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Lateralization of the Subthalamic Nucleus with Age in Parkinson's Disease

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Abstract

Age-related changes in subthalamic nucleus (STN) position have not been well characterized in patients with Parkinson's disease (PD). We report a systematic retrospective analysis of age-related changes in radiographic and final deep brain stimulator (DBS) STN coordinates in PD patients. The charts of 134 PD patients (97 males, 28–84 years) representing 255 STN were reviewed. Multiple linear regression, stepwise regression, and relative importance of regressors analysis was performed to determine the significance of the relationship between STN position and age. Across all subjects, both radiographic STN localization and final DBS position within the STN showed a lateralization of the STN target with age ($R^2=0.1096, p=6.9 \times 10^{-8}$ and $R^2=0.0433, p=8.7 \times 10^{-4}$, respectively). Lateralization with age was observed regardless of MR field strength (1.5T and 3.0T) ($R^2=0.0946, p=7.6 \times 10^{-6}$ and $R^2=0.2687, p=9.2 \times 10^{-5}$, respectively). No other consistent or clinically significant age-related changes were identified. Multiple linear regression revealed that the third ventricle width and age are statistically significant predictors of radiographic STN lateralization ($R^2 = 0.2404$, $p = 1.51 \times 10^{-5}$ and $p = .00784$ respectively). Stepwise regression demonstrated that age is a non-redundant predictor of STN lateralization relative to third ventricle width. Similar to healthy controls, STN position appears to shift laterally with age in PD. This highlights limitations of indirect targeting and atlas-based stereotactic surgery and argues for reliance on patient specific anatomy since factors such as age and 3rd ventricular width can contribute to patient-specific variability in STN localization.

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Keywords

deep brain stimulation; Subthalamic nucleus; targeting; Parkinson's disease

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INTRODUCTION

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) provides significant benefit with respect to management of the motor symptoms of advanced Parkinson's disease (PD) [1–8]. Given its small size and proximity to other critical subcortical structures, precise targeting is essential and is a cornerstone of stereotactic neurosurgery [4,9]. While each surgeon has slight variations in targeting methodology, a common first step is “indirect targeting,” in which standardized coordinates relative to the anterior and posterior commissures (AC-PC) are applied to the individual patient.

The limitations of indirect targeting are well recognized, the most important of which is that the atlases from which these coordinates are derived are based on a limited number of non-representative subjects. Nowinski and colleagues have characterized the probability distribution of optimal STN stimulation relative to AC-PC, demonstrating significant variability across subjects [10]. Patil and colleagues also described the variability in STN dimensions and reported that the Schaltenbrand-Wahren (SW) atlas [11], the most commonly used atlas of the human basal ganglia for neurosurgical procedures [12], is a poor predictor of the amount of STN traversed during intraoperative microelectrode recordings (MER) [13]. While additional steps are often used to improve localization, such as direct target visualization on MRI, MER, and intraoperative testing, it is important to recognize factors that may affect target position in order to improve the efficiency, efficacy and potentially the safety of stereotactic surgery.

Age-related changes in brain morphology are inherently unaccounted for in brain atlases such as the SW atlas [14–15]. The effect of age specifically on STN position remains undercharacterized, particularly in PD patients. While some have described a lateral shift of STN with age in postmortem and high-field magnetic resonance imaging (MRI) studies in non-PD subjects, others have failed to identify such age-related changes [16–19].

In order to provide better insight into age-related changes in STN position in PD, we report a systematic retrospective analysis of radiographic targeting coordinates and final DBS STN coordinates in PD patients undergoing DBS surgery.

MATERIALS AND METHODS

Clinical records were retrospectively reviewed to identify all patients who had undergone STN DBS implantation for PD at UCLA between 1999 and 2013. Of the patients identified, clinical data extracted included age at time of imaging and implantation, MR field strength for imaging, radiographically planned AC-PC coordinates, and AC-PC coordinates of the electrode tip (target) which is influenced by a combination of preoperative radiographic target determination, intraoperative MER findings, as well as macrostimulation testing for both efficacy and side effects. The AC-PC coordinates of the final electrode tip position

were used as a surrogate of “clinically-defined STN”, understanding that multiple factors may influence this final positions but that it should reflect a conglomerate of data that guides clinical definition of STN [20]. This study was approved by the institutional review board.

Surgical technique evolved over time. Between 1999 and 2007, planning MRI were acquired at 1.5T and stereotactic localization was performed based on CT fusion using BrainLab software [21–22]. Between 2007 and 2008, 1.5T MRI-guided implants were performed without CT fusion [23]. Between 2008 and 2013, planning MRI were acquired at 3T and stereotactic localization was performed based on intraoperative CT fusion using BrainLab [23]. Radiographic targeting aiming to traverse the dorsolateral STN and terminate in the ventromedial STN. MER and macrostimulation testing was performed in a similar manner throughout the entire period. Targeting coordinates used for analysis were those originally used for planning and therefore were blind of this study’s goals.

To evaluate the relationships of AC-PC coordinates relative to age, X, Y, and Z positions were linearly regressed against age and evaluated with Pearson’s correlation. To evaluate the effect of MR field strength, subanalyses were performed for subjects imaged and implanted at low field (1.5T) and high field (3T). Tests were conducted using Bonferroni adjusted alpha levels of .004 (.05/12).

The statistical software *R* was used to determine potential interactions between third ventricular width and age on predicting STN lateralization (X coordinate). A multiple linear regression was performed as a function of age, third ventricle width, radiographic Y, Z position, and target Y, Z position. The maximal model was subject to backward stepwise linear regression to identify the non-redundant predictors. The Akaike Information Criteria (AIC), a measure of goodness-of-fit in model selection, was used as the penalty term in the stepwise regression. AIC penalizes for adding additional parameters, discouraging overfitting. Given the set of candidate models, the preferred model had the minimum AIC value. The relative importance of the selected predictors for STN lateralization was quantified using the *lmg* in the *relimpo* package for *R* [24].

The effect size for the relationship between STN lateralization and age was calculated using the linear regression slope (mm/year). The uncertainty of this estimator was approximated with bootstrap resampling. The data pairs (planned STN lateral position, age) 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% confidence interval.

RESULTS

The charts and operative reports of 134 PD patients (97 males and 37 females, 28–84 years) representing 255 STN were retrospectively reviewed. Ranges and average STN coordinates for both radiographic and physiologic targeting are provided in table 1.

Age-related changes in STN based on radiographic measures

Across all subjects, radiographic targeting of the STN revealed a lateralization of the STN target with age ($R^2=0.1096, p=6.9 \times 10^{-8}$). While a statistically significant posterior shift of the STN target was identified with age ($R^2=0.0433, p=8.7 \times 10^{-4}$, Figure 1), this is likely physiologically and clinically insignificant given the submillimetric effect. Sub-analyses of STN targets at 1.5T also revealed lateralization and a posterior shift of the STN target with age ($R^2=0.0946, p=7.6 \times 10^{-6}$ and $R^2=0.0620, p=3.2 \times 10^{-4}$, retrospectively)(Figure 1). However, subanalysis of 3T radiographic targets only revealed a lateralization of the STN target with age ($R^2=0.2687, p=9.3 \times 10^{-5}$) without a concomitant posterior shift of the STN target with age ($R^2=0.0005, p=0.87$)(Figure 1). No relationships between age and the superior-inferior location of STN relative to AC-PC were identified (Figure 1).

Age-related changes in clinically-defined STN position

Across all subjects, the laterality of the final DBS lead position was significantly correlated with age ($R^2=0.038, p=0.0018$)(Figure 1). The R-squared, which provides an estimate of the proportion of total variation of outcomes explained by the model, is notably lower than that reported for radiographic measures but is still significant. No correlation, however, was identified between the anterior/posterior and superior/inferior position of the final electrode tip in STN relative to age (Figure 1).

Predictors of radiographic measured STN lateralization

To determine if the variation in STN lateralization explained by age was independent of related factors such as third ventricular width, multivariate analysis was performed. Across all subjects, the laterality of the radiographic STN position was significantly predicted by third ventricle width and age ($R^2=0.2404$; $p=1.51 \times 10^{-5}$ and $p=7.84 \times 10^{-3}$, respectively) with normalized multiple regression coefficients of 0.3226 and 0.1904, respectively, indicating that the third ventricle width is a relatively stronger predictor than age. The collinearity of the predictors, to account for predictor redundancy, was quantified with a backward stepwise linear regression. The original maximal model predictors (third ventricle width, age, anterior-posterior radiographic position, anterior-posterior target position, superior-inferior radiographic position, superior-inferior target position) were reduced to the third ventricle width, age, and anterior-posterior radiographic position to minimize the AIC criteria. However, only third ventricle width and age were statistically predictive of radiographic STN lateralization. Thus, age provides additional information about radiographic STN lateralization not accounted for by the third ventricle width.

Relative importance of predictors of STN lateralization

Analysis of the relative importance of the predictors on radiographic STN lateralization can be quantified by the proportion of the multiple linear regression model R-squared ($R^2=0.2404$) accounted for by each predictor. The two statistically significant predictors, third ventricle width and age, account for 55.25% (32.26–70.27%, 95% C.I.) and 30.60% (11.79–50.27%, 95% C.I.) of the R^2 value, respectively (Figure 2). While the third ventricle width accounts for the most variation in radiographic STN lateralization in the model, age still accounts for a significant portion.

The effect size of age on STN target lateralization

Given that age is an independent predictor of radiographic STN lateral position we measured the effect size as the slope of the linear regression analysis between the two variables (mm/year). This revealed an STN lateral shift of 0.03526 mm/year (0.0235, 0.0470 mm/year 95% C.I.). The linear regression analysis between the radiographic STN lateral position and age, along with the 95% C.I. regression lines, are illustrated in Figure 3.

DISCUSSION

Despite the common use of STN DBS for PD management, questions remain regarding age-related changes in the location of this important subcortical target [16–19, 25–26]. The current results suggest age, at least in part, contributes to relative STN position in patients with PD, based on both radiographic targeting as well as final DBS lead position guided by integration of multiple factors including radiographic and intraoperative physiological testing. The relationship between the laterality of STN and age based on radiographic targeting was identified regardless of field strength of the MRI (1.5T and 3T), consistent with a recent report using high-field 7T imaging in normal subjects [18]. Defining the potential effects of age on STN position is important for understanding how brain anatomy can change with age but also the validity of indirect targeting for DBS targeting.

Den Dunnen and Staal evaluated STN position in 12 postmortem brains (age 29–85), finding that the STN not only changes its shape with age but also its position, with a more superior, anterior, and lateral position with increasing age [16]. However, this directly contrasts with a high resolution 9.4T MR and histologic study by Massey et al. who showed no consistent age-related changes in the position of STN in 8 postmortem brains (age 38–95) [19]. More recently, Keuken and colleagues analyzed the STN with 7T MRI in 31 healthy subjects, avoiding potentially confounding postmortem changes in brain shape, again reporting a lateral displacement of the STN with age [18].

Etiologically, such a lateral shift could happen either due to changes in the intrinsic anatomy of the STN or external factors such as enlargement of the third ventricle or due to loss of tissue lateral to the STN that results in ex vacuo shift of the nucleus laterally (which can also cause secondary expansion of the third ventricle). Both Daniluk and colleagues and Keuken and colleagues described a direct relationship between STN laterality and the width of the third ventricle [17–18]. In their multifactorial analysis, Keuken and colleagues found that the lateral shift of STN can entirely be accounted for by age without significant contribution from third ventricular width. The multivariate analysis presented here goes further to suggest that although third ventricular width is a relatively stronger predictor, age does portend additional predictability of STN laterality unaccounted for by its potential effect on ventricular width. Such a lateral shift could be due to loss of tissue lateral to the STN, namely the internal capsule [27–28]. Using voxel based analyses, Kim and colleagues demonstrated diffuse deficits in the whole corticofugal tract, including the internal capsule, in PD patients relative to age-matched control [27]. Given these prior results in conjunction with the results of our multivariate analysis, we propose that this positional change may also be influenced by alterations in the anatomy of structures lateral to the STN, such as the internal capsule and other components of the basal ganglia, which may have varying effects

on third ventricular width enlargement and STN disposition. A future study using diffusion-weighted imaging to allow for investigation of changes in white matter tissue (e.g. the internal capsule [29]) may be done to evaluate for such explanation of lateral shift of the STN with age.

In addition to these anatomical factors, one must consider intrinsic factors that may alter imaging characteristics as well. While the variability of STN across patients is well described [16–18, 25–26, 30–33], imaging characteristics of the STN may also change with age and this may be a contributing factor as well. On T2 weighted imaging, iron deposition accounts for the hypointensity of the STN seen on MRI. The posterior half of the nucleus is less heavily laden with iron and therefore less readily visualized on MRI [34]. The observed lateralization of the STN with age may be attributed in part to increasing iron deposition within the lateral STN with increasing age [12]. Given the potential of this factor however, Aquino and colleagues have previously showed that the level of iron deposition in the STN stabilizes at the age of twenty-five [35], mitigating this potential confounding effect in our cohort of patients aged 28 – 84 years. Furthermore, the consistency of the results across both radiographic targeting as well as clinically defined STN suggests that a potential increase in iron deposition alone cannot explain the lateralization of STN with age. Second, image distortion of MRI may also present a potential confound. While consideration can be given to potential image distortion effects at high field however, such distortion has been shown to be relatively minimal in the basal ganglia, even at 7T [36].

There are limitations inherent in this retrospective analysis, some of which may merit further exploration but none of which would negate the final interpretation of the current analysis although could provide better insight into the etiology of the observed effects. In this study, we use the STN DBS target as a surrogate for STN localization, but believe it a fair estimate of STN position given the consistent clinical targeting throughout the study period and the assumption that the DBS STN target should shift and correlate with the overall STN position. While we do not include or stratify results by clinical outcomes (due to lack of comprehensive quantified outcomes across this patient pool), large scale multi-center studies demonstrate the efficacy of STN DBS across large groups, suggesting inter-subject variability in the accuracy of STN localization is compensated for at the group level. [7,8]. We recognize that final electrode tip position is influenced not only by preoperative radiographic targeting and physiological identification of STN (i.e., MER and macrostimulation testing), but also by the intent of minimizing stimulation-related adverse effects. These additional factors likely in part account for the decreased correlation coefficient between age and final electrode tip position relative to that seen between radiographic target and age. Future analyses should evaluate optimal STN stimulation site (i.e., contact) and age to further incorporate clinical outcomes into assessment. Moreover, further detailed analysis of MER-confirmed length of STN relative to age would provide further insight into age-related changes in STN. Unfortunately, due to the retrospective nature of this dataset, this information is not available for the current analysis. Despite these inherent limitations, the consistency of results with regards to lateralization across imaging field strengths and based on both radiographic and clinical guidance argues strongly for a true relationship between age and laterality.

CONCLUSIONS

Similar to healthy controls, STN position appears to shift laterally with age in PD, based on both radiographic and physiologically-guided DBS placement. This highlights limitations of indirect targeting and atlas-based stereotactic surgery and argues for using patient-specific anatomy as visualized on individual MRI since factors such as age and 3rd ventricular width can contribute to patient-specific variability in STN localization.

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References

1. Lozano AM, Lipsman N. Probing and regulating dysfunctional circuits using deep brain stimulation. *Neuron*. 2013; 77(3):406–424. [PubMed: 23395370]
2. Miocinovic S, Somayajula S, Chitnis S, Vitek JL. History, applications, and mechanisms of deep brain stimulation. *JAMA Neurol*. 2013; 70(2):163–171. [PubMed: 23407652]
3. Rodriguez-Oroz MC, Obeso JA, Lang AE, et al. Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. *Brain*. 2005; 128(Pt 10):2240–2249. [PubMed: 15975946]
4. Benabid AL, Koudsie A, Benazzouz A, Le Bas JF, Pollak P. Imaging of subthalamic nucleus and ventralis intermedius of the thalamus. *Mov Disord*. 2002; 17(Suppl 3):S123–129. [PubMed: 11948766]
5. Limousin P, et al. Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet*. 1995; 345:91–95. [PubMed: 7815888]
6. Limousin P, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med*. 1998; 339:1105–1111. [PubMed: 9770557]
7. Deuschl G, Schade-brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med*. 2006; 355(9):896–908. [PubMed: 16943402]
8. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA*. 2009; 301(1):63–73. [PubMed: 19126811]
9. Voges J, Volkmann J, Allert N, et al. Bilateral high-frequency stimulation in the subthalamic nucleus for the treatment of Parkinson disease: correlation of therapeutic effect with anatomical electrode position. *J Neurosurg*. 2002; 96(2):269–279. [PubMed: 11838801]
10. Nowinski WL, Thirunavuukarasuu A, Liu J, Benabid AL. Correlation between the anatomical and functional human subthalamic nucleus. *Stereotact Funct Neurosurg*. 2007; 85(2–3):88–93. [PubMed: 17167237]
11. Schaltenbrand, G.; Wahren, W. *Atlas for Stereotaxy of the Human Brain*. 2. Stuttgart: Georg Thieme; 1977.
12. Dormont D, et al. Is the subthalamic nucleus hypointense on T2-weighted images? A correlation study using MR imaging and stereotactic atlas data. *AJNR Am J Neuroradiol*. 2004; 25:1516–1523. [PubMed: 15502130]
13. Patil PG, Conrad EC, Aldridge JW, Chenevert TL, Chou KL. The anatomical and electrophysiological subthalamic nucleus visualized by 3-T magnetic resonance imaging. *Neurosurgery*. 2012; 71(6):1089–1095. discussion 1095. [PubMed: 22948201]
14. Meunier D, Achard S, Morcom A, Bullmore E. Age-related changes in modular organization of human brain functional networks. *Neuroimage*. 2009; 44(3):715–723. [PubMed: 19027073]
15. Meunier D, Stamatakis EA, Tyler LK. Age-related functional reorganization, structural changes, and preserved cognition. *Neurobiol Aging*. 2013

16. den Dunnen WF, Staal MJ. Anatomical alterations of the subthalamic nucleus in relation to age: a postmortem study. *Mov Disord.* 2005; 20(7):893–898. [PubMed: 15809991]
17. Daniluk S, K GD, Ellias SA, Novak P, Nazzaro JM. Assessment of the variability in the anatomical position and size of the subthalamic nucleus among patients with advanced Parkinson's disease using magnetic resonance imaging. *Acta Neurochir (Wien).* 2010; 152(2):201–210. discussion 210. [PubMed: 19806309]
18. Keuken MC, Bazin PL, Schafer A, Neumann J, Turner R, Forstmann BU. Ultra-high 7T MRI of structural age-related changes of the subthalamic nucleus. *J Neurosci.* 2013; 33(11):4896–4900. [PubMed: 23486960]
19. Massey LA, Miranda MA, Zrinzo L, et al. High resolution MR anatomy of the subthalamic nucleus: imaging at 9.4 T with histological validation. *Neuroimage.* 2012; 59(3):2035–2044. [PubMed: 22036997]
20. Wodarg F, et al. Stimulation site within the MRI-defined STN predicts postoperative motor outcome. *Mov Disord.* 2012; 27:874–879. [PubMed: 22517070]
21. De Salles AA, Frighetto L, Behnke E, et al. Functional neurosurgery in the MRI environment. *Minim Invasive Neurosurg.* 2004; 47(5):284–289. [PubMed: 15578341]
22. Lee MW, De Salles AA, Frighetto L, Torres R, Behnke E, Bronstein JM. Deep brain stimulation in intraoperative MRI environment – comparison of imaging techniques and electrode fixation methods. *Minim Invasive Neurosurg.* 2005; 48(1):1–6. [PubMed: 15747209]
23. Pezeshkian P, DeSalles AA, Gorgulho A, Behnke E, McArthur D, Bari A. Accuracy of frame-based stereotactic magnetic resonance imaging vs frame-based stereotactic head computed tomography fused with recent magnetic resonance imaging for postimplantation deep brain stimulator lead localization. *Neurosurgery.* 2011; 69(6):1299–1306. [PubMed: 21725253]
24. Grömping, Ulrike. Relative Importance for Linear Regression in R: The Package relaimpo. *Journal of Statistical Software.* 2006; 17(1):1–27.
25. Ashkan K, et al. Variability of the subthalamic nucleus: the case for direct MRI guided targeting. *Br J Neurosurg.* 2007; 21:197–200. [PubMed: 17453788]
26. Patel NK, Khan S, Gill SS. Comparison of atlas- and magnetic-resonance-imaging-based stereotactic targeting of the subthalamic nucleus in the surgical treatment of Parkinson's disease. *Stereotactic and Functional Neurosurgery.* 2008; 86:153–161. [PubMed: 18334857]
27. Kim HJ, Kim SJ, Kim HS, et al. Alterations of mean diffusivity in brain white matter and deep gray matter in Parkinson's disease. *Neurosci Lett.* 2013; 550:64–68. [PubMed: 23831353]
28. Pal D, Trivedi R, Saksena S, et al. Quantification of age- and gender-related changes in diffusion tensor imaging indices in deep grey matter of the normal human brain. *J Clin Neurosci.* 2011; 18(2):193–196. [PubMed: 21183352]
29. Kawaguchi H, Obata T, Ota M, Akine Y, Ito H, Ikehira H, Kanno I, Suhara T. Regional heterogeneity and age-related change in sub-regions of internal capsule evaluated by diffusion tensor imaging. *Brain Res.* 2010; 1354:30–39. [PubMed: 20682306]
30. Richter EO, Hoque T, Halliday W, Lozano AM, Saint-Cyr JA. Determining the position and size of the subthalamic nucleus based on magnetic resonance imaging results in patients with advanced Parkinson disease. *J Neurosurg.* 2004; 100:541–546. [PubMed: 15035292]
31. Schlaier J, Schoedel P, Lange M, Winkler J, Wernat J, Dorenbeck U, Brawanski A. Reliability of atlas-derived coordinates in deep brain stimulation. *Acta Neurochir (Wien).* 2005; 147:1175–1180. discussion 1180. [PubMed: 16133776]
32. Zhu XL, Hamel W, Schrader B, Weinert D, Hedderich J, Herzog J, Volkmann J, Deuschl G, Muller D, Mehdorn HM. Magnetic resonance imaging-based morphometry and landmark correlation of basal ganglia nuclei. *Acta Neurochir (Wien).* 2002; 144:959–969. discussion 968–959. [PubMed: 12382123]
33. Kitajima M, Korogi Y, Kakeda S, Moriya J, Ohnari N, Sato T, Hayashida Y, Hirai T, Okuda T, Yamashita Y. Human subthalamic nucleus: evaluation with high-resolution MR imaging at 3.0 T. *Neuroradiology.* 2008; 50:675–681. [PubMed: 18443775]
34. Lambert C, et al. Confirmation of functional zones within the human subthalamic nucleus: patterns of connectivity and sub-parcellation using diffusion weighted imaging. *NeuroImage.* 2012; 60:83–94. [PubMed: 22173294]

35. Aquino D, Bizzi A, Grisoli M, Garavaglia B, Bruzzone MG, Nardocci N, Savoiardo M, Chiapparini L. Age-related iron deposition in the basal ganglia: quantitative analysis in healthy subjects. *Radiology*. 2009; 252:165–172. [PubMed: 19561255]
36. Duchin Y, Abosch A, Yacoub E, Sapiro G, Harel N. Feasibility of using ultra-high field (7 T) MRI for clinical surgical targeting. *PLoS One*. 2012; 7(5):e37328. [PubMed: 22615980]

Figure 1.

Scatter plots of STN location (x-first column, y-second column, z-third column) relative to age. Separate plots for radiographic targeting (first row), subanalysis of 1.5T targeting (second row), subanalysis of 3T targeting (third row), and physiologically-guided targeting (fourth row).

Figure 2.

Relative importance of regressors analysis for the predictors of radiographic STN 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. The vertical bars depict the 95% confidence intervals. (AP: anterior-posterior, SI: superior-inferior)

Linear Regression of Radiographic STN Lateral Position and Age

Figure 3.

Scatter plot of radiographic STN lateralization and age. Red line: linear regression model of radiographic STN lateralization as a function of age (Intercept = 8.58197, Slope= 0.03526 mm/year). Black lines: 95% confidence interval linear regression lines (Intercept: (7.846, 9.342), Slope:(0.0235, 0.0470)).

Table 1

Range and average X, Y, and Z coordinates for radiographically and physiologically-defined STN DBS targets relative to the midcommisural point (MCP). All measures are in mm.

	Radiographic Minimum	Radiographic Maximum	Radiographic Average $\pm$ SD	Physiologically Guided Minimum	Physiologically Guided Maximum	Physiologic Guided Average $\pm$ SD
X	7.8	14.2	10.7 $\pm$ 1.0	5.0	14.1	10.3 $\pm$ 1.5
Y	-6.5	-0.5	-3.3 $\pm$ 0.9	-10.6	1.4	-3.1 $\pm$ 1.7
Z	-8.7	4.0	-6.6 $\pm$ 0.8	-14	0	-6.5 $\pm$ 2.1