Neuromodulatory Influence over Cortico-Thalamic Basal Ganglia Function

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Freezing of Gait (FoG) is a debilitating symptom in Parkinson's disease in which patients experience paroxysmal cessation of walking despite an intention to do so. The underlying pathophysiology of FoG involves the basal ganglia which is a complex subcortical system involving an array of different nuclei that are both functionally and anatomically segregated. Classically, dopamine has been viewed as the primary neuromodulator for this circuit, as it facilitates activity in the direct pathway, but inhibits activity in the indirect pathway. Unfortunately, the simplicity of the dopaminergic influence of the basal ganglia circuitry inherently misses the complexity of other neuromodulatory influences of the basal ganglia in the context of FoG.

To remedy this problem, we extended a working neural mass model of the cortico-thalamic basal ganglia system by incorporating parameters that mimicked the impact of dopaminergic, cholinergic, serotonergic modulation on the cortico-thalamic basal ganglia model.

BACKGROUND

- Basal ganglia include several distinct sub-circuits, such as the direct, indirect and hyper-direct pathway, each of which integrates cortical and thalamic projections to mediate motor, cognitive and limbic function[1].

- Parkinson's disease (PD) is due to the loss of dopaminergic modulation of the basal ganglia, which gives rise to numerous motor, cognitive and limbic dysfunction.

- Freezing of Gait (FOG) is a debilitating symptoms of PD, that causes patients to experience an inability to progress in their walking despite an intention to do so.

- We have extended a working neural mass model of the cortico-thalamic basal ganglia system[2] by incorporating parameters that attempt to mimic the Parkinsonian depleted dopaminergic basal ganglia.

AIMS

To understand the neural mechanisms giving rise to freezing of gait in PD, we will modulate the activity of the subthalamic nucleus.

METHODS

- Mimic Parkinsonian depleted dopaminergic basal ganglia by increasing the relative strength of cortico-striatal projections to the indirect pathway (D2) and decreasing projections that give rise to the direct pathway (D1).

- Mimic freezing of gait state by driving 'bursty firing' of the subthalamic nucleus through altering both the decay (α) and the rise (β) response rates of the postsynaptic potentials (PSPs):

$$D_{\alpha\beta} = \frac{1}{\alpha\beta}\frac{d^2}{dt^2} + \left(\frac{1}{\alpha} + \frac{1}{\beta}\right)\frac{d}{dt} + 1$$

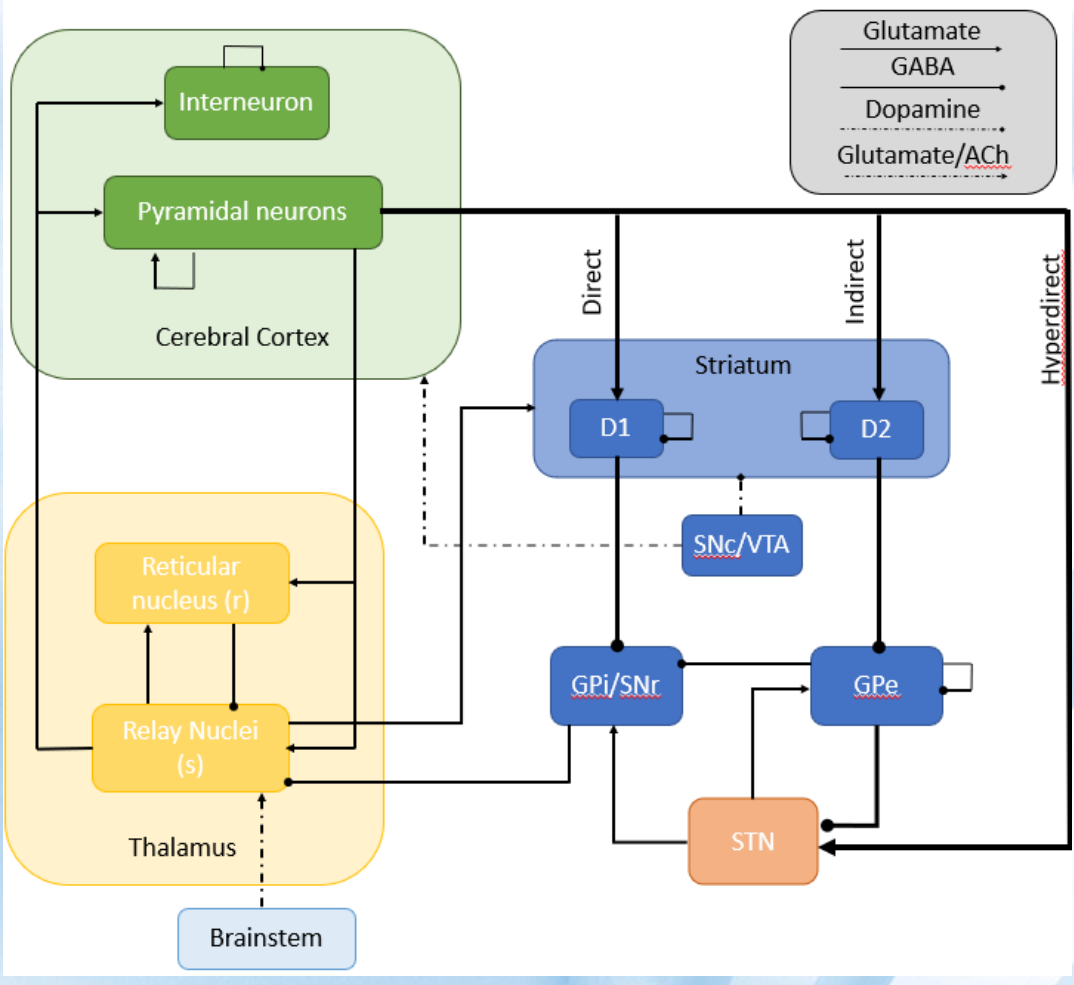
- The gains of the system represent the additional activity generated in postsynaptic nuclei per additional input from presynaptic nuclei.

- We will calculate the gains of the direct, indirect pathways, and the loop gain of the hyperdirect – STN – Gpi - Thalamus.

$$G_{ab} = \rho_a v_{ab}$$

METHODS

Cortico-Thalamic Basal Ganglia Model

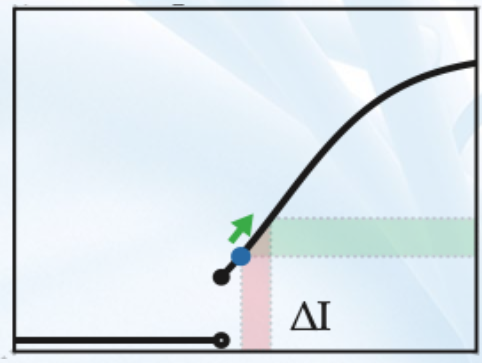


METHODS

Neuron Measures

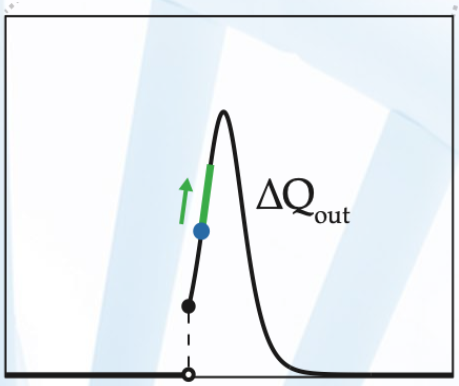
Modifying the postsynaptic potentials (PSPs), we can shape the likelihood of eliciting action potentials across groups of neurons.

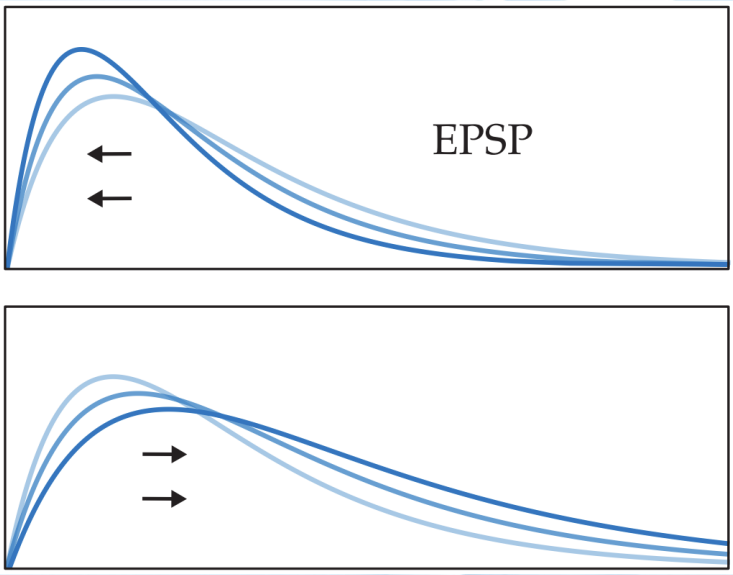
Spike Rate



$\frac{dQ}{dI}$

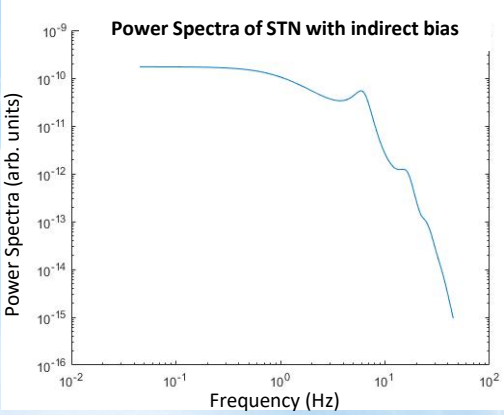
Gains



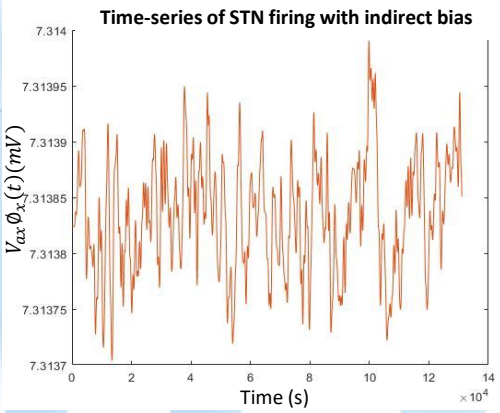


RESULTS

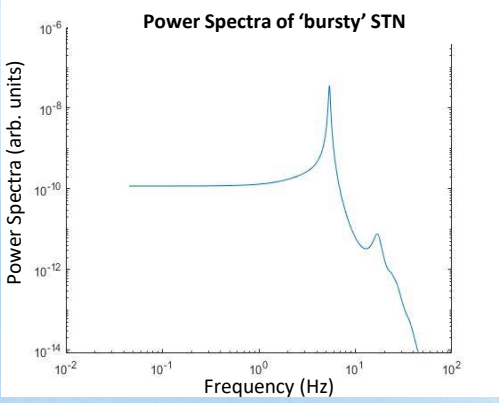
Preliminary Results of Model Simulation



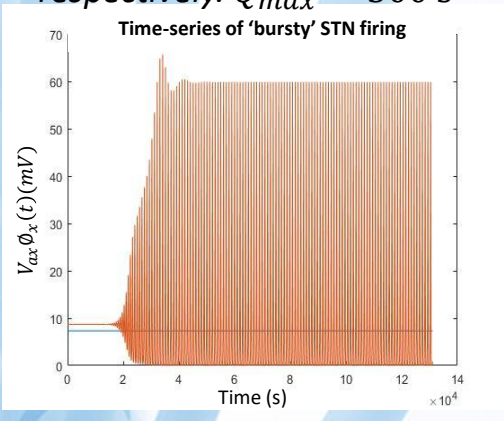
Power spectrum of STN firing rate with indirect bias of $V_{d2-e} = 0.75\ mV$



Time-series of STN firing under indirect bias of activity, with rise and decay rate as $\alpha=50s^{-1}$ *and* $\beta=200\ s^{-1}$, *respectively.* $Q_{max} = 500\ s^{-1}$



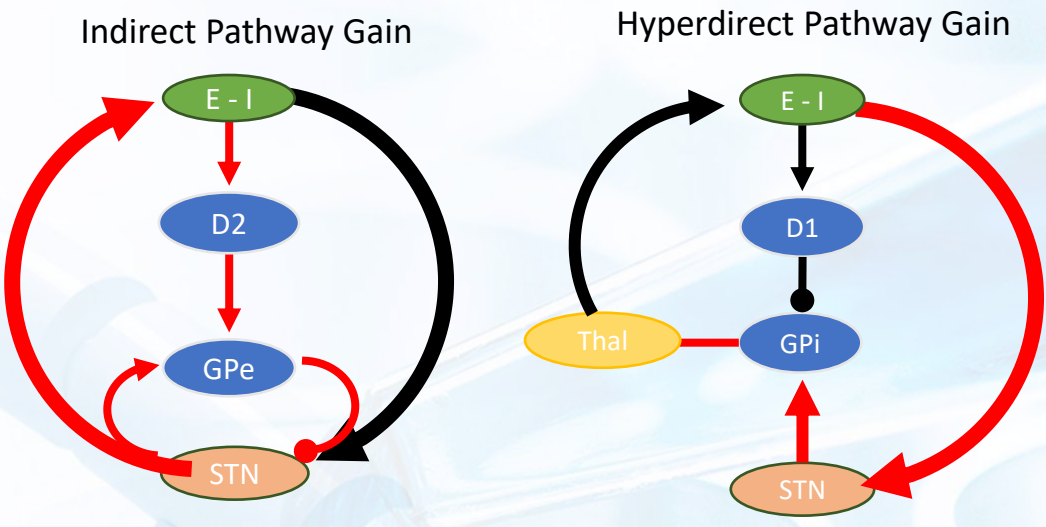
Power spectrum of STN firing rate with indirect bias of $V_{d2-e} = 0.75\ mV$, *and* $V_{stn-e} = 1\ mV$



Time-series of STN firing under indirect bias of activity, with rise and decay rate as $\alpha=35s^{-1}$ *and* $\beta=140\ s^{-1}$, *respectively.* $Q_{max} = 500\ s^{-1}$

CONCLUSION

Comparison of Loop Gains



We propose that modulating the STN 'bursty' activity in a neural mass model can give insights into the neural mechanisms underpinning freezing of gait in Parkinson's Disease.

REFERENCES

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2. Muller, E. J., and Robinson, P. A., 2018 PloS Comp. Biol. 14(5) e1006217
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