Predictive Modelling the Effect of Neurostimulation on Memory Biomarkers in Epileptic Patients

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Rationale: Many epileptic patients suffer from memory dysfunction. Neurostimulation has emerged as a novel treatment option for seizure control in patients with medically refractory epilepsy, and it has the additional potential to enhance memory in these patients. One of the first challenges to enhance memory using neurostimulation is to identify optimal stimulation parameters. We present a modeling approach to predict the effect of different stimulation parameters and locations on memory biomarkers.

Methods: Sixty four patients who underwent intracranial EEG monitoring completed experiment sessions of free recall memory tasks. For each patient, calculated measures of specific EEG band power was combined with memory task performance to produce a scalar biomarker for memory performance. Following the identification of the memory biomarker, a target in the brain was selected for neurostimulation. A grid search of the stimulation parameter space was conducted in an exploratory fashion: frequency of pulse (P), 10, 25, 50, 100, or 200Hz; amplitude between 0.25 to 3.0mA in steps of 0.25mA; duration of 250, 500, or 1000ms. A positive change in the biomarker indicated an improvement in memory performance; conversely, a negative change indicated poor performance. For each stimulation, we recorded the pre-stimulation biomarker, stimulation frequency, stimulation duration, stimulation amplitude, and post-stimulation change in the biomarker. For each location, we used a linear least-squares model to predict change in biomarker from combinations of pre-stimulation biomarker and stimulation parameters. In the first analysis, we looked at prediction using stimulation alone, pre-stimulation biomarker, and a combination. Mean squared error (MSE) between predicted and actual biomarker change was used to judge performance with leave-one-out cross-validation. In the second analysis, we looked at the influence each predictor had on change in biomarker by examining the t-stat p-value of each term after fitting the model. We again used MSE but with k-folds (k=30) cross-validation.

Results: Analysis of post-implantation imaging grouped stimulator probes into twenty-one unique anatomic locations. Not all subjects were able to complete the same full set of stimulation sequences and so the grid was sparsely sampled in some areas; however, there were a total of 81,716 stimulation observations collected across all subjects. Figure 1 shows the predictability of the post-stimulation changes in the memory biomarker as a function of the anatomical location, stimulation parameters, and the biomarker before stimulation. Combining stimulation parameters and the pre-stimulation value of the biomarker is the best predictor of the changes in the memory biomarkers after stimulation. Figure 2 shows the influence each of the predictors has on change in biomarker at three locations. The biomarker itself is most significant followed by amplitude, while duration appears to have no significant influence.

Conclusions: This presents a predictive modelling approach for exploring the effects of stimulation on electrophysiological biomarkers of cognitive performance in epileptic patients. These findings will inform subsequent experiments to determine potential anatomical targets and interesting areas in the neurostimulation parameter space.

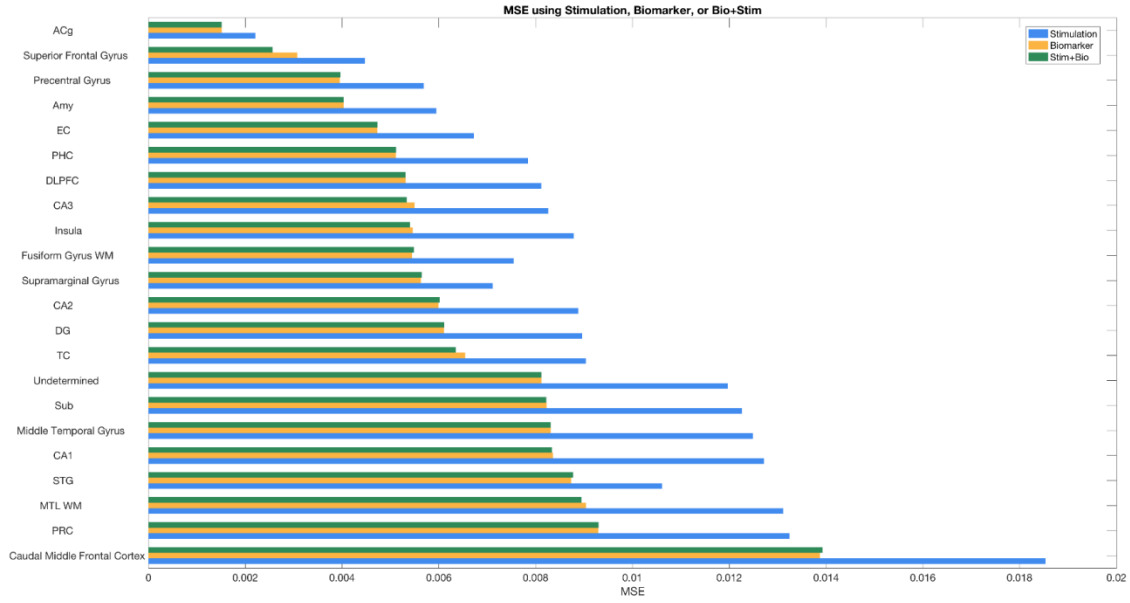

Figure 1. Generalization accuracy of the predictive model based on the anatomical distribution of the neurostimulation and different predictors: stimulation parameters, pre-stimulation biomarker, and a combination of these two predictors (Stim+Bio)

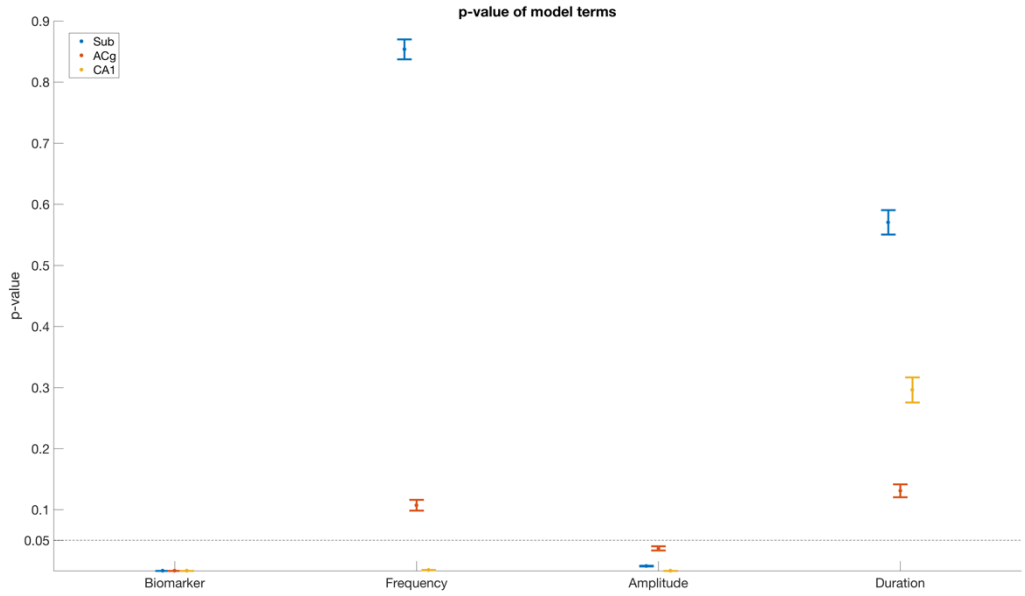

Figure 2. Contribution of each predictor to the model accuracy at three representative stimulation locations. The p-value after model fit indicating the significance of effect on change in biomarker (mean and standard error over k-folds=30) after stimulation. The pre-stimulation state of the biomarker has the most significant impact. Amplitude also has next most influence. Duration has no significant influence.