Validating Graph Theory Based Classification of Brain States under Propofol Sedation using Measurements of Plasma Drug Levels

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**Background:** The neuroanatomical basis of consciousness is intensely debated. While classical approaches involve the comparison of neural responses to stimuli in awake and sedated states, emerging evidence suggests that resting state fMRI during anesthesia/sedation may provide additional insights. We used the anaesthetic drug propofol to modulate consciousness and designed a classifier to discriminate states of sedation based on graph theoretic properties. We also designed a rigorous framework to compare the classifications returned with measured plasma propofol levels.

**Methods:** Resting state fMRI was acquired from 25 adults, 19-52 years old (mean=34.62) on a Siemens Trio 3T scanner (WBIC, Cambridge). Propofol was administered aiming to achieve three target plasma levels - no drug (baseline), 0.6 µg/ml (mild) and 1.2 µg/ml (moderate sedation). ROIs from the AAL atlas (132) were used to extract time series from preprocessed fMRI data (156 volumes, TR=2s, eyes closed). Networks constructed were based on correlation between ROI pairs and were thresholded at various densities. Graph properties computed included global efficiency, transitivity, modularity, eigenvector centrality, participation coefficient, and betweenness centrality. Classifiers (support vector machine, decision trees, and K-nearest neighbour), were trained using different graph properties at each network density as separate sets of features. The top 20 classifiers were ranked by leave-one-out cross-validation accuracy on the training set and were tested on a blind data set from the same subjects at the recovery stage. Classifications from the top 20 classifiers were combined incrementally using a Bayesian combination rule. Classification labels were only assigned when the confidence level of the combined classifier reached 95% for each sample. Classification labels were compared to plasma propofol levels measured during each stage of sedation and recovery. Classification labels were assigned to the recovery networks based on proximity of recovery drug level to drug levels during different stages of sedation.

**Results:** Classification labels returned by the pipeline matched the targets assigned based on physiological anaesthetic levels in 71% of subjects. When parameters of the methodology –both in the classification pipeline and in assigning target labels – were optimised, accuracy increased to 81%.

**Conclusions:** The classification pipeline was able to classify sedation stages in agreement with plasma drug level measurements in the majority of subjects tested. This is validation of the methodology’s potential in a clinical setting as well as a significant first step in understanding the mechanics of anaesthesia’s effects on brain network connectivity. Further work is required to localize major changes in network structure.