Night-Time Brain Inter-Hemispheric Asynchrony in Sleep Apnea Patients Carry Information on Neuropsychological Impairment

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***Abstract*—Obstructive sleep apnea (OSA) is a serious sleep disorder with diurnal symptoms including neuropsychological impairments such as excessive daytime sleepiness and loss of attention. There are no efficient tools to measure these impairments in current clinical practice. In this paper, we explore the feasibility of measuring neuropsychological impairments using electroencephalography (EEG) data acquired during the standard clinical sleep diagnostic test known as polysomnography (PSG). We hypothesized that left-right hemispheric EEG asynchrony could quantitatively characterize neuropsychological impairment in OSA in a population of sleep laboratory patients. We acquired EEG data from 50 subjects undergoing routine PSG, using symmetric electrode derivations of C4-A2 and C3-A1. Their neuropsychological performance was assessed via a psychomotor vigilance task (PVT). We computed the left-right EEG asynchrony and developed a logistic regression model (LRM) to classify patients according to their PVT performance. Leave-one-out cross-validation studies on a LRM model with two-class PVT performance achieved a sensitivity of 83% (95% CI: 66-100%) and a specificity of 78% (95% CI: 64-92%). These results indicate that EEG asynchrony during sleep carries information on daytime neuropsychological impairments in OSA subjects.**

Keywords—asynchrony, electroencephalography, neuropsychological, obstructive sleep apnea, psychomotor vigilance task

I. Introduction

Obstructive sleep apnea (OSA) is a serious sleep disorder characterized by breathing interruptions during sleep. Complete cessation of airflow is defined as obstructive apnea and a partial decrease is defined as obstructive hypopnea. The total number of apnea and hypopnea events per hour of sleep is known as the respiratory disturbance index (RDI) [1].

The reference standard for OSA diagnosis is attended Type 1 polysomnography (PSG) [1]. RDI is the major outcome of PSG but it also provides information related to the neurophysiological aspects of sleep such as the arousal index (ArI), sleep latency (SL), and sleep architecture.

Long-term risks of OSA includes diabetes, obesity, and cardiovascular disease [2]. The immediate daytime consequences are neuropsychological impairments [3] such as excessive daytime sleepiness, loss of attention, and impairment of memory and executive functions.

Neuropsychological impairments cause medical, economic and social costs to society. According to the national highway traffic safety administration, USA, drowsy driving causes 100,000 motor vehicle crashes per year resulting in 1,550 deaths, 71,000 injuries and $12.5 billion in damage [4]. OSA patients are 2-9% more likely to have motor vehicle and industrial accidents [4].

Neuropsychological manifestations are direct consequences of OSA but there are no efficient tools to measure these. At present, sleep physicians depend on surrogate clinical measures and subjective analysis to evaluate the neuropsychological aspects of OSA. These measures are (i) sleep latency (from a multiple sleep latency test (MSLT) [5]), arousal index, and subjective questionnaires (such as Epworth sleepiness scale (ESS) [6]) and (ii) interview with the patients.

The main outcome of MSLT is sleep latency, defined as the time required for falling asleep. It provides an indirect quantitative measure of "sleepiness". MSLT is expensive, resource intensive, subjective (in scoring sleep onset), and is not available for routine clinical use on all OSA patients. It requires specialized equipment and several hours of expert care. The arousal index, defined as the number of EEG arousals per hour of sleep, is available from a routine in-facility PSG test as another quantitative measure. However, it is only weakly correlated with diurnal neuropsychological manifestations of OSA limiting its clinical utility.

The ESS is a questionnaire which provides a measure of the general level of daytime sleepiness based on subject self-assessment. However, the self-reporting of sleepiness is not that reliable when subjects have cognitive deficiencies clouding their capacity for judgment. ESS, despite its subjective nature and the narrow focus on sleepiness, is widely used in clinical practice.

Tests such as the psychomotor vigilance task (PVT) can also be used to assess different facets of neuropsychological impairment in OSA. These tests are time consuming, can be expensive, and may not be suitable for the elderly or people with disabilities. Neuropsychological tests, despite their

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potential, are not available as a routine clinical tool in managing OSA.

In this paper, we explore the hypothesis that regional brain asynchrony as manifested in sleep EEG carries information of neuropsychological impairments in OSA patients as captured in PVT results. The rationale behind our hypothesis is illustrated in Fig. 1. It is based on the observations (a) OSA patients suffer from neuropsychological impairment [3, 7, 8] and (b) OSA patients suffer brain asynchrony due to brain structural [9-11] and functional changes [12-15]. Thus, it is conceivable brain asynchrony and neuropsychological impairments have an association in OSA.

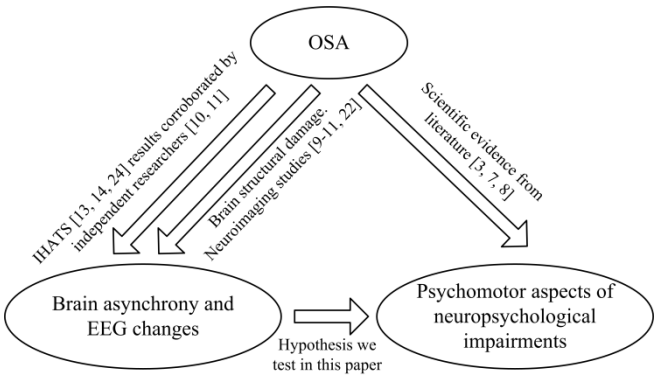

Fig. 1. Conceptual framework of the proposed research.

II. Material and Method

A. Setting and Subjects

Data recording environment for this study is the sleep diagnostic laboratory of the Princess Alexandra Hospital (PAH), in Brisbane, Australia. All subjects undergoing PSG for suspected sleep disordered breathing were approached for participation. The experimental procedures involving human subjects described in this paper were approved by the institutional review board.

In this work, we studied data from 50 subjects. Subjects on medications for neurological disorders such as Parkinson's, epilepsy, schizophrenia, etc. were excluded from the dataset. Demographic characteristics of the subjects are as follows: male to female ratio=20:30, mean age=54.8±16.0 years, mean BMI=36±9kg/m^2, mean ESS=11.7±6.0, and mean RDI=29.83±38 (n=14 for RDI<5; n=12 for 5≤RDI<30, and n=24 for RDI≥30).

B. Psychomotor Vigilance Task

PVT test was performed on the evening of the scheduled PSG study. A portable tablet computer loaded with an open-source software system (PEBL) [16] was used to conduct the test. The PEBL allows design and run simple-response-time (SRT) task similar to the one described in the original PVT test [17]. Test was conducted in a quiet examination room. Subjects were instructed to respond to the appearance of a visual stimulus (an 'X' in the middle of the screen) by pushing a response button as quickly as possible. The test ran for 10-15 minutes with visual stimuli appearing at random time intervals spanning from 250–2500ms. Subject reaction times (RTs) were recorded from each PEBL-SRT trial.

According to existing literature, sleepiness and sleep loss are associated with increased variability in the reaction time [17, 18] which could be evaluated using the following PVT measures: (i) mean 1/RT measuring response speed, (ii) median RT, (iii) fastest 10% of RT, (iv) the slowest 10% of RT, and (v) number of lapses defined as number of RT≥500ms.

Even though SRT-PVT test has proven capability to capture aspects of neuropsychological impairment in OSA, it suffers from the non-availability of published normative data. Considering that our use of SRT-PVT data is limited to answering the question that whether EEG asynchrony carries information on neuropsychological impairment, we followed a process of PVT clustering to overcome the absence of normative data.

Inspired by existing literature, we clustered subjects into two groups, G1 and G2, based on five PVT parameters: (i) mean of 1/RT, (ii) median of RT, (iii) mean of fastest 10% of RT, (iv) mean of slowest 10% of RT, and (v) lapse count. The good PVT group (G2) has lower RT values and a lower lapse count and the inferior PVT group (G1) has them relatively higher.

We used the standard k-means algorithm [19] on these parameters to group the subjects into two groups. It should be noted that this clustering algorithm is an unsupervised technique and hence 'discover' the two clusters based on the parameters themselves. Once we form the two groups G1 and G2, our next task reduces to finding out if EEG asynchrony-based features can be used to build classification models that can map subjects to the associated group (G1 or G2) with reasonable accuracy.

In Section C, we describe the method we followed to extract mathematical features from the EEG asynchrony data.

C. Inter-Hemispheric Asynchrony Time Series

Previously, we have developed the concept of inter-hemispheric asynchrony time series (IHATS) [14] to compute the inter-hemispheric asynchrony as manifested in sleep EEG. EEG channels C4-A2 (from right hemisphere) and C3-A1 (from left hemisphere) recorded during PSG were segmented into epochs of 30 seconds. We then calculated the spectral correlation between the two hemispheric data (for each epoch of 30s) in different frequency bands for all sleep epochs. The frequency bands we used followed the convention used in clinical EEG analysis: delta (0.1–4 Hz), theta (4.1–8 Hz), alpha (8.1–12 Hz), beta (12.1–16 Hz), high beta (16.1–25 Hz), and gamma (25.1–35 Hz). The collection of correlations at contiguous 30 epochs is called an IHAT. Thus we got one IHAT per each frequency band from each patient [14, 15]. Finally, four statistical features were computed. These are mean, standard deviation, skewness, and kurtosis. A total of 24 statistical features (4 statistical features × 6 frequency bands) form the final feature vector.

D. Classification Model

Exhaustive feature selection is used to identify a subset of features from the candidate feature vector computed earlier. Once a reduced feature set is selected, we train a logistic regression model (LRM) to map each patient to one of the groups, G1 or G2.

LRM is a generalized linear model which uses several independent features to estimate the probability of a categorical event (dependent variable). In this work, the

dependent variable Y is assumed to be equal to "one" (Y=1) for 'poor PVT performance subjects in G1' and "zero" (Y=0) for 'good PVT performance subjects in G2'. A model is derived using a regression function to estimate the probability Y=1, (that is, subject belongs to group G1) given the independent variable (IHATS statistical features) as follows:

$$P\left(Y=1|_{f_1,f_2,\ldots f_F}\right)=\frac{e^z}{e^z+1} \quad (1)$$

where

$$z=\beta_0+\beta_1 f_1+\ldots\beta_F f_F \quad (2)$$

$f_1, f_2, \ldots, f_F$ are independent variables (IHATS features), β_0 is the intercept, and $\beta_1, \beta_2, \ldots, \beta_F$ are the regression coefficients of independent variables.

We used leave-one-out cross-validation (LOOCV) technique for LRM design. That is, one subject was left out for testing and the remaining subjects used for training the model, one at a time. The performance of the model is evaluated using sensitivity and specificity, assuming the PVT based k-means grouping of G1/G2 as the reference technique. We also provide confidence intervals of the estimates.

III. Results

A. PVT Performance and Subject Characteristics

EEG and PVT data from 50 subjects is analyzed. In the absence of adult normative data for PVT tests, in section II-B we separate 50 subjects into two groups, G1 and G2, based on the outcomes of the PVT test. Group G1 represents subjects with poor PVT performance and G2 represents subjects with good PVT performance. The clustering results are given in Table I.

In order to get some understanding on the performance of the clustering technique we used, the silhouette technique [20] was used. The silhouette values ranges from -1 to +1; the higher the value the better the separation of a cluster from its neighbors. The mean silhouette for the two clusters G1 and G2 in our study is 0.82, indicating a successful clustering. Note that if we seek 3 clusters, the value reduces to 0.78. Seeking more clusters led to further reduction in the silhouette values. This shows that two is the best number of clusters for this dataset and, overall, the points in the two clusters are well separated.

Furthermore, the mean RDI and mean ArI were significantly high in G1 subjects compared to subjects in G2, indicating the detrimental effects of apnea/hypopnea/arousal events on neuropsychological functions. Interestingly, no significant difference between two groups of subjects is seen in measures such as sleep efficiency, total sleep time, and Epworth sleepiness scale.

The most dominant PVT outcome in grouping subjects, as determined using one-way ANOVA, was the mean of slowest 10% of RT (p<0.001) followed by lapses (p=0.0999) and mean 1/RT (p=0.1201). This is consistent with [18] where, in a study of 74 subjects, metrics related to lapses and measures of psychomotor speed (mean 1/RT and mean of slowest 10% 1/RT) are proposed as the primary outcome metrics to categorize sleep deprived and alert subjects.

TABLE I. Distribution after separating subjects into two groups according to PVT performance using k-means clustering algorithm.

	G1	G2	ANOVA (p-value)
Num. of subjects	18	32	–
Mean 1/RT (1/seconds)	2.3±0.6	2.5±0.6	0.1201
Median RT (ms)	494±200	432±191	0.2832
Mean of Fastest 10% RT (ms)	338±94	338±125	0.9975
Mean of Slowest 10% RT (ms)	2429±1512	707±296	9.3565×10^{-8}
Lapses	43±37	25±35	0.0999
RDI	51±52	18±20	–
ArI	32±25	21±15	–
SE	72±19	67±18	–
TST (min)	316±96	296±84	–
ESS	12±6	12±6	–
BMI (kg/m^2)	36±10	36±8	–
Age (years)	53±21	55±14	–
Gender (M:F)	6:12	14:18	–

B. Prediction of PVT Performance Using Inter-Hemispheric Asynchrony Time-Series Features

Using the EEG electrode configuration (C4-A2 and C3-A1), as described in Section II-C, the IHA time series was computed separately for the delta, theta, alpha, beta, high-beta, and gamma bands of EEG, in sleep epochs. As such, a total of 24 statistical features were computed. Exhaustive feature selection was then performed, searching up to a maximum of 6 feature combinations, to select a subset of features which give best validation performance.

Table II gives LOOCV results as a contingency table. The LRM was able to predict subjects with poor PVT performance with sensitivity of 83% (95% CI: 66-100%) and a specificity of 78% (95% CI: 64-92%). The 95% confidence interval (CI) values were computed as given in [21].

IV. Discussion and Conclusion

We analyzed PVT test performance of OSA subjects and their inter-hemispheric asynchrony of the brain as manifested in EEG signal recorded during PSG. The sensitivity and specificity performance of the models indicate that there is a non-random, non-trivial relationship between EEG asynchrony and PVT measures indicative of neuropsychological impairment in OSA.

Our results indicate that IHATS properties have potential to characterize the illusive neurocognitive impairments in OSA. As far as we know, this is the first study investigating the association between daytime neuropsychological impairment and night-time inter-hemispheric EEG asynchrony in OSA subjects.

There is some evidence in existing literature to explain this association. There exists irrefutable scientific evidence [3, 7, 8] supporting the association between OSA and neuropsychological impairments. Evidence on the brain EEG asynchrony in OSA comes from two independent pathways, structural and functional. Several neuroimaging studies [9-11] on moderate to severe OSA patients have found unilateral structural damage in brain regions that also lead to

TABLE II. PERFORMANCE OF LRM IN PREDICTING PATIENTS WITH POOR PVT PERFORMANCE USING IHATS FEATURES.

		Subject Group (PVT Clustering)		
		G1	G2	
Predicted Group (IHATS-LRM)	G1	15	7	PPV = 68.18%
	G2	3	25	NPV = 89.29%
		Sensitivity = 83.33%	Specificity = 78.13%	Accuracy = 80.00%

functional alterations, including areas responsible for neuropsychological functions. Affected areas include frontal and parietal cortex, temporal lobe and hippocampus [9, 10]. MRI imaging study [22] on OSA patients have shown reduced neuronal density in brain regions regulating memory and executive functions. Evidence for functional changes in brains of OSA patients can be gathered from studies in [23, 24]. Our own research on EEG in OSA have showed that left-right hemispherical asynchrony changes when sleep state changes from NREM to REM sleep [15], within different sleep stages of NREM [25] and sleep state transitions due to apnea and arousal events [15].

Neuropsychological manifestations of OSA are the most conspicuous daytime symptoms in OSA [3, 7]; they can have a major impact on patients' daily activities and occupational safety as well as long term metabolic health. Despite the importance of neuropsychological measures, currently there are no efficient and objective tools to measure them in clinical practice. This paper provides a pioneering solution to this problem. It delivers fully automated, objective technology that can quantify neuropsychological manifestations of OSA using standard PSG data.

Proposed technology may also help in clinical decision making. At present, the decision to begin OSA treatment is not straightforward. The PSG-provided RDI alone is insufficient for the purpose. The physician has to make a judgment call on how severe the effects of OSA are on a given patient. Proposed technology may help in this process by providing an objective method to quantify neuropsychological manifestations of OSA. At present clinicians rely on self-reported questionnaires such as ESS.

The dataset used in this study is small (n=50) and the results need to be interpreted taking it into account. Further validation will be required on large data sets.

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