Association of Deep Brain Stimulation Washout Effects With Parkinson Disease Duration

Scott E. Cooper, MD, PhD; Cameron C. McIntyre, PhD; Hubert H. Fernandez, MD; Jerrold L. Vitek, MD, PhD

Background: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) improves symptoms of Parkinson disease (PD), including bradykinesia. When stimulation ceases abruptly, bradykinesia returns gradually. The duration of the gradual, slow washout varies across patients, and although the origin of this variability is unclear, it is hypothesized to be related to 1 or more clinical characteristics of patients.

Objective: To determine if a correlation exists between clinical characteristics of patients with Parkinson disease (age, age at disease onset, disease severity, disease duration, medication dose, or time since surgery) and the washout rate for bradykinesia when STN DBS is discontinued.

Design: Serial quantitative assessments of bradykinesia were performed during a defined period following cessation of STN DBS.

Setting: Academic research.

Patients: Twenty-four patients with Parkinson disease who underwent STN DBS were enrolled in the study. Patients were assessed while off medication (medication had been discontinued 101/2 to 161/2 hours before testing), and stimulator settings were unchanged for a mean (median) of 20 (14) months.

Main Outcome Measures: We measured bradykinesia in the dominant hand by assessing finger tapping (item 23 on the Unified Parkinson Disease Rating Scale), which was quantified using an angular velocity transducer strapped on the index finger. Finger tapping was assessed every 2 minutes for 20 seconds at a time. This was performed during a 20-minute period with DBS on (baseline period), during a 50-minute period following discontinuation of STN DBS for the dominant hand, and again during a 20-minute period after turning on the device.

Results: When STN DBS was turned off, an initial fast but partial loss of benefit was observed, which was followed by a further slow washout of the residual therapeutic effect. The half-life of the slow washout phase varied significantly across patients, and this variation was strongly related to disease duration: patients with shorter disease duration experienced slower washout, while patients with longer disease duration experienced faster washout.

Conclusions: Washout of STN DBS effects varies with Parkinson disease duration. Estimates of proper washout time based on one patient population may not apply to populations with different disease durations. In DBS clinical trials, washout intervals should be chosen conservatively or adjusted for individual variation in the rate at which washout occurs.


Deep brain stimulation (DBS) of the subthalamic nucleus (STN) improves symptoms of Parkinson disease (PD), including bradykinesia.1 When stimulation ceases abruptly, bradykinesia returns gradually.2 It was recently demonstrated that this occurs in 2 phases (as an initial abrupt, partial loss of therapeutic benefit, followed by a further gradual loss of the residual benefit) and that the proportion of abrupt vs slow loss of benefit varies with electrode position.3 The duration of the gradual, slow washout varied across patients, and although the origin of this variability was unclear, it was hypothesized to be related to 1 or more clinical characteristics of patients.

METHODS

Details of these experiments were published in an earlier article.3 To avoid redundancy, some of that material is available in an eAppendix (http://www.jamaneuro.com).

PATIENTS

We studied 24 patients with PD who underwent STN DBS. All had been diagnosed by a movement disorders neurologist, showed a clear response to levodopa therapy, and demonstrated no symptoms of dementia. All had
a minimum of 5 years’ PD duration, had undergone implantation at least 3 months earlier, and had completed the initial postoperative period of stimulator adjustments. Characteristics of the patients are summarized in Table 1. This study was approved by the Cleveland Clinic Institutional Review Board, and informed consent was obtained by the study coordinator or the principal investigator (S.E.C.).

PROCEDURE

Bradykinesia testing was performed off medication (range, 10½ to 16½ hours before testing) under stimulation-on and stimulation-off conditions. Patients were blinded to the time when their stimulator was tuned off using the following procedure: they were told that their stimulator settings would be changed but not how or how many times. Stimulation was turned on or off as the patients performed a distraction task (visual choice reaction time). The experimenter (S.E.C.) pressed buttons on the programmer device randomly (only one button press actually had effect) to further disguise any cues.

Quantitative measurements of bradykinesia were made using an angular velocity transducer strapped on the index finger. Finger tapping was assessed every 2 minutes by requiring the patient to rapidly tap the tips of the thumb and index finger for 20 seconds at a time (item 23 on the Unified Parkinson Disease Rating Scale). The total power of index finger angular velocity in the 1-Hz to 10-Hz band was the variable assessed to quantitate bradykinesia (lower power indicates greater bradykinesia).

Finger tapping was assessed every 2 minutes during a 20-minute period with DBS on (baseline period), then every 2 minutes during a 50-minute period with the contralateral stimulator off, and again every 2 minutes during a 20-minute period after the stimulator was turned back on. We studied only patients who demonstrated a clear clinical improvement in bradykinesia with stimulation and who met a stationarity criterion that bradykinesia must improve with turning the stimulator back on. Twenty of 24 patients tested demonstrated stationarity. We excluded those who did not demonstrate stationarity because this could occur as the result of fatigue.

DATA ANALYSIS AND STATISTICAL ANALYSIS

Data were analyzed by fitting an exponential decay function (first-order linear differential equation) to the plot of bradykinesia vs time during the stimulation-off interval (Figure 1) using Nelder-Mead iterative minimization of summed, squared error (scipy.optimize.fmin [http://docs.scipy.org/doc/scipy-0.7.x/reference/generated/scipy.optimize.fmin.html]).

Clinical characteristics of the patients (Table 1) were obtained by review of their medical records. Plots and tests of statistical significance were performed using the R statistical programming language. We report herein the association

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Dominant Hand</th>
<th>Age at Time of Testing, y</th>
<th>Disease Duration, y</th>
<th>Off UPDRS Motor Score</th>
<th>Total Levodopa Equivalent Daily Dose, mg</th>
<th>Time Since Electrode Implantation, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right</td>
<td>62</td>
<td>27</td>
<td>28</td>
<td>1954</td>
<td>1033</td>
</tr>
<tr>
<td>2</td>
<td>Right</td>
<td>65</td>
<td>13</td>
<td>...</td>
<td>2148</td>
<td>1258</td>
</tr>
<tr>
<td>3</td>
<td>Right</td>
<td>58</td>
<td>19</td>
<td>50</td>
<td>1275</td>
<td>550</td>
</tr>
<tr>
<td>4</td>
<td>Right</td>
<td>53</td>
<td>18</td>
<td>16</td>
<td>935</td>
<td>992</td>
</tr>
<tr>
<td>5</td>
<td>Right</td>
<td>70</td>
<td>24</td>
<td>42</td>
<td>1234</td>
<td>500</td>
</tr>
<tr>
<td>6</td>
<td>Left</td>
<td>64</td>
<td>15</td>
<td>14</td>
<td>1113</td>
<td>956</td>
</tr>
<tr>
<td>7</td>
<td>Right</td>
<td>63</td>
<td>16</td>
<td>29</td>
<td>1250</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Right</td>
<td>72</td>
<td>9</td>
<td>28</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>9</td>
<td>Right</td>
<td>74</td>
<td>26</td>
<td>...</td>
<td>...</td>
<td>28</td>
</tr>
<tr>
<td>10</td>
<td>Left</td>
<td>52</td>
<td>7</td>
<td>30</td>
<td>1239</td>
<td>300</td>
</tr>
<tr>
<td>11</td>
<td>Right</td>
<td>57</td>
<td>&gt;10</td>
<td>...</td>
<td>1125</td>
<td>400</td>
</tr>
<tr>
<td>12</td>
<td>Right</td>
<td>69</td>
<td>12</td>
<td>13</td>
<td>1150</td>
<td>483</td>
</tr>
<tr>
<td>13</td>
<td>Right</td>
<td>54</td>
<td>15</td>
<td>39</td>
<td>1193</td>
<td>617</td>
</tr>
<tr>
<td>14</td>
<td>Right</td>
<td>64</td>
<td>12</td>
<td>43</td>
<td>1439</td>
<td>750</td>
</tr>
<tr>
<td>15</td>
<td>Right</td>
<td>64</td>
<td>11</td>
<td>33</td>
<td>650</td>
<td>300</td>
</tr>
<tr>
<td>16</td>
<td>Right</td>
<td>61</td>
<td>13</td>
<td>21</td>
<td>706</td>
<td>283</td>
</tr>
<tr>
<td>17</td>
<td>Right</td>
<td>73</td>
<td>17</td>
<td>30</td>
<td>1683</td>
<td>821</td>
</tr>
<tr>
<td>18</td>
<td>Right</td>
<td>67</td>
<td>10</td>
<td>25</td>
<td>542</td>
<td>701</td>
</tr>
<tr>
<td>19</td>
<td>Right</td>
<td>57</td>
<td>13</td>
<td>29</td>
<td>2252</td>
<td>550</td>
</tr>
<tr>
<td>20</td>
<td>Right</td>
<td>62</td>
<td>19</td>
<td>47</td>
<td>863</td>
<td>200</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients Not Meeting the Stationarity Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 Right 62 11 38 551 300 18 18</td>
</tr>
<tr>
<td>22 Right 59 16 21 1200 650 25 25</td>
</tr>
<tr>
<td>23 Right 47 27 14 800 625 65 65</td>
</tr>
<tr>
<td>24 Right 55 16 55 867 200 5 5</td>
</tr>
</tbody>
</table>

Abbreviations: Ellipsis, missing data; NA, not applicable because the patient was implanted only on the dominant side.

a Time from the onset of symptoms to the time of testing.

b Unified Parkinson Disease Rating Scale (UPDRS) motor score in the off-medication, deep brain stimulation-naive state.

c Details of how the levodopa equivalent was computed are given in the eAppendix.

d Dominant side.

e Nondominant side.
between the rate of the slow washout phase and patients’ clinical characteristics.

## RESULTS

### PATIENT CHARACTERISTICS

Table 1 gives the characteristics of the patients. Briefly, their mean (SD) age was 61.8 (6.8) years. Their mean (SD) off-medication and off-stimulation Unified Parkinson Disease Rating Scale motor score was 30.7 (11.9). Their total levodopa equivalent daily dose before surgery was 1125.8 (507.3) mg and at the time of testing was 531.3 (319.7) mg. The mean (SD) time since surgery was 37.8 (30.6) months.

### STIMULATION CHARACTERISTICS

Stimulation parameters were the same as each patient’s usual settings, which had been clinically optimized before and independent of the experiment. Stimulator settings were unchanged for a mean (median) of 20 (14) months. Table 2 gives the detailed stimulation parameters. Briefly, the mean (SD) voltage was 3.26 (0.45) V, the frequency was 155.8 (26.1) Hz, and the pulse width was 75.0 (17.7) microseconds. Eleven patients (1 of whom had 2 cathodes) were stimulated in monopolar mode, while the remaining 13 patients (2 of whom had 2 cathodes) were stimulated in bipolar mode.

### ASSOCIATION OF THE HALF-LIFE OF THE SLOW WASHOUT PHASE WITH DISEASE DURATION

We found a strong correlation between disease duration and the reciprocal of the half-life (ie, the rate constant of the differential equation describing the slow washout phase). That is, the rate of the slow washout phase was linearly related to disease duration over the range of disease durations (7-27 years) in our sample. This accounted for more than half of the variance in washout rates ($R^2 = 0.55, P < .001$) (Figure 2).

The following equation was used:

$$\frac{1}{\text{Half-life in Seconds}} = (3.123 \times 10^{-4}) \times \text{Disease Duration in Years} - (2.085 \times 10^{-3}).$$

The SEs were $6.541 \times 10^{-3}$ for slope and $1.079 \times 10^{-3}$ for intercept.

### OTHER CLINICAL VARIABLES

The following clinical variables had no statistically significant effect on the rate of washout for bradykinesia after stimulation: age, age at disease onset (ie, age minus disease duration), total levodopa equivalent daily dose before surgery, current total levodopa equivalent daily dose, and off-medication and off-stimulation Unified Parkinson Disease Rating Scale motor score. Age at disease onset had a significant effect on the washout rate ($P = .006$ in simple regression analysis). However, in a multiple regression analysis, age at disease onset was not significant ($P = .54$), whereas disease duration remained sign-

The rate of the slow washout phase varied greatly across patients and was strongly related to PD duration (ie, washout was faster [half-life shorter] with longer disease duration). These data suggest that washout times will vary with disease duration; as such, in DBS clinical trials, estimates of proper washout time based on one patient population may not apply to patients with different disease characteristics (eg, disease durations). Washout intervals should be chosen conservatively or should accommodate individual variation in the rate at which washout occurs.

Limitations of this study include the modest sample size, which could have prevented us from detecting other weaker correlations. Results may also be different for symptoms other than bradykinesia, and because our shortest disease duration at the time of testing was 7 years, we do not know if a relationship exists from the time of onset to that period. In addition, worsening symptoms

![Figure 1](http://archneur.jamanetwork.com/pdfaccess.ashx?url=/data/journals/neur/926242/)
when the stimulator was off may have unblinded some patients to the testing condition, in which case the nocebo phenomenon (placebo worsening of symptoms) could conceivably account for our results but only if its temporal dynamics bore a strong and consistent relationship to disease duration, which is speculative.

In principle, fatigue could have confounded our results. We attempted to minimize fatigue effects by ensuring that finger tapping occupied only 20 seconds of every 2 minutes. In addition, we excluded patients in whom bradykinesia did not improve with turning the stimulator back on because in these cases changes in bradykinesia during the testing interval could be caused by fatigue rather than DBS washout. If, despite these attempts to minimize fatigue, a confounding effect occurred, it would require a strong (>/%0 of variance) linear relationship between disease duration and the rate at which fatigue increased over time. This would be a noteworthy observation in its own right. Nevertheless, we do not believe that fatigue accounts for our results because there was no tendency for bradykinesia to increase over time during the stimulation-on periods at the beginning and end of each experiment.

Therefore, the present observations suggest an association of slow-phase washout time with PD duration after discontinuation of STN DBS. A better understanding of the biological basis for this finding may provide insight into the mechanisms of the therapeutic effect of DBS on PD motor symptoms. For example, Lee et al studied DBS-induced accumulation of extracellular neurotransmitter (glutamate) in an animal model and used microdialysis to measure the rate of neurotransmitter washout: they obtained half-lives similar to what we measured.
for washout of DBS therapeutic effects (more recent work by the same group used cyclic voltammetry in humans⁹). This suggests¹ that extracellular neurotransmitter accumulation might contribute to the slow washout of DBS therapeutic effects.

Accepted for Publication: April 9, 2012.
Published Online: October 15, 2012. doi:10.1001/jamaneurol.2013.581
Correspondence: Scott E. Cooper, MD, PhD, Center for Neurological Restoration, Department of Neurology, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195 (coopers2@ccf.org).

Author Contributions: Study concept and design: Cooper, McIntyre, and Vitek. Acquisition of data: Cooper. Analysis and interpretation of data: Cooper, McIntyre, Fernandez, and Vitek. Critical revision of the manuscript for important intellectual content: McIntyre, Fernandez, and Vitek.

Funding/Support: This research was supported in part by grant K23NS052523 from the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH) (Dr Cooper).

Conflict of Interest Disclosures: Dr McIntyre is a consultant for IntElect Medical and Boston Scientific Neuromodulation. Dr Fernandez has received research support from Abbott, Acadia, Biotie Therapeutics, EMD-Serono, Huntington Study Group, Ipsen, Merz Pharmaceuticals, Michael J. Fox Foundation, Movement Disorders Society, National Parkinson Foundation, NINDS of the NIH, Novartis, Parkinson Study Group, and Teva; honoraria from University of South Florida Continuing Medical Education (CME), Cleveland Clinic CME, Medical Communications Media, Health Professions Conferencing, Ipsen, Merz Pharmaceuticals, and US World Meds; and royalty payments from Demos Publishing, Manson Publishing, and Springer Publishing; he is also a consultant for Merz Pharmaceuticals, Ipsen Pharmaceuticals, and United Biosource Corporation and received a stipend from the Movement Disorders Society for serving as medical editor of the Movement Disorders Society website. Dr Vitek has received research grant funding from the NINDS of the NIH, NeuroNexus, and Great Lake NeuroTech (doing business as Cleveland Medical); he has also received consulting fees from Medtronic, Boston Scientific, St Jude Medical, and Ceregene, along with an honorarium for speaking for Teva Neuroscience.


REFERENCES