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Modeling Laterality of the Globus Pallidus Internus in Patients With Parkinson's Disease

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Introduction

When motor symptoms of Parkinson's disease (PD) become refractory to medication, neurosurgical interventions such as deep brain stimulation (DBS) of the globus pallidus internus (GPi) play a role, and provide significant therapeutic benefit to patients [1–5]. Precise targeting in such procedures is essential in the ultimate postoperative outcome [4, 6]. The GPi has been shown to be somatotopically organized [7]; moreover, within the GPi itself, electrode or lesion location has been shown to significantly affect postoperative therapeutic outcome [4, 8]. Therefore, millimetric changes in the location of the electrode can lead to suboptimal placement of electrodes, and thus suboptimal therapeutic benefit. This may in part have contributed to the lack of initial enthusiasm for pallidal DBS in the era of ventriculography prior to the advent of direct image-based stereotactic targeting.

When planning DBS surgery, an initial first target is often estimated using “indirect” atlas-based targeting, using coordinates relative to the anterior and posterior commissures (AC-PC) derived from the Schaltenbrand-Wahren atlas [9]. Indirect targeting alone has been shown to be an inadequate predictor of postoperative outcome [10]. A significant disadvantage of the Schaltenbrand-Wahren atlas, often used to localize the GPi in surgical procedures, is that all slices used to illustrate the basal ganglia were derived from only three patients, two of which were 40 years old and one of which was 51, and all of which were male [11]. Early studies have shown that there is substantial variation in subcortical structures such as the globus pallidus between patients [12]. Manual selection of AC-PC coordinates themselves has been shown to vary amongst neurosurgeons, and such intersurgeon variance has been shown to significantly affect planned GPi localization based

on indirect targeting [13]. Given such variability in targeting, it is generally accepted that direct targeting is superior to indirect targeting.

This report provides a systematic retrospective analysis of GPi lateralization; both radiographically targeted and neurophysiologically defined, in PD patients undergoing DBS surgery. The aim of this report is to highlight factors that may contribute to differences in GPi localization.

Methods

Clinical records of all patients who had undergone GPi DBS implantation for PD at UCLA between 2010 and 2015 were retrospectively reviewed. In all patients, the ventral posterolateral segment of the GPi was targeted to implant the DBS lead in the motor region of the GPi. Data extracted for each subject include age at time of implantation, gender, AC-PC distance, and third ventricular width (measured as the maximal third ventricular width on axial slices by a single investigator). Both radiographically planned AC-PC coordinates of the lead tip as well as final AC-PC coordinates of the final implanted lead tip were evaluated. The latter is influenced by preoperative radiographic target determination, but also intraoperative microelectrode recording (MER) findings and macrostimulation testing for both efficacy and side effects.

Planning MRI was acquired at 3T using 1 mm isotropic T1 and T2-weighted MR sequences, targeting the posterior ventrolateral region of the GPi, usually between 2 and 4 mm anterior to the mid-commissural point and approximately 2 mm anterolateral to the margin of the GPi with the posterior limb of the internal capsule. Stereotactic localization was performed based on intraoperative MRI and CT fusion using BrainLab [14]. In all cases, patients were awakened following craniotomy for intraoperative MER and neurophysiological testing to target the motor part of the GPi. Both preoperative targeting coordinates (radiographically defined target) and final lead tip position (clinically defined target) (Fig. 1) used in the analysis were those originally used for planning and in treatment, and thus were blind to the goals of this study.

Preoperative high-resolution T2-weighted noncontrast MRI in coronal (A) and axial (B) views of planned electrode location (red tracing). Dashed lines indicate that the tracing spans planes other than that shown.

The statistical software *R* was used to determine potential interactions between third ventricular width, age, gender, AC-PC distance on both the radiographically planned target and the final electrode position. A normalized multiple linear regression was performed with either planned target or final target separately as a function of third ventricular width, age, gender, and AC-PC distance. As there were no obvious nonlinear relationships seen, a linear multivariate regression model was chosen for ease of model interpretation and to reduce the risk of overfitting the model, as is a known pitfall of nonlinear models [15, 16]. The appropriateness of a linear model was further determined by analyzing the residuals (defined as the actual data subtracted by the regression line) of the model. The Kolmogorov–Smirnov test, which is commonly used to assess the goodness of fit of sample data to the normal

distribution, was applied to the residuals [17]. In the Kolmogorov–Smirnov test, an approximately normal distribution of the residuals about 0 indicates that the linear model is without systematic errors in representing the data, alleviating the need for a nonlinear model. A p -value of less than 0.05 rejects the null hypothesis of a normal distribution of the residuals, thus supporting the use of a nonlinear regression model.

Backward stepwise linear regression was performed to identify nonredundant predictors. The Akaike Information Criteria (AIC), which is a measure of goodness-of-fit model selection, was employed as the penalty term in the stepwise regression. In addition to the multiple linear regression, Pearson's correlation coefficient was used to individually determine the strength of linearity between the individual factors (age, gender, third ventricular width, and AC-PC distance) and either planned or final target. The relative importance of the selected predictors for GPi lateralization was quantified using the *lmg* in the *relimpo* package for *R* [18]. Additionally, adverse effect thresholds were analyzed against third ventricular width, age, gender, AC-PC distance via normalized multiple linear regression to determine if there were any significant correlations between threshold level and laterality or any of the variables.

The effect size for the relationship between GPi lateralization and all predictors was calculated by using a multiple linear regression of the predictors (ventricular width, age, AC-PC distance, gender) to determine coefficients in the model (mm shift/mm of ventricular width, mm shift/mm AC-PC distance, mm/year in age, and mm shift/gender). Ninety-five percent confidence intervals (CI) were calculated using two standard errors about the multiple linear regression coefficients.

Effect size was also calculated for individual predictors using a linear regression slope. The uncertainty of this estimator was approximated with bootstrap resampling. The data pairs (e.g.: age, radiographically targeted GPi lateral position) were resampled with replacement 10,000 times and the linear regression coefficients (y-intercept and slope) were recomputed for each bootstrap data set. The 2.5th and 97.5th percentile slope coefficients were used as the limits of the 95% CI.

Results

The charts and operative reports of 201 GPi implanted in 101 PD patients (70 males and 31 females, aged 11–78 years at time of operation) were retrospectively reviewed. Mean age for all patients was 62.01 ± 11.29 (mean $\pm$ standard deviation) years at time of operation. Third ventricular width ranged from 3.2 to 16.0 mm, with mean 7.1 ± 2.1 mm. AC-PC distance ranged from 22.62 to 33.98 mm, with mean 26.86 ± 1.79 mm. Radiographically planned GPi target ranged from 16.00 to 25.45 mm lateral to midline, with mean 20.13 ± 1.21 mm. Clinically defined GPi target ranged from 15.52 to 23.06, with mean 19.78 ± 1.37 mm lateral to midline.

Changes in Radiographically Defined GPi Lateralization

For radiographically defined target, multiple linear regression for target vs. third ventricular width, gender, AC-PC distance, and age were significant for normalized linear regression

coefficients of 0.333 ($p = 9.65 \times 10^{-7}$), 0.206 ($p = 0.00219$), 0.168 ($p = 0.0119$), and 0.159 ($p = 0.0136$), respectively. Third ventricular width was thus deemed the best predictor, followed by gender, AC-PC distance, and finally, age. As a whole, the model predicts the radiographically planned GPi target with an R^2 value of 0.357 ($R = 0.597$). The Kolmogorov–Smirnov normality test demonstrated the residuals approximately fit a normal distribution ($p = 0.462$), supporting the use of a linear instead of nonlinear regression model. AIC showed that the model is best with all four variables included. R -values for each variable individually were 0.506, 0.362, 0.400, and 0.292 for third ventricular width, gender, AC-PC distance, and age, respectively.

Changes in Clinically Defined GPi Lateralization

In the case of clinically defined GPi target, 64 patients representing 127 GPi had postoperative CT with spatial resolution high enough for electrode tip localization. Similar to radiographically defined target, multiple linear regression for target vs. third ventricular width, gender, AC-PC distance, and age were significant for a normalized linear regression coefficient of 0.232 ($p = 0.00965$) for third ventricular width, 0.217 ($p = 0.0117$) for gender, 0.185 ($p = 0.0380$) for AC-PC distance, and 0.179 ($p = 0.0345$) for age. Third ventricular width was again thus deemed the best predictor, followed by gender, AC-PC distance, and finally, age. As a whole, the model predicts final target with an R^2 value of 0.293 ($R = 0.542$). The Kolmogorov–Smirnov normality test had p -value 0.848, again demonstrating the appropriateness of a linear vs. nonlinear regression model. AIC showed that the model is best with all four predictors. R -values for each variable individually were 0.424 for third ventricular width, 0.335 for gender, 0.279 for age, and 0.395 for AC-PC distance.

Internal capsule stimulation side effects were additionally analyzed in conjunction with final clinically defined target. Internal capsular adverse effects in all patients included dysarthria, twitching, pulling sensation, tightness, heaviness, lip pursing, and coughing. Across all included patients, intraoperative voltage threshold necessary to induce an adverse effect ranged from 1.0 – 5.0 volts. Of note, internal capsule thresholds were between 1 and 2V in two subjects at the most ventral contact, but capsular thresholds were above 2V at more dorsal contacts with very low thresholds therapeutic benefits, prompting the decision to leave these leads in the original position. Intraoperative internal capsule threshold did not significantly correlate with age, AC-PC distance, third ventricular width, or gender, with normalized multiple linear regression coefficients of 0.102 ($p = 0.990$), 0.040 ($p = 0.183$), -0.116 ($p = 0.546$), and 0.274 ($p = 0.140$), respectively. Finally, the threshold did not vary with the measured laterality, with a normalized multiple linear coefficient of -0.195 ($p = 0.293$).

Finally, to further estimate targeting accuracy, the error between the laterality of the radiographically and clinically defined target was evaluated to better determine how precise and accurate targeting was and if there was a systematic shift between the intended target and final lead tip localization. Mean difference in clinically defined and radiographically defined target laterality (clinically defined minus radiographically defined) was -0.044 mm (-1.90 mm to 1.81 mm, 95% CI).

Relative Importance of Predictors of GPi Lateralization

Analysis of the relative importance of the predictors on radiographic GPi lateralization can be quantified by the proportion of the normalized multiple linear regression model R^2 -squared ($R^2 = 0.357$) accounted for by each predictor. Third ventricle width, gender, AC-PC distance, and age each account for 44.06% (21.38–65.69%, 95% CI), 20.82% (10.51–35.88%), 21.46% (8.28–37.05%), and 13.66% (2.62–28.64%) of the R^2 value, respectively (Fig. 2). While the third ventricle width accounts for the most variation in radiographic GPi lateralization in the model, other predictors still account for a significant portion.

Relative importance of regressors analysis for the predictors of radiographic GPi lateralization. The vertical axis contains the percent of the multiple linear regression model R^2 value accounted for by each predictor and the horizontal axis contains the predictors. Vertical bars depict the 95% confidence intervals.

Effect Size of Predictors on Radiographic GPi Lateralization

Multiple linear regression analysis yielded regression coefficients for third ventricular width (mm lateral shift/mm width), gender (mm lateral shift/gender [x1 if male, x0 if female]), AC-PC distance (mm lateral shift/mm anteroposterior distance), and age (mm lateral shift/year in age). Regression coefficients with 95% CI, as well as levels of significance, are displayed in Table 1. Regression coefficients can be used together to result in the following equation to predict laterality of radiographic GPi target based on all predictors:

Given that each factor in question was a nonredundant predictor of radiographic GPi lateral position, we also measured the effect size as the slope of the linear regression analysis between the each variable individually and radiographic target (mm/year for age, mm/mm for ventricular width and AC-PC distance, and finally, mm by gender). This revealed a GPi lateral shift of 0.02882 mm shift/mm ventricular width (0.01988, 0.03686 mm/mm 95% CI), 0.2689 mm shift/mm AC-PC distance (0.1674, 0.3735 mm/mm 95% CI), and 0.03117 mm shift/year in age (0.01113, 0.04949 mm/year 95% CI). We calculated effect size for gender as the difference in mean GPi laterality between males (20.423 mm [20.239, 20.623 mm 95% CI]) and females (19.480 mm [19.204, 19.740 mm 95% CI]), difference of which was significant ($p < 1.0 \times 10^{-5}$), and resulting in an effect size of 0.9429 (0.6199, 1.277 95% CI) mm-lateral shift in males relative to females.

Discussion

This model highlights factors that may contribute to differences in GPi localization and that surgeons might consider, similar to thalamic targets which are modified based on third ventricular width. Such variation of the GPi DBS target is consistent with prior findings with other nearby structures such as the subthalamic nucleus, where lateralization with age [19–23], third ventricular width [21–23] and with male gender [21, 22] have been previously identified. These factors, which are readily available to the neurosurgeon following preoperative imaging, have been used in previous work in the subthalamic nucleus [23] to predict laterality.

Previous research has shown a greater GPi laterality in PD patients when compared to that of dystonia patients, both in preoperative imaging and in postoperative DBS lead location [4]. This can be interpreted to be due to a higher average age among PD patients relative to dystonia patients, which contributes to age-related atrophy [24]. Consistent with this, the width of the third ventricle in PD patients is greater than that of dystonia patients. Thus, the observed increase in laterality with age may be due to an ex vacuo shift, which is also consistent with a secondary expansion of the third ventricle.

Outcomes following GPi DBS are significantly correlated with the precise anatomical lead position [4, 6, 25, 26]. Accordingly, direct visualization of target under MRI with adjunctive MER and/or macrostimulation testing have largely supplanted indirect targeting alone. In this series, the final electrode tip position is influenced not only by preoperative radiographic targeting and physiological identification of GPi (i.e., MER and macrostimulation testing), but also by the intent of minimizing stimulation-related adverse effects, and intraoperative brain shift due to pneumocephalus [27–29]. It is these additional factors, along with the lesser number of patients available with postoperative CT, that likely in part account for the decreased correlation coefficient between the model and final electrode tip position relative to that seen between radiographic target and the model.

In this retrospective study, GPi DBS electrode tip is used as a surrogate for GPi localization. The lack of result stratification by clinical outcomes may limit the interpretation of this study. Nevertheless, we believe electrode location to be a fair estimate of GPi location given the consistent clinical targeting throughout the study period. Large-scale multicenter studies have demonstrated the efficacy of GPi DBS across large groups [1, 5], suggesting that intersubject variability will be compensated for at a group level. Moreover, we additionally analyzed thresholds for internal capsular stimulation adverse effects, which showed that the laterality of the final lead position did not change the average level of stimulation required to elicit capsular side effects, further arguing that the leads were targeted similarly within the motor region of the GPi across subjects. Finally, no systematic shift was detected between the laterality of the clinically and radiographically defined target, suggesting both precise and accurate targeting. A future, more definitive study may be prospective in nature, taking into account outcome with respect to UPDRS-III reduction, but the current findings provide the first comprehensive analysis to date to provide any insight with respect to this issue. Despite this limitation, the consistency of results across both radiographic and clinical guidance argues strongly for true relationships between the predictors—age, third ventricular width, AC-PC distance, and gender—and GPi laterality.

Conclusion

The current results suggest that GPi position shifts laterally with age, male gender, third ventricular width, and AC-PC distance, based on both radiographic and physiologically guided DBS placements. This variability highlights the limitations of indirect targeting alone, and argues for the continued use of patient-specific guidance, using techniques such as MRI or intraoperative physiological testing to account for such factors that contribute to patient-specific variability in GPi localization.

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Figure 1. Preoperative high-resolution T2-weighted noncontrast MRI in coronal (A) and axial (B) views of planned electrode location (red tracing). Dashed lines indicate that the tracing spans planes other than that shown.

Figure 2.

Relative importance of regressors analysis for the predictors of radiographic GPi lateralization. The vertical axis contains the percent of the multiple linear regression model R^2 value accounted for by each predictor and the horizontal axis contains the predictors. Vertical bars depict the 95% confidence intervals.

Table 1

Predictor Effect Sizes.

Parameter	Coefficient	95% CI	p-value
1. Effect size calculated by multiple linear regression analysis for third ventricular width, gender, AC-PC distance, and age. Y-intercept additionally depicted in the first row.			
Intercept (mm)	14.33	(12.15, 16.50)	$<1 \times 10^{-15}$
Ventricular Width (mm)	0.19	(0.11, 0.26)	$<1 \times 10^{-6}$
Gender (Female = 0, Male = 1)	0.54	(0.19, 0.88)	0.0022
AC-PC distance (mm)	0.11	0.024, 0.21)	0.012
Age (years)	0.017	(0.0033, 0.031)	0.014

GPI laterality in mm = 14.33 mm + Ventricular Width in mm (0.19) + AC-PC Distance in mm (0.11) + Age in years (0.017) + 0.54 mm if Male Gender