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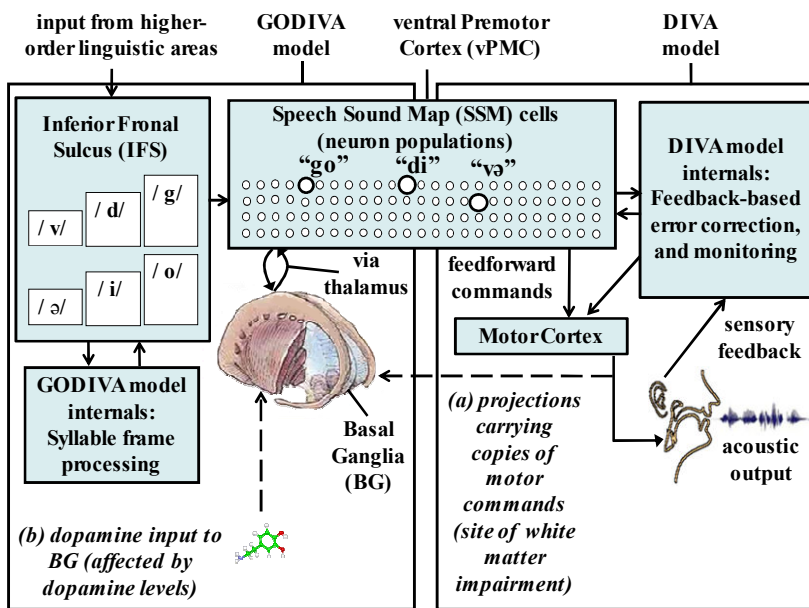
Both dopamine excess and white matter impairment induce dysfluencies in a neural queuing model of multi-syllabic speech

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Recent findings of neural abnormalities in the brains of persons who stutter provide the best evidence for a neurological basis of stuttering. We hypothesize that some or all of these neural abnormalities lead to an impairment in the ability of persons who stutter to read out motor commands for well-learned syllables (*feedforward commands*). This impairment may lead to different types of dysfluency: sound/syllable repetition, prolongation or block.

We propose that the integrity of the basal ganglia (BG) - thalamus - left ventral premotor cortex (vPMC) loop is essential for proper readout of feedforward commands. Neural abnormalities may disturb this circuit in at least two hypothesized ways (dashed lines in the figure): (a) due to white-matter impairment in the corticostriatal projections carrying copies of motor commands, and (b) due to increased dopamine binding in the striatum leading to a ceiling effect, i.e., multiple thalamic neuron populations have maximum activation. In both hypotheses, dysfluencies result from delayed activation of the vPMC neuron population responsible for reading out the feedforward commands for the next syllable.



Most past hypotheses concerning BG dysfunction in stuttering cannot be tested using imaging data because they cannot predict whether particular brain regions would be over- or under-activated during stuttering. The BG's internal circuits are very complex, including many inhibitory connections, and as a result the relationship between metabolism and signaling is unclear, making it difficult to predict neural activations. We overcome this problem by testing our hypotheses with the GODIVA and DIVA models [1]. As neurobiologically specified models, they are able to predict the blood-oxygenation-level-dependent (BOLD) response of the brain during simulated speech tasks (cf. [2]).

Simulations of the combined models producing /godivə/ (see figure) demonstrated that both white-matter impairment and increased dopamine binding can account for key aspects of stuttering. Furthermore, the neural activations predicted by the simulations agree with most published results: hyper-activation in the putamen and thalamus, and deactivation in GPi and vPMC. The simulations also account for the alleviation of stuttering with D2 antagonists. In both

hypotheses, the D2 antagonists strengthen the indirect pathway of the BG by preventing dopamine from exerting its inhibitory effect on the putamen D2 neurons. The strengthening of the indirect pathway counteracts over-excitation of the direct pathway of the BG (in the increased dopamine binding hypothesis), and compensates for the impaired inputs to the striatum (in the white-matter impairment hypothesis). Simulations of future variants of the models could clarify how other drugs, such as the partial D2 agonist aripiprazole, affect the frequency of stuttering.

The models can also account for variability of stuttering. Because dopamine levels fluctuate over time, frequently due to emotional state, the increased dopamine binding hypothesis can account for day-to-day variability in stuttering, as well as modulation of the disorder by emotions.

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[1] Bohland, J., Bullock, D. & Guenther, F.H. *J. Cogn. Neurosci.* **22**, 1504–1529 (2010).

[2] Guenther, F.H., Ghosh, S.S. & Tourville, J.A. *Brain Lang.* **96**, 280-301 (2006).

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