Supplementary Online Content


**eAppendix. Methods.**

This supplementary material has been provided by the authors to give readers additional information about their work.
**eAppendix. Methods**

**Subjects**
Subjects were patients with Parkinson's disease and STN DBS devices at the Cleveland Clinic. All had 1) a diagnosis of PD by a movement disorders neurologist 2) at least 5 years disease duration, 3) clear levodopa response 4) no dementia and 1) were at least 3 months post-implantation on the tested side 2) had completed the initial postoperative period of stimulator adjustments, and reached stable stimulator settings in the judgement of the treating clinician 3) were obtaining satisfactory and expected clinical benefit from the stimulation. Mean (median) time from last clinical change of stimulator settings to time of experiment was 20 (14) months.

Subjects’ clinical characteristics are given in Table 1a. The levodopa equivalents given in that table were computed as follows: Total levodopa equivalents = \((\text{regular levodopa dose} \times 1 + \text{levodopa continuous release dose} \times 0.75) \times 0.25\) with carbidopa and either tolcapone or entacapone + pramipexole dose x 67 + ropinirole dose x 16.67 + pergolide dose x 100 + bromocriptine dose x 10 + cabergoline dose x 50 + amantadine dose x 0.5 + oral selegiline dose x 10 + rasagiline dose x 100 + rotigotine dose x 57. (The figure of 57 is taken from Table 2 in reference 9, and is the midpoint between the mean (62) and median (52) value in that table. Other values are directly from the text of that paper.) 1.25 mg sublingual selegiline considered equal to 10 mg oral.


**Surgical Procedure**
The initial target was MR image-based, and the angulation adjusted to avoid cortical sulci, blood vessels, and, when possible, ventricles. The target was further refined using intraoperative microelectrode recording and microstimulation. Intraoperative stimulation through the DBS electrode was used to confirm a satisfactory therapeutic window between therapeutic effects and side effects.

**Testing Procedure**
Testing was in the off-medication state: mean (median) delay between medication withdrawal and testing was 12.8 (12.0) hours (range: 10.5-16.5). The dominant hand and contralateral stimulator were tested.

Each bradykinesia measurement consisted of a 20 second block of continuous finger-tapping (UPDRS item 23) maintaining an interval of about 2 minutes between consecutive measurements. The time of each bradykinesia measurement was known to an accuracy of one second. This continued for 20 minutes constituting the initial stimulation-on period, designated Epoch 0.

At the conclusion of Epoch 0, the stimulator was turned off using a Medtronic model 8840 or 7451 programmer. Bradykinesia measurements then resumed for a further 50 minutes with the stimulator now off: this constituted the stimulation-off period, designated Epoch 1.

At the conclusion of Epoch 1, the stimulator was turned back on again and measurements resumed with the stimulator back on again, for a further 20 minutes designated Epoch 2.

Stimulation was turned on/off using the following procedure: Subjects were told that their stimulator settings would be changed, but not how, or how many times. Stimulation was turned off/on while subjects performed a distractor task (visual choice reaction time). Timing was controlled by a computer-generated voice-synthesized count-down, over headphones, so that the experimenter, but not the subject, could hear it. The experimenter pressed buttons on the programmer device randomly (only one button-press actually had effect) to further disguise any cues.

**Bradykinesia Measurements**
To measure bradykinesia, we used an instrumented version of UPDRS item 23 ("finger tapping"), in which subjects tapped the tip of the thumb and index finger together "as fast as possible" and "as wide as possible" for 20 seconds. An angular velocity sensor (model G-1, NeuroKinetics, Edmonton, Alberta, Canada) was taped to first phalange of the index finger to detect metacarpophalangeal flexion/extension. We used total power in the angular velocity signal, in the 1-10 Hz frequency band, as a measure of bradykinesia (lower power = more bradykinesia). We conducted separate experiments to validate this measure against blinded UPDRS ratings [3].

Data Analysis

All data analysis was done using the pylab, numpy, and scipy libraries (www.enthought.com or www.scipy.org) The angular velocity signals were sampled (PCI-6025E, National Instruments, Austin, TX) at 16 bits x 10 KHz resolution. A power spectrum was then computed (Welch’s method, with window 2^15 = 32768 samples) and the total power computed in a band of 1.0 to 10.0 Hz.

Ideally, the subject is a stationary system, and all changes over time reflect only the dynamics of the subject’s response to stimulation. However, factors, such as fatigue or boredom may also cause changes over time. Therefore, we imposed a stationarity criterion: we excluded from analysis four (out of 24) experiments in which bradykinesia did not improve when the stimulator was turned back on again at the end of the experiment (the Epoch-1 to Epoch-2 transition), since, in such experiments, changes during Epoch-1 could not reliably be attributed to turning off the stimulation.

Curve Fitting

Curves were fit to the graph of tapping-power vs. time (see Fig 1) using Nelder-Mead iterative minimization of summed, squared error (scipy.optimize.fmin function).

To the three epochs of the experiment, we fit the piecewise equation

\[
Y = \begin{cases} 
  f(t) & : t \leq t_{off} \\
  g(t) & : t_{off} < t < t_{on} \\
  h(t) & : t \geq t_{on}
\end{cases}
\]

where \( t \) = time and \( Y \) = tapping power, and where \( t_{off} \) and \( t_{on} \) are the time stimulation was turned off, and on, respectively. \( f(t) \), \( g(t) \), and \( h(t) \) correspond to epochs 0, 1, and 2, respectively.

To choose the form of \( g(t) \), we assumed that after stimulation ceased, as time passed, \( g(t) \) eventually would reach a plateau; this is supported both by biological plausibility and previously published data (e.g. [2]). The simplest functions meeting that constraint have first derivative, \( g'(t) \), decreasing monotonically over time, approaching zero asymptotically. The simplest is the linear differential equation

\[
g'(t) = -kg(t)
\]

whose solution is

\[
g(t) = e^{-kt}
\]

where \( t_{off} \) is defined as time zero.

Note that we made no a priori assumption that the equation was continuous across the boundaries between epochs, allowing for the possibility of abrupt changes when stimulation was turned on/off. In fact, such abrupt changes occurred, and were the subject of our earlier paper [3], which reported systematic variations in the size of the abrupt changes (STEP parameter, see Figure 1 in that paper).
In this paper, we report systematic variations in HALF-LIFE (time to decrease by a factor of 2, see Figure 1 in the present paper), which is the reciprocal of the rate constant \( k \) in the function \( g(t) \). Strictly speaking \( 1/k \) is the time constant—the time to decrease by a factor of 2.718... (\( e \): the base of the natural logarithms). The half-life is simply the time constant times a constant factor of 0.69314..., which is \( \log_2 \). We used half-lives, rather than time constants, because they are more familiar to clinicians accustomed to drug half-lives.