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Return of bradykinesia after subthalamic stimulation ceases: Relationship to electrode location

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ABSTRACT

In 20 subjects we quantified the rate at which subthalamic nucleus deep brain stimulation effects on Parkinson's bradykinesia "washed-out" after stimulation ceased. We found that wash-out was a two-step process, consisting of an initial fast decrease in stimulation's therapeutic effect, followed by a further, slow decline. Moreover, the relative contribution of the fast and slow components differed between patients. Finally, we found that lateral stimulation caused more of the fast-decaying component, while medial stimulation caused more of the slow-decaying component. This implies the existence of at least two separate mechanisms by which subthalamic nucleus deep brain stimulation improves bradykinesia, associated with activation of spatially separate zones in the vicinity of the subthalamic nucleus.

Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment for symptoms of Parkinson's disease (PD) (Deuschl et al., 2006). It is well known that the therapeutic effects of STN DBS do not cease instantaneously when stimulation is turned off, but, rather, decay gradually (Temperli et al., 2003). The implications of this observation for the design of clinical trials are well recognized, but little work has been done to quantify precisely the rate of decay, or to establish how it varies from one patient to another. Temperli et al. (2003) give average figures for time to 75%, or 90% of maximum and these results justify a 1–2 hour washout period. However, Keresztenyi et al. (2007) reported much faster rates of decay. These differences could be related to study design or inter-subject variability. The present study was designed to assess inter-subject variability with respect to both rapid and slow decay of DBS effects.

In addition to its practical implications, the decay of DBS effects provides important clues to the physiological mechanisms by which DBS exerts its therapeutic effect. Temperli et al. (2003) pointed out that the slow decay of STN DBS therapeutic effect implicated physiological mechanisms capable of persistent changes. We have suggested that DBS-induced synaptic plasticity is such a mechanism (Cooper et al., 2008, 2009). Given that current theories on DBS mechanisms propose that it overrides a native, pathological pattern of activity it is possible that slow decay of DBS therapeutic effects could reveal whether a particular DBS-induced change in neuronal activity (i.e. power in the beta frequency band) has a causal relation to DBS therapeutic effects (Eusebio and Brown, 2009): if beta-suppression causes therapeutic effects, then it should persist, after DBS ceases, for about as long as the therapeutic effects do (Bronte-Stewart et al., 2009). While this proposition is not without controversy (Foffani et al., 2006), it does provide further motivation to understand the factors affecting the decay of DBS therapeutic effects.

In the present paper we measure STN DBS therapeutic effect on bradykinesia, and report on rates of decay of that effect after stimulation is turned off. We found that inter-subject variation was high, but non-random, exhibiting both a fast- and a slow-decaying process. Moreover, these did not represent two separate patient populations but rather two separate physiological processes which could occur simultaneously in the same patient. As a result, we found that individuals differed in the relative contributions of fast and slow processes to their net DBS effect. Finally, we associated the fast and slow processes with spatially distinct sites of stimulation. These results address ambiguities in the previous literature and point

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toward a better understanding of physiological mechanisms underlying the therapeutic effect of DBS.

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) 5 or more 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 judgment 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.

Details of subjects' pre- and postoperative medication regimens are given in Supplementary Material.

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.

Subjects performed three tasks, in rotation: A) a 20 second block of continuous finger-tapping (UPDRS item 23), B) a 20 second block of muscle-tone testing using the device developed by Patrick et al. (2001), and C) a 30 second block of a visual choice reaction time task (only the finger-tapping results are reported here), maintaining an interval of about 2 min between consecutive bradykinesia measurements. The time of each bradykinesia measurement was known to an accuracy of 1 s. This continued for 20 min 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. Subjects then resumed performing the three tasks in rotation for a further 50 min 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 tasks resumed in rotation with the stimulator back on again, for a further 20 min designated Epoch 2.

The procedure for turning on/off stimulators is detailed in Supplementary Material.

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 s. Angular velocity sensors (model G-1, NeuroKinetics, Edmonton, Alberta, Canada) were taped to the first phalange of thumb and index finger to detect metacarpophalangeal flexion/extension. Validation of the quantitative tapping measurement procedure against UPDRS_III is presented in Supplementary Material.

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 × 10 kHz resolution and the Euclidean sum $\sqrt{(x^2+y^2)}$ taken. A power spectrum was then computed (Welch's method, with window $2^{15}=32{,}768$ 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 excluded from analysis four 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

$$Y = \begin{cases} f(t) & : t \le t_{off} \\ g(t) & : t_{off} < t < t_{on} \\ h(t) & : t \ge t_{on} \end{cases}$$

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. 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.

The derivation of f(t), g(t), and h(t) is discussed in detail in Supplementary Material. Briefly, for g(t) we used a simple decaying exponential (see Fig. 1); the form of f(t) and h(t) did not affect our results. In this paper, we report HALFLIFE (time to decrease by a factor of 2), and STEP, defined as the fraction of total (from initial to asymptotic value) change which occurred *abruptly* when DBS was turned off (see Fig. 1).

Statistics

Regression and tests of significance were done with the R statistical programming language (R development core team, 2009).

Electrode localizations

In subjects with sufficient perioperative clinical data (see Table 1) we created a patient-specific DBS computer model using Cicerone v1.2, a freely available academic DBS research tool (Miocinovic et al., 2007), following our previously described methodology (Butson et al., 2007) (see Supplementary Material). Four subjects were excluded from the electrode localization analysis because of incomplete data due to: 1) operated at another institution (surgical records not available), 2) "frameless" stereotaxic system used (incompatible with Cicerone software 3), incomplete surgical records and 4) incomplete radiological records.