CHARLOTTE LUFF - 05

c.luff16@imperial.ac.uk

Neurophysiological characterisation, and investigation into the mechanism of action of temporal interference (TI) non-invasive brain stimulation

Charlotte E. Luff, Ho-Jun Suk, Edward. S. Boyden, Nir Grossman

UK Dementia Research Institute- Imperial College London, Massachusetts Institute of Technology

Introduction: Temporal interference (TI) stimulation is a novel and potentially revolutionary technique for non-invasive deep brain stimulation. During TI, two very high frequency (>1kHz) (f1 - (carrier frequency) and f2) currents, that differ in frequency by a small amount (df), are applied to the brain. Where the two electric fields overlap within the brain, the envelope amplitude of the combined field changes periodically at the difference frequency (df) (temporal interference). Neurons in the overlap of the two electric fields are stimulated to fire at df. Focality of stimulation, however, is currently unable to rival that of deep brain stimulation (DBS), and the physiological mechanism of action of TI is unknown.

Objective: To facilitate improvement of this technology, characterisation of the neuronal response to TI must be undertaken, and the mechanism of action investigated. We hypothesise that TI stimulation works via a frequency multiplexing mechanism that occurs due to non-linear polarisation at the cell membrane- caused by a nonlinearity in the neuron or neuronal network.

Methodology: TI-induced depolarisation was investigated using single compartment Hodgkin-Huxley (H-H) modelling and *in vivo* automated whole cell patch clamp.

Results: Characterisation of TI using H-H modelling revealed that the current threshold for action potential firing decreases as carrier frequency increases. This is supported in a trend in the electrophysiology data, however the results are not significant due to small n numbers. H-H modelling also suggests that as difference frequency increases, current threshold decreases.

H-H modelling suggests that TI stimulation exerts its effects via a nonlinearity in the cell membrane capacitance and that magnitude of depolarisation is dependent on the product of the two applied currents, rather than the amplitude of the envelope.

These results are in support of the hypothesis, suggesting that TI stimulation drives neural activity via frequency multiplexing at the cell membrane, the origin of which is a nonlinearity in the cell membrane capacitance. Future work will aim to validate these results experimentally *in vivo.* Elucidation of the mechanism of action of TI stimulation has the potential to accelerate improvement and clinical adoption of the technology.