A possible mechanism for the efficacy of subthalamic nucleus deep brain stimulation

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Deep brain stimulation (DBS):

Focus on DBS of the subthalamic nucleus:
How can STN-DBS help alleviate parkinsonian motor symptoms?

Boxes and arrows...

- □ = inhibition
- ▶ = excitation

Thalamocentric view:

- **VL thalamus:** job is to relay inputs between cortical areas
- **GPi/SNr:** inhibitory “interference”
- **Idea:** STN-DBS can help if it allows appropriate thalamic function
- **Questions:** under what conditions can the thalamus do a good job? does STN-DBS set up these conditions?
An interesting paradox:

- **PD:** $\uparrow$ inhibition from GPi to thalamus compromises relay
- **STN-DBS:** data show GPi activity $\uparrow$ further
Inhibition 6 45 28 44
5.5–7.0 Excitation 19 73 33 63
2.5–4.5 Excitation 63 41 83 52
1.0–2.5 Inhibition 31 77 56 67

Inhibition was greater and more tightly coupled to each stimulation pulse during higher-frequency stimulation, as observed in previous studies (man et al., 1992). Although the increased firing rate in GP neurons in spinal or nigral dopamine neurons (Curtis et al., 1960; Holler et al., 1995; Beurrier et al., 2001). We also observed a decrease in the expression of STN neuronal output during STN HFS (Benazzouz et al. • Effects of STN Stimulation on Pallidal Neurons J. Neurosci., March 1, 2003 • 23(5):1916–1923 • 1919).

The latency of monosynaptic EPSPs of STN orthodromic activation of STN was 0.3 msec and 0.5 msec reported in the rat (Nakanishi et al., 1991) and that of STN–GPe and STN–GPi pathways or by the refractory period of the underlying the short-latency excitation and inhibition observed in this study, it is likely that the earliest excitatory response (peak, 0.3 msec after the stimulation pulse) could occur as a result of split-axonal activation of GPe at 1.0 msec, and split-axonal activation of GPi at 0.3 msec. This would also be consistent with previous observations in Japanese macaques of antidromic activation of GPe at 1.0 msec, and GPe at 0.3 msec, and also with single neuron staining studies in the rat (Kita and Kitai, 1994) and the monkey (Shink et al., 1996; Sato et al., 2000).

Changes in the shape of action potentials were observed during periods of prolonged stimulation lasting 5 min, 15 min, and 30 min. This effect was greatest at 136 Hz stimulation (Filion and Tremblay, 1991; Bergman et al., 1994), periodic oscillations of pallidal activity during motor cortex HFS (Bergman et al., 1994; Nini et al., 2000), and synchronization of GPi (Bergman et al., 1994; Nini et al., 2000) have all been noted to be similar to the change preceding depolarization block as observed in previous studies in anesthetized rats that showed a strong shift to excitation in both GPe and GPi.

The consistent pattern and precise latencies of the responses indicate a significant difference in on versus off stimulation conditions. Significant effect of the short-latency excitatory responses after each stimulation pulse. The increased mean firing rate reflected the dominant excitatory periods at 4 and 8 msec, indicating a regular firing pattern with peaks at 4 and 8 msec, and ISIs of 2, 4, and 8 msec. The interstimulus interval (ISI) histograms of GPi neurons into a high-frequency regular pattern of discharge (Fig. 4). The interstimulus interval (ISI) histograms of GPi neurons into a high-frequency regular pattern of discharge (Fig. 4). The interstimulus interval (ISI) histograms of GPi neurons into a high-frequency regular pattern of discharge (Fig. 4). The interstimulus interval (ISI) histograms of GPi neurons into a high-frequency regular pattern of discharge (Fig. 4). The interstimulus interval (ISI) histograms of GPi neurons into a high-frequency regular pattern of discharge (Fig. 4). The interstimulus interval (ISI) histograms of GPi neurons into a high-frequency regular pattern of discharge (Fig. 4). The interstimulus interval (ISI) histograms of GPi neurons into a high-frequency regular pattern of discharge (Fig. 4).

Discussion
Our experimental setting closely reproduces the HFS system used in humans, and the results demonstrated that STN stimulation of STN neuronal activity, as observed in previous studies, was greater and more tightly coupled to each stimulation pulse during higher-frequency stimulation.
McIntyre et al., *J. Neurophysiol.*, 2004: simulations
Back to the paradox:

- **PD**: ↑ inhibition from GPi to thalamus compromises relay
- **STN-DBS**: data show GPi activity ↑ further (e.g. Hashimoto et al., 2003); consistent with simulations (McIntyre et al.)
- *Why should this ↑ in inhibition relieve PD symptoms?*
Main idea:

- In PD, GPi outputs become *rhythmic* (*woodpecker*), not just stronger.

- **STN-DBS** cuts the rhythmicity: *stronger inhibition is less of a nuisance if it’s more regular* (*window fan*)
This talk - simulation and analysis results in support of this idea:

1. **GPI data** into biophysical thalamocortical relay (TC) cell model
2. biophysical models for basal ganglia/thalamic neurons → mechanism

papers:
- Guo, Rubin, McIntyre, Vitek, and Terman, *J. Neurophysiol.*, accepted
Data-driven computational model:

- Use GPi spike trains recorded from primates in normal/PD/sub-therapeutic DBS/therapeutic DBS to generate inhibitory inputs
- Use elevated spike time (EST) as measure of input burstiness
- Feed inhibitory inputs to conductance-based TC cell model
- Consider TC cell relay of simulated excitatory inputs
- Quantify relay performance with error index
  \[ \text{error index} = \frac{\text{misses} + \text{bursts}}{\text{excitatory inputs}} \]
KEY RESULTS:

A. GPi signal
   - control
   - GPi spike train
   - excitatory input
   - TC potential

B. Parkinsonian without DBS

C. Sub-therapeutic DBS

D. Therapeutic DBS

E. Periodic input
   - Error index
   - EST

F. Random input
   - Error index
   - EST
WHY? Biophysical basal-ganglia-TC network model:

Individual TC cell equations:

\[ C_m v' = -I_L - I_{Na} - I_K - I_T - I_{GPi\rightarrow TC} - I_{signal} \]

\[ h'_T = (h_{T\infty}(v) - h_T)/\tau_{h_T}(v) \]

\[ h' = (h_{\infty}(v) - h)/\tau_h(v) \]

\[ s' = \alpha(1 - s)exc(t) - \beta s, \quad exc(t) = \Sigma H(t - t_{on})(1 - H(t - t_{off})) \]

\[ I_L = g_L(v - v_L) \]

\[ I_T = g_T m_{T\infty}^2(v) h_T(v - v_{Ca}) \]

\[ I_{Na} = g_{Na} m_{\infty}^3(v) h(v - v_{Na}) \]

\[ I_{GPi\rightarrow TC} = g_{GPi}(v - v_{inh}) \Sigma_j(s_{GPi})_j \]

\[ I_K = g_K n^4(v - v_K) \]

\[ I_{signal} = g_{signal} s(v - v_{exc}) \]

\[ X_{\infty}(v) = (1 + \exp(v - \theta_X)/\sigma_X)^{-1}; \quad X \in \{ m, h, m_T, h_T \} \]

STN voltage equation:

\[ C_m v'_{STN} = -I_L - I_{Na} - I_K - I_T - I_{Ca} - I_{AHP} - I_{GPe\rightarrow STN} + DBS \]

GPe voltage and synaptic equations (GPi is similar):

\[ C_m v'_{GPe} = -I_L - I_{Na} - I_K - I_T - I_{Ca} - I_{AHP} - I_{STN\rightarrow GPe} - I_{GPe\rightarrow GPe} \]

\[ s'_{GPe} = \alpha_{GPe}(1 - s_{GPe})inh(v_{GPe}, t) - \beta_{GPe}s_{GPe} \]
Simulation results with model - Normal case:

Excitatory inputs
Parkinsonian case:
DBS case (extreme example):
More examples and summary:

periodic input

Poisson input

normal

park

DBS

\text{error index} = (\text{misses} + \text{bursts})/\text{(excitatory inputs)}
Similar qualitative results in a reduced thalamic model:

\[
v'_{Th} = -(I_L + I_T) - I_{signal} - I_{inh}
\]

\[
h'_{Th} = (h_\infty(v_{Th}) - h_{Th})/\tau_h(v_{Th})
\]
Analysis

Quick reminder - relaxation oscillators and coupling:

\[
\begin{align*}
\dot{v} &= f(v, h) - I_{\text{exc}} - I_{\text{inh}} \\
&\quad \begin{cases} <0 & \text{if } f>0 \\ >0 & \text{if } f<0 \end{cases} \\
\dot{h} &= \epsilon g(v, h), \quad 0 < \epsilon \ll 1
\end{align*}
\]
Phase planes for reduced thalamic model:

\[
v'_{Th} = -(I_L + I_T) - \frac{I_{signal}}{I_S \text{ or } I \text{ below}} - g_{GPi} \frac{s_{GPi}}{S \text{ below}} (v_{Th} - v_{inh})
\]

\[
h'_{Th} = \frac{h_\infty(v_{Th}) - h_{Th}}{\tau_h(v_{Th})}
\]

key idea: for ANY constant inhibition, \(I_T\) equilibrates and strong enough inputs at reasonable rate evoke reliable responses
Cartoon view:

normal:

DBS:

Numerics:

normal:

DBS:
- responses 2 and 3 (partially) are blocked by left branch
- the response after 4 is inappropriately huge
Full thalamic model:

- **constant inhibition (normal or DBS):**
  - $I_{Na}$, rather than $I_T$, equilibrates
  - $h_T$ is so slow that it is $\sim$ constant
- **parkinsonian:**
  - phasic inhibition means $I_{Na}$ and $I_T$ both participate
  - reminiscent of bursts within sleep spindle oscillations

Bazhenov and Timofeev, Scholarpedia (from Timofeev and Bazhenov, 2005)
Normal case in the full model:

A) Excitatory input vs. $v$

B) $v$ vs. $h_T$

C) $h$ vs. $v$

D) $h$ vs. $v$

E) $h$ vs. $v$
DBS in the full model:

- Excitatory input
- No input

Graphs showing the dynamics of the system with DBS intervention.
Parkinsonian case in the full model:
BACK TO DATA:
Signals preceding each type of TC response

• average over 25 msec of GPi activity, consisting of 20 msec of activity preceding each TC response and 5 msec of activity following response

• cluster by 3 TC response types (miss, bad, successful)

• result is consistent with predictions from theory!
Apply GPi data to heterogeneous TC population:
TC miss at the same time in PD/subDBS, not in tDBS!
How general is model performance?

Consider stochastic inputs:
- let many GPi cells inhibit a biophysical model TC cell
- use Poisson processes to generate GPi firing
- vary correlation between GPi cells and GPi burst rate (EST)
- **PD** ≈ moderate correlation and **EST**
- **DBS** ≈ high correlation and **EST**
- **error index** = (misses + bursts)/(excitatory inputs)
Simulation results:

error index varies with inhibitory input correlation and EST
Results from jittered data also separate correlation and burstiness:
Quantitative Analysis:
Markov chains for arbitrary stochastic input trains

idea - use a *Markov chain*, based on transitions between bins defined in silent phase, to compute firing statistics:

**step 1: define bins**

![Diagram showing 5 bins with excitation on and off phases]

- use time $S$, the min time between excitatory inputs
- bins (non-Markovian) are
  \[
  I_k = [w_{E,RK}^E \cdot kS, w_{E,RK}^E \cdot (k + 1)S], \text{ if } k + 1 < N,
  \]
  \[
  I_{N-1} = [w_{E,RK}^E \cdot (N - 1)S, w_{L,K}^E]
  \]
  \[
  I_N = [w_{L,K}^E, w_{FP}^0].
  \]

- states of Markov chain are $(I_k, m), m \geq 1$, where $m - 1 =$ number of inputs since last fired
**step 2:** compute transition probabilities $p_{(j,m)\rightarrow(k,m+1)}$:

example:

\[
\begin{array}{c|c|c|c}
M^3_S(w^E_{RK}) & M^3_S(w^E_{RK}) & M^3_S(w^E_{RK}) & M^3_S(w^E_{RK}) \\
M^2_S(w^E_{RK}) & M^2_S(w^E_{RK}) & M^2_S(w^E_{RK}) & M^2_S(w^E_{RK}) \\
M^1_S(w^E_{RK}) & M^1_S(w^E_{RK}) & M^1_S(w^E_{RK}) & M^1_S(w^E_{RK}) \\
\end{array}
\]

\[
p_{(1,1)\rightarrow(2,2)} = 1, \quad p_{(2,2)\rightarrow(3,3)} = \lambda, \\
p_{(2,2)\rightarrow(4,3)} = 1 - \lambda, \quad p_{(3,3)\rightarrow(4,4)} = 1, \\
p_{(4,3)\rightarrow(1,1)} = 1, \quad p_{(4,4)\rightarrow(1,1)} = 1
\]

in general, **transition probabilities** can be computed recursively
**Theorem:** This (excitation-only) Markov chain is aperiodic and irreducible, with **limiting distribution** $Q$, if and only if cells can move across multiple bins in a single iteration (as in the above example).

**interpretation:**

- probability of firing to next input $= \Sigma_{m=1}^{N} Q[(I_N, m)]$
- expected number of failures $= E_f = \Sigma_{j=1}^{N-1} j F_j$, where $F_j =$ probability of $j$ failures $= \frac{\left(\frac{\Sigma_{k=1}^{N-1} Q(I_k, 1)}{\Sigma_{k=1}^{N} Q(I_k, 1)}\right) \left(\frac{\Sigma_{k=2}^{N-1} Q(I_k, 2)}{\Sigma_{k=2}^{N} Q(I_k, 2)}\right) \ldots \left(\frac{\Sigma_{k=j}^{N-1} Q(I_k, j)}{\Sigma_{k=j}^{N} Q(I_k, j)}\right)}{\left(\frac{\Sigma_{k=j+1}^{N} Q(I_k, j + 1)}{\Sigma_{k=j+1}^{N} Q(I_k, j + 1)}\right)}$  

- also extends to inhibition + excitation (see below), homogeneous population with differing inputs, heterogeneous population with identical inputs
**example:** 2-d TC cell with uniform distribution of intervals between excitatory inputs

- **0 inhibition** ⇒ bins (1,1), (2,1), (2,2), (3,2), (3,3) with
  
  \[ v^0 = [0.3404, 0.1135, 0.0922, 0.3617, 0.0922] \]
  
  \[ v^0_{num} = [0.3276, 0.1289, 0.0878, 0.3629, 0.0878], \]

  firing to \(\sim 45\%\) of inputs, \(\sim 1.2\) failures per spike

- **max inhibition** ⇒ 5 bins, 12 states with
  
  \[ v^I = [0.2290, 0.0763, 0.0859, 0.1622, 0.0215, 0.0569, 0.0624, 0.0005, 0.0004, 0.2211, 0.0833, 0.0005] \]
  
  \[ v^I_{num} = [0.2272, 0.0784, 0.0726, 0.1927, 0.0194, 0.0388, 0.0669, 0.0022, 0.0007, 0.2171, 0.0820, 0.0002], \]

  firing to \(\sim 30\%\) of inputs, \(\sim 2.28\) failures per spike

- **similar results with other distributions**

- **E inputs + jumps in I** ⇒ similar agreement, with firing to \(< 10\%\) of inputs and large \(Q(I_1, 1)\) after onset of inhibition: PD case!
SUMMARY:

• Hypothesis 1: PD yields bursting oscillations (GPe, STN, GPi), not just changes in firing rates
  – massive experimental support
  – STN-GPe loop may generate (Plenz and Kitai, 1999; Terman, Rubin, et al., 2002)

• Hypothesis 2: phasic or bursty inhibition compromises TC relay
  – seen in sleep spindles
  – seen robustly in model due to $I_T, I_{Na}$ interaction

• Hypothesis 3: STN DBS restores TC relay reliability
  – slow process can equilibrate during sustained inhibition

• Hypothesis 4: compromised relay is related to PD symptoms, while restored relay contributes to alleviation of symptoms
  – only therapeutic DBS restores relay in model
  – *in a heterogeneous population, the effect is enhanced:* rhythmic inhibition causes cells to fail together, while failures with regular inhibition are spread out
Tests:

- VL thalamic burstiness ↑ in PD, ↓ in therapeutic DBS?
- change in thalamus/cortex correlations in DBS, relative to PD?
- motor symptoms associated with thalamic burstiness?
- speed-up of $T$-current (de)inactivation in TC should help in PD
- do perturbations in VL inputs affect cortical processing when combined with other (e.g. Vim) thalamic inputs in cortex?

Future directions:

- more detailed analysis of local impact of DBS (McIntyre et al.)
- multi-cell GPi recordings and larger scale simulations
- optimization of DBS (Feng et al., 2007)
- multi-site stimulation (Tass et al.): mechanisms?
- role of hyperdirect pathway (Leblois et al., 2006)?
- thalamocortical relay/thalamic reticular/cortical interactions?