A Method for Predicting the Outcomes of Combined Pharmacologic and Deep Brain Stimulation Therapy for Parkinson's Disease

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Abstract. Deep brain stimulation (DBS) is an established therapy for the management of advanced Parkinson's disease (PD). However, the coupled adjustment of pharmacologic therapy and stimulation parameter settings is a time-consuming process and treatment outcomes are not always optimal. In this study, we develop a linear function that relates the DBS parameters, the levodopa dosage, and patient-specific preoperative clinical data with the actual treatment motor outcomes. To this end, we incorporate image-based patient-specific computer models of the volume of tissue activated by DBS in a multi-linear regression analysis (6 PD patients; 60 follow up visits). The resulting predictor function was highly correlated with the actual motor outcomes ($r = 0.76$; $p<0.05$). These results demonstrate that the outcomes of a combined pharmacologic-DBS therapy can be predicted and may facilitate patient-specific treatment optimization for maximal benefits and minimal adverse effects.

1 Introduction

Deep brain stimulation (DBS) of the subthalamic region is an effective treatment for the motor symptoms of advanced Parkinson's disease (PD) [1, 2]. Following the surgery, the neurologist is faced with the challenge of balancing the patient's drug and stimulation treatments to maximize therapeutic benefit and minimize adverse effects. This complex process is currently driven by clinical experience and typically incorporates guidelines developed based on previous clinical studies [3]. However, treatment optimization often requires time-consuming follow-up visits with the patient because of the extremely large treatment parameter space [4]. Clinical decision support systems (CDSS) that incorporate patient-specific computer models to help customize DBS parameter settings to the patient have been developed in the past decade [5–7]. The first generation of commercial DBS CDSS are now available in Europe (e.g. Optivise by Medtronic (MN, USA) or GUIDE by Boston Scientific (MA, USA)).

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Table 1. Six advanced Parkinson's disease patients participated in this study (60 follow up office-visits). Age refers to the patient's age at time of DBS surgery. Unified Parkinson's disease rating scale, part III (UPDRS-III) preoperative scores are presented.

Patient #	Sex (M/F)	Age (years)	Follow up #visits	Follow up #months	Preoperative UPDRS-III off meds.
01	M	68	13	55	35
02	F	63	3	13	48
03	F	74	10	47	54
04	M	71	9	27	22
05	M	53	11	21	39
06	M	54	14	35	23

These current CDSS systems provide guidance regarding the electrical stimulation but ignore the pharmacology side of patient management. Therefore, we set out to define the foundation for a comprehensive CDSS that couples stimulation and medication.

2 Methods

In this study we develop a linear formula to predict treatment outcomes that combines the patient-specific PD symptoms, clinical history, levodopa equivalent daily dosage (LEDD), and the overlap between estimated volume of tissue activated (VTA) by DBS and a therapeutic target volume. The VTA was computed using standard techniques [6], with models that have been validated in monkey [8] and human [9] experiments. The target volume was defined via statistical mapping of therapeutic DBS VTAs [10], and validated in prospective clinical testing [7]. Our new formula is generated by a multi-linear regression analysis that best fits the above data with the actual outcomes using a linear weighted sum function. The advantage of using a weighted sum function in comparison to advanced machine learning (ML) methods is that it can be more simply interpreted by the target clinical users. The disadvantage is that the linear formula is probably less accurate than ML methods, which will be the focus of future investigations.

2.1 Patients and Data Extraction

Motor Symptoms

Six PD patients that underwent bilateral subthalamic DBS treatment were included in this study that was authorized and approved by the Institutional Review Board of the University Hospitals and Case Western Reserve University School of Medicine. The details of the patients are presented in Table 1. All patients met accepted selection criteria for DBS and signed informed consent for the surgery. The third subsection (motor score) of the unified PD rating scale [11] (UPDRS-III; range 0-108; the larger

the score, the symptoms are worsen) was assessed preoperatively both off (>12 hours) and on dopaminergic medication. Postoperatively, UPDRS-III was assessed at a total of 60 follow-up visits of the six patients, each visit under one of the following setups: 1) on-meds on-stimulation; 2) on-meds off-stimulation; 3) off-meds on-stimulation, or; 4) off-meds off-stimulation). The relative improvement of motor symptoms on-medication in the preoperative state, and on/off-medication on/off-stimulation in the postoperative state were defined as follows to avoid false correlations that may arise using the non-normalized UPDRS scores [12]:

$$100\times\frac{PRE_{off}-PRE_{on}}{PRE_{off}} \text{ and } 100\times\frac{PRE_{off}-POST_{comb}}{PRE_{off}}, \quad (1)$$

respectively, where PRE_{off}, PRE_{on}, *and* $POST_{comb}$ represent the UPDRS-III score preoperative off-medication, preoperative on-medication and a postoperative combination of on/off-medication and on/off-stimulation, respectively.

Pharmacological Information

Levodopa equivalent daily dosage (LEDD) was computed from each patient's medications records as suggested by Tomlinson et al. [13] and the relative change in LEDD was defined as follows.

$$100\times\frac{LEDD_{pre}-LEDD_{post}}{LEDD_{pre}} \quad (2)$$

Deep Brain Stimulation Information

To estimate the effect of DBS on the motor symptoms of PD, we incorporate a preferred therapeutic stimulation area, named here *target* zone (Fig. 1). The target zone was defined to cover most VTAs that were associated with effective DBS outcomes in an earlier study on a different set of patients and it is not limited to a specific anatomical structure [10]. The target zone is relative to the Harvard-Oxford brain atlas [14] with representation of the subthalamic nucleus [15]. The following protocol steps were followed for each patient to estimate the effect of DBS on patient's motor outcomes. 1) First, the anatomical atlas (with target volume) was registered to the patient's preoperative MRI (Fig. 1a); 2) a 3D geometrical model of the implanted electrode was fitted to its postoperative CT image counterpart; 3) the CT image was registered to the MRI and the 3D electrode model was transformed to MRI coordinates (Fig. 1a); 4) Then, for each DBS parameter setup that was tested and recorded postoperatively (n=60), a VTA was computed around the electrode (Figs. 1b and 1c) with a validated method that incorporates artificial neural network to model the spread of activation [16]; 5) Last, the volume of the overlap between the VTA and the target zone was computed, and its percentage from the total volume of the target was defined as follows to predict the effectiveness of stimulation.

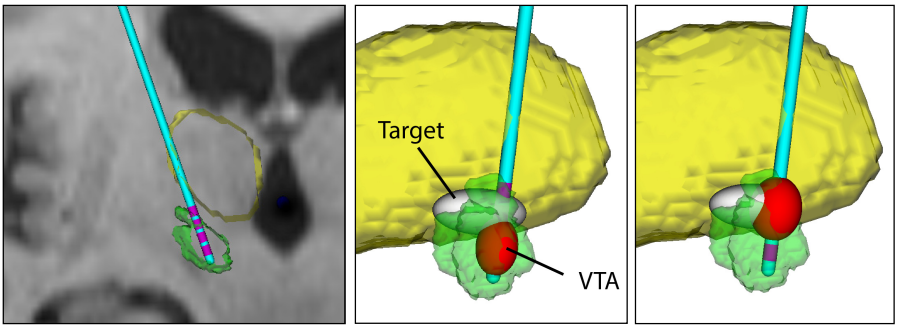

Fig. 1. Image based efficacy estimation of deep brain stimulation (DBS) treatment. Brain atlas was registered to the patient's MRI (a; the thalamus (yellow) and subthalamic nucleus (green) contours are presented). The electrode was identified on the postoperative CT image and transformed to MRI coordinates (a). Then, for each stimulation setup, volume of tissue activated (VTA, red) was computed and compared with a preferred therapeutic *target* area (grey). Our results show that stimulation setups that are associated with small overlap (b) are in general less effective in comparison to setups that yield large overlap (c).

$$100 \times \frac{|target\_zone \cap VTA|}{|target\_zone|} \tag{3}$$

where *target_zone* is the preferred stimulation area, *VTA* is the computed zone of tissue activated, and $|x|$ denotes the volume of x. Typical MRI size was 256x256x190 with voxel size of 1x1x1 mm^3. Typical CT image size was 512x512x40 with voxel size of 0.36x0.36x2.4 mm^3. Brain shift of < 3mm at the frontal area was an inclusive criterion for the subjects in this study and was assessed in CT images. 3D-Slicer [17] was used for the MRI-CT registration. Cicerone [18] was used for the atlas/MRI fitting, the 3D electrode-model fitting and computation of VTAs and their overlap with the target area.

2.2 Data Analysis

Correlations of candidate predictors and actual outcomes were computed. To compare specific symptom improvement, the UPDRS-III (motor) section was broken up into 5 composite symptom scores as follows: 1) Speech (section 18; max 4); 2) Tremor (sections 20–21; max 28); 3) Rigidity (section 22; max 20); 4) Limb bradykinesia (sections 23–26; max 32), and Axial bradykinesia (sections 19 and 27–31; max 24). The candidate predictors tested in this study are (Fig. 2, y-axis top-down): 1) patient's age at time of surgery; 2) number of months since surgery at the time of follow-up visit; 3) relative improvement in the preoperative on-medication UPDRS-III total- or sub-scores; 4) relative change in levodopa equivalent daily dosage, and; 5) mean overlap of VTA and target area over right and left hemispheres.

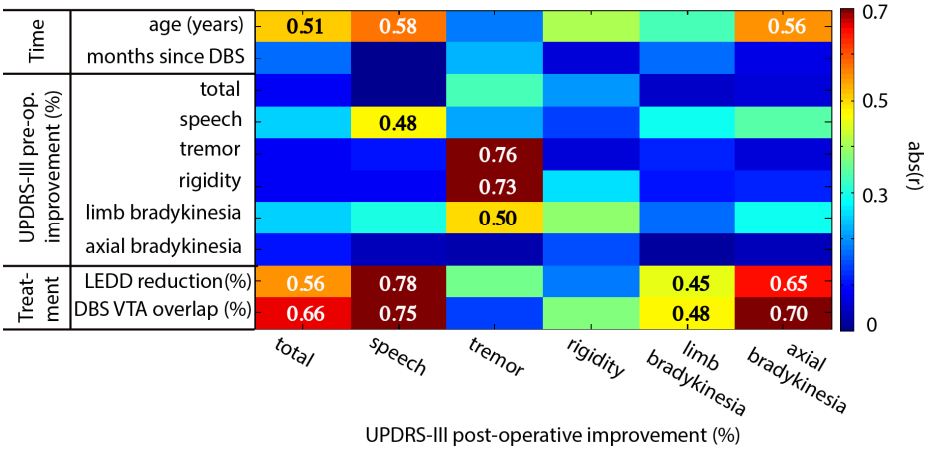

Fig. 2. Color-coded correlation table of post-operative DBS treatment outcomes (columns) and candidate predictors (rows). The predictors include time, preoperative motor relative improvement by levodopa, relative postoperative levodopa equivalent daily dosage (LEDD) reduction, and overlap of volume of tissue activated (VTA) with the preferred therapeutic area. The absolute values of the correlation coefficients were color-coded as illustrated in the bar to the right. The correlation numbers were added when the correlation was significant ($p<0.05$; after Bonferroni correction for multiple comparisons). It is demonstrated that the UPDRS-III total postoperative improvement is insignificantly correlated with the preoperative relative response to levodopa (leftmost column, third row). In contrast, LEDD reduction and VTA overlap are significantly correlated with the postoperative improvement of motor symptoms.

Disease duration was not considered because different subtypes of PD (e.g. tremor-dominant, postural-and-gait disorders, etc.) are associated with different disease progression [19]. The absolute correlation values were color-coded and augmented with specific values when the correlation was significant ($p<0.05$ after Bonferroni multiple comparison correction (MCC)) in order to present a comprehensive correlation map between possible predictors and actual outcomes (Fig. 2). Then, multi-linear regression analysis was conducted and regression coefficients were computed to best fit the predictors with actual outcomes using Matlab (version R2012b, by MathWorks Inc., Natick, MA, USA).

3 Results

Fig. 2 presents the measured correlations between predictors and actual outcomes for the UPDRS-III total- and sub-scores. The relative improvement in UPDRS-III total score was significantly correlated with relative changes in LEDD and overlap volume between VTA and target area (Fig. 2; $r = 0.56$ and 0.66, respectively, $p<0.05$, after MCC). Improvements in tremor with levodopa in the preoperative tests were significantly correlated with the postoperative relative improvement of tremor (Fig. 2; $r = 0.76$, $p<0.05$, after MCC).

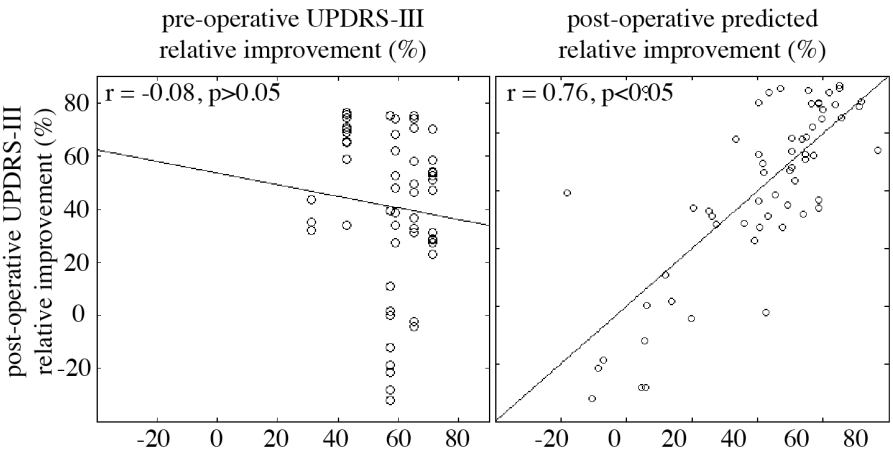

Fig. 3. Comparison of the commonly used pre-operative UPDRS-III (left) and the suggested linear formula (right; Eq. 4) as predictors for post-operative UPDRS-III measures of motor outcomes.

Interestingly, such correlation was not observed in the total UPDRS-III score (Fig. 3, left; the result was similar also when considering only the on-stimulation on-medication states). Our multi-linear regression analysis suggests that the expected postoperative relative improvement (%) of combined DBS-levodopa treatment for a given patient can be estimated as follows.

$$\text{UPDRS-III} \approx 0.99a - 0.69m - 0.09u + 0.30l + 1.02d - 28.2 \quad (4)$$

where, '*a*' denotes age at surgery, '*m*' denotes months since DBS surgery, '*u*' denotes the preoperative relative response to levodopa as measured with UPDRS-III, '*l*' denotes the postoperative relative change to LEDD values, and '*d*' denotes the overlap between VTA and target area as a result of DBS. A significant correlation (Fig. 3, right; $r = 0.76$, $p<0.05$, after MCC) was observed between the actual UPDRS-III scores and the values computed with the above equation. This correlation is higher than any other value observed for a single predictor (Fig. 2). The mean±SD (range) errors in prediction of relative improvement in UPDRS-III scores were 0±20% (-68 – 45 %).

4 Discussion

Our results show that the suggested linear combination of relative preoperative response to levodopa, relative change in LEDD, and VTA overlap with target zone are highly correlated with the actual motor outcomes, more than any other single measurement. Therefore, our novel predictor equation may assist in the selection of optimal combined pharmacological-DBS treatment setup for Parkinson's disease patients. This measure alone should not be considered as the expected outcome itself

since large differences between the prediction and actual outcomes were observed. Yet, its high correlation with the actual outcome suggests that it can assist with comparing various candidate treatment setups. Note that the computed formula represents the outcomes in our center and its validity should be further investigated incorporating data from other centers. A validation method, such as leave-one-out, was not conducted in this study since linear regression coefficients change very little with the exclusion of one dataset for testing. We do plan to incorporate this validation method in our extended study incorporating more patients and accurate machine learning methods. Another interesting and important observation is the lack of correlation between preoperative response to levodopa and DBS treatment outcome. Preoperative response to levodopa is typically a prerequisite indication for DBS. Our results support recent studies calling to revise this requirement [12], and suggesting that a subset of non-levodopa-responsive PD patients can still have significant benefits from DBS [20].

5 Conclusions

The formula proposed in this study represents a novel tool for incorporation into clinical decision support systems for the treatment of PD.

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