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A Model of Pathological Oscillations in the Basal Ganglia and Deep Brain Stimulation in Parkinson's Disease.

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Abstract— **A model of pathological oscillatory activity within the basal ganglia in Parkinson's disease is presented. Synchronous oscillatory activity of the subthalamic nucleus (STN) and globus pallidus external (GPe) is simulated at both the parkinsonian tremor (3-9) Hz and beta (15-30) Hz frequencies. The model extends previous models to incorporate cortical inputs to the subthalamic nucleus through the 'hyperdirect' pathway, changes in coupling between STN neurons due to dopamine depletion and the plateau potential generating capacity of STN neurons. The effect of deep brain stimulation (DBS) across a range of frequencies on the oscillatory activity is examined. High frequency DBS attenuates synchronous oscillatory activity within the STN-GPe network at both the tremor and beta frequencies. The efficacy of the DBS input in quenching the pathological oscillations is shown to vary systematically with the frequency, pulse width and amplitude of the applied stimulus.**

I. INTRODUCTION

There is increasing evidence that synchrony between neurons and oscillatory phenomena within the basal ganglia plays a key role in several movement disorders including Parkinson's disease [1]. Experiments with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated primates and data in patients with Parkinson's disease show significant changes in neural discharge patterns including increased firing rates and strong synchrony and abnormal oscillatory bursting in the different nuclei of the basal ganglia [2], [3], [4], [5]. Increased oscillatory bursting is observed in Parkinson's disease within specific frequency bands, the 3-9 Hz (tremor band) range [3], [4] and 15-30 Hz (beta band) range [6], [7]. Recent studies have shown that oscillations in the Subthalamic Nucleus (STN) at the tremor frequency are correlated with tremor in specific limbs [8], while abnormal synchrony in the beta-band is related to the symptoms of bradykinesia and akinesia [6], [9].

It has been demonstrated *in vitro* that the STN and Globus Pallidus external (GPe) could constitute a central pacemaker, forming a feedback system modulated by striatal inhibition of the GPe, that may partially account for the pathological low-frequency oscillations observed under dopamine deficient conditions [10], [11]. An alternative possibility is that increased oscillatory activity within the STN-GPe network may result from increased sensitivity of the STN to rhythmic inputs transmitted from the motor cortex through the 'hyperdirect' pathway [12]. Consistent with this, an increase in coherence between cortex and the basal ganglia in the beta band is observed in Parkinson's disease [1]. Recent studies have also suggested that the generation of plateau potentials, an important property of the STN, may play a key role in generating oscillatory bursting observed in Parkinson's disease [13], [14]. In addition, coupling within the STN results in pulses or switch-like activities and this may further contribute to bursting activities at low frequencies in Parkinson's disease [13], [14]. In addition, coupling within the STN results in pulses or switch-like activities and this may further contribute bursting activities at low frequencies in Parkinson's disease [15].

One of the most physiologically plausible and comprehensive models of the basal ganglia in Parkinson's disease is a conductance based model of the STN-GPe network developed by Rubin and Terman [16]. Firing patterns of STN and GPe neurons were examined with various excitatory-inhibitory networks [16] and the model was later extended to include GPi and thalamus neurons to illustrate how deep brain stimulation (DBS) may restore the ability of the thalamus to relay excitatory inputs [17]. The model developed by Rubin and Terman has been used as the basis with which to investigate the effect of DBS stimulus parameters and target sites on pathological oscillations in the basal ganglia at the parkinsonian tremor frequency [18], [19]. In these models, oscillations at the tremor frequency are generated intrinsically by the STN-GPe network, modulated by increased striatal inhibition.

The aim of this study was to develop a new model to incorporate increased sensitivity of the STN to rhythmic cortical inputs transmitted through the hyperdirect pathway. Local interactions within the STN nucleus and voltage-dependent generation of a plateau potential in STN neurons were also incorporated. The model was used to simulate oscillatory activity within both the tremor and beta frequency ranges, arising from increased sensitivity of the STN-GPe network to external inputs from the cortex and striatum. The effect of DBS in quenching the tremor and beta oscillations was then examined as the frequency, pulse-width and amplitude of the DBS waveforms were varied.

II. METHOD

In this study, a single-compartment conductance-based model was used to represent each neuron in the STN and GPe. 8 cells of each type were developed for the simulations described in this study . The STN-GPe network includes both the indirect and hyperdirect pathways and the GPe receives both inhibitory input from the striatum and excitatory input

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from the STN. In addition, there is inhibitory synaptic connection within GPe cells. The STN receives inhibitory input from the GPe and excitatory input from the cortex. There is also STN functional interconnectivity between cells. The model structure is shown in Fig. 1.

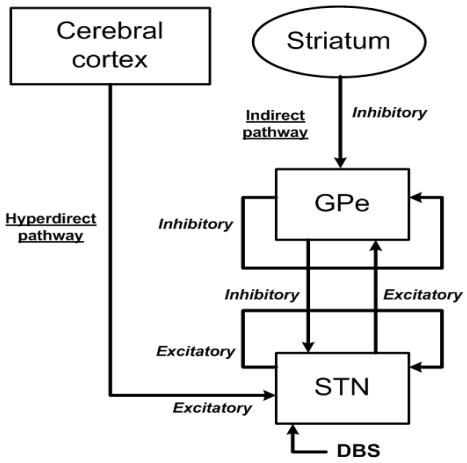

Fig. 1. Schematic diagram of the model, indicating connections between GPe (Globus Pallidus external), STN (Subthalamic Nucleus), Cortex and Striatum. DBS is injected directly into the STN

1) STN Neurons: There are several computational models for STN neurons which can generate plateau potentials [13], [20]. The model chosen here is that developed by Otsuka *et al.* [13] as it captures critical STN properties in a single compartment model. The membrane potential, $V_{m_{STN}}$ is described by

$$C_{m_{STN}}\frac{dV_{m_{STN}}}{dt} = -I_{Na_{STN}} - I_{K_{STN}} - I_{A_{STN}} - I_{L_{STN}} - I_{T_{STN}} - I_{Ca-K_{STN}} - I_{l_{STN}} - I_{\alpha\to\beta} + I_{app} \quad (1)$$

where $C_{m_{STN}}$ is membrane capacitance. $I_{Na_{STN}}$ is the sodium current, $I_{K_{STN}}$ is the delayed rectifier K^+ current and $I_{A_{STN}}$ is the voltage dependent A-type K^+ current. For Ca^{2+} currents, a L-like long-lasting Ca^{2+} current, $I_{L_{STN}}$, and low threshold T-type Ca^{2+} current, $I_{T_{STN}}$ are included. Finally, the model includes a Ca^{2+}-activated K^+ current, $I_{Ca-K_{STN}}$, and a leak current, $I_{l_{STN}}$.

2) GPe Neurons: The model for the GPe cells was adapted from [16] and [17]. Similar to the equation for the STN neurons, the membrane potential, $V_{m_{GPe}}$ is described by

$$C_{m_{GPe}}\frac{dV_{m_{GPe}}}{dt} = -I_{L_{GPe}} - I_{K_{GPe}} - I_{Na_{GPe}} - I_{T_{GPe}} - I_{Ca_{GPe}} - I_{AHP_{GPe}} - I_{\alpha\to\beta} + I_{app} \quad (2)$$

Here, $C_{m_{GPe}}$, $I_{L_{GPe}}$, $I_{K_{GPe}}$, $I_{Na_{GPe}}$, $I_{T_{GPe}}$, $I_{Ca_{GPe}}$, $I_{AHP_{GPe}}$ indicate the membrane capacitance, leak, potassium, sodium, low-threshold T-type Ca^{2+}, high-threshold Ca^{2+} and voltage-independent "afterhyperpolarization" K^+ current, respectively.

In both (1) and (2), $I_{\alpha\to\beta}$ represents the synaptic current from cell α to cell β. I_{app} is the applied current from the cortex to the STN and from the striatum to the GPe. Details of the equations and parameters used may be found in [13] for the STN neurons and [16], [17] for the GPe neurons.

To describe synaptic connection between the GPe and STN and for intrapallidal connection, the structured sparsely-connected architecture of [16] was chosen as it can generate both irregular and synchronous oscillatory bursting. To implement STN coupling [15], each cell was simulated to excitate all other STN cells. The details are illustrated in Fig. 2.

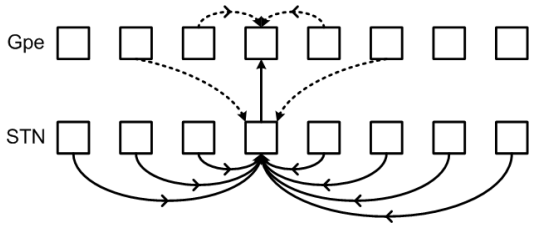

Fig. 2. Network structure indicating connections between GPe and STN cells. 8 GPe and 8 STN cells were implemented. Solid lines indicate excitatory synaptic inputs and dotted lines indicate inhibitory synaptic inputs.

To simulate DBS a rectangular pulse train, I_{DBS} was injected directly to the target 8 STN neurons synchronously similar to the approach described in [17]. The stimulation waveform had an amplitude of 250 pA/μm^2, 6 ms pulse duration and 0.6 ms pulse width. The frequency of the DBS signal was approximately 167 Hz.

To implement STN-GPe oscillatory activity at the parkinsonian tremor frequency, the parameter $g_{g\to g}$ was adjusted to 0.0 and the striatal input was injected using a sine function with the amplitude of 5 pA/μm^2 and frequency of 5 Hz. To induce beta band oscillations, the external input, which represents possible cortical input through the hyperdirect pathway, was introduced using a sine function with an amplitude of 10 $\mu A/cm^2$ and frequency of 20 Hz. In addition, interconnectivity between the STN neurons was increased with $g_{s\to s}$ set to 0.05. STN neurons received an applied current of -2.5 $\mu A/cm^2$, while GPe neurons received an applied current of -5.5 pA/μm^2.

III. RESULTS

A. Spontaneous Activities in Isolated STN and GPe Neurons

Both STN and GPe neurons fire regular spontaneous action potentials under normal conditions. STN neurons exhibit slow firing rates between 3 and 10 Hz at 25°C [14], while GPe neurons exhibit high frequency discharge at ∼100 Hz interrupted by long pauses [21], [22]. Spontaneous firing of the simulated STN and GPe neurons occurred under normal conditions at approximately 3.5 Hz and 110 Hz. respectively.

B. STN-GPe Network under Normal and Parkinsonian Conditions

The irregular and asynchronous firing patterns of the STN and GPe under normal conditions change to regular and synchronous bursting under parkinsonian conditions [3], [4]. In this study, oscillatory activity was considered at two

different frequencies, the parkinsonian tremor frequency and the beta band frequency.

1) Tremor Band Oscillations: Inhibitory input to GPe from the striatum was enhenced and synaptic conductance for intrapallidal connection was decreased. Fig. 3 shows the STN-GPe network activity in the parkinsonian tremor state.

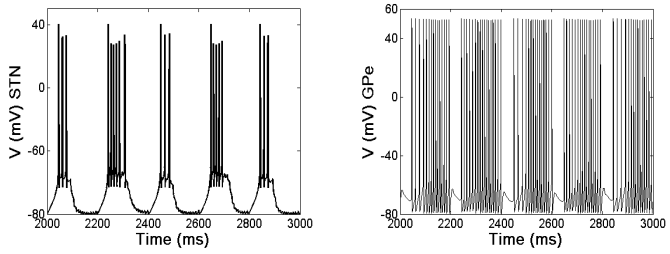

Fig. 3. Activity of STN and GPe cells under parkinsonian conditions (tremor band oscillations): STN and GPe cells exhibit periodic bursting at 5 Hz, with regular and synchronous firing patterns.

2) Beta Band Oscillations: In addition to neurons exhibiting oscillations at the tremor frequency, local field potentials recorded in the STN in Parkinson's disease show increased oscillatory activity in the beta frequency range 15-30 Hz [6], [7]. After injection of cortical input, both the STN and GPe were observed to exhibit oscillatory bursting at 20 Hz as shown in Fig. 4.

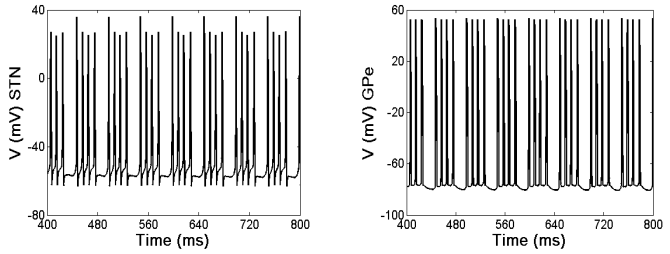

Fig. 4. Activity of STN and GPe cells under parkinsonian conditions (beta band oscillations): STN and GPe cells exhibit beta frequency oscillations at approximately 20 Hz, with regular and synchronous firing patterns.

C. Applied DBS

Application of DBS resulted in synchronized firing of the STN and GPe neurons at the DBS frequency in both tremor and beta bands abolishing the pathological tremor and beta frequency oscillations as shown in Fig 5.

D. Variation with DBS Frequency at Different Pulse Widths

The effect of varying the frequency of the DBS at different pulse widths is shown in Fig. 6 and 7, which present the power in the STN neuron in the tremor and beta bands as the DBS frequency was increased. As the frequency of DBS increases the power in the STN activity at the pathological tremor and beta band frequency decrease.

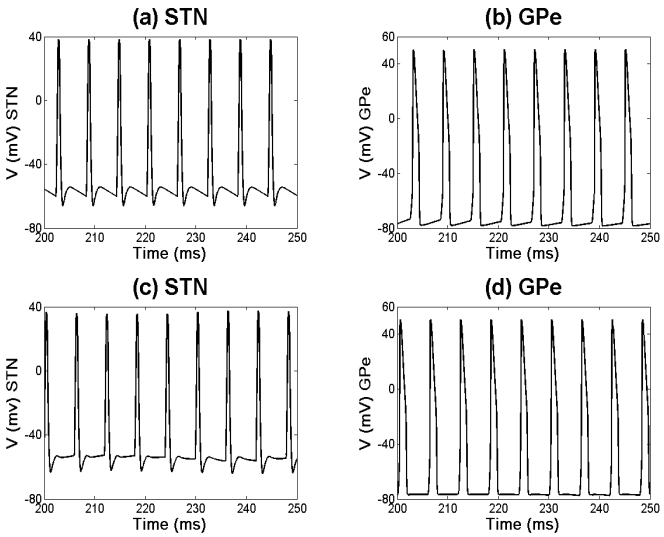

Fig. 5. The STN-GPe network responding to DBS at the frequency of 167 Hz. DBS completely removes oscillatory bursting at the frequency of 5 Hz in (a) STN and (b) GPe and 20 Hz in (c) STN and (d) GPe.

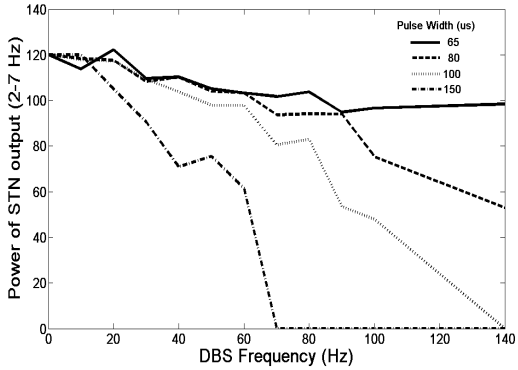

Fig. 6. Tremor band oscillation: Effect of DBS frequency on the total power of a representative STN neuron in the tremor band frequency range (2-7 Hz).

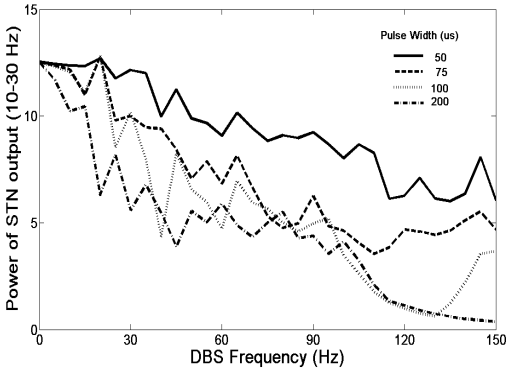

Fig. 7. Beta band oscillation: Effect of DBS frequency on the total power of a representative STN neuron in the beta band frequency range (10-30 Hz).

IV. DISCUSSION

The model extends previous models of the basal ganglia network which have simulated synchronous oscillations generated intrinsically in the STN-GPe network at the parkinsonian tremor frequency [17]. The model is adapted to incorporate STN neurons, with the ability to generate the voltage-dependent generation of a plateau potential [13], interconnectivity between the STN neurons [15] and cortical input through the hyperdirect pathway [23].

In addition to exhibiting oscillations at the tremor frequency, Fig. 3, consistent with [17], STN and GPe neurons in the model were shown to exhibit oscillatory activity within the beta frequency range, Fig. 4. Beta band oscillations were observed within the network in response to increased sensitivity of the STN, under dopamine depleted conditions, to rhythmic inputs at this frequency transmitted from the cortex through the hyperdirect pathway. Increasing evidence suggests that oscillations within the beta-band frequency range are exaggerated in STN and GPe in the parkinsonian state and may play a critical role in the motor symptoms of akinesia and bradykinesia in Parkinson's disease [6], [9]. Consistent with this, the level of oscillatory power in local field potentials changes with levodopa-induced improvements in rigidity and bradykinesia [9]. Furthermore, a reduction in beta band power is observed immediately following DBS [24].

Abnormal oscillatory bursting at both tremor and beta frequencies in the model was abolished by the application of high frequency DBS to the STN, Fig. 5. Injection of a high frequency input can attenuate unwanted low-frequency oscillations in closed loop systems by reducing the effective gain around the loop, due here to dopamine depletion [25]. The efficacy of the DBS input in quenching the pathological oscillatory STN-GPe activity depended on the frequency of the DBS input, with the total STN power in the tremor and beta bands reducing as the frequency of the DBS input was increased, and also on the pulse width and amplitude Fig. 6 and 7.

V. CONCLUSIONS

A model of pathological oscillations in the basal ganglia is presented. Under the conditions simulated, intrinsically generated slow oscillations of the STN-GPe network, similar to those observed *in vitro* [10], were observed to act as a central pacemaker modulated by additional rhythmic inputs from either the cortex or striatum to generate oscillations within both the tremor and beta frequency bands. The pathological oscillations were abolished by the application of high frequency DBS of the appropriate pulse width and amplitude.

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