Basic mechanisms of DBS for Parkinson’s disease: computational and experimental studies on neural dynamics
Çanan, H.

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Summary

Deep Brain Stimulation (DBS) has become an accepted therapy of last resort for Parkinson's disease (PD). The acceptance of DBS for the management of PD motor symptoms is based on its success rate and contrasts sharply with ones understanding of the pathophysiology underlying the disease state and mechanism of DBS. Theoretical and experimental studies at a neuronal and population level continue to shed light on the mechanism of DBS. In this thesis, we employ computational models in order to test certain hypothesis put forward in the field regarding the mechanism of DBS and efficacy of high frequency stimulation. Moreover, we make use of cellular recordings in order to test the validity of observations made using computational models. We incorporate population level recordings, obtained from PD patients, into a theoretical population level model in order to infer possible neuronal mechanisms underlying the differences observed in the recordings, arising from different experimental conditions. Last but not least, we analyze experimental recordings obtained from PD patients and assess which signal properties are selective to certain brain regions of interest.

Utilizing theoretical models for investigating mechanism of Deep Brain Stimulation

In chapter 2, we investigated 1) functional importance of correlated Basal Ganglia (BG) activity associated with PD motor symptoms by analyzing effects of globus pallidus internum (GPI) bursting frequency and synchrony on a thalamocortical relay (TCR) neuron, which received GABAergic projections from this nucleus; 2) effects of subthalamic nucleus (STN) DBS on the TCR neuron’s response to synchronized GPI oscillations; and 3) functional basis of the inverse relationship that has been reported between DBS frequency and stimulus amplitude, required to alleviate PD motor symptoms (Benabid et al., Lancet, 337, 403-406, 1991). The TCR neuron selectively responded to and relayed synchronized GPI inputs bursting at a frequency located in the range of 2-25 Hz. Input selectivity of the TCR neuron is dictated by low threshold calcium current dynamics and passive membrane properties of the neuron. STN-DBS prevented the TCR neuron from relaying synchronized GPI oscillations to cortex. Our model indicates that DBS alters BG output and input selectivity of the TCR neuron; providing an explanation for the clinically observed inverse relationship between DBS frequency and stimulus amplitude.
In chapter 3, we investigated membrane properties of a TCR neuron using numerical bifurcation analysis and observed that the TCR neuron exhibits bistability (i.e. non-spiking or sub-threshold oscillations and rebound spiking locked to the bursting frequency of the pre-synaptic GABAergic GPi neurons). The TCR neuron model is also used to investigate possible mechanisms underlying the existence of a clinically effective stimulation window, i.e. low stimulation amplitude and high frequency. To this end, we studied the effect of DBS parameters on thalamocortical relay of excitatory cortical inputs and pathological BG oscillations. We observed that low amplitude high frequency stimulation suppressed relay of pathological BG oscillations. However, excessively high amplitude high frequency stimulation blocked relay of excitatory cortical inputs. Together, this gave rise to a parameter window, where relay of low frequency oscillatory BG input is suppressed and relay of excitatory cortical input is preserved.

Parameters used during Deep Brain Stimulation

As an extension to the theoretical models, in chapter 4, we investigated whether theoretical observations made regarding DBS parameter dependency of thalamocortical function can be reproduced experimentally. To this end, we used an in-vitro rat thalamic slice preparation to investigate how low frequency (LF, 2-6 Hz) and high frequency (HF, 30-130 Hz) sinusoidal current injections modulate the membrane dynamics of TCR neurons. We observe that LF sinusoidal current injection induces phase related firing. Amplitude of the LF input determines phase of TCR spiking. Superimposing a HF sinusoidal input, initially delays spiking activity phase locked to the LF component. Increasing the amplitude of the HF component gives rise to action potential generation at sub-harmonics of the LF input and further increasing the amplitude of the HF component, completely suppresses spiking activity. Application of a pulse-train, phase locked to the LF sinusoidal input, modulates the response of TCR neurons in a similar fashion. Overall effect of the phase-locked pulse-train is dependent on at which phase of the LF sinusoidal input the pulse train is applied and amplitude of the LF input.

Deep Brain Stimulation and target localization

Micro electrode recording (MER) along surgical trajectories is commonly applied for refinement of the target location during DBS surgery. In chapter 5, we utilize automatically detected MER
features in order to locate the STN, employing an unsupervised algorithm. The automated algorithm makes use of background noise level, compound firing rate and power spectral density along the trajectory and applies a threshold based method to detect the dorsal and the ventral borders of the STN. Depending on the combination of measures used for detection of the borders, the algorithm allocates confidence levels for the annotation made (i.e. high, medium and low). The algorithm has been applied to 258 trajectories obtained from 84 STN DBS implantations. MERs used in this study have not been pre-selected or pre-processed and include all the viable measurements made. Out of 258 trajectories, 239 trajectories were annotated by the surgical team as containing the STN versus 238 trajectories by the automated algorithm. The agreement level between the automatic annotations and the surgical annotations is 88%. Taking the surgical annotations as the golden standard, across all trajectories, the algorithm made true positive annotations in 231 trajectories, true negative annotations in 12 trajectories, false positive annotations in 7 trajectories and false negative annotations in 8 trajectories. We conclude that our algorithm is accurate and reliable in automatically identifying the STN and locating the dorsal and ventral borders of the nucleus; and in a near future could be implemented for on-line intra-operative use.

Merging neuronal recordings with theoretical models

Modulatory effect of dopaminergic treatment during PD on the network dynamics and properties of the basal ganglia-thalamocortical loop remains unknown. In chapter 6, we employ dynamic causal modeling to study the physiological causes underlying the differences observed in cortical evoked potentials (cEPs) arising from administration of Levodopa. We use neural mass models to characterize nuclei making up the basal ganglia-thalamocortical loop, preserving the type of projection neurons and projection types (i.e. Glutamatergic, GABAergic) and estimate the parameters that determine the underlying neural dynamics, using the cEPs and the network architecture of the basal ganglia-thalamocortical loop. Three variants of the model, which differ with respect to connections that are allowed to exhibit off-on dopamine-specific changes, are compared using Bayesian Model Comparison. This comparison was used to establish which connectivity changes within the basal ganglia-thalamocortical loop best explain the differences in the cEPs arising from administration of Levodopa.