Simulating neural impairments to syllable-level command generation in stuttering

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Summary

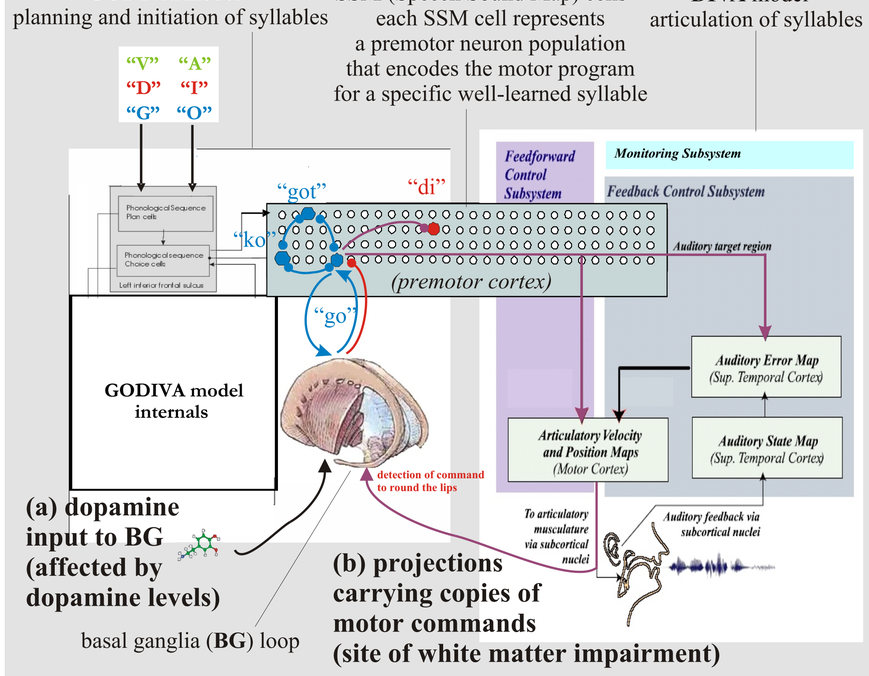
The hypothesis that stuttering partly results from neural abnormalities leading to impaired readout of motor commands for well-learned syllables was investigated with GODIVA and DIVA, neurobiological models of speech production. Two brain abnormalities associated with stuttering were investigated: elevated 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 antagonists.

Introduction

Two recent findings of neural abnormalities in the brains of persons who stutter (PWS) are a hyperactive dopaminergic system (Wu et al., 1997; cf. Rastatter & Harr, 1988), and structural impairment in white matter fibers beneath the left precentral gyrus (Chang et al., 2008; 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 loop is essential for proper readout of feedforward commands. Neural abnormalities may disturb this circuit in at least two hypothesized ways (see diagram below):
(a) due to increased dopamine (DA) binding in the striatum 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 (cf. 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 of speech (pause). If the CNS initiates airflow before full activation, the result is 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., accepted).

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., in press). As neurally specified models, they are also able to predict the blood-oxygenation-level-dependent (BOLD) response of the brain during simulated speech tasks (Guenther, 2006; Tourville et al., 2008).



Order of events in fluent production of "go.di.va":
Selection of "go". The GODIVA model primes the SSM cells for "go", "god", and "ko" (motor programs that most closely match the phonological syllable "go"), which then compete with each other. However, because the BG bias competition in favor of the "go" SSM cell, it is the cell that wins the competition and becomes active.
Execution of "go". The SSM cell for "go" reads out the motor program (by activating the appropriate motor neurons in a specific order) and sensory expectations for that syllable, while preventing (by inhibition) other SSM cells (as the cell for "di") from turning on. The DIVA model articulates the commands of the program, sending to the BG a copy of each command being executed.
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. The "di" SSM cell is not inhibited anymore, and becomes active. And so on ...

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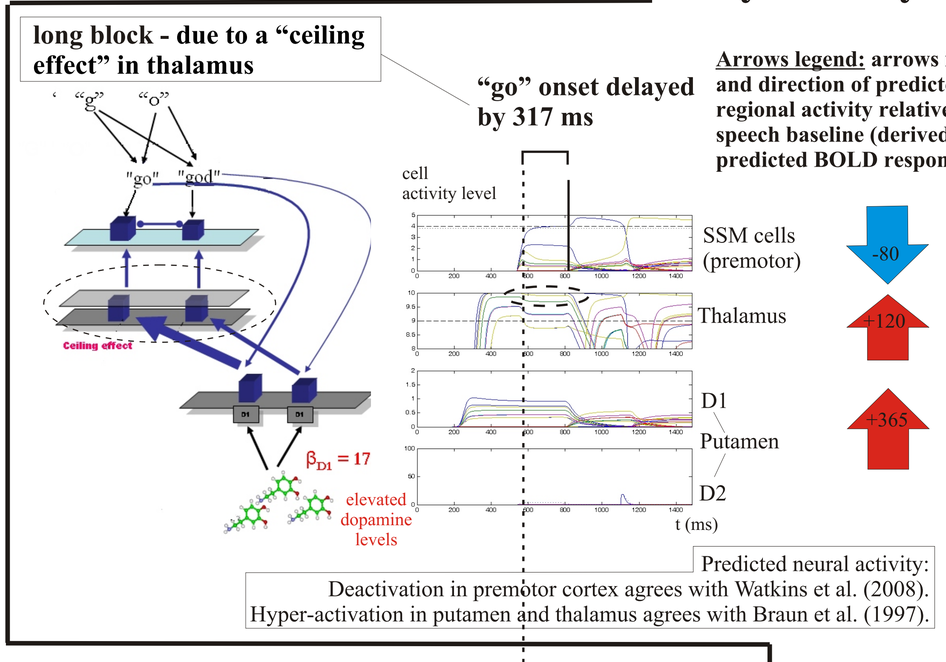
Simulations of dysfluencies (blocks of speech) in the word "go.di.va"

2. Dysfluency due to elevated dopamine

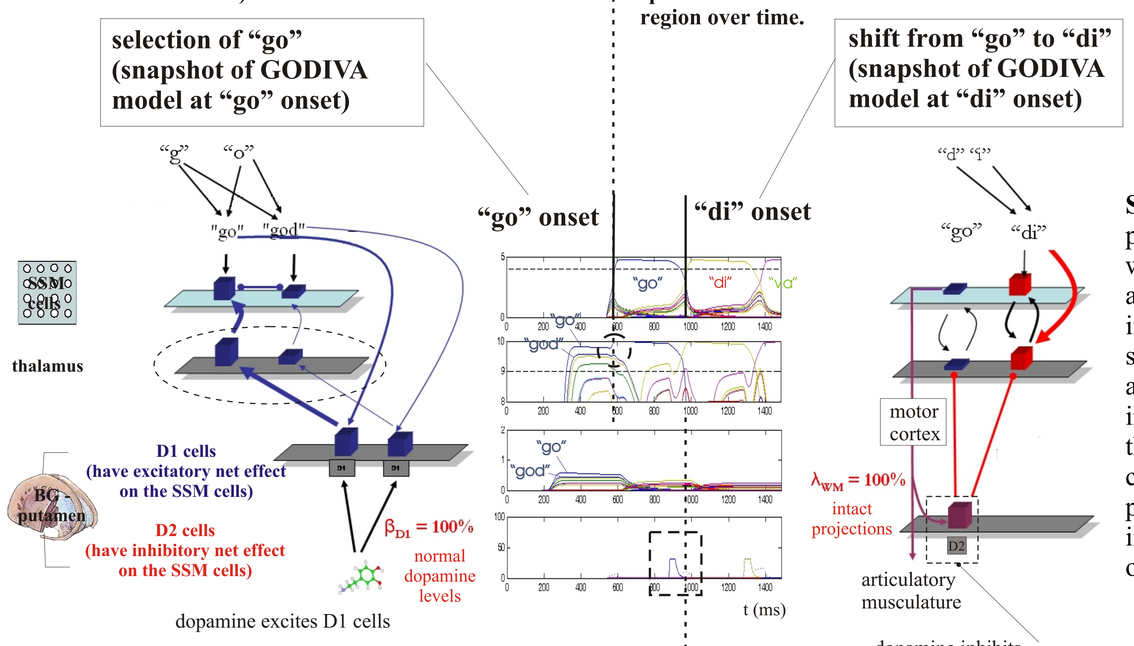


The D1 cells, being over-excited due to the dopamine excess, are exciting the thalamus, pushing the activation of the thalamic cell for the desired syllable ("go") to the highest possible level; unfortunately, it does the same to cells of other syllables (e.g., "gop", "god"). Although the "go" thalamic 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 ellipse, 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".**

1. Fluent speech

Diagrams legend: The height of the bars represents the neural activation level of the cell. The arrows represent projection fibers (arrowhead = excitatory, circle = inhibitory) or net effect (for the arrows from D1 and D2 cells to the thalamus).

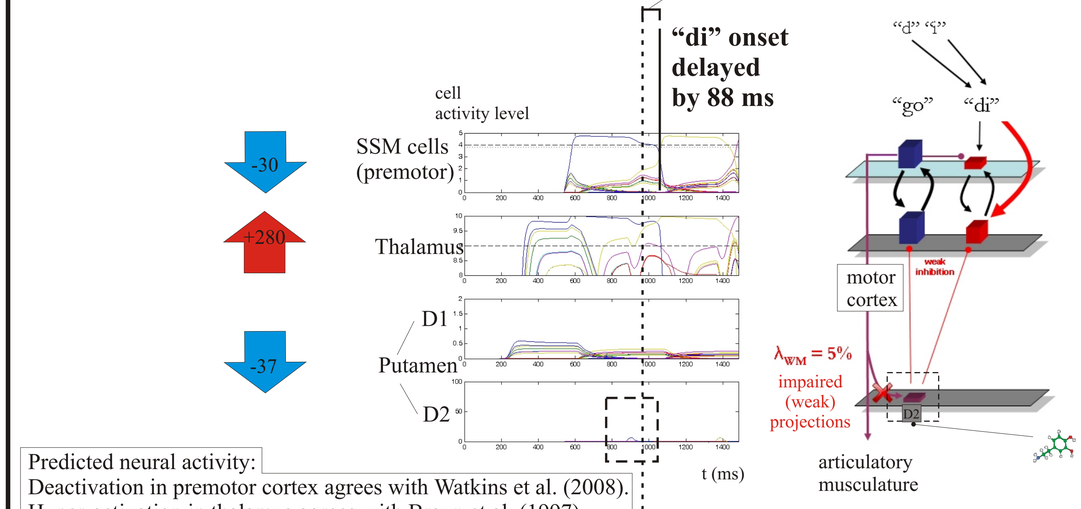
Plots legend: each subplot shows the activation levels of neurons in a specific brain region over time.



Selection of "go". 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 ellipse) 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).

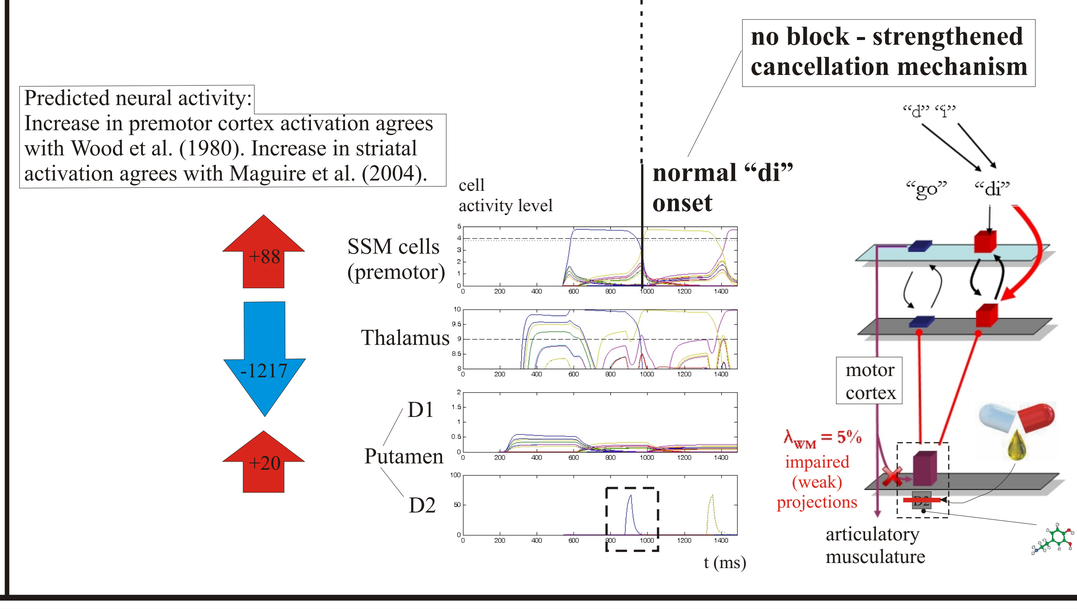
Shift from "go" to "di". The production of "go" is underway, when the D1 cell receives a copy of a motor command that indicates imminent termination of the syllable. The D1 cell becomes active (see dashed square) and inhibits all thalamic cells. While the activity of the "go" thalamic cell is canceled, the "di" cell is pushed above threshold due to the input it receives, and the production of "di" is initiated (at "di" onset).

3a. Dysfluency due to bad white matter



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 square). 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".**

3b. Using D2 antagonists to prevent dysfluency due to bad white matter



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). 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 square) that can inhibit the SSM cell of the currently active syllable, **allowing a rapid shift to the next syllable "di".**

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 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 due to elevated dopamine levels (Civier et al., in preparation). Simulations of future variants of the model could also 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.
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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