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Robustness of ultrasonic modulation of the subthalamic nucleus to GABAergic perturbation

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BMC Neuroscience 2020, **21(Suppl 1)**:P196

Introduction: Deep brain stimulation (DBS) is a surgical treatment for movement and neuropsychiatric disorders. Here, the subthalamic nucleus (STN) is the most common target for the treatment of advanced Parkinson's disease (PD). Although DBS has proven effective, the procedure is associated with surgical risks such as infection and haemorrhage. Consequentially, we investigated the possibility of using ultrasound (US) as a non-invasive and reversible alternative of conventional DBS. Here, we expand on our study on the spiking behaviour of a computational STN model [1], insonicated with continuous-wave and pulsed US of different intensities. In particular, the sensitivity of the simulated STN response to hyperpolarizing input (e.g., GABAergic globus pallidus afferents) is investigated.

Methods: A computational model for insonication of the STN is created by combining the Otsuka-model of a plateau-potential generating STN neuron [2] with the bilayer sonophore model [3,4]. After careful validation of our model implementation by comparison with theoretical and experimental literature, simulations are performed of the STN-neuron insonicated with different ultrasonic intensities and pulse waveforms. The robustness of the simulated response to GABAergic input is tested by injecting brief hyperpolarizing currents.

Results: Our model results predict intensity dependent spiking modes of the STN neurons. For continuous waveforms, three different observed spiking modes in order of increasing ultrasonic intensity are low-frequency spiking, high-frequency (>120 Hz) spiking with significant spike-frequency and spike-amplitude adaptation, and a silenced mode. Simulation results indicate that only the silenced mode is robust to brief hyperpolarizing input. In contrast, the STN response will saturate robustly to the pulse repetition frequency in pulsed US, for sufficiently large intensity and pulse repetition frequency.

Conclusion: Model results of the ultrasonically stimulated plateau-potential generating STN predict intensity dependent spiking modes that could be useful for the treatment of PD. High-frequency spiking of the STN might "jam" pathological network activity or result in the creation of an information lesion due to short-term synaptic depression, which are potential mechanisms ascribed to conventional DBS. In contrast, the silenced mode in which the STN transmembrane potential is fixed to a stable plateau might be functionally equivalent to subthalamotomy and to depolarization blockage of STN efferents during DBS. The former and latter STN mode is induced robustly by pulsed and continuous wave US, respectively.

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Computational modelling of the Locus Coeruleus

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BMC Neuroscience 2020, **21(Suppl 1)**:P197

The locus coeruleus (LC) is one of the most dominant noradrenergic systems in the brain that supplies the central nervous system with norepinephrine through widespread efferent projections. Consequently, it plays an important role in attention, feeding behaviour and sleep-to-wake transition [1]. Moreover, studies have shown that the locus coeruleus is correlated to the anticonvulsive action of vagus nerve stimulation (VNS) [2]. To date, the underlying mechanisms of VNS and the LC are, however, not fully understood. Therefore, we derived a computational model, such that in silico investigations can be performed. Based on the work of Carter et al. [3], we created a single compartment model that matched our in vivo measurements. These were extracted from rat brains at the 4Brain lab. The original model created by Carter et al. was a conductance-based model of the locus coeruleus and hypocretin neurons, used for the investigation of the sleep-to-wake transition. When the hypocretin neurons are omitted, our measured tonic firing rate of 3.35 $\pm$ 0.49Hz could not be reached with the original two compartment model by means of continuous current injection. The maximal achievable tonic firing rate was 0.75 Hz for a current of 0.4 A/m^2, while a bursting behaviour followed by depolarization block was observed for higher inputs. When combined into a single compartment model, the required frequency is reached with a 0.39 A/m^2 current injection. There were no notable differences in state occupancies that could explain the difference in firing rate. Therefore, we concluded that the lower firing rate observed in the two compartment model is solely due to spatial filtering. Finally, we compared the pinch response. The pinch was modelled as a rectangular current pulse. With an amplitude of 0.0314 A/m^2 and pulse duration of 0.9 s, an equivalent firing rate (13.64 $\pm$ 2.75Hz vs.13.86Hz) and refractory period (1.186 $\pm$ 0.234s vs.1.09s, the measurements and model, respectively) are observed.

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Voltage-dependent synaptic plasticity in magnetic tunnel junctions

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BMC Neuroscience 2020, **21(Suppl 1)**:P198

Spike-timing-dependent plasticity (STDP) is a fundamental learning mechanism that shapes plastic synaptic strengths in brain networks according to pre- and post-synaptic spike times [1]. Later, a model of voltage-based STDP was proposed based on the postsynaptic membrane potential to explain experimentally observed connectivity patterns in cortex [2]. Synaptic plasticity plays a key role in memory retention by modulating functional cortical circuitry in memory networks. The development of solid-state devices in recent years provided a means for computational implementation and experimental realization of neuromorphic structures designed to emulate adaptive behavior of synapses in brain. Particularly, spin-polarized transport through magnetic tunnel junctions (MTJs) is a well-characterized

BMC Neurosci 2020, **21**(Suppl 1):54
https://doi.org/10.1186/s12868-020-00593-1

BMC Neuroscience

MEETING ABSTRACTS

Open Access

29th Annual Computational Neuroscience Meeting: CNS*2020

Virtual. 18–22 July 2020

Published: 21 December 2020