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Effect of Subthalamic Nucleus Interconnectivity at Deep Brain Stimulation Onset and Offset: A Simulation Study

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Abstract— **Deep brain stimulation (DBS) has been demonstrated to effectively improve the motor symptoms of Parkinson's disease. However, the underlying mechanisms are not known. It has been reported that a period of time is required before the full effect on motor symptoms is realized after DBS is initiated and that suppression of symptoms persists after DBS ends under parkinsonian conditions. A computational model is presented to investigate the hypothesis that interconnectivity and transmission delays within the subthalamic nucleus (STN) neurons may induce a gradual decay and recovery of pathological oscillations at DBS onset and offset under simulated parkinsonian conditions. Interconnectivity strength between the STN neurons and the number of STN neurons directly stimulated by DBS are both varied to examine the gradual decay and recovery of oscillatory STN activity. Weaker interconnectivity and lower numbers of STN neurons directly receiving DBS input were found to result in longer decay and recovery times at the onset and offset of DBS, respectively.**

I. INTRODUCTION

The subthalamic nucleus (STN) is one of five nuclei of the basal ganglia and, as the only excitatory projection in the basal ganglia, plays a crucial role in control of movement [1]. Under normal conditions there is robust oscillatory activity in the STN [2], while under parkinsonian conditions abnormal synchrony and increases in firing rates and oscillatory activity within the frequency ranges of 3-9 Hz (tremor band) and 15-30 Hz (beta band) have been reported [3], [4]. These oscillatory activities have been shown to be related to motor symptoms of Parkinson's disease. In particular, the strength of beta band oscillations has been related to levels of bradykinesia, askinesia and rigidity, while suppression of beta band power is correlated to improvement of those symptoms [5], [6].

The STN has been identified as one of the most promising targets for deep brain stimulation (DBS) to improve motor symptoms both in parkinsonian monkeys [7] and in patients [8]. However, the underlying mechanisms of DBS are not fully known and it has been shown that improvement in parkinsonian symptoms may occur gradually after DBS is activated or that the effects of DBS may prolong following cessation of DBS [9], [10]. Similar effects have been also found with DBS applied in dystonia patients [11] and for Tourettes syndrome [12]. As they may influence the effect of DBS and final outcome, the mechanisms by which delays occur during DBS onset and offset, are of clinical interest. However, these effects have not been investigated in detail. Interconnectivity within STN neurons may be one of several possible contributory factors, although the effect that this may have on DBS application is not known. Debate exists on whether interconnectivity is present between STN neurons. It has been shown that axon collaterals in the rat STN may exist and terminate within the STN itself [13] and these axon collaterals may influence synchrony in the STN neurons [14]. In a previous computational model it has been shown that interconnectivity within STN neurons can cause interconnected STN neurons to be in a uniform high state in response to a direct cortical input to the STN and change to a low state with inhibitory input [15]. In contrast, Wilson *et al.* suggested that there is no evidence of such interconnectivity within the STN in extracellular recordings made from rat STN neurons and hence synchrony within the STN neuron does not result from the network in the STN but the other basal ganglia nuclei [16].

In this study, a computational model has been developed to investigate the potential contribution of interconnectivity and transmission delays between STN neurons to the gradual effect of DBS onset and offset on pathological beta band oscillations within the basal ganglia network. The model is based on a previous model [17]. The model was used to investigate the hypothesis that DBS may directly stimulate a subset of STN neurons while remaining neurons are stimulated through interconnectivity within the nucleus. This may lead to gradual onset and offset of the effects of DBS due to synchronization and desynchronization of the STN neurons in the network of the computational model. The effect of the number of STN neurons receiving DBS input directly and strength of interconnectivity within the STN was also examined.

II. METHOD

The cortico-basal ganglia network model used in this study extended the previous model developed in [17] to include 200 STN, Globus Pallidus external (GPe), Globus Pallidus internal (GPi), thalamus and cortical neurons with indirect and hyperdirect pathways. Each neuron was represented by a single-compartment conductance-based model. There was an excitatory input to the STN from the cortex, to the GPe and GPi from the STN, and to the cortex from the thalamus. Inhibitory inputs were directed to the STN and GPi from the GPe and to the thalamus from the GPi. Functional interconnectivity and self-inhibition were present within the

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STN neurons and within the GPe neurons, respectively. The model structure is detailed in Fig. 1.

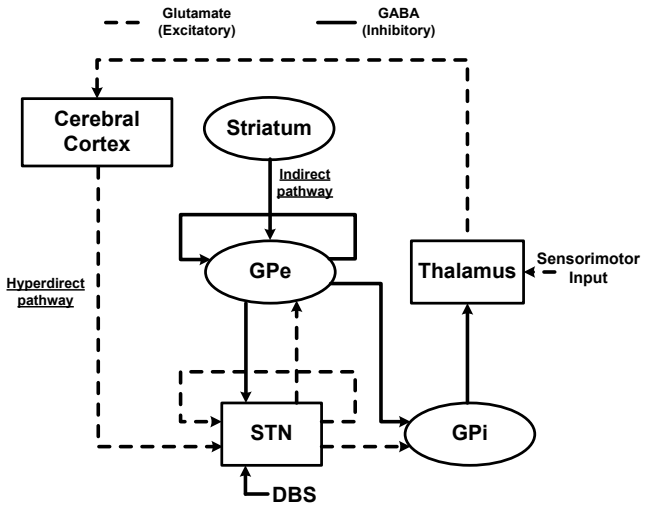

Fig. 1. Schematic diagram of the model, indicating connections between GPe (Globus Pallidus external), GPi (Globus Pallidus internal), STN (Subthalamic Nucleus), cortex and striatum. DBS is injected directly into the STN

A. Cell Models

STN, GPe, GPi and thalamic neurons were simulated using the previous computational model based on Hodgkin-Huxley type equations to describe ion channel dynamics [17]. The membrane potential for each neuron is described as follows:

$$\frac{dV_m}{dt} = -\frac{1}{C_m}\left(\sum_i I_i + I_{syn}\right) \tag{1}$$

where C_m is membrane capacitance and V_m is membrane potential. I_i denotes the individual ionic currents required to generate the membrane potential for each neuron and I_{syn} indicates the synaptic currents. STN neurons were given 6 μA/cm^2 of external current, 0.5 pA/μm^2 and 1.5 pA/μm^2 for GPe and GPi, respectively. Details of the model are provided in [17]. To simulate cortical neurons a simple spiking model developed by Izhikevich [18] was used as it can demonstrate physiological properties of cortical neurons providing effective computational simulation. Details for the equations and parameter values are provided in [17].

B. Synaptic Connectivity

The synaptic connection was sparsely structured as follows: each STN neuron was synaptically connected to its two nearest neighbors, Fig. 2. Each STN neuron was connected to 2% of all STN neurons in the network. This is close to the minimum connectivity estimated in [15]. Following Rubin and Terman [19], the synaptic current injected by neuron α into neuron β is given by an expression involving the transmembrane voltage of neuron α, V_α, the synaptic reversal potential, $E_{\alpha\to\beta}$ and sum of conductances over all paths connecting other neurons to neuron β, all multiplied by a gain term, $g_{\alpha\to\beta}$. In this paper, $g_{\alpha\to\beta}$ is denoted by $g_{s\to s}$ and is to be interpreted as a gain term associated with each path coupling any STN neuron to its two nearest neighbours on either side. A 2 ms transmission delay was also incorporated. In the modelling study by Gillies and Willshaw [15] it has been assumed that STN neurons are proximally located. As the delay time in transmission from STN to GPe is 6 ms [20], the transmission delay with the STN neuron was set to 2 ms. STN neurons also received excitatory synaptic input from the cortex, Cortex_{i-3} + Cortex_{i-2} + Cortex_{i-1} + Cortex_{i+1} + Cortex_{i+2} + Cortex_{i+3} $\rightarrow$ STN_i and inhibitory synaptic input from GPe, GPe_{i+2} $\rightarrow$ STN_i.

GPe neurons received excitatory synaptic input from STN, STN_i $\rightarrow$ GPe_i and GPi neurons were given both inhibitory synaptic input from GPe, GPe_i $\rightarrow$ GPi_i and excitatory input from STN, STN_i $\rightarrow$ GPi_i.

Inhibitory synaptic input was added from the GPi to the thalamus, GPi_i + GPi_{i+1} + GPi_{i+2} + GPi_{i+3} + GPi_{i+4} $\rightarrow$ Thalamus_i and excitatory synaptic input from thalamus to cortex, Thalamus_i + Thalamus_{i+1} + Thalamus_{i+2} + Thalamus_{i+3} + Thalamus_{i+4} $\rightarrow$ Cortex_i were present. STN synaptic connectivity is presented in Fig. 2.

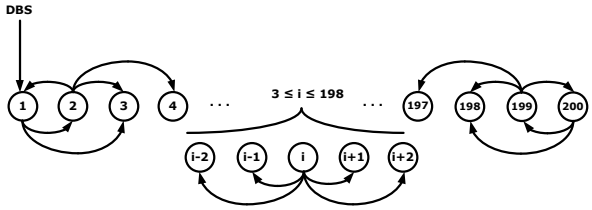

Fig. 2. Synaptic connection within the STN neurons. 200 STN neurons were implemented. DBS is directly applied to neuron 1 or neuron 1 and 2.

C. DBS Application

The DBS input was simulated as a series of periodic rectangular current pulses and directly added to the membrane potential of the STN neuron. The number of STN neurons which received the excitatory DBS current and the strength of interconnectivity among the STN neurons were varied to examine their effect on the gradual onset and offset of the effect of DBS under parkinsonian conditions generating 20 Hz oscillations. Five sets of computational simulations were performed as following: two sets with different number of STN neurons receiving DBS input, one and two STN neurons with fixed interconnectivity strength and three sets with different strength of interconnectivity, $g_{s\to s}$ 0.2, 0.25 and 0.3 with fixed number of STN neurons receiving DBS input. The decay time was defined as the duration from the time at which DBS was applied to the time at which the relative beta band power was reduced to 10% of its baseline level. The recovery time was similarly defined as the duration from the time at which DBS was turned off to the time at which the relative beta band power returned back to its baseline level. The gradual decay and recovery of 20 Hz oscillations in the STN neurons during DBS onset and offset was examined with DBS input which had a frequency of 150 Hz, amplitude of 300 μA/cm^2 and pulse duration of 100 μs.

III. RESULTS

Beta band oscillations were generated and DBS was directly applied to the first STN neuron. Averaged membrane potential and relative beta band power of STN neurons are shown in Fig. 3. A decay time of 1200 ms and recovery time 1600 ms following DBS onset and offset for suppression of beta band oscillations were observed when DBS was applied for 2 s.

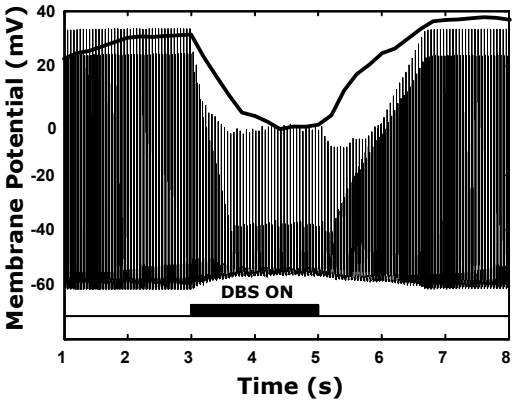

Fig. 3. Averaged membrane potential of 200 STN neurons under parkinsonian conditions is presented. Thick line indicates relative beta band power extracted from the membrane potential. DBS applied to the first STN neuron for 2 s is also shown.

A. Variations with STN Interconnectivity Strength

The effect of varying the strength of STN interconnectivity is shown in Fig. 4, which presents the relative beta band power of the averaged membrane potential of all STN neurons. The delay at decay and recovery times decreased as the synaptic gain for interconnectivity within the STN neurons increased. Fig. 5 presents decay and recovery times during DBS onset and offset depending on the synaptic gain.

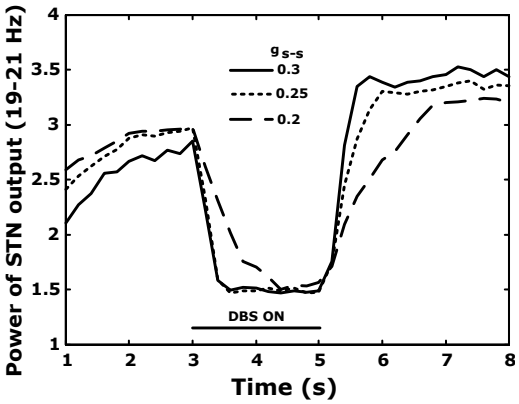

Fig. 4. Variation in STN beta band power with strength of interconnectivity within the STN neurons at onset and offset of DBS. The effect of DBS onset and offset becomes more gradual as synaptic gain decreases. $g_{s\to s}$ indicates the synaptic gain from one STN neuron to another.

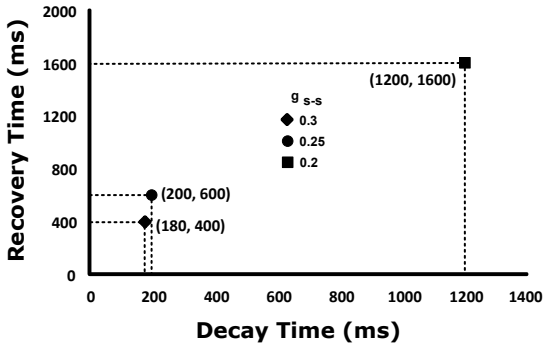

Fig. 5. Both decay time and recovery time increase as synaptic gain, $g_{s\to s}$ is decreased. As shown in Fig. 2, only the first neuron on the left receives DBS input.

B. Variations with Number of STN Neurons Receiving DBS Input

The effect of varying the number of STN neurons which are directly stimulated by DBS input is shown in Fig. 6. With the synaptic connectivity, $g_{s\to s}$ of 0.2, longer decay and recovery times resulted when smaller number of STN neurons received the DBS input directly, Fig. 6(a). However, there was little difference in decay and recovery rates with $g_{s\to s}$ of 0.3, Fig. 6(b).

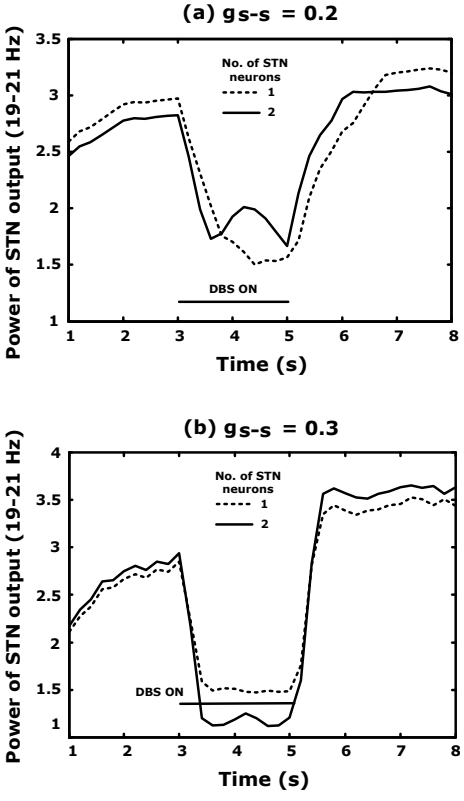

Fig. 6. With weaker synaptic gain the rates of decay and recovery both become faster as number of STN neurons stimulated is increased 1 to 2. This phenomenon is not evident when the synaptic gain is higher. $g_{s\to s}$ indicates the synaptic gain from one STN neuron to another.

IV. DISCUSSION

The model presented incorporates interconnectivity and transmission delays among STN neurons to investigate the hypothesis that the combination of these effects may cause a gradual decay and recovery of pathological beta band oscillations within the STN following DBS onset and offset. In the model, interconnectivity between the STN neurons provides a path for the DBS input to spread across the STN network. In this way, the DBS input gradually and indirectly affects the STN neurons through the interconnectivity with transmission delays between neurons. The simulated, pathological beta band power therefore gradually decreased once DBS was activated, Fig. 3. After DBS was turned off, a similar phenomenon occurred with the high frequency synchronization of neuronal firing remaining when DBS was turned off and decaying gradually. The recovery rate was observed to be slower than the decay rate.

Interconnectivity strength affected the decay and recovery rates of the simulated beta band oscillations, Fig. 4. As the synaptic gain increased both the decay time and recovery time decreased, Fig. 5. The high level of interconnectivity caused the synchronization of neuronal firing to the DBS input to spread quickly through the network, resulting in short duration decay and recovery.

In Fig. 6 the number of STN neurons directly receiving DBS input was varied with a fixed level of synaptic strength. Higher rates of decay and recovery were shown when more STN neurons received DBS input. This may be related to DBS strength. If DBS amplitude increases more STN neurons will be directly stimulated and this will quickly spread to remaining STN neurons through interconnectivity within the STN. However, this effect is only shown when interconnectivity is weak between STN neurons. This implies that the interconnectivity strength may have stronger influence on gradual effect of DBS onset and offset.

Experimental studies *in vivo* have observed therapeutic latencies during DBS offset and onset [9], [10], concluding that it may take minutes, hours or days for symptoms to worsen again after DBS is turned off or improve following activation of DBS. There are many factors which may affect this phenomenon such as alterations in synaptic plasticity and the underlying mechanisms have not been yet investigated. The computational model presented here indicates that neuronal activities return back to the original state within millisecond or seconds due to the effect of interconnectivity and transmission delays within the STN neurons. It is suggested that short duration delays in the quenching and recovery of pathological oscillatory activity occur as a result of the gradual synchronization and desynchronization of neurons following direct stimulation of a relatively small number of interconnected neurons.

V. ACKNOWLEDGMENTS

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REFERENCES

[1] R. L. Albin, A. B. Young, and J. B. Penney, "The functional anatomy of disorders of the basal ganglia." *Trends Neurosci*, vol. 18, no. 2, pp. 63–64, Feb 1995.

[2] P. Brown, A. Oliviero, P. Mazzone, A. Insola, P. Tonali, and V. D. Lazzaro, "Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease." *J Neurosci*, vol. 21, no. 3, pp. 1033–1038, Feb 2001.

[3] H. Bergman, T. Wichmann, B. Karmon, and M. R. DeLong, "The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism." *J Neurophysiol*, vol. 72, no. 2, pp. 507–520, Aug 1994.

[4] P. Brown, "Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease." *Mov Disord*, vol. 18, no. 4, pp. 357–363, Apr 2003.

[5] P. Brown and C. D. Marsden, "Bradykinesia and impairment of EEG desynchronization in Parkinson's disease." *Mov Disord*, vol. 14, no. 3, pp. 423–429, May 1999.

[6] A. A. Kühn, A. Tsui, T. Aziz, N. Ray, C. Brücke, A. Kupsch, G.-H. Schneider, and P. Brown, "Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity." *Exp Neurol*, vol. 215, no. 2, pp. 380–387, Feb 2009.

[7] A. Benazzouz, C. Gross, J. Fger, T. Boraud, and B. Bioulac, "Reversal of rigidity and improvement in motor performance by subthalamic high-frequency stimulation in mptp-treated monkeys." *Eur J Neurosci*, vol. 5, no. 4, pp. 382–389, Apr 1993.

[8] P. Limousin, P. Pollak, A. Benazzouz, D. Hoffmann, J. F. L. Bas, E. Broussolle, J. E. Perret, and A. L. Benabid, "Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation." *Lancet*, vol. 345, no. 8942, pp. 91–95, Jan 1995.

[9] P. Temperli, J. Ghika, J.-G. Villemure, P. R. Burkhard, J. Bogousslavsky, and F. J. G. Vingerhoets, "How do parkinsonian signs return after discontinuation of subthalamic dbs?" *Neurology*, vol. 60, no. 1, pp. 78–81, Jan 2003.

[10] A. Hristova, K. Lyons, A. I. Trster, R. Pahwa, S. B. Wilkinson, and W. C. Koller, "Effect and time course of deep brain stimulation of the globus pallidus and subthalamus on motor features of parkinson's disease." *Clin Neuropharmacol*, vol. 23, no. 4, pp. 208–211, 2000.

[11] J. K. Krauss, J. Yianni, T. J. Loher, and T. Z. Aziz, "Deep brain stimulation for dystonia." *J Clin Neurophysiol*, vol. 21, no. 1, pp. 18–30, 2004.

[12] J. L. Houeto, C. Karachi, L. Mallet, B. Pillon, J. Yelnik, V. Mesnage, M. L. Welter, S. Navarro, A. Pelissolo, P. Damier, B. Pidoux, D. Dormont, P. Cornu, and Y. Agid, "Tourette's syndrome and deep brain stimulation." *J Neurol Neurosurg Psychiatry*, vol. 76, no. 7, pp. 992–995, Jul 2005.

[13] H. Kita, H. T. Chang, and S. T. Kitai, "The morphology of intracellularly labeled rat subthalamic neurons: a light microscopic analysis." *J Comp Neurol*, vol. 215, no. 3, pp. 245–257, Apr 1983.

[14] A. J. Gillies and D. J. Willshaw, "A massively connected subthalamic nucleus leads to the generation of widespread pulses." *Proc Biol Sci*, vol. 265, no. 1410, pp. 2101–2109, Nov 1998.

[15] A. Gillies and D. Willshaw, "Models of the subthalamic nucleus. The importance of intranuclear connectivity." *Med Eng Phys*, vol. 26, no. 9, pp. 723–732, Nov 2004.

[16] C. L. Wilson, M. Puntis, and M. G. Lacey, "Overwhelmingly asynchronous firing of rat subthalamic nucleus neurones in brain slices provides little evidence for intrinsic interconnectivity." *Neuroscience*, vol. 123, no. 1, pp. 187–200, 2004.

[17] G. Kang and M. M. Lowery, "A model of pathological oscillations in the basal ganglia and deep brain stimulation in Parkinson's disease." *Conf Proc IEEE Eng Med Biol Soc*, vol. 2009, pp. 3909–3912, 2009.

[18] E. M. Izhikevich, "Simple model of spiking neurons." *IEEE Trans Neural Netw*, vol. 14, no. 6, pp. 1569–1572, 2003.

[19] J. E. Rubin and D. Terman, "High frequency stimulation of the subthalamic nucleus eliminates pathological thalamic rhythmicity in a computational model." *J Comput Neurosci*, vol. 16, no. 3, pp. 211–235, 2004.

[20] H. Kita, Y. Tachibana, A. Nambu, and S. Chiken, "Balance of monosynaptic excitatory and disynaptic inhibitory responses of the globus pallidus induced after stimulation of the subthalamic nucleus in the monkey." *J Neurosci*, vol. 25, no. 38, pp. 8611–8619, Sep 2005.