A neural modeling study of stuttering and fluency enhancement by drugs that partially block dopamine action

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Summary

The hypothesis that stuttering partly results from neural abnormalities leading to impaired readout of motor commands for well-learned syllables was investigated with GODIVA and DIVA, neurobiological models of speech production. Two brain abnormalities associated with stuttering were investigated: elevated dopamine levels, and impairment in white matter fibers. Introducing either abnormality into the model could account for dysfluent speech and associated abnormal brain activations. For both abnormalities, the affected circuit is a loop involving basal ganglia, thalamus and left ventral premotor cortex. The model also simulates alleviation of stuttering with D2 dopamine antagonists.

Introduction

Two recent findings of neural abnormalities in the brains of people who stutter (PWS) are a hyperactive dopaminergic system (Lan et al., 2010; Wu et al., 1997; cf. Rastatter & Harr, 1988), and structural impairment in white matter fibers beneath the left precentral gyrus (Chang et al., 2008; Cykowski et al., 2010; Kell et al., 2010; Sommer et al., 2002; Watkins et al., 2008). We hypothesize that one or both abnormalities lead to an impairment in the ability of PWS to read out motor commands for well-learned syllables (feedforward commands), resulting in dysfluencies.

We propose that the integrity of the basal ganglia (BG) - thalamus - left ventral premotor cortex (vPMC) circuit, or BG-vPMC loop, is essential for proper readout of the feedforward commands. The circuit is a loop because the vPMC not only receives projections from the BG via the thalamus, but also sends projections back to the BG. According to our proposal, the function of the BG-vPMC loop is to decide when the conditions for program execution are satisfied, and then to facilitate fast syllable initiation by biasing cortical competition in favor of the premotor neuron population responsible for reading out the correct motor program for the next syllable.

Neural abnormalities may disturb the BG-vPMC loop in at least two hypothesized ways (see Fig. 1): (a) due to increased dopamine binding in the striatum (Maguire et al., 2004) leading to a ceiling effect in the thalamus (cf. Alm, 2004), and (b) due to white-matter impairment in the corticostriatal projections that carry a copy of each motor command sent to the muscles (see Alm, 2004).

In both hypotheses, dysfluencies result from delayed activation of the premotor neuron population responsible for reading out the motor program for the next syllable. The type of dysfluency is decided by the response of the central nervous system (CNS) to the delay. Here we

simulate scenarios in which the CNS waits until the premotor neuron population is fully activated; hence, the outcome is a block. If the CNS initiates airflow before full activation, the result is a prolongation. If the CNS starts producing the next syllable, although the neuron population is not fully activated yet, the motor program is read out improperly, and production errors prevail. While sensory feedback control can correct some of these errors, repetition arises when error grows too large, causing the motor system to "reset" and repeat the current syllable (Civier et al., 2010).

Methods: The GODIVA and DIVA models

GODIVA (Gradient Order DIVA) and DIVA (Directions Into Velocities of Articulators) are biologically plausible models capable of simulating speech development and production (Guenther et al., 2006; Bohland et al., 2010). As neurally specified models, they are also able to predict the blood-oxygenation-level-dependent (BOLD) response of the brain during simulated speech tasks (Golfinopoulos et al., 2010; Guenther, 2006; Tourville et al., 2008). DIVA models circuits that control articulation of sounds and well-learned syllables, whereas GODIVA models higher-level aspects of speech production, including syllable sequence planning and readout (controlled initiation) of successive plan constituents. The GODIVA model circuit outputs to the DIVA circuit through a premotor cortex stage that consists of speech sound map (SSM) cells (see Fig. 1). Each SSM cell represents a premotor neuron population that encodes the motor program for a specific well-learned syllable. The GODIVA model decides which SSM cell should be active at each point, and the DIVA model executes the articulatory program coded by that cell.

Fig. 1 shows the models' contribution when fluently producing the syllable "go" of the syllable sequence "go.di.və" ("go diva"). The syllables "di" and "və" are produced in a similar fashion.

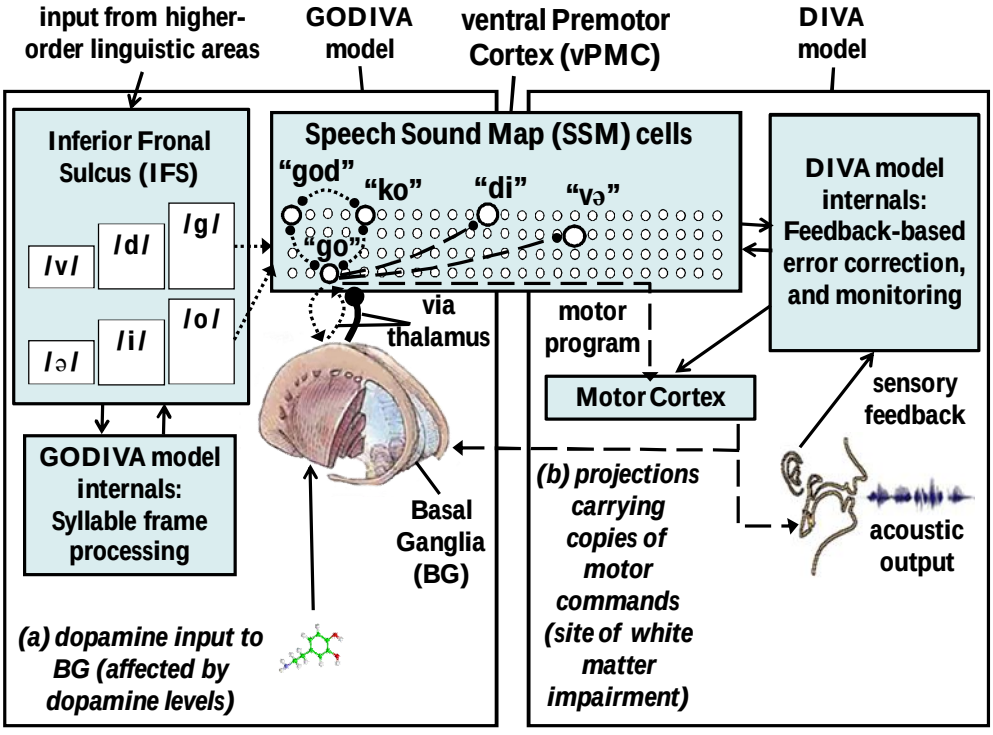


Figure 1: Schematic of the GODIVA and DIVA models producing the first syllable of "go.di.və".

The order of events in Fig. 1 is as follows:

Processing of inputs

The input to the simulation is a graded set of pulses sent in parallel, assumed to arrive from higher-order linguistic areas. In the inferior frontal sulcus (IFS) stage of the GODIVA model, these inputs create an activity gradient across the /g/, /d/, and /v/ phoneme cells (each cell represents an IFS neuron population) in the onset consonant's queue, and a gradient across the /o/, /i/, and /ə/ phoneme cells in the vowel nucleus's queue (see Bohland et al., 2010).

Selection of "go"

Because both the /g/ and /o/ phoneme cells have the highest activity in their corresponding queues within the IFS, these cells drive initial activity in the premotor cortex stage. Multiple SSM cells representing motor programs for syllables become active, each partially matching the phonological sequence representation in the IFS. Three such cells are depicted in Fig. 1: "go", "god", and "ko". These cells compete with each other for a variable time interval that depends on inputs via the BG-thalamus. Under normal conditions, these inputs promote competitive selection in favor of the cell with the best match to the phonological sequence representation. In this case, the "go" SSM cell (see dotted arrows in Fig. 1. Arrowheads and circles indicate excitation and inhibition, respectively).

Execution of "go"

After competitive selection, the SSM cell for "go" reads out the motor program for that syllable, while inhibiting other SSM cells (e.g., the cells for "di" and "və"). The motor cortex stage of the DIVA model articulates the commands of the program, sending to the BG a copy of each executed command (see dashed arrows in Fig. 1).

Selection of "di"

Similar to the selection of "go".

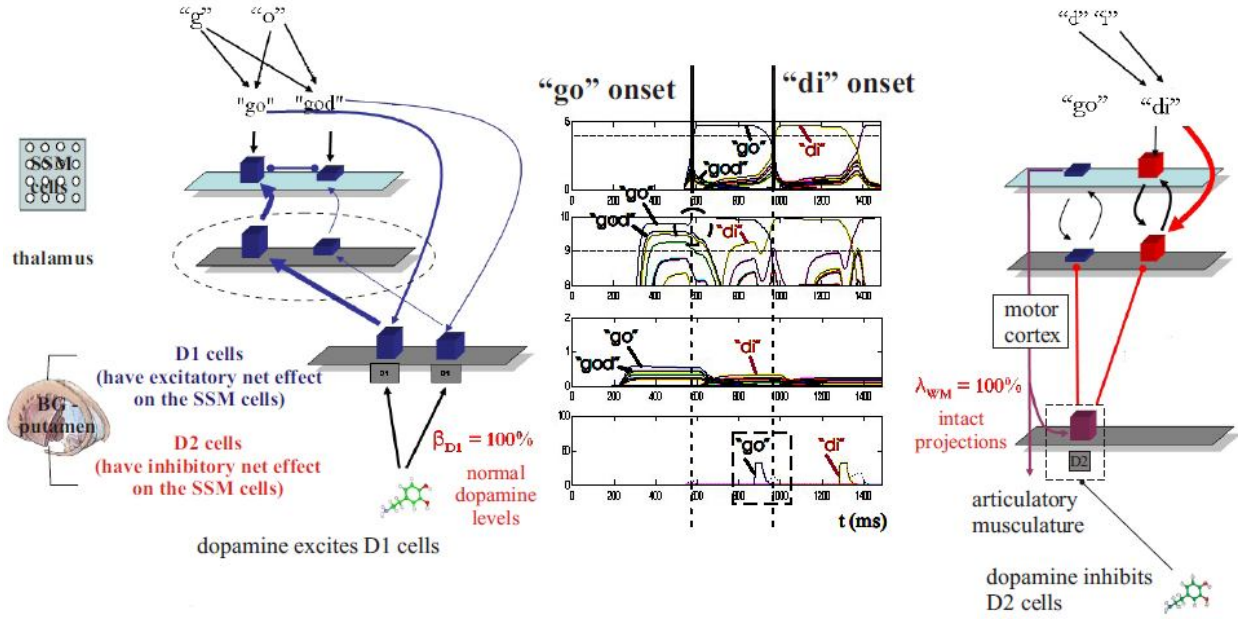
Shifting from "go" to "di"

Although selected, the SSM cell for "di" cannot become active due to the inhibition it receives from the currently active SSM cell ("go"). Yet, when the BG receive a copy of a command that executes toward the end of the syllable "go" (e.g., the command to fully round the lips), they know (based on prior experience) to terminate the activation of the "go" SSM cell (see thick arrow from the BG to the "go" SSM cell in Fig. 1). The "di" SSM cell is not inhibited anymore, and becomes active.

Results

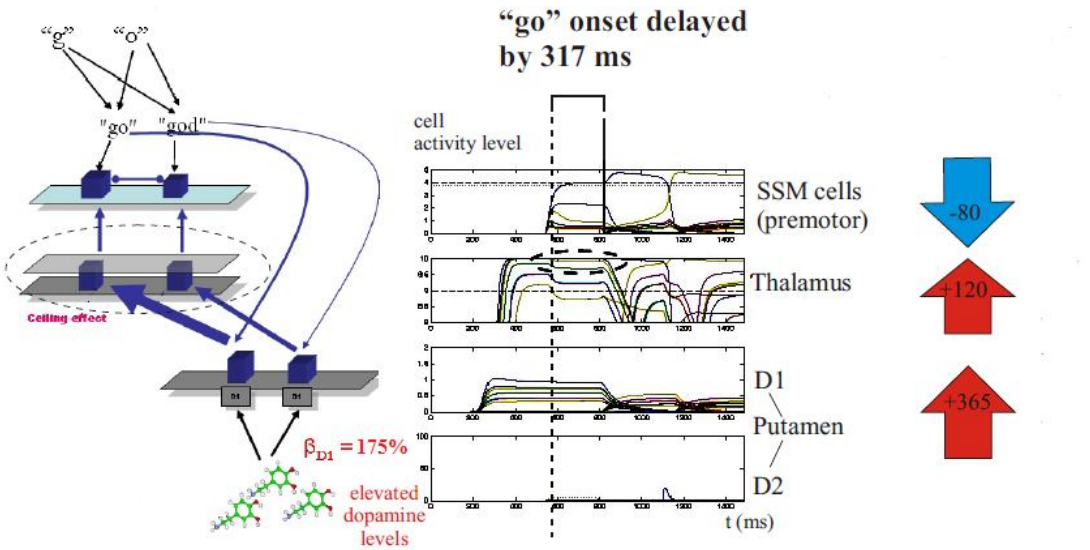
Computer simulations of the models producing "go.di.və" were performed to test mechanisms by which elevated dopamine levels or white-matter impairment could lead to stuttering. The first simulation used normal dopamine levels (β_{D1}=100%) in combination with intact white matter fibers (λ_{WM}=100%), and served as a baseline (Fig. 2). In the second simulation, we raised the parameter for dopamine tone (β_{D1}=175%), while keeping other parameter values constant (Fig. 3). In the last two simulations, we lowered the parameter for white matter integrity (λ_{WM}=5%), once without drug treatment (Fig. 4), and once under the influence of D2 dopamine antagonists (Fig. 5). Before the

simulations, the motor programs for the 300 most frequent syllables from the CELEX database were acquired by the DIVA model.



(a) (b) (c)

Figure 2 (above): Simulation 1. Activities in key cell types of the BG-vPMC loop during fluent production of "go.di.və" at normal conditions. (a) Snapshot at the baseline initiation time of the syllable "go". (b) Time course of activities at the four loop stages (c) Snapshot at the baseline initiation time of the syllable "di".



(a) (b) (c)

Figure 3 (above): Simulation 2. Activities in key cell types of the BG-vPMC loop during dysfluent production of "go.di.və" due to elevated dopamine levels. (a) Snapshot at the baseline initiation time of the syllable "go". (b) Time course of activities at the four loop stages. (c) Predicted changes in regional neural activity.

The time course of activity in key cell types of the BG-vPMC loop is shown in Fig. 2(b), 3(b), 4(b), and 5(b). Each plotted line shows the activity of a single cell representing a neuron population (the lines that show the activity of the cells for "go", "god", and "di" are marked in Fig. 2(b)). The figures include the activity of premotor SSM cells, thalamic cells, putamen cells that express D1 dopamine receptors (D1 cells), and putamen cells that express D2 dopamine receptors (D2 cells). The vertical dashed lines mark the baseline initiation times of the syllables "go" and "di". Fig. 2(a) and 3(a) show snapshots of the BG-vPMC loop at the baseline initiation time of the syllable "go", while Fig. 2(c), 4(c), and 5(c) show snapshots of the BG-vPMC loop at the baseline initiation time of the syllable "di". The bars in these figures represent cells, with bar height indicating the neural activation level of the cell. Notice that the cells are organized in columns; the cells of each column pertain to control of the syllable indicated above the column. For clarity, the diagrams only include the cells for "go" and "god" (Fig. 2(a) and 3(a)), or the cells for "go" and "di" (Fig. 2(c), 4(c), 5(c)). The arrows in these figures represent projection fibers, or for the arrows from the D1 or D2 cells to the thalamus, net effect. Arrow thickness indicates the strength of excitation (arrowhead) or inhibition (circle).

Next we describe the behavioral outcomes and neural dynamics in each of the simulations.

Simulation 1: fluent speech

Fig. 2 shows results from a simulation at normal conditions.

Selection of "go"

Fig. 2(a) and (b) show that the D1 cells enhance the contrast of their inputs regarding the relative activation of the competing syllables, exciting the SSM cell for "go" (via the thalamus, see dashed ellipses) much more than the cell for "god". The production of the "go" syllable starts when the activity of the "go" SSM cell exceeds threshold (at "go" onset).

Shift from "go" to "di"

Fig. 2(b) and (c) show that the production of "go" is underway, when the D2 cell receives from the motor cortex stage a copy of a motor command that indicates imminent termination of the syllable. The D2 cell becomes active (see dashed squares) and inhibits all thalamic cells. While the activity of the "go" thalamic cell is canceled, the "di" thalamic cell is pushed above threshold due to the input it receives (see thick arrow in Fig. 2(c)), and the production of "di" is initiated (at "di" onset).

Simulation 2: dysfluency due to elevated dopamine

Fig. 3 shows results from a simulation using elevated dopamine levels.

Fig. 3(a) and (b) show that the D1 cells, being over-excited due to the dopamine excess, are exciting the thalamus, pushing the activation of the thalamic cell for the desired syllable ("go") to the highest possible level; unfortunately, it does the same to cells of other syllables (e.g., "gop", "god"). Although the "go" thalamic cell is still receiving stronger net excitation than its competitors are, its activation cannot be increased above theirs because the cell has reached its ceiling (see dashed ellipses, cf. Alm, 2004). The SSM choice cell for "go", which does not have a competitive advantage anymore, needs more time to overcome the other SSM cells, delaying the selection of the syllable "go". The result is a long block on the syllable "go".

The large arrows in Fig. 3(c) indicate size and direction of predicted changes in regional neural activity relative to the fluent speech baseline from simulation 1 (derived from predicted BOLD response). The deactivation in premotor cortex agrees with Watkins et al. (2008). The hyper-activation in putamen and thalamus agrees with Braun et al. (1997).

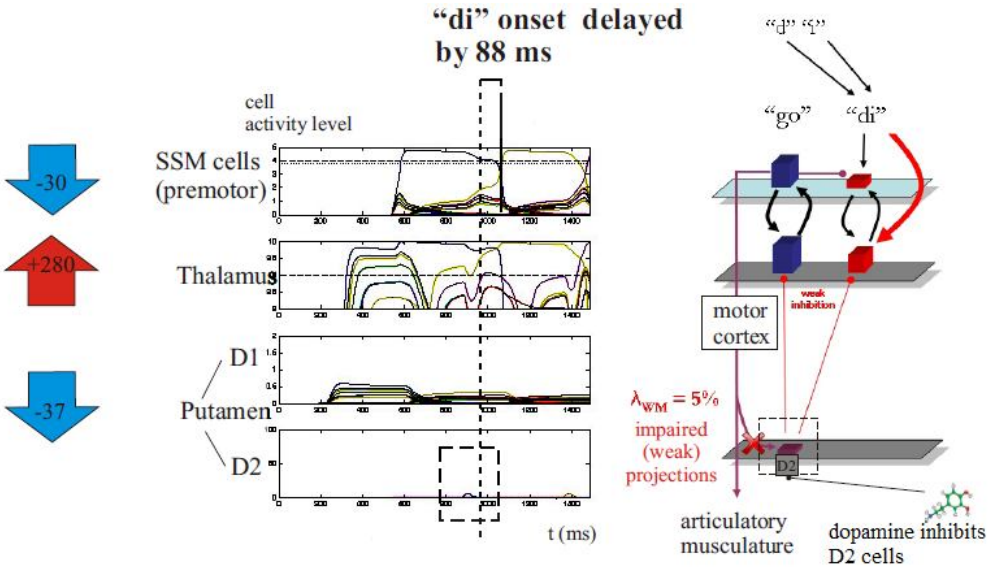


Figure 4 (above): Simulation 3a. Activities in key cell types of the BG-vPMC loop during dysfluent production of "go.di.və" due to impaired white matter fibers. (a) Predicted changes in regional neural activity. (b) Time course of activities at the four loop stages. (c) Snapshot at the baseline initiation time of the syllable "di".

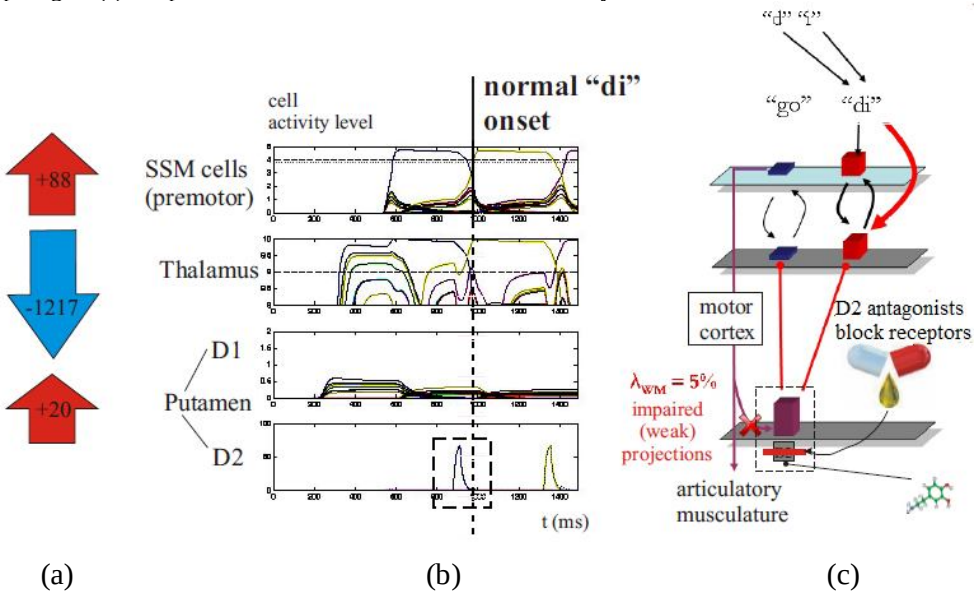


Figure 5 (above): Simulation 3b. Activities in key cell types of the BG-vPMC loop during fluent production of "go.di.və" due to D2 antagonists counteracting the effect of the white-matter impairment. (a) Predicted changes in regional neural activity. (b) Time course of activities at the four loop stages. (c) Snapshot at the baseline initiation time of the syllable "di".

Simulation 3a: dysfluency due to bad white matter

Fig. 4 shows results from a simulation with white-matter impairment.

Fig. 4(b) and (c) show that due to the white-matter impairment, which is assumed to affect the corticostriatal projections from the motor cortex to the putamen nucleus of the BG (Alm, 2004), the putamen D2 cells cannot reliably detect the motor command which indicates the imminent completion of syllable articulation (simulated as weak D2 cell activation, see dashed squares). This prevents the D2 cells from exerting strong inhibition on the thalamus, and the activity of the SSM cell for the currently executed syllable cannot be rapidly canceled. Thus, introducing a delay to the shift to the next syllable "di". The result is a block on the syllable "di".

The large arrows in Fig. 4(a) indicate size and direction of predicted changes in regional neural activity relative to the fluent speech baseline from simulation 1 (derived from predicted BOLD response). The deactivation in premotor cortex agrees with Watkins et al. (2008). The hyper-activation in thalamus agrees with Braun et al. (1997).

Simulation 3b: using D2 antagonists to prevent dysfluency due to bad white matter

Fig. 5 shows results from a simulation with white-matter impairment under the influence of D2 antagonists.

The simulation accounts for the reduction in the frequency of fluencies with the atypical D2 (or D2-like) antagonists risperidone and olanzapine (Maguire et al., 2004). Fig. 5(b) and (c) show that by blocking the inhibitory D2 receptors, D2 antagonists remove the normal inhibition of D2 cells by dopamine. Although the corticostriatal projections are still impaired, the D2 cells can once again generate a strong signal (see dashed squares) that can inhibit the SSM cell of the currently active syllable, allowing a rapid shift to the next syllable "di". The result is an elimination of the block that occurred in simulation 3a.

The large arrows in Fig. 5(a) indicate size and direction of predicted changes in regional neural activity relative to the fluent speech baseline from modeling experiment 1 (derived from predicted BOLD response). The increase in premotor cortex activation agrees with Wood et al. (1980). The increase in striatal activation agrees with Maguire et al. (2004).

Conclusions

Simulations of the GODIVA and DIVA models showed that both elevated dopamine levels and white-matter impairment can account for stuttering. In the elevated dopamine hypothesis, over-excitation of the D1 cells leads to over-excitation of the thalamus, and thus, to a ceiling effect there. The BG cannot help, then, to select the next syllable. In the bad white-matter hypothesis, impaired input to the D2 cells prevents the BG from detecting the command that indicates the termination of the syllable. The BG cannot shift, then, to the next syllable.

The simulations make sense of two apparently unrelated findings by demonstrating that stuttering due to white-matter impairment can be alleviated with D2 dopamine antagonists (Brady, 1991; Maguire et al., 2004; Stager et al., 2005). This drug treatment strengthens the putamen D2 cells by preventing dopamine from inhibiting them, and thus, compensates for the weak inputs they receive. Additional simulations (not shown) demonstrated that D2 antagonists can also alleviate stuttering caused by elevated dopamine levels (Civier et al., in preparation). Moreover, simulations of future variants of the model could clarify how dopamine system stabilizer drugs (as the partial

D2 agonist aripiprazole, see Tran et al., 2008), as well as changes in emotional state (Alm, 2004), affect the frequency of stuttering.

Lastly, the simulations predict neural activations in stuttering, generally in agreement with published results. Predictions common to both hypotheses are deactivation of left ventral premotor cortex (Watkins et al., 2008), and hyper-activation of the thalamus (Braun et al., 1997).

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