

# Global and local excitation and inhibition shape the network dynamics for the control of movement and reward

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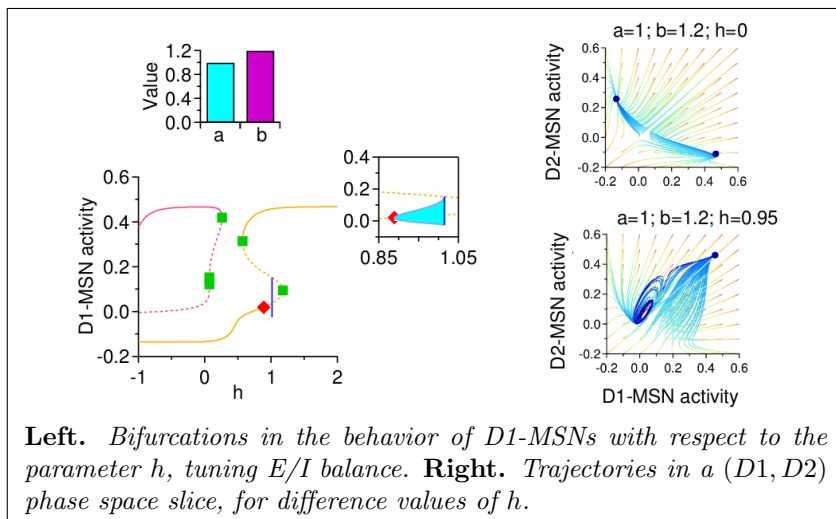
The cortico-striatal-thalamo-cortical (CSTC) pathway is a brain circuit that controls movement execution, habit formation and reward. Hyperactivity in the CSTC pathway is commonly observed in patients affected by obsessive compulsive disorder (OCD), a neuropsychiatric disorder characterized by the execution of repetitive involuntary movements. The striatum shapes the activity of the CSTC pathway through the coordinated activation of two classes of medium spiny neurons (MSNs) expressing D1 or D2 dopamine receptors. The exact mechanisms by which balanced excitation/inhibition (E/I) of these cells controls the network dynamics of the CSTC pathway remain unclear. We use non-linear modeling of neuronal activity and bifurcation theory to investigate how global and local changes in E/I of MSNs regulate the activity of the CSTC pathway. Our findings indicate that subtle changes in the relative strength of E/I of MSNs can powerfully control the network dynamics of the CSTC pathway in ways that are not easily predicted by its synaptic connections.

Our current understanding of the wiring diagram of the CSTC pathway, based on functional neuroimaging studies, indicate that this circuit has an equivalent organization in rodents and humans of either sex and age. In normal conditions, oscillations and synchronous activity in distinct domains of the CSTC pathway are crucial to ensure the execution of habitual actions. In contrast, hyperactivity in specific domains or throughout the circuit are thought to underlie the manifestation of obsessive compulsive disorder (OCD) and Tourette’s syndrome. The striatum, one of the main nodes of the CSTC pathway, is largely composed of two types of MSNs that can be distinguished for their expression of either D1 or D2 dopamine receptors. Activation of D1-MSNs facilitates movement initiation and activation of D2-MSNs inhibits initiation of competing actions. Recent findings indicate that repetitive optogenetic activation of cortico-striatal glutamatergic afferents to the striatum triggers OCD-like behaviors in mice, whereas optogenetic stimulation of feed-forward inhibition onto D1- and D2-MSNs relieves OCD-like behaviors in a genetic mouse model of OCD. These findings are important because they suggest that a fine regulation of excitation and inhibition (E/I) onto D1- and D2-MSNs might be crucial to control the onset of hyperactivity in the CSTC pathway.

We address this question theoretically, using a mathematical model of the excitatory (glutamatergic) and inhibitory (GABAergic) connections in a model of the CSTC pathway [1]. By using bifurcation theory in a system of seven-dimensional coupled Wilson-Cowan equations, we determine how global and local changes in excitation and inhibition contribute to orchestrate the activity of D1- and D2-MSNs and of the entire CSTC pathway.

Our findings indicate that there are wide parameter ranges that confer bi-stability to the system (see Figure), with the hyper-space  $D1 = D2$  delimiting the attracting basins for two different stable regimes: one with high D1- and low D2-MSN activity, a second with low D1- and high D2-MSN activity. While global changes in E can push the system into a different such steady-state, simultaneous changes in global or local E/I can lead to the onset of oscillatory bursting behaviors.

Taken together, these findings allow us to analyze the effects of small perturbations on the activity of D1- and D2-MSNs and of the entire CSTC pathway. They highlight that local inhibition, among all other factors, can powerfully regulate the activity of the entire system, possibly contributing to the hyperactivity patterns observed in patients with OCD.



**Left.** Bifurcations in the behavior of D1-MSNs with respect to the parameter  $h$ , tuning E/I balance. **Right.** Trajectories in a  $(D1, D2)$  phase space slice, for difference values of  $h$ .

## References

- [1] Rădulescu A, Herron J, Kennedy C, Scimemi A, 2017. *Global and local excitation and inhibition shape the dynamics of the cortico-striatal-thalamo-cortical pathway.* Sci Rep, 7(1): 7608.