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Reduction of Dopamine in Basal Ganglia and its Effects on Syllable Sequencing in Speech: A Computer Simulation Study

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Abstract

Background: Reduction of dopamine in basal ganglia is a common cause of Parkinson's Disease (PD). If dopamine-producing cells die in the substantia nigra, as seen in PD, a typical symptom is freezing of articulatory movements during speech production.

Goal: It is the goal of this study to simulate syllable sequencing tasks by computer modelling of the cortico-basal ganglia-thalamus-cortical action selection loop using different levels of dopamine in order to investigate the freezing effect in more detail.

Method: This simulation was done using the Neural Engineering Object (Nengo) software tool. In the simulation, two dopamine level parameters (lg and le), representing the effect of D1 and D2 receptors, and therefore the level of dopamine in striatum respectively, can be differentiated and modified.

Results: By a decrease of the dopamine level parameters lg and le to 50% we replicated a freezing effect after less than 5 syllable productions. Furthermore freezing of action selection in speech was greater for dopamine level reduction in D1 than D2 receptors.

Conclusions: In this study using a neuro-functional brain model, the speech freezing effect results from simulating a reduction of dopamine level in striatum.

Keywords: Neural engineering framework; basal ganglia; action selection; syllable sequencing; Parkinson's disease; freezing of speech movements

1 Introduction

In a specific contextual situation (e.g. reading silently, speaking aloud, being involved in a communication process etc.), a specific number of actions are available for cortex to perform such as activation of a cognitive representation of a word in the mental lexicon (Levelt et al. 1999, Li et al. 2004, Indefrey & Levelt 2004) or activation of cognitive, auditory, somatosensory, and motor representations of a word or syllable at hyper- and unimodal cortical levels (Guenther 2006, Golfinopoulos et al. 2010, Eckers et al. 2013, Kröger et al. 2009, Kröger et al. 2014). All of these actions are represented as potentially available cognitive, sensory, or motor actions to the basal ganglia and thalamus. Due to the specific situational context, one of these actions can then be selected by the basal ganglia-thalamus system (e.g. DeLong & Wichmann 2009; Gurney et al. 2001a and 2001b).

Two pathways define action selection within the basal ganglia, often referred to as the direct and indirect pathways. However, we adopt the analysis of Gurney at al. (2001a and 2001b), which suggests that there is rather a “selection pathway” and a regulating or modulation pathway, called the “control pathway”. In both pathways all neural activity starts with the cortex stimulating the striatum (see also Fig. 1). The striatum inhibits both the substantia nigra (SN) and the globus pallidus (GP). Both the SN and the GP consists of two parts. There is the substantia nigra pars compacta (SNc) and pars reticularis (SNr), as well as the globus pallidus pars externa (GPe) and pars interna (GPi). When the striatum inhibits the SN and the GP, SNr and GPi themselves cannot continue inhibiting the thalamus. This is the selection pathway, which largely relies on mechanisms of disinhibition. In addition, the GPe inhibits the GPi and the subthalamic nucleus (STN), which in turn reduce their excitatory input into the GPe, GPi and the SNr. As mentioned above, a less active SNr and GPi positively influence the neural activity of the thalamus (i.e., via disinhibition). This is the control pathway. Both the control and selection pathways are modulated by the SNc, which effects the striatum by modulating the dopamine level. Activation of the dopamine D1 receptor results in the inhibition of the SN and the GPi by the striatum, and activation of the D2 receptor results in the inhibition of the inhibition (i.e., disinhibition) of the GPe by the striatum. In both cases, dopamine influences result in increased thalamic activity, suggesting that the pathways work synergistically.

This process of action selection is highly dependent on the dopamine level in the striatum (Gerfen & Surmeier 2011). Following Gurney et al. (2001a and 2001b), in our basal ganglia-thalamus action selection model two parameters can be introduced in order to describe the dopamine level in striatum. The lg parameter affects the selection pathway and modulates the stimulating influence of the SNc on the striatum. Specifically, it determines the amount of dopamine, which interacts with the D1 receptor. The second parameter is the le parameter, which reflects the amount of dopamine from the SNc binding to the D2 receptor. The D2 receptor results in an inhibitory effect on the parts of the striatum which inhibit the GPe causing this inhibitory effect on GPe to decrease (disinhibition). The result is a more active GPe now inhibiting the GPi and the STN which then decreases excitatory influence on the SNr and the GPi so that both of these structures decrease their inhibitory effect on the thalamus. The D1 receptor, however, has an excitatory effect on the striatum, so the striatum itself can inhibit the SN and the GP, which subsequently cannot inhibit the thalamus (disinhibition).

Because of this complexity, an imbalanced dopamine system is thought to cause different neuropsychiatric disorders, such as the Parkinson's disease (PD) (e.g. Goetz and Pal 2014), schizophrenia (e.g. Shen et al. 2012) or AD/HD (e.g. Kasahara et al. 2013). In the case of PD, both the degeneration of dopaminergic cells within the substantia nigra and the resulting loss of dopamine in the striatum result in Parkinsonian symptoms such as tremor, bradykinesia, rigidity and difficulty with walking and gait (Goetz and Pal 2014). More than a third of PD patients also suffer from a so-called freezing effect (Gonçalves and Pereira 2013, Vercruysse et al. 2014). During freezing, patients suddenly interrupt an action which is already under execution, or interrupt an action sequence. This can occur in tasks like walking, reaching or speaking. In the case of walking, freezing may lead to falling, resulting in a loss of independence for these patients (Okuma 2014).

Patients suffering from Parkinson's Disease typically produce specific symptoms in speech production like reduced loudness, poor voice quality, voice tremor, reduced prosodic variability in pitch and loudness, unprecise or reduced articulation of consonants and vowels, short rushes of speech, hesitations, and passages of dysfluency. These symptoms can be subsumed as hypokinetic dysarthria (Duffy 2005, Sapir 2014). When confronted with a syllable repetition task in speech (rapid repetition of one syllable or of an ordered sequence of syllables) in addition speech freezing can be observed in Parkinsonian patients (Ackermann et al. 1993, Erro et al. 2014). Erro et al. (2014, p. 561) describe freezing of speech seen in Parkinsonian patients as "a brief, episodic absence or marked reduction of forward progression of the speech, despite the intention to speak, bearing resemblance with FoG" (freezing of gait). While other symptoms of hypokinetic dysarthria are well investigated, this does not hold for the symptom complex of hesitations, dysfluency, and freezing of speech. Freezing of speech (FoS) can be interpreted as a subform of repetitive speech in Parkinson's Disease (Erro et al. 2014, Benke et al. 2000) and in its extreme form leads to a stoppage of articulation or at least to a break of articulation for a duration of a couple of syllables. Ziegler (2002) reports that he excluded all trials in an endless syllable repetition task (oral diadochokinesis), which comprised less than eight produced syllables (ibid., p. 561). Thus, we are unable to compare the freezing phenomena presented here with quantitative human data, and instead focus on reproducing the effect qualitatively and investigating the neural mechanisms that may be involved.

In past work, it was shown via simulation experiments by using a neurocomputational model of cortical and subcortical parts of the brain that pathological dopamine levels within basal ganglia can result in dysfluencies in speech (Civier et al. 2013). In that work, data were gathered with the neurocomputational speech production model GO-DIVA, containing basal ganglia, thalamus and left ventral premotor cortex, which is assumed to simulate the syllable-sequencing circuit. It was shown that an elevated dopamine level in striatum disturbs normal thalamus activity and leads to a stuttering effect (repetition of a sound or syllable following a complete stop of articulation during a first production trial of that sound or syllable). Civier (2013 p. 264) confirms as well, that an imbalanced dopamine system is associated with disorders of movement and decision making.

It is our hypothesis that speech freezing in Parkinson's disease (Ackerman et al. 1993, Vercryuice et al. 2014) results from dysfunctions in syllable repetition or syllable sequencing as well. It will be shown in this paper on the basis of computer simulation using a neurofunctional model of cortical and subcortical structures that the speech freezing effect can be simulated by a decrease in

the dopamine level of striatal neurons in our basal ganglia model and therefore can be attributed to a modified functioning (a “dysfunction”) of our model with respect to the cortico-basal ganglia-thalamus-cortex action selection circuit.

2 Computer modelling of neural processes

In order to investigate the functional role of specific regions of the brain in humans (e.g., cortical regions, basal ganglia, and thalamus) imaging techniques are most commonly used (for a review see Raichle & Mintun 2006). While these techniques allow the identification of the most active brain regions depending on the cognitive or sensorimotor task under execution, the detailed functional processes occurring in the local neural networks in these brain regions cannot be explored. Thus, computational modeling of neural processes can be helpful (Markram 2006, Izhikevich & Edelman 2008, Eliasmith & Trujillo 2014).

In order to investigate the basic functioning of the action selection loop including basal ganglia and thalamus, the brain model Spaun (Semantic Pointer Architecture Unified Network, Eliasmith et al. 2012) provides a simultaneous large-scale and neutrally detailed account. Spaun was implemented using the Nengo (Neural ENGineering Object) software tool (Bekolay et al. 2014). This neural simulation package incorporates the three principles of the Neural Engineering Framework (Eliasmith and Anderson 2003), here formulated in non-mathematical terms: (i) Information is coded as time-varying numerical vectors and is represented by spike activity of model neurons within neuron ensembles. The model neurons can be any of a variety of neural models, although here we use simple leaky integrate and fire neurons. The current state of activity of all neurons within a neuron ensemble can be called the *neural state* of an ensemble (see section 3 of this paper). (ii) The transformation of information – i.e. the transformation of neural states – is modeled by specifying the weights of the connections between all model neurons of two or more neuron ensembles. (iii) The dynamic behavior of neuron ensembles – i.e. the temporal progression of a neural state within a neuron ensemble or of several states within a network of interacting neuron ensembles – is modeled by introducing recurrent connections within neuron ensembles as well as between different neuron ensembles.

In addition, several constraints need to be formulated in order to replicate the neural architecture representing the central nervous system and the associated sensory and motor systems. We adopt the Semantic Pointer Architecture (SPA) as a general approach for building this architecture (Eliasmith 2013, Stewart & Eliasmith 2014). The Spaun model is currently the largest-scale example of an SPA model and includes cognitive processes, visual perception and motor control of arm movements. A central part of the SPA is the modeling of action selection, i.e. modeling of the cortico-basal ganglia-thalamus-cortical circuit. Action selection includes processing of cognitive as well as of sensory and motor information. In parallel with Humphries & Gurney (2006), Humphries, Khamassi et al. (2012), and Humphries, Stewart et al. (2012), a spiking neuron model of action selection has been developed in Nengo, which forms the core of action selection in the SPA. This model has been introduced and implemented by Stewart et al. (2010) and is based on the modeling work of Gurney et al. (2001a) and Gurney et al. (2001b), already described above. In the SPA, neural representations are generally understood as so called *semantic pointers*, which represent cognitive, sensory or motor states on the one hand, as well as being neural activation patterns within specific neuron ensembles

on the other hand. From a mathematical viewpoint, a semantic pointer can be considered as a n-dimensional numerical vector where the number of dimensions in the case of Spaun simulations is 16 or higher in order to be able to represent a variety of different states (e.g. 200 different syllables) within one neuron ensemble at different points in time with sufficient accuracy.

3 Method

The neural processes of the action selection loop can be computer simulated using Nengo. Using this tool, a large-scale neural network was created for simulating the syllable sequencing task (Fig. 2). Recall that in our basal ganglia model two parameters (lg and le) exist which quantify the dopamine level at the striatum. One (lg) operates for D1 receptors and the other (le) on the D2 receptors, both located in the striatum. Modulating these parameters allows us to simulate different dopamine levels and therefore to test its influence on the performance of the syllable repetition or sequencing task and with it of the action selection process.

3.1 The architecture of the model

The large-scale model for simulating the syllable repetition task comprises cortical neuron ensembles, i.e. neuron ensembles for visual, auditory, somatosensory, premotor, and motor state representations (see Fig. 2). The basal ganglia comprises neuron ensembles representing the striatum, substantia nigra, subthalamic nucleus, and globus pallidus (see Fig. 2). As can be seen, the action selection loop exhibits connections from cortex to basal ganglia, from basal ganglia to thalamus, and back from thalamus to cortex (Fig. 2). An additional subcortical part is included as a motor execution or delay network, which simulates the production of each syllable and feeds back a neural signal towards the somatosensory state network, when the execution of the syllable ends.

Activation of several already learned syllables (e.g. /ba/, /da/, /ga/, /pa/, /ta/, /ka/) can be simulated within this network at a cognitive phonemic level (phonemic state network, Fig. 2), at sensory levels, e.g. activation of the learned auditory and somatosensory image or expectation of a syllable (auditory expectation and somatosensory state network, Fig. 2), as well as at the level of the primary motor network (motor state network, Fig. 2), where the currently activated syllable is ready for execution. Syllables were encoded as semantic pointers, i.e. as specific neural activation patterns within the cortical neuron ensembles, existing in this large-scale network. These neural activation patterns or semantic pointers were named e.g. BA, DA, GA in the cognitive, premotor and auditory expectation networks and named BA_EXEC, DA_EXEC, GA_EXEC in the primary motor and execution network and in the somatosensory network, where the feedback signal resulting from syllable execution is processed. The duration of syllable execution varies between 100 and 400 ms and is introduced as a delay time constant in our neural network.

The difference between premotor and motor state is that in the premotor or planning network the execution of the syllable is not spelled out in detail (cf. Riecker et al. 2005) while in the motor state network (M1) a direct activation of motor neurons occurs, signaling that the execution of the syllable is about to start. Because we model typical syllable sequencing or syllable repetition tasks, we exclusively select and execute frequent syllables, i.e. syllables, which are already learned and for which an auditory as well as a somatosensory image of that syllable is already stored in a mental

syllabary (Eckers et al. 2013, Kröger & Heim 2013). These higher level motor and sensory representations are activated always synchronously with the phonemic state (i.e., the cognitive state) of a syllable (Kröger et al. 2014). If the primary motor state is activated for a syllable, motor execution starts and the motor execution network (Fig. 2) feeds back the end of motor execution after a predefined delay time (100ms, 200ms, or 400ms in case of our simulation experiments) towards the somatosensory state network.

The action selection process works as follows: An initial visual signal, always representing the syllable BA for 200 ms and beginning at a specific point in time (250ms after start of a simulation), induces the syllable state BA in the neuron ensemble representing the visual state network (Fig. 2 and Fig. 3). The basal ganglia-thalamus system is guided by a task-specific rule system, here in order to perform the syllable repetition or sequencing task in a way that this initial visual neural pulse activates the phonemic as well as the auditory expectation for that syllable (Fig. 2 and Fig. 3). Furthermore the primary motor state is activated for the syllable BA as well (see BA_EXEC in the primary motor network, Fig. 3). 200 ms later, the somatosensory state network gives a feedback signal BA_EXEC (Fig. 3) towards the basal ganglia, indicating that the syllable has been executed successfully. This initializes the phonemic activation of the next syllable (i.e., DA) and so on (see Fig. 3). In the case of normal task execution, the syllables BA, DA, GA, PA, TA, KA will be repeated now without any ending (Fig. 3). Thus, in this example a total of 14 potential actions (coded by 14 different semantic pointers) are prepared to be selected at any time by the basal ganglia thalamus system: BA, DA, GA, PA, TA, KA, BA_EXEC, DA_EXEC, GA_EXEC, PA_EXEC, TA_EXEC, KA_EXEC, ZERO, NEUTRAL. ZERO and NEUTRAL are semantic pointers, describing non-speech actions, which occur within the visual system (ZERO, if no syllable occurs at the screen), or within the cortical system of the mental syllabary (NEUTRAL, if no syllable is currently under selection).

Each neuron ensemble within basal ganglia and thalamus comprise 50 model neurons leading to 2000 neurons in basal ganglia and 400 in thalamus. In the cortical areas of the model each neuron ensemble comprises 50 neurons per semantic pointer dimension. We used 32 dimensional semantic pointers in order to guarantee a clear separation of the representation of up to 50 semantic pointers per neuron ensemble. All other Nengo parameters are set on default values.

Nengo source code for this model can be downloaded at http://www.phonetik.phoniatrie.rwth-aachen.de/bkroeger/documents/syllable_sequencing.ipynb (in IPython notebook format). This source code requires Nengo (version 2.0; Bekolay et al. 2014), which can be downloaded at http://www.nengo.ca/download. The simulation of single model neurons, their activations, and interactions with other model neurons within and between neuron ensembles is described in detail in Eliasmith (2013) and Stewart & Eliasmith (2014). The mathematical background concerning the implementation of all neuron ensembles and the interconnections representing the basal ganglia and thalamus is described in Stewart et al. (2010) and Eliasmith (2013).

3.2 Results of the simulation experiments

3.2.1. Variation of dopamine levels

After Gurney et al. (2001a, 2001b), two parameters (lg and le) exist which quantify the dopamine level at the striatum. One parameter (lg) operates on D1 receptors and the other (le) on D2 receptors, both

of which are located in the striatum. Within our network architecture, lg (D1) mainly influences the selection pathway, while le (D2) mainly influences the control pathway. As described above, the effect of D1 and D2 receptors is a more active thalamus, communicated by means of disinhibition.

In this study all combinations of lg and le are measured in steps of 0.02 from 0.2 (where value 0.2 represents a normal dopamine level as occurs in healthy persons) to 0 (no dopamine available), i.e. 121 combinations. Four simulation trials were done for each le-lg-value pair. Simulation time is 5.5s for each of these four simulation trials. Thus, in total 484 simulation trials were done. The duration of syllable production stays constant at 200ms, and the number of available syllables is always six in these simulation trials. A syllable is defined as not executed in our model if activation for a specific syllable at a primary motor state neuron ensemble does not exceed the level of 10% of maximum activity for the semantic pointer of this syllable (i.e., does not exceed 10% of semantic pointer similarity). In the case of a normal dopamine level (lg and le value set to 0.2), the process of action selection and thus the syllable sequencing task is executed without any error. Syllable sequencing always works correctly until the end of simulation time (which is set to 5.5 seconds of simulated time in order not to extend the real computation time above 5 minutes). If the dopamine level is reduced for one parameter le or lg as well as for both parameters, the syllable sequencing task begins to show syllable activation levels below 10% of maximum activation for semantic pointers representing specific syllables (Fig. 4), which is interpreted as not executed syllables (freezing of speech articulation).

From Fig. 5 and Tab. 1 we can see that the number of executed syllables becomes smaller if the dopamine level is reduced by the parameters lg and le. The effect is a little more prominent for lg than for le (see Tab. 1, especially the area for normal syllable sequencing, marked by green colour is more enlarged for the lg dimension).

Detailed behavioural results concerning percentage of executed syllables relating to intended number of syllables within action sequencing by varying dopamine level parameters le and lg are given in Fig. 5 and Tab. 1. Here all 121 parameter combinations of le and lg were displayed. We can see that freezing occurs over wide areas of le and lg (blue area in Tab. 1 at low le and lg levels). Only within a small area (lg from 0.2 to 0.16 and le from 0.2 to about 0.08) we can find the condition of error-free syllable repetition within the syllable sequencing task (red area in Tab.1: no freezing effect; normal syllable sequencing without stops; minimum of correct sequencing over 90% of the whole simulation time range, i.e. minimum of 16 correct sequenced syllables per simulation). The blue area in Tab. 1 indicates freezing of syllable production at least after 5 syllable executions per simulation (minimum: 25% of the whole simulation time range is covered by correct syllable sequences). The white area in Tab. 1 area indicates a transition region from normal speech (no freezing) to freezing within the syllable sequencing task.

3.2.2. Variation of duration of syllable production

Actions (i.e., syllables in the context of this study) vary in length of execution time. In terms of our Nengo simulation network, the delay time for motor execution, which is located in between the primary motor network and the somatosensory state network (Fig. 2), needs to be set to different values. In this study, we checked whether syllable duration (i.e., action execution time) influences action selection behavior at different levels of dopamine for same le and lg levels (le=lg). Syllable duration

was set to 100ms, 200ms and 400ms respectively and four runs for simulating syllable sequencing behavior over 5.5 sec were performed for each combination of dopamine level and syllable duration time. It can be seen from Fig. 6 that in the whole range of dopamine levels the absolute number of correctly sequenced syllables does not show significant differences for different syllable durations. The hypothesis “different mean values” was checked using a Mann-Whitney U Test at each dopamine level for all combinations of syllable duration. In all cases the hypothesis was not supported because significance level was $p>.05$ for each combination at each dopamine level.

3.2.3. Variation of number of potentially executable syllables

The performance of action selection may also vary with the number of syllables potentially activated or pre-activated, i.e., with the number of syllables that have to be uttered within the syllable sequencing task. Again, we checked the variation of this parameter at different levels of dopamine for the same le and lg levels (le=lg). The number of pre-activated syllables were 3, 6, 12, 24 syllables, i.e., /ba. da, ga/ in case of 3 syllables, /ba, da, ga, pa, ta, ka/ in case of 6 syllables, /ba, da, ga, pa, ta, ka, bi, di, gi, pi, ti, ki/ in case of 12 syllable and all combinations of /b, d, g, p, t, k/ with four vowels /a, i, o, u/ in the case of 24 syllables. In terms of our Nengo simulation network that means that the number of semantic pointers including all syllable related cognitive and execution pointers and including two default pointers ZERO and NEUTRAL are 8, 14, 26, and 50 predefined semantic pointers, in the case of 3, 6, 12, and 24 syllables respectively. Four runs for simulating syllable sequencing behavior over 5.5 sec were done for each combination of dopamine level and number of syllables. It can be seen from Fig. 7 that for the le=lg levels 0.2, 0.16, 0.12, 0.08, 0.04, 0 the absolute number of correctly sequenced syllables does not vary significantly for these different amounts of potentially activated syllables at any dopamine level. The hypothesis “different mean values” was checked using Mann-Whitney U Test at each dopamine level for all combinations of number of syllables. In all cases the hypothesis was not supported because significance level was $p>.05$ for each combination at each dopamine level.

3.2.4. Variability of syllable sequencing

Even when all model parameters are fixed (le, lg, syllable duration, number of potentially executable syllables), different simulation trials show variability with respect to different features. First, the number of correctly sequenced syllables varies from trial to trial. For example, in the case of lg = 0.18, le = 0.10, 200ms syllable duration, and six potentially executable syllables we found that freezing occurred after 11, 5, 9, or 10 successfully sequenced syllables respectively from trial 1 to trial 4. A systematic evaluation of this variability is documented by the range of values of successfully sequenced syllables for the case of le=lg in sections 3.2.2 and 3.2.3. Secondly, in some of the trails with le and lg parameter combinations occurring within the transition region between normal production (no freezing) and freezing (white area in table 1), the effect of re-stabilization of syllable sequencing can be seen after a short period of freezing. This can be labelled as episodic freezing or stuttering. The trial shown in Fig. 8 demonstrates re-stabilization of production of the syllable /ga/ after about one second freezing between 3.5s to 4.5s. Thus, here we have no re-stabilization towards correct syllable sequencing, but at least toward the repetition of one syllable. The trial shown in Fig. 9, in contrast,

demonstrates re-stabilization toward correct syllable sequencing, but here we have no complete freezing between 3.2s and 4.0s, only a reduction of activation of the syllable initiating semantic pointers.

In other trials within the le-lg-transition region (white area in table 1) we found that one syllable is reproduced over and over again without freezing. One typical simulation trial for this is shown in Fig. 10. Here the repetition (or stuttering) of the syllable /ga/ starts directly after cessation of correct syllable sequencing at around 1.5s. Moreover, it can be seen from this example that the timing of syllable production in the case of repetitive speech becomes more irregular and syllable production becomes slower in comparison to the case of correct syllable sequencing at the beginning of this simulation trial.

These examples of variability in syllable sequencing from trial to trial indicate that our approach does not exclusively model freezing as a complete stoppage of speech production after a period of correctly sequenced syllables, but also models local or episodic freezing and syllable repetitions. Local freezing and syllable repetitions can be subsumed as repetitive speech or as stuttering, which is often described as a frequent symptom in speech production occurring in patients suffering from Parkinson's disease (e.g. Benke et al. 2000, Erro et al. 2014).

4. Discussion and Conclusions

In this paper we systematically varied the D1 and D2 dopamine level during a syllable sequencing task. This systematic variation of control of the dopamine level is only possible using computer simulation. Therefore, we used a functional model of the cortico-basal ganglia-thalamus-cortical action selection circuit (Stewart et al. 2010) and gave it a syllable sequencing task to do, which at normal dopamine level it could easily perform. In case of decreasing the dopamine level in the striatum, we see that the action selection system halted after a certain number of produced syllables. These results are reminiscent of a behaviour called "freezing" seen in more than one third of patients with Parkinson's disease (Goncalves and Pereira 2013).

Particularly, we find that there is a difference between the impact of the lg and the le parameter. We see that the decrease of the lg parameter (which affects D1) more quickly results in a destabilised basal ganglia than the decrease of the le parameter (which affects D2). When setting the le parameter to 50% of the normal dopamine level we still do not observe freezing symptoms. But, decreasing the lg parameter to 50%, syllable sequencing stops after about 9 syllables (i.e. 49%, see Tab. 1). This result supports the theory by Gurney et al. (2001a) of a selection and a control pathway, assuming that the selection pathway is the main pathway to effect the actual action selection process (represented by the lg parameter) and the control pathway (represented by the le parameter) is regulating, modulating and supervising this process (Gurney et al. 2001a). We also showed that neither the duration of the syllables nor the number of preselected actions affect the freezing behaviour significantly.

However the cause of freezing is still not fully understood, but our findings hint to an involvement of a low dopamine level, or possibly a low density of the D1 and D2 receptors, within the striatum in the origin of the symptom of freezing. This would also explain freezing in other functional

domains of body movements beside speech (vocal tract articulator movements), which is including e.g., gait (lower limb movements), gesturing, pointing or grasping (upper limb movements) (Shine JM et al. 2011, Vercruysse et al. 2014).

In addition to these empirically relevant results, the present work suggests an important role for modelling studies. The behaviour resulting from these modelling experiments cannot be measured easily in patients, because we cannot control or measure their dopamine level in vivo. As well, a lot of other parameters and effects may influence the speech behaviour in natural subjects. We believe that the SPA, with its detailed modeling of action selection and action sequencing (Stewart et al. 2010) seems a good choice for this kind of studies because it uses a spiking neuron approach and thus allows a detailed modelling of timing (ibid., see “response latencies”, p. 239). Furthermore, a detailed representation of each nucleus of the basal ganglia is implemented here by using neuron ensembles and not by just representing each nucleus by one or a few “nodes” as it is the case in Gurney et al. (2001a and 2001b).

A shortcoming of this simulation study is that it focuses on reproducing freezing, despite patients suffering from Parkinson’s Disease showing many deficits in speech production; e.g. repetition of syllables and restarts of syllable productions after a time interval of freezing. It is a part of our ongoing work to establish an extended version of the model which includes a neural mechanism for transferring short-term knowledge - like the phonological information concerning the syllable sequence - from cortical regions to the basal ganglia-thalamus complex. In our current model, this knowledge is directly stored at the level of the basal ganglia-thalamus complex. Other symptoms of Parkinson’s Disease in speech production, like unclear or reduced articulation of consonants and vowels, result from lower level parts of the speech production hierarchy (e.g. how syllable specific semantic pointers at the primary motor level are transferred in concrete muscle activation patterns) and are therefore a target for future work that incorporates our model, but is not currently a planned extension in our ongoing work.

Given our results, it now would be interesting to do clinical studies in order to try to investigate whether or not there is a day-to-day variation of the freezing effect, or if there is an influence of emotions. Both would be another sign of an involvement of the dopamine level in the symptom of freezing (e.g. Ashby et al. 1999).

References

Ackermann H, Gröne BF, Hoch G, Schönle PW (1993) Speech freezing in Parkinson's disease: a kinematic analysis of orofacial movements by means of electromagnetic articulography. Folia Phoniatrica 45(2): 84-89 (Link)

Ashby FG, Isen AM, Turken AU (1999) A neuropsychological theory of positive affect and its influence on cognition. Psychol Rev 106(3): 529-550 (Link)

Bekolay T, Bergstra J, Hunsberger E, DeWolf T, Stewart TC, Rasmussen D, Choo X, Voelker AR, Eliasmith, C (2014) Nengo: a Python tool for building large-scale functional brain models. Frontiers in Neuroinformatics 7: 48 (Link)

Benke T, Hohenstein C, Poewe W, Butterworth B (2000) Repetitive speech phenomena in Parkinson's disease. J Neurol Neurosurg Psychiatry 69: 319-324 (Link)

Civier O, Bullock D, Max L, Guenther FH (2013) Computational modeling of stuttering caused by impairments in a basal ganglia thalamo-cortical circuit involved in syllable selection and initiation. Brain & Language 126: 263–278 (Link)

de Lau LM, Breteler MM (2006) Epidemiology of Parkinson's disease. *Lancet Neurol* 5 (6): 525–535 (Link)

DeLong M, Wichmann T (2009) Update on models of basal ganglia function and dysfunction. Parkinsonism Relat Disord. 3: 237-240 (Link)

Duffy JR (2005) Motor Speech Disorders (2nd ed.). St. Louis, MO: Mosby (Link)

Eckers C, Kröger BJ, Sass K, Heim S (2013) Neural representation of the sensorimotor speech-action repository. Frontiers in Human Neuroscience 7:121 (Link)

Eliasmith C (2013) How to Build a Brain: A Neural Architecture for Biological Cognition. Oxford University Press. (Link)

Eliasmith C, Anderson CH (2003) Neural Engineering: Computation, Representation, and Dynamics in Neurobiological Systems. Cambridge, MA: MIT Press (Link)

Eliasmith C, Stewart TC, Choo X, Bekolay T, DeWolf T, Tang Y, Rasmussen D (2012) A large-scale model of the functioning brain. Science 338: 1202-1205 (Link)

Eliasmith C, Trujillo O (2014) The use and abuse of large-scale brain models. Current Opinion in Neurobiology 25: 1-6 (Link)

Erro R, Tedeschi MR, Vitale C, Buonocore S, Orefice G (2014) A (single case) rehabilitation program based on cueing for freezing of speech. Eur J Phys Rehabil Med. 50(5): 561-565 (Link)

Gerfen CR, Surmeier DJ (2011) Modulation of striatal projection systems by dopamine. Annu Rev Neurosci 34: 441-466 (Link)

Goetz CG, Pal G (2014) Initial management of Parkinson's disease. BMJ 349: g6258 (Link)

Golfinopoulos E, Tourville JA, Guenther FH (2010) The integration of large-scale neural network modeling and functional brain imaging in speech motor control. Neuroimage 52: 862–874 (Link)

Gonçalves G, Pereira J (2013) Freezing and gait disorders in Parkinson's disease. Revista Medica de Chile 141: 758-764 (Link)

Guenther FH (2006) Cortical interaction underlying the production of speech sounds. J Commun Disord 39: 350–365 (Link)

Gurney K, Prescott TJ, Redgrave P (2001a) A computational model of action selection in the basal ganglia. I. A new functional anatomy. Biological Cybernetics 84: 401-410 (Link)

Gurney K, Prescott TJ, Redgrave P (2001b) A computational model of action selection in the basal ganglia. II. Analysis and simulation of behaviour. Biological Cybernetics 84: 411-423 (Link)

Herman T, Giladi N, Hausdorff JM (2013) Neuroimaging as a window into gait disturbances and freezing of gait in patients with Parkinson's disease. Curr Neurol Neurosci Rep. 13(12): 411 (Link)

Humphries MD, Gurney K (2012) Network effects of subthalamic deep brain stimulation drive a unique mixture of responses in basal ganglia output. European Journal of Neuroscience 26: 2240-2251 (Link)

Humphries MD1, Khamassi M, Gurney K (2012) Dopaminergic Control of the Exploration-Exploitation Trade-Off via the Basal Ganglia. Front Neurosci. 6:9. doi: 10.3389/fnins.2012.00009 (Link)

Humphries MD, Stewart RD, Gurney KN (2006) A Physiologically Plausible Model of Action Selection and Oscillatory Activity in the Basal Ganglia. The Journal of Neuroscience 26: 12921-12942 (Link)

Indefrey P, Levelt W J (2004) The spatial and temporal signatures of word production components. Cognition 92, 101–144 (Link)

Izhikevich EM, Edelman GM (2008) Large-scale model of mammalian thalamocortical systems. Proceedings of the National Academy of Sciences of United States of America 105: 3593-3598 (Link)

Kasahara Y, Kubo Y, Sora I (2013) Analysis of dopamine transporter knockout mice as an animal model of AD/HD. Nihon Shinkei Seishin Yakurigaku Zasshi 33(5-6): 185-189 (Link)

Kröger BJ, Heim S (2013) How could a self-organizing associative speech action repository (SAR) be represented in the brain? Hallesche Schriften zur Sprechwissenschaft und Phonetik 45: 61-68

Kröger BJ, Kannampuzha J, Kaufmann E (2014) Associative learning and self-organization as basic principles for simulating speech acquisition, speech production, and speech perception. EPJ Nonlinear Biomedical Physics 2: 2

Kröger BJ, Kannampuzha J, Neuschaefer-Rube C (2009) Towards a neurocomputational model of speech production and perception. Speech Communication 51: 793-809

Levelt WJM, Roelofs A, Meyer A (1999) A theory of lexical access in speech production. Behav Brain Sci 22: 1–75 (Link)

Li P, Farkas I, MacWhinney B (2004) Early lexical development in a self-organizing neural network. Neural Netw 17: 1345–1362 (Link)

Markram H (2006) The blue brain project. Nature Reviews Neuroscience 7: 153-160 (Link)

Okuma Y (2014) Freezing of gait and falls in Parkinson's disease. J Parkinsons Dis. 4(2): 255-260 (Link)

Raichle ME, Mintun MA (2006) Brain work and brain imaging. Annual Review of Neuroscience 29: 449-476 (Link)

Riecker A, Mathiak K, Wildgruper D, Erb M, Hertrich I, Grodd W, Ackermann H (2005) fMRI reveals two distinct cerebral networks subserving speech motor control. Neurology 64: 700-706 (Link)

Sapir S (2014) Multiple factors are involved in the dysarthria associated with Parkinson's disease: a review with implications for clinical practice and research. J Speech Lang Hear Res 57: 1330-1343 (Link)

Shen LH, Liao MH, Tseng YC (2012) Recent advances in imaging of dopaminergic neurons for evaluation of neuropsychiatric disorders. J Biomed Biotechnol 2012: 259349 (Link)

Shine JM, Naismith SL, Lewis SJ (2011) The pathophysiological mechanisms underlying freezing of gait in Parkinson's Disease. J Clin Neurosci. 18(9): 1154-1157 (Link)

Stewart TC, Choo X, Eliasmith C (2010) Dynamic behaviour of a spiking model of action selection in the basal ganglia. Proceedings of 10th International Conference on Cognitive Modeling (Philadelphia, PA) pp. 235-240 (Link)

Stewart TC, Eliasmith C (2014) Large-scale synthesis of functional spiking neural circuits. Proceedings of the IEEE 102: 881-898 (Link)

Vercruysse S, Gilat M, Shine JM, Heremans E, Lewis S, Nieuwboer A (2014) Freezing beyond gait in Parkinson's disease: a review of current neurobehavioral evidence. Neurosci Biobehav Rev. 43: 213-227 (Link)

Ziegler W (2002) Task-related factors in oral motor control: speech and oral diadochokinesis in dysarthria and apraxia of speech. Brain Lang 80: 556-575 (Link)

Figure Captions

Figure 1. Model of the cortico-basal ganglia-thalamus-cortical circuit following Gurney et al. (2001a and 2001b). The green lines symbolize excitatory pathways, the red lines inhibitory pathways.

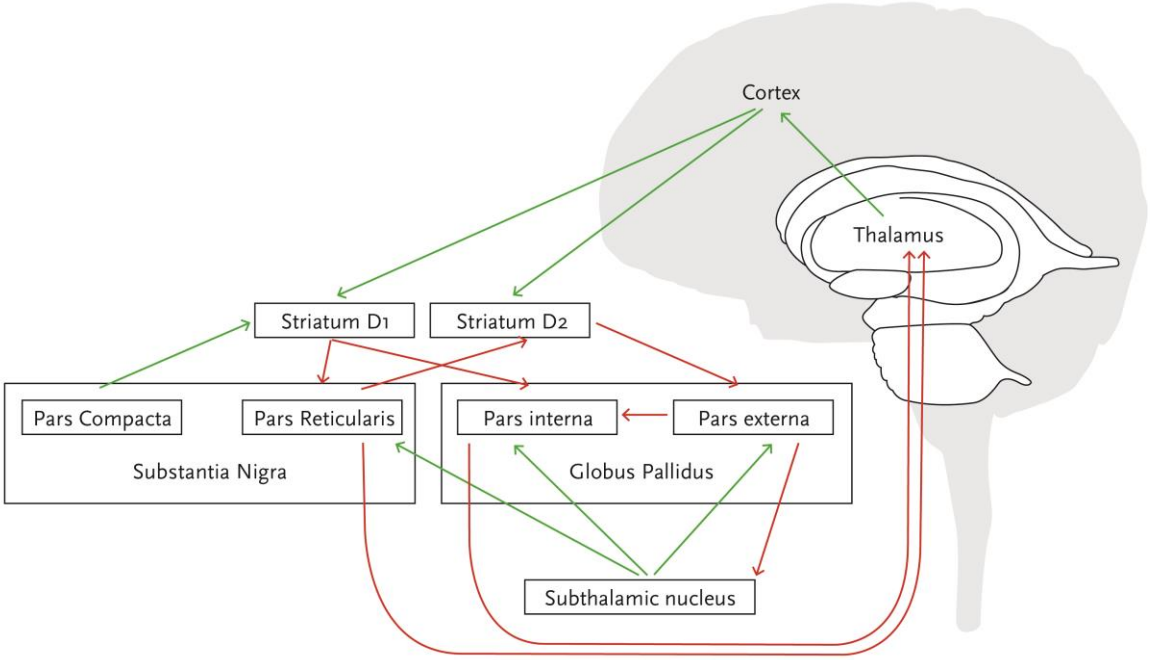
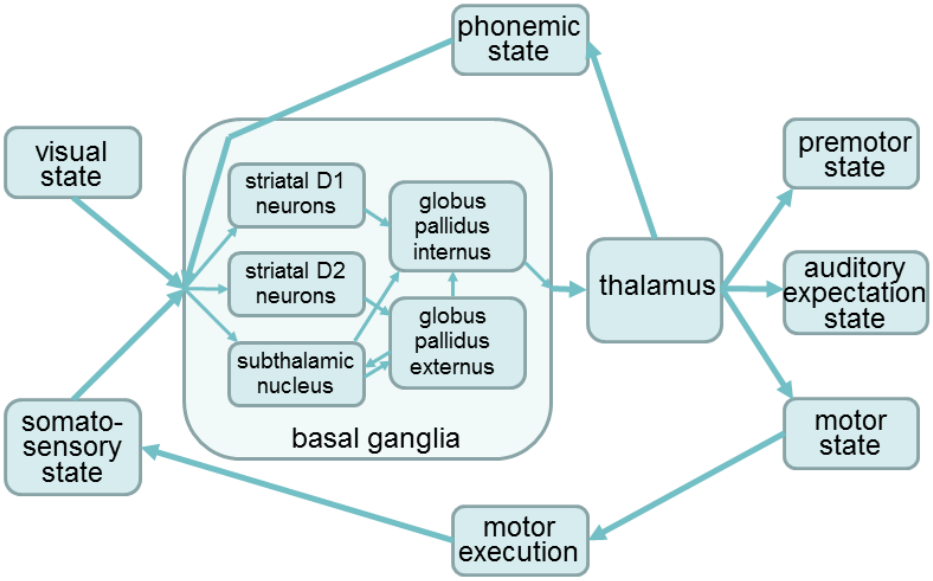


Figure 2. Architecture of the large-scale neural network for simulating the syllable repetition task. Top: block diagram of model; Bottom: Nengo diagram of the model, automatically generated from source code using the Nengo GUI (graphics user interface). Basal ganglia (bg) and thalamus constitute the central part of the network. Other parts except motor execution are cortical.



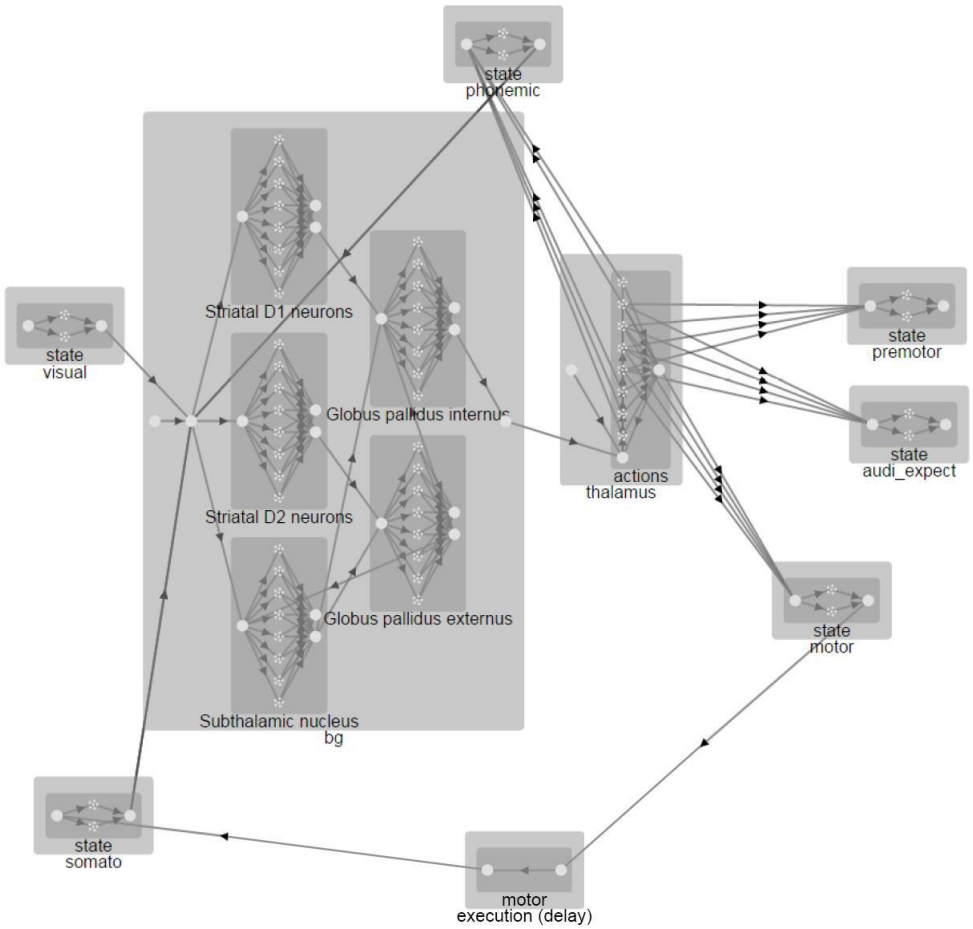


Figure 3. Neural activity in different neural networks (neuron ensembles) represented as the degree of similarity between the current neural activity and the activity for predefined semantic pointers. Colors for the semantic pointers are given at the right side of the figure; the network name is given at the left side. The diagram represents a simulation time from 0s to 5.5s. The delay time for syllable execution (delay between motor network and somatosensory network) is 200ms in this simulation example (see delay of semantic pointer peaks between the Motor and Somato neuron ensembles) and the syllable repetition or sequencing task comprises six syllables (see text).

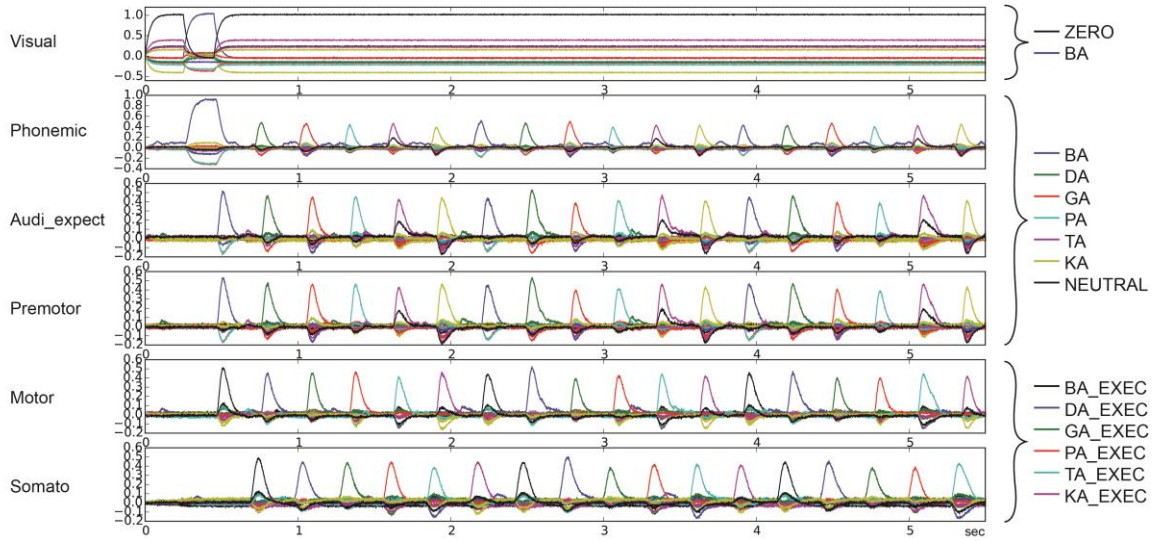


Figure 4. Effect of freezing (i.e. stopping of syllable sequencing) in the case of reduced dopamine level: syllable activation and syllable execution here ends after four syllable productions (lg=0.14, l le=0.14) syllable duration is 200ms, number of available syllables is six.

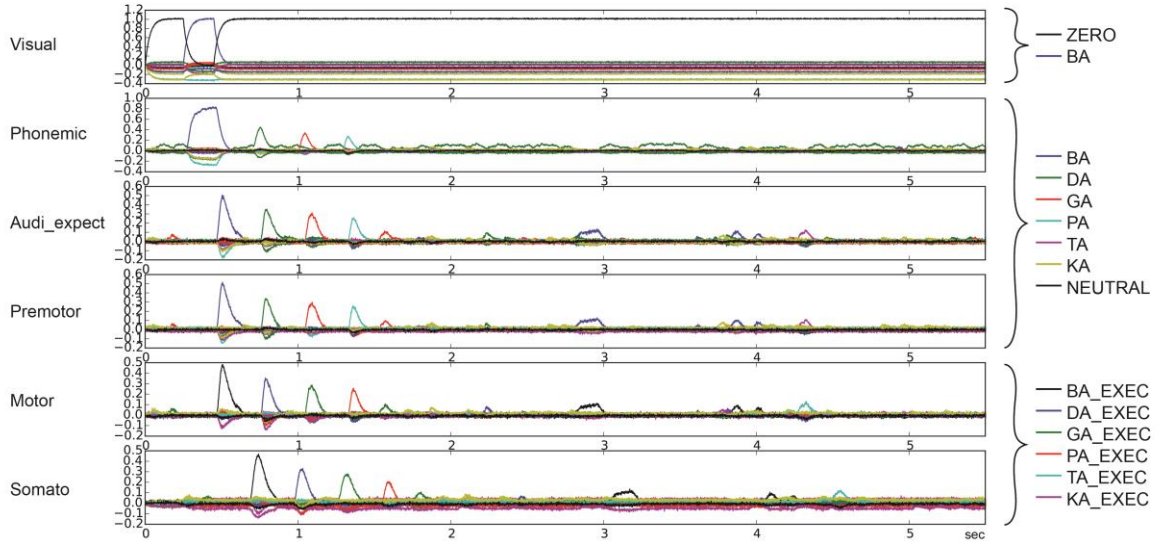


Figure 5. Percentage of accumulated number of correctly sequenced syllables over 121 simulations of a syllable sequencing task as function of parameters le and lg. Duration of syllable production is 200ms; number of available syllables is six.

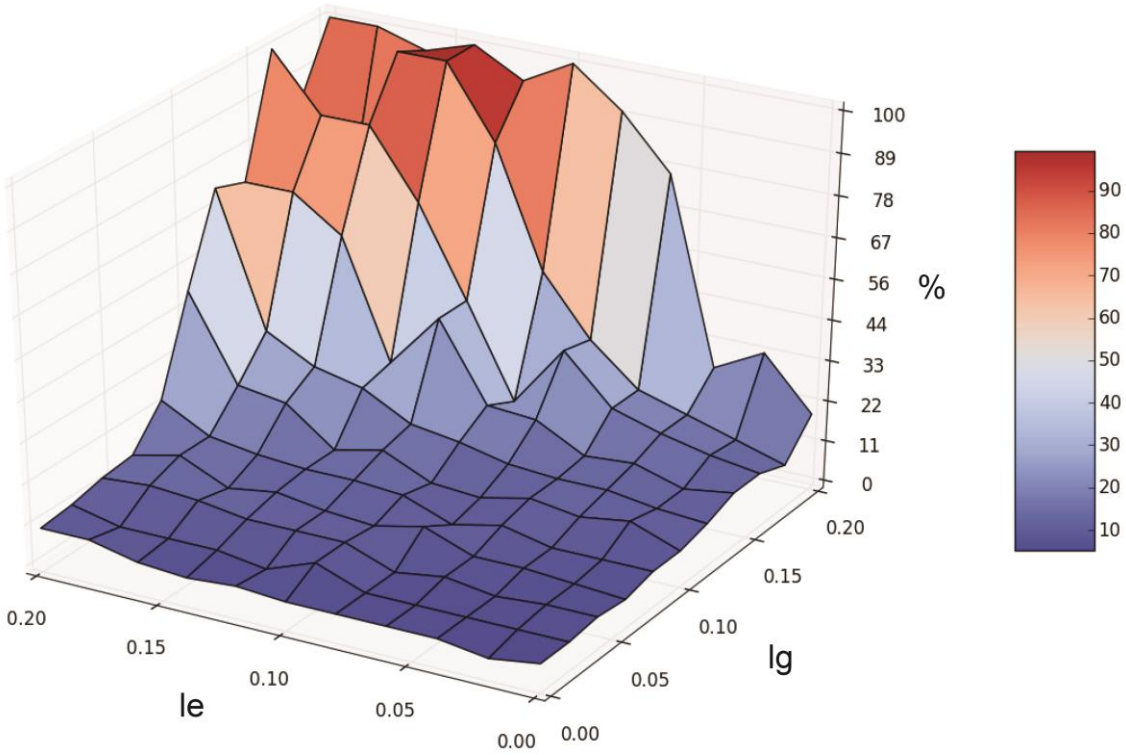


Figure 6. Accumulated number of correctly sequenced syllables summarized for four trials (top) and range of numbers and median value per trial of correctly sequenced syllables (bottom) for different syllable durations: 100ms (blue), 200ms (red), 400ms (green) and for different dopamine levels: le = lg = 0.2, 0.16, 0.12, 0.08, 0.04, 0.

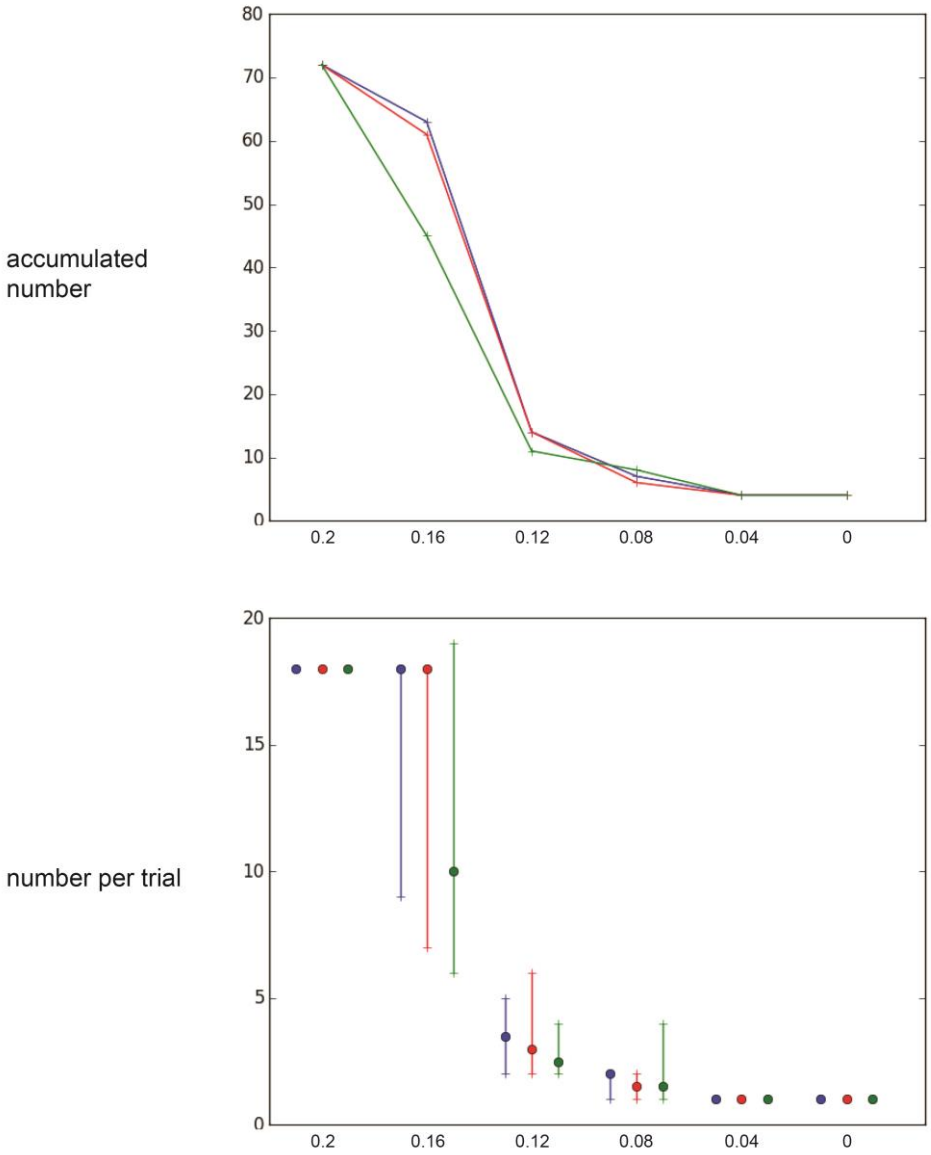


Figure 7. Accumulated number of correctly sequenced syllables summarized for four trials (top) and range of numbers and median value per trial of correctly sequenced syllables (bottom) for different numbers of syllables: 3 (blue), 6 (red), 12 (green), 24 (magenta) and for different dopamine levels: le = lg = 0.2, 0.16, 0.12, 0.08, 0.04, 0.

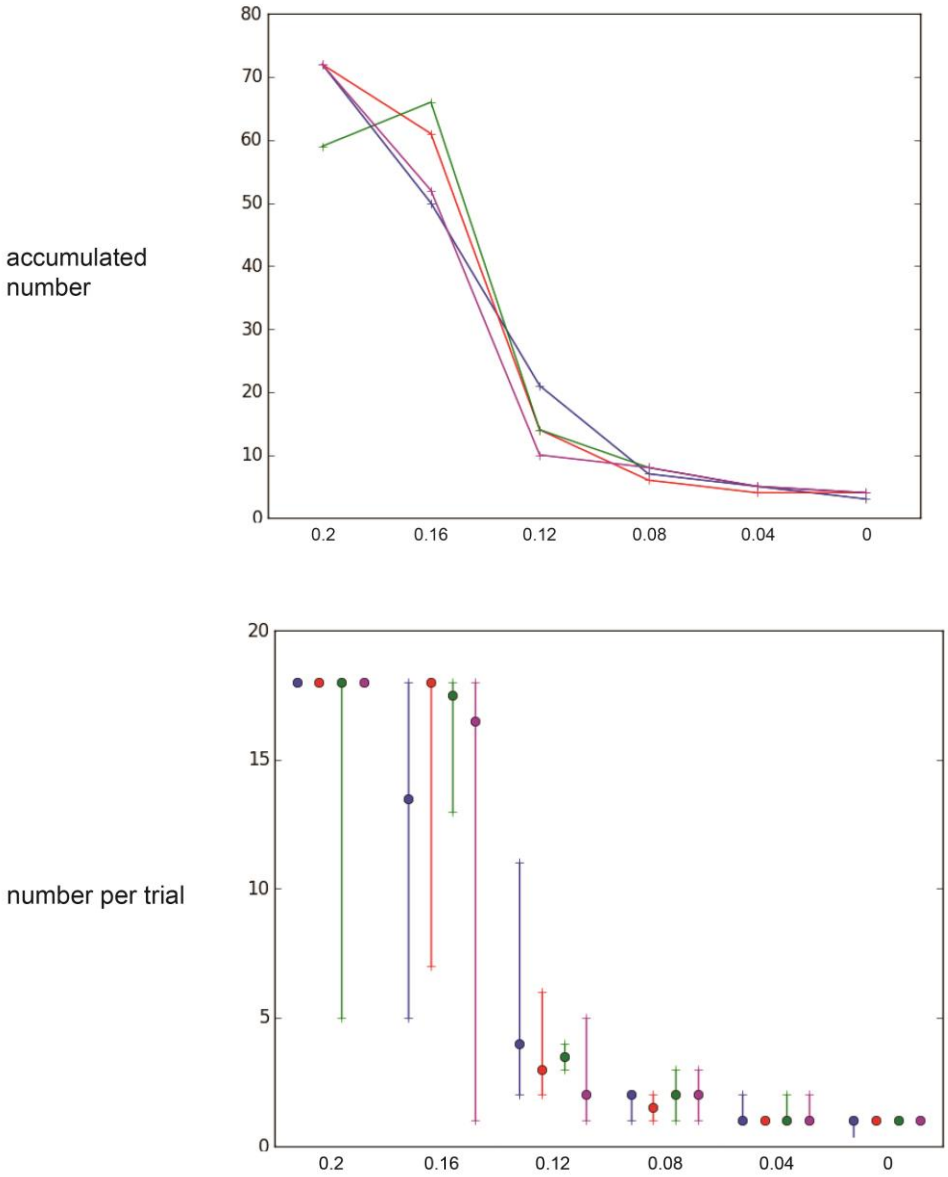


Figure 8. Effect of local freezing; here: interruption of syllable sequencing between 3.5s and 4.5s; parameters: lg = 0.12, le = 0.18, syllable duration is 200 ms, number of available syllables is six.

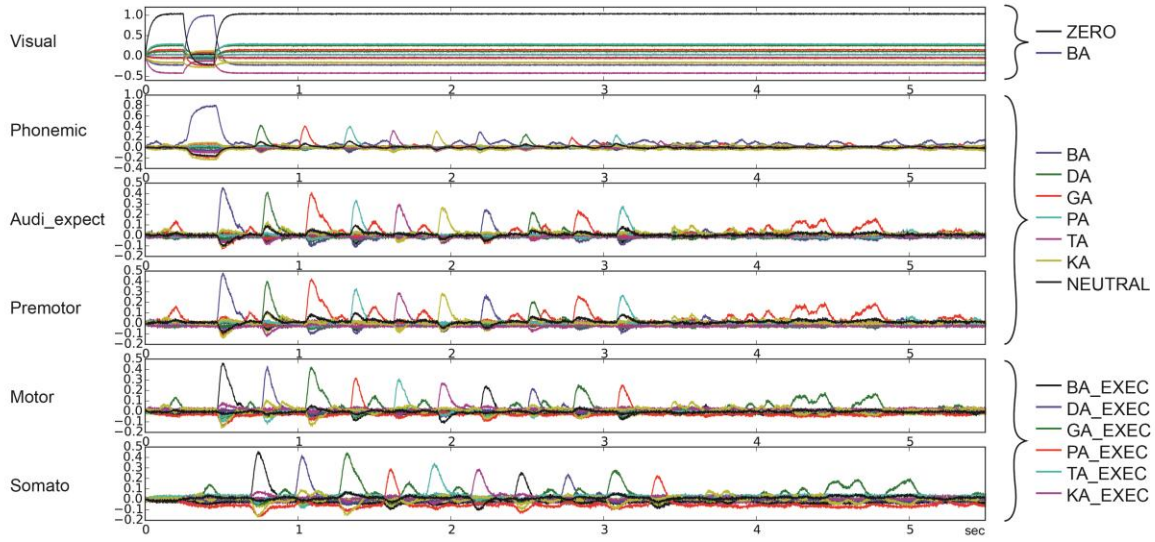


Figure 9. Effect of local freezing; here: interruption of syllable sequencing (at least reduction of activation of semantic pointers) between 3.2s and 4.0s; parameters: lg=0.16, le=0.14, syllable duration is 200ms, number of available syllables is six.

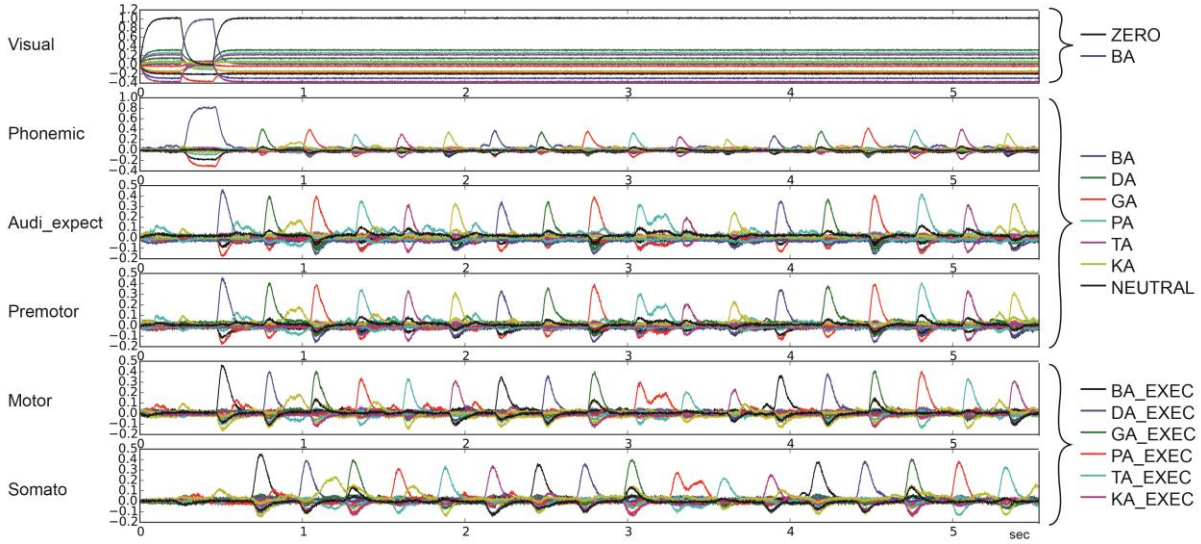
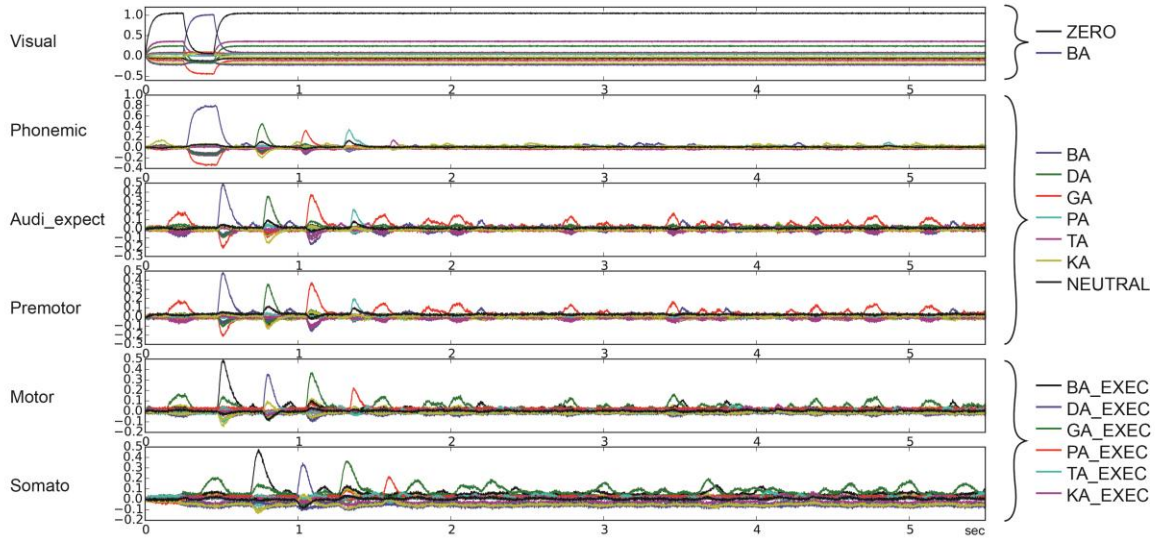


Figure 10. Effect of repetitive speech; here: repetition of syllable /ga/ after 1.5s; parameters: lg=0.12, le=0.18, syllable duration is 200ms, number of available syllables is six.



Tables

le / lg	0.2	0.18	0.16	0.14	0.12	0.10	0.08	0.06	0.04	0.02	0.00
0.2	1,00	1,00	0,96	1,00	0,93	1,00	0,90	0,76	0,26	0,33	0,19
0.18	0,83	0,58	1,00	1,00	0,81	0,49	0,33	0,22	0,18	0,14	0,10
0.16	1,00	0,85	0,85	0,67	0,43	0,18	0,35	0,22	0,18	0,15	0,13
0.14	0,69	0,69	0,60	0,28	0,43	0,22	0,21	0,14	0,15	0,11	0,13
0.12	0,72	0,36	0,29	0,26	0,19	0,17	0,14	0,13	0,13	0,11	0,10
0.10	0,49	0,26	0,24	0,14	0,17	0,11	0,10	0,13	0,11	0,13	0,08
0.08	0,24	0,17	0,15	0,14	0,14	0,13	0,08	0,11	0,08	0,08	0,08
0.06	0,14	0,17	0,11	0,13	0,11	0,10	0,13	0,08	0,08	0,07	0,06
0.04	0,13	0,14	0,13	0,11	0,11	0,11	0,06	0,08	0,06	0,07	0,07
0.02	0,11	0,08	0,08	0,08	0,06	0,11	0,06	0,06	0,06	0,06	0,06
0.00	0,10	0,10	0,07	0,06	0,07	0,06	0,06	0,06	0,06	0,04	0,06

Table 1. Percentage(/100%) for 121 simulations described in Text (see also Fig. 5). Red area: no freezing; blue area: early freezing; white area: transition from normal speech (no freezing) to freezing.