Brain Functional Connectivity as Biomarker for Propofol-Induced Alterations of Consciousness

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***Abstract*—Understanding neural correlates of consciousness and its alterations poses a grand challenge for modern neuroscience. Even though recent years of research have shown many conceptual and empirical advances, the evolution of a system that can track anesthesia-induced loss of consciousness is hindered by the lack of reliable markers. The work presented herein estimates the functional connectivity (FC) between 21 scalp electroencephalogram (EEG) recordings to evaluate its utility in characterizing changes in brain networks during propofol sedation. The sedation dataset in the University of Cambridge data repository was used for analyses. FC was estimated using the debiased estimator of the squared Weighted Phase Lag Index (dWPLI2). Spectral FC networks before, during, and after sedation was considered for 5 EEG sub-bands. Results demonstrated significantly higher alpha band FC during baseline, mild and moderate sedation, and recovery stages. A striking association between frontal brain activity and propofol-sedation was also noticed. Furthermore, inhibition of frontal to parietal and frontal to occipital connections were observed as characteristic features of propofol-induced alterations in consciousness. A random subspace ensemble framework using logistic model tree as the base classifier, and 18 functional connections as features, yielded a cross-validation accuracy of 98.75% in discriminating baseline, mild and moderate sedation, and recovery stages. These findings validate that EEG-based FC can reliably distinguish altered conscious states associated with anaesthesia.**

Keywords: **Functional connectivity (FC), electroencephalogram (EEG), consciousness, propofol sedation.**

I. Introduction

Identifying robust and objective signatures for consciousness and its alterations induced either naturally as in sleep, or meditation, and externally as in disorders of consciousness (DoC) or drug-induced sedation, is a challenge for modern neuroscience. Although several standardized questionnaires like the Coma Recovery Scale (CRS-R) [1], and Richmond Agitation-Sedation Scale (RASS) [2] exist, and are even considered as gold standards for identifying altered states of consciousness associated with DoC or sedation, administering them requires knowledge and expertise of clinicians. Moreover, these questionnaires are heavily based on changes in behavioral responses and lack any evidence of a subject's conscious content, thus making them rather subjective and prone to diagnostic errors [3].

The study reported herein investigates surface electroencephalography (EEG) based functional connectivity (FC) as an objective marker for the reversible altered conscious states induced by propofol, an anaesthetic drug commonly used in clinical medicine [4]. Even though EEG is relatively economic, easy to measure from the scalp, and has long been known to implicate anaesthetic-induced changes in brain dynamics [5], EEG-based assessment of depth of anaesthesia in an individual is still not widely used in clinical settings. This is despite the fact that intraoperative awareness during anaesthesia continues to result in pain and prolonged and unwanted outcomes, including post-traumatic stress disorder or depression in patients [6]. The absence of a reliable 'depth of anaesthesia' monitor in an operating room can be partly attributed to the lack of robust EEG markers which can reliably track the loss and re-establishment of consciousness [7], [8]. This study attempts to incorporate EEG-based FC measures into machine learning algorithms to establish a classification scheme that can distinctly identify altered conscious states during anaesthesia.

The sedation dataset available for public access in the University of Cambridge data repository [9] was used for analyses. The debiased estimator of the squared Weighted Phase Lag Index (dWPLI2) [10] was used as a metric of FC between 21 EEG electrode sites, covering the whole brain. FC between all possible pairs of electrodes was computed and used as features for the proposed classification scheme. Boruta based feature selection was performed to identify an appropriate feature subset [11], which was further used to develop a random subspace ensemble classifier framework [12] for discriminating altered conscious states during anaesthesia.

II. Methodology

A. Dataset Description

The propofol sedation database available for public access in the University of Cambridge Data Repository [9] was used for analyses presented in this paper. The dataset comprises EEG recorded in 20 healthy participants [11 females, and 9 males, Age: 30.9 +/- 11.0 years (mean+/-SD)], who were given the sedative propofol. For each participant, there are 4 datasets each with approximately 7 minutes of EEG at rest, recorded at baseline, during mild sedation (propofol concentration measured in blood plasma is 0.6 μg/ml), moderate sedation (propofol concentration measured in blood plasma is 1.2 μg/ml), and finally at recovery.

B. Data Pre-processing and Labelling

EEG data sampled at 250Hz from 21 channels over the scalp surface as per 10-20 system (Fig. 1) were used for analysis. Time series data were filtered between 0.5-45Hz, segmented into 10-second epochs, cleaned and preprocessed to remove artifacts, and referenced to the average of all channels.

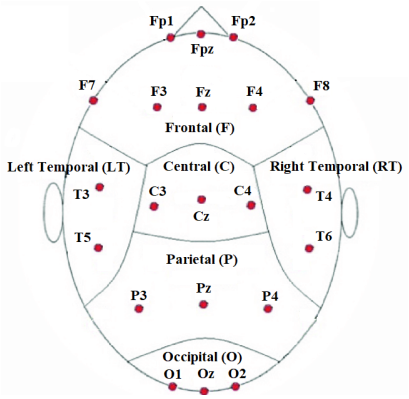

Fig. 1. EEG electrode placement covering all lobes

The generated epochs were further labeled as baseline (BL), mild, moderate (MOD), and recovery (REC) based on the data collection phase. TABLE I illustrates a summary of generated epochs.

TABLE I
SUMMARY OF EPOCHS GENERATED

Label	BL	MILD	MOD	REC
# Epochs	755	780	751	796
	Total: 3082			

C. Functional Connectivity Estimation

FC between all possible pairs of EEG electrodes was computed using the dWPLI2 metric, resulting in a feature vector of dimension 210 for each epoch. The metric proposed by Vinck et al. [10] is a measure of phase synchronization that is based solely on the imaginary component of the cross-spectrum of two time series. Mathematically, dWPLI2 can be expressed as:

$$\text{dWPLI2} = \frac{\sum_{j=1}^{N}\sum_{k\neq j} Im\{X_j\}Im\{X_k\}}{\sum_{j=1}^{N}\sum_{k\neq j} |Im\{X_j\}Im\{X_k\}|} \quad (1)$$

where $Im\{X\}$ denotes the imaginary component of the cross-spectrum of the complex-valued random-variable X and N denotes the number of trials.

In comparison to the previous phase synchronization measures, the dWPLI2 metric is known to have increased sensitivity to detect true interactions (even when the interacting sources are spatially close) and increased robustness to noise [13], [14]. Furthermore, the metric also debiases connectivity based on the number of epochs, thereby preventing any sample size bias from being introduced by a direct estimator [10]. This debiasing can cause the dWPLI2 to be negative and, therefore, its value ranges from -1 to 1.

D. Feature Selection and Classification

The FC metric was computed separately for 5 specific EEG bands viz., Delta (0.5-4 Hz), Theta (4-8 Hz), Alpha (8-12 Hz), Beta (12-30 Hz), and Low Gamma (30-45 Hz).

This was followed by feature selection, which is an important pre-processing step in the machine learning pipeline to identify a subset of the most pertinent features. Boruta, an "all-relevant" feature selection algorithm [11] was used in this study. It yields a set of all appropriate features from the feature set instead of selecting only the non-redundant ones. Boruta-based feature selection was done separately for each EEG band to identify all appropriate functional connections in each band.

The identification of conscious states during anaesthesia was formulated as a 4-level classification problem with BL, MILD, MOD, and REC as target classes. A random subspace ensemble (RSE) learning framework [12] was used for classification. RSE has recently gained more attention in functional magnetic resonance imaging (fMRI) based classification of brain images and was found to be more effective than some of the most widely used classifier ensembles such as Bagging, AdaBoost, Random Forest, and Rotation Forest [15].

In RSE, the training data is modified such that random subspaces of feature space are chosen and classifiers are built for each subspace. The results of these classifiers with different accuracy scores are further aggregated by utilizing a majority voting. Thus, RSE benefits from the aggregated decision of such classifiers and provides better predictive results than a single classifier built on the original training set in the entire feature space [16]. Four parameters viz., base classifier, number of iterations, seed and subspace size were tuned carefully during the implementation of RSE so as to achieve the best performance. Eight classifiers viz., Naive Bayes, REP Tree, Random Tree, Multilayer Perceptron, k-NN, SVM, Random Forest, and Logistic Model Tree were applied to identify the best base classifier. The 10-fold cross-validation accuracy was chosen as the performance index.

III. RESULTS AND DISCUSSIONS

The whole-brain functional connectivity in 5 EEG bands viz., delta, theta, alpha, beta, and low-gamma during baseline, mild and moderate sedation, and recovery stages were assessed to investigate the impact of propofol on the oscillatory neural interactions. The assessment was done by averaging FC values of all 210 connections across multiple epochs for each band during specific stages. Results are summarized in Fig.2.

A pairwise comparison of means was performed using the Bonferroni's method to determine if the differences are statistically significant. As can be seen from Fig.2, the alpha band FC is significantly higher during baseline, mild and moderate sedation, and recovery stages. It may also be noted that the connectivity in the alpha band decreases as the sedation level increases from mild to moderate, although the decrease is not statistically significant. Nevertheless, the alpha band connectivity increases significantly as subjects proceed to the recovery stage from the moderate sedation stage, indicating that alpha connectivity is indeed compromised during sedation. This warrants a more detailed investigation of the connectivity in the alpha band. Fig. 3 is an illustration of the average alpha band connectivity map of 20 subjects during four stages of the sedation study.

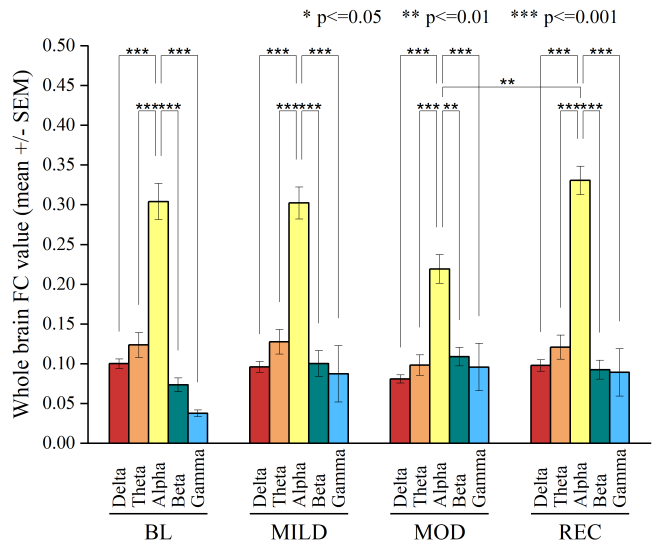

Fig. 2. Summary of whole-brain connectivity changes during different experimental phases. Significant differences after multiple comparisons using Bonferroni's method are presented.

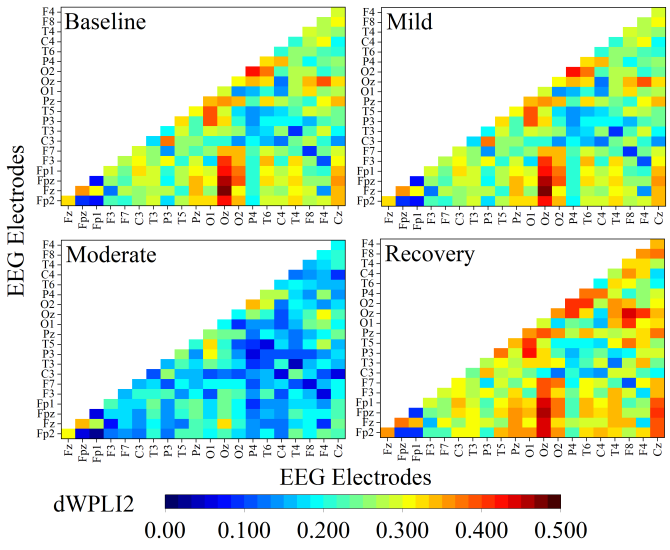

Fig. 3. Alpha band whole-brain connectivity maps during different experimental phases, averaged across 20 subjects.

The map demonstrates that the loss of consciousness during moderate sedation is accompanied by a decrease in corticocortical connectivity from frontal to parietal and occipital regions of the brain. This, in turn, contributes to the overall reduction in whole-brain connectivity. However, it may be noted that these connections are more or less preserved during mild sedation. These findings converge with the existing literature that highlights the reduction in the efficiency of cortical networks during propofol sedation [7], [17]. A similar disintegration in the alpha connectivity has also been reported with other anaesthetic agents like ketamine and sevoflurane [18], [19].

Further, Boruta based feature selection was performed separately for each specific EEG band to identify the "all-relevant" feature subset, that can effectively distinguish the target classes. Results are summarized in TABLE II.

TABLE II
CONNECTIONS CONFIRMED AS SIGNIFICANT BY BORUTA

EEG Band	# Connections	Significant Connections
Delta	4	Fz-F7, Fpz-C4, Fp1-T4, F4-Cz
Theta	3	Fz-C4, Fz-Cz, Fpz-F8
Alpha	7	Fp2-C4, Fpz-P3, Fpz-O2, Fpz-C4, F3-F4, T4-T5, F8-C4
Beta	3	Fpz-Fz, Fp1-Fz, Fp1-F3
Low Gamma	1	Fp2-F4

It may be noted that 17 out of 18 connections identified as significant, involve electrodes in the frontal lobe of the brain. Also, a total of 7 connections belong in the frontal region. These may be indicative of an association between frontal brain activity and propofol-induced unconsciousness. In this context, it is worth noting that wave-like patterns in the frontal EEG are known to provide an estimation of intraoperative anaesthetic depth during sevoflurane surgical anaesthesia [20]. Two connections along the anterior-posterior axis of the brain viz., Fpz-P3, Fpz-O2 were identified as significant in the alpha band. This is in line with previous evidence highlighting the inhibition of frontal to parietal and frontal to occipital connections as neurophysiologic correlates of general anaesthesia [21] and disruption of frontal-parietal communication as a common feature of anaesthesia-induced alterations in consciousness [22].

The Boruta-selected connections were further used as features to develop RSE frameworks for classification. The performance measures of classification models developed using features from specific EEG bands as well as their concatenation are summarized in TABLE III.

It may be noted that the highest cross-validation accuracy of 98.75% was achieved while using all 18 features spread across 5 EEG sub-bands. Logistic Model Tree was used as the base classifier for the model. The maximum number of iterations was set at 10, seed at 1, and the subspace size at 0.51 to achieve this performance. This accuracy is higher than some of the recent works reporting the use of EEG-based spectral analysis and machine learning techniques to estimate the depth of anesthesia. Mirsadeghi *et al.* [23] studied 25 subjects and developed a machine learning method to distinguish awake and anesthetized patients using EEG features like power in different bands (delta, theta, alpha, beta, and gamma), total power, spindle score, and entropy. They reported an accuracy of 88.4%. Similarly, Shalbaf *et al.* [24] used multiple EEG features to classify four states viz., awake, light, general, and deep anesthesia, during sevoflurane sedation. The model yielded an accuracy of 92.91% and demonstrated generalizability on propofol and volatile anesthesia patients with 93% accuracy.

Classification accuracy of the reported order, yielded by the proposed model, is indeed an indication of the utility of functional connections across the human brain as characteristic signatures and potentially reliable correlates of conscious states associated with propofol sedation. The fact that the proposed classification framework utilizes only 18 functional connections involving 14 EEG channels has entailed advantages in a clinical setting. The reduced number of electrodes can make the system less cumbersome. Moreover, as a majority of these electrodes are in the frontal lobe, it allows

TABLE III
PERFORMANCE MEASURES OF DIFFERENT CLASSIFICATION MODELS

	EEG Band: Delta					EEG Band: Theta				
Class	Accuracy (%)	TP Rate	FP Rate	ROC Area	PRC Area	Accuracy (%)	TP Rate	FP Rate	ROC Area	PRC Area
BL	52.50	0.60	0.15	0.78	0.60	42.50	1.00	0.47	0.77	0.42
MILD		0.35	0.03	0.87	0.70		0.00	0.00	0.57	0.28
MOD		0.70	0.27	0.79	0.59		0.70	0.30	0.70	0.38
REC		0.45	0.18	0.73	0.53		0.00	0.00	0.50	0.25
	EEG Band: Alpha					EEG Band: Beta				
BL	43.75	0.00	0.00	0.52	0.26	43.75	0.75	0.32	0.78	0.54
MILD		0.00	0.00	0.55	0.27		0.10	0.08	0.58	0.31
MOD		0.85	0.28	0.78	0.46		0.75	0.25	0.82	0.60
REC		0.90	0.47	0.72	0.38		0.15	0.10	0.58	0.32
	EEG Band: Low Gamma					EEG Band: 0.5-45 Hz				
BL	42.50	0.60	0.18	0.73	0.43	98.75	1.00	0.02	1.00	1.00
MILD		0.45	0.23	0.62	0.33		1.00	0.00	1.00	1.00
MOD		0.65	0.35	0.70	0.36		0.95	0.00	1.00	1.00
REC		0.00	0.00	0.59	0.30		1.00	0.00	1.00	1.00

Accuracy: Proportion of unseen instances that are correctly classified during the 10-fold cross-validation; True Positive rate (TP Rate): Proportion of positive instances that are correctly classified as positive; False Positive rate (FP Rate): Proportion of negative instances that are erroneously classified as positive; ROC area: Area under the Receiver Operating Characteristics (ROC) curve; PRC area: Area under the Precision/Recall (PRC) plot.

for rapid placement of electrodes below the hairline. Results also highlight that a learning model developed using only alpha band features can distinguish the moderate sedation and recovery phases reliably. This is of utmost significance in the context that the sedation safety standards put forth by the Association of Anaesthetists of Great Britain and Ireland (AAGBI) [25] has identified the transition from sedation to recovery as a period of high risk to the patient and has recommended continued monitoring until full recovery.

IV. CONCLUSIONS

The work presented here attempts to identify differences if any, in the FC at different levels of consciousness associated with propofol sedation: from the overall connectivity strength in each state to the numbers of connections of particular brain areas, and disruptions of specific functional correlations. This is envisaged as a precursor to further studies that will help in understanding the neuronal basis of consciousness and its alterations, thereby enabling the discovery of objective and accurate markers for them.

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