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IMPACT OF CORTICAL INPUT ON SUBTHALAMIC ACTIVITY DURING DEEP BRAIN STIMULATION

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ABSTRACT

Cortical afferences (e.g., primary motor cortex M1, and supplementary motor area SMA) are believed to play a role in the generation of abnormal oscillatory activity in the subthalamic nucleus (STN) in Parkinson's disease (PD). Using a computational model, we investigate how cortical inputs impact STN activity during deep brain stimulation (DBS). When cortical input to the STN is constant, high-frequency DBS is able to suppress pathological, low-frequency STN oscillations. On the contrary, when cortical input to the STN is oscillatory, DBS capacity to suppress STN abnormal oscillations is compromised. We propose that DBS induces a functional decoupling between cortex and STN. This functional decoupling may originate from spike cancellation following antidromic activation of cortical afferences.

KEY WORDS

Computational modelling, Parkinson's disease, cortex, deep brain stimulation.

1 Introduction

Chronic, electrical deep brain stimulation (DBS) of the subthalamic nucleus (STN) in Parkinson's disease (PD) is a symptomatic treatment of growing importance, even if its physiological mechanisms remain elusive (see McIntyre et al., 2004 for a review). In PD, neuronal activity in the STN becomes abnormally synchronized at low-frequencies (≈ 5 Hz), and neurons have a strong tendency to burst (Rodriguez-Oroz et al., 2001). These low-frequency oscillations are thought to be actively involved in the generation of Parkinsonian tremor, usually observed at ≈ 5 Hz (Rodriguez-Oroz et al., 2001).

In a previous study (Modolo et al., 2007a), a population dynamics model based on the Izhikevich neuronal model was developed. This model is used to investigate the dynamics of large neuronal assemblies, with realistic patterns of discharge (Izhikevich, 2003) and a computing time independent of the number of neurons simulated. The main equation of the model is a PDE,

$$\frac{\partial}{\partial t} p(\vec{w}, t) = -\vec{\nabla} \cdot \vec{J}(\vec{w}, t) \quad (1)$$

where $p(\vec{w}, t)$ is the population density function (giving the number of neurons per state, where \vec{w} is the state vector of the neuron) and $\vec{J}(\vec{w}, t)$ the term accounting for both individual dynamics and neuronal interactions (Modolo et al., 2007a). We used the model of the complex formed by the STN and the external part of the globus pallidus (GPe) detailed in Modolo et al. (2008), written under simplified form as:

$$\frac{\partial}{\partial t} p_E = -\vec{\nabla} \cdot \{ \vec{F}_E(\vec{w}) p_E + \vec{G}_{EE}(t) - \vec{H}_{IE}(t) \} \quad (2)$$

$$\frac{\partial}{\partial t} p_I = -\vec{\nabla} \cdot \{ \vec{F}_I(\vec{w}) p_I - \vec{H}_{II}(t) + \vec{G}_{EI}(t) \} \quad (3)$$

where $p_{E/I} = p_{E/I}(\vec{w}, t)$, E/I denote STN and GPe respectively, that are excitatory and inhibitory neuronal populations; and G/H_{ij} the excitation/inhibition contribution from population i to population j (see Modolo et al., 2007b for detailed expressions). A schematic view of the STN-GPe network is presented in Fig. 1:

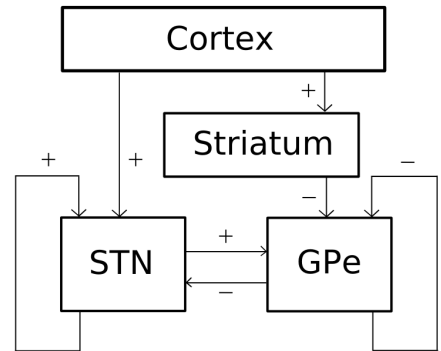


Figure 1. Schematic representation of relationships between and within the STN and the GPe, completed with some of their external inputs. The cortico-striatum pathway is not included into the model but see discussion.

When this model exhibits a stable, low-activity state for the two nuclei, it is called a physiological or healthy

state. When the model exhibits an oscillatory, low-frequency (≈ 5 Hz), synchronized activity caused by an increase of striatal inhibition to the GPe, it is termed a pathological state (Modolo et al., 2008). The behaviour of the model when control parameters are modified is consistent with experimental studies (Albin et al., 1989; Levy et al., 2000). Furthermore, bursting activity of STN model cells disappears when a DBS current with parameter values in the therapeutical range are used (Modolo et al., 2008). This observation is also in line with experimental results (Garcia et al., 2005).

2 Simulations

2.1 Constant cortical input

We introduced a depolarization current term $I^{Cx}(t)$ in the equations of the Izhikevich model for STN neurons (Modolo et al., 2008) to simulate a cortical input (taking into account cortico-STN projections, also called the hyperdirect pathway, Nambu et al., 2006). If we denote by $I^{DBS}(t)$ the DBS current, the Izhikevich model for STN neurons expresses as

$$\frac{dv}{dt} = 0.04v^2 + 5v + 140 - u + I^{Cx}(t) + I^{DBS}(t) \quad (4)$$

$$\frac{du}{dt} = a(bv - u) \quad (5)$$

$$v > 30 \text{ mV} \rightarrow v = c, u = u + d \quad (6)$$

with $a = 0.005, b = 0.265, c = -65, d = 1$. Then the Izhikevich model with cortical and DBS inputs is included in our main population equation to describe the dynamics of a large assembly of STN neurons. We first examine the impact of a constant level of cortical input is illustrated in Fig. 2.

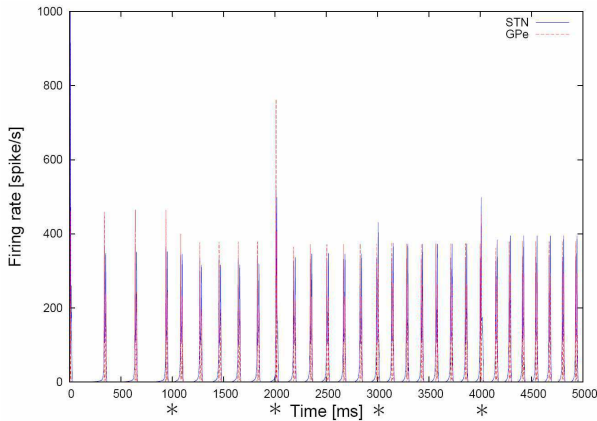


Figure 2. Impact of increasing level of cortical input on STN activity ($I^{Cx} = 0, 2, 3, 4, 5$ pA, with value changed each second of simulation, represented by “*”).

One can observe (Fig. 2) that increasing the amplitude of the cortical input progressively increases the frequency of STN bursting behaviour. Next, we ran the same simulation by applying a DBS current with therapeutic parameters values ($f = 130$ Hz, $I^{DBS} = 250$ pA, pulse width $100 \mu\text{s}$) to the STN. DBS is modelled as a train of biphasic, asymmetric pulses (with the positive part first), such as used in clinical applications. Results are presented in Fig. 3.

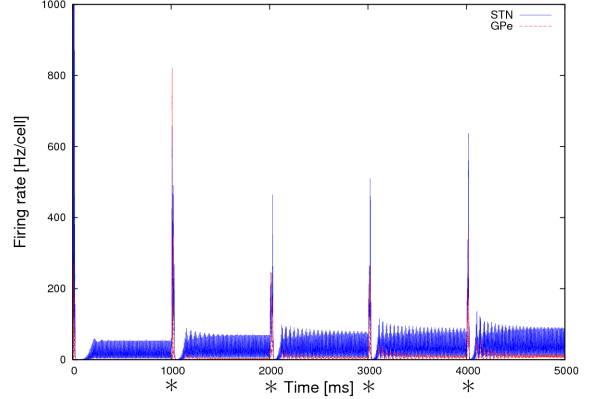


Figure 3. Effect of DBS (not shown) on STN activity under increasing levels of constant cortical input to the STN ($I^{Cx} = 0, 2, 3, 4, 5$ pA). Vertical bars are transients.

Under increasing levels of cortical excitatory input, abnormal oscillations are suppressed and neuronal activity is decreased in STN model cells by DBS. Because pathological low-frequency oscillations are suppressed, we conclude that in this situation, DBS is *efficient*.

2.2 Oscillatory cortical input

Cortical input to the STN was then modelled using a sine function $I^{Cx} = I_0 \times \text{abs}(\sin(2\pi f^{Cx}))$ with $f^{Cx} = 10$ Hz, to incorporate the oscillatory nature of cortical activity (Silberstein et al., 2005). Simulations results are presented in Fig. 4.

Our simulation results (Fig. 4) indicate that an oscillatory cortical input, in a frequency band close to oscillations present in the STN of patients with PD, can modulate STN activity pattern. This holds even when this input has a weak amplitude. Next, we ran the same simulation and applied a DBS current with therapeutic parameters values to the STN (Fig. 5).

As opposed to the case of a constant cortical input, low-frequency cortical input compromises the efficiency of DBS in our computational model: strong oscillations of STN activity persist. Thus, DBS appears *non-efficient* when the STN receives low-frequency cortical input.

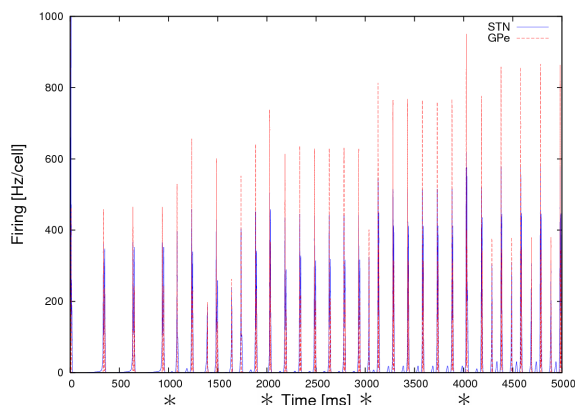


Figure 4. Impact of increasing low-frequency level of cortical input to the STN ($I_0 = 0, 2, 3, 4, 5$ pA, with value changed each second of simulation, represented by “*”).

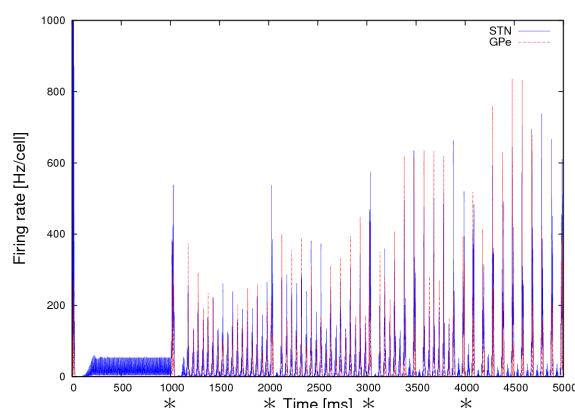


Figure 5. Effect of DBS (not shown) with therapeutic parameters ($f = 130$ Hz, $I^{DBS} = 250$ pA, pulse width $100 \mu s$) on STN activity under various levels of a 10 Hz cortical input to the STN.

3 Discussion

Using a mathematical model of a complex formed by two basal ganglia nuclei implied in the generation of pathological neuronal activity in PD, we note that DBS efficiency is closely related to the level of low-frequency cortical input to the STN. Indeed, if cortical input to the STN is constant, then high-frequency DBS is able to suppress pathological, low-frequency STN oscillations. On the contrary, in the case of a low frequency oscillatory cortical input to the STN, DBS capacity to suppress STN abnormal oscillations is compromised. This may indicate that a complementary mechanism not explicitly included into the model, such as an antidromic activation (Lozano and Mahant, 2004; Li et al., 2007), perturbs cortical input to the STN and allows the suppression of abnormal STN oscillations by DBS.

We propose that the cortico-STN or *hyperdirect* pathway (Nambu et al., 1996) constitutes a *resonant* pathway

in PD, i.e., STN activity increases when cortical afferences arrive at a similar frequency (which is the case in PD, Silberstein et al., 2005). In the healthy state, one of the roles played by dopamine is to modulate the impact of cortical afferences on STN cells (Magill et al., 2001). Indeed, it has been observed in rat brain slices that in the presence of dopamine, the amplitude of glutamatergic excitatory postsynaptic potentials is reduced (Hamani et al., 2005). Thus it appears plausible that, in the parkinsonian state, the absence or limited amount of dopamine available leads to a stronger interaction, and possibly to a resonance between cortex and STN. This proposition is supported by a recent clinical study (Plaha et al., 2008), in which the hypothesis that the STN is highly responsive to α (3-15 Hz) and β (15-30 Hz) motor cortical input in PD was verified, but see Mallet et al. (2008) for the delayed nature of the effect.

Let us note that limitations of our model include (1) an absence of projections from the cortex to the striatum, with the latter projecting inhibitory fibers to the GPe; (2) a simplified application of the same DBS current to each STN cell, whereas in reality a decay of the electric field generated by the electrode occurs with distance (McIntyre et al., 2004); and (3) a non explicit representation of the motor cortex in the model, that should allow a more detailed investigation of antidromic activation of cortical afferences to the STN on motor cortex activity. Furthermore, in our model we assume that only STN neurons receive the DBS current. However, it has been shown that the stimulation via electrodes located near the STN (Zona Incerta) produced equally good or even more effective clinical benefits (Plaha et al., 2006; Guehl et al., 2008). Thus it cannot be ruled out that efficient DBS stimulates not only part of the STN, but also fibers of passage. Finally, a possible extension of the present work would be to extend the model with a contribution of indirect cortical afferences to the GPe *via* the striatum.

4 Conclusion

In summary, we explored the influence of constant and oscillatory cortical inputs on STN activity in PD during DBS. Our model suggests that a probable resonance between low-frequency activity occurring in the motor cortex (e.g., M1, SMA) and the STN underlies the strong oscillatory activity that DBS current alone cannot suppress or decrease in STN. Disrupting cortical afferences to the STN could functionally decouple the motor cortex from the STN, a condition which is fulfilled by dopamine under healthy conditions. This decoupling may be part of (the) underlying mechanism(s) of DBS in PD.

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