BMC Neuroscience

Poster presentation

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Theoretical approach to the basal ganglia thalamocortical network: oscillators and modulators

Dimitrios A Perakis*[1], George A Tagaris[2] and Konstantina S Nikita[1]

Address: [1]Biomedical Simulations and Imaging Laboratory, National Technical University of Athens, Greece and [2]Department of Neurology, "Georgios Gennimatas" Athens General Hospital, Greece

Email: Dimitrios A Perakis* - dperakis@biosim.ntua.gr

* Corresponding author

from Eighteenth Annual Computational Neuroscience Meeting: CNS*2009
Berlin, Germany. 18–23 July 2009

Published: 13 July 2009

BMC Neuroscience 2009, **10**(Suppl 1):P245 doi:10.1186/1471-2202-10-S1-P245

This abstract is available from: http://www.biomedcentral.com/1471-2202/10/S1/P245

The Basal Ganglia Thalamo-Cortical complex is comprised of dynamically coupled, parallel, interconnected and polysynaptic closed loops [1]. Each individual loop is made up of nodes (the various nuclei of the network) and the connections between these nodes, comprising an oscillator. Each closed loop oscillates in a different fundamental frequency and the interaction between various oscillators can provide the abundance of frequencies and rhythms which can be seen in the recorded Local Field Potentials (LFPs) [2]. The fundamental frequency of a single oscillator is predominantly determined by the conduction delay of each connection and, to a lesser extent, by the synaptic delays and ion channel kinetics of the neurons involved.

To understand the role and function of each nucleus in the whole complex as well as determine the source of physiological and pathophysiological frequencies apparent in the LFPs recorded, we split the network to several closed loops. Every circuit then is classified into one out of four possible loops: (1) positive feedback loops promoting movement execution, (2) negative feedback loops associated with termination or inhibition of an unwanted motor program, (3) feed-forward loops operating to bring about millisecond precision of spike timing [3] and (4) regulatory loops that stabilize the network's activity.

By examining the properties of each circuit and assuming a linear approach, we come to some interesting conclusions as far as the whole network behavior, the oscillatory activity and the exact role of each nucleus are concerned. First, the gamma oscillations related with voluntary motor preparation and execution, and the beta oscillations related with motor inhibition and exemplified in the Parkinson's disease are associated with certain circuits that operate in these frequency domains. For example, the striatal-globus pallidus internal (GPi)-thalamic (CM/Pf) positive feedback loop oscillates with a period of approximately 15 msec and therefore in the gamma frequency domain. Second, the subthalamic nucleus (STN) is always part of a negative feedback circuit and thus we characterize it as the braking nucleus of the Basal Ganglia. It is interesting to remind STN's hyperactivity in Parkinson's disease, which leads to akinesia and bradykinesia, and the alleviation of the symptoms by the STN high frequency stimulation [4]. Third, striatal neurons integrate the information flow from the cortical regions and, depending on the dopamine levels, act to direct the flow of the information through the direct or the indirect pathway. Fourth, globus pallidus external (GPe) modulates the STN's firing rate and regulates the precise spike timing of the Basal Ganglia. Therefore it is not the STN but the STN-GPe-GPi feed-forward circuit that sets the "clock inside the Basal Ganglia" [5]. Finally, due to small differences on the conduction and synaptic delays between different subjects, it is reasonable to expect some variability in the applied frequency of the therapeutic "high frequency stimulation" of the Basal Ganglia and therefore the need for a more personalized treatment in Parkinsonian patients.

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