Subthalamic Nucleus Visualization on Routine Clinical Preoperative MRI Scans: A Retrospective Study of Clinical and Image Characteristics Predicting Its Visualization

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Keywords

Parkinson disease · Deep brain stimulation · Subthalamic nucleus · Magnetic resonance imaging · Visualization

Abstract

Background: The visualization of the subthalamic nucleus (STN) on magnetic resonance imaging (MRI) is variable. Studies of the contribution of patient-related factors and intrinsic brain volumetrics to STN visualization have not been reported previously. **Objective:** To assess the visualization of the STN during deep brain stimulation (DBS) surgery in a clinical setting. **Methods:** Eighty-two patients undergoing pre-operative MRI to plan for STN DBS for Parkinson disease were retrospectively studied. The visualization of the STN and its borders was assessed and scored by 3 independent observers using a 4-point ordinal scale (from 0 = not seen to 3 = excellent visualization). This measure was then correlated with the patients' clinical information and brain volumes. **Results:** The mean STN visualization scores were 1.68 and 1.63 for the right and left STN, respectively, with a good interobserver reliability (intraclass correlation coefficient: 0.744). Older age and decreased white matter volume were

negatively correlated with STN visualization ($p < 0.05$). **Conclusion:** STN visualization is only fair to good on routine MRI with good concordance of interindividual rating. Advancing age and decreased white matter are associated with poor visualization of the STN. Knowledge about factors contributing to poor visualization of the STN could alert a surgeon to modify the imaging strategy to optimize surgical targeting.

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Introduction

The subthalamic nucleus (STN) is the most common therapeutic target in deep brain stimulation (DBS) for Parkinson disease (PD). The STN can be visualized on magnetic resonance imaging (MRI) scans in part due to its iron content, allowing direct DBS targeting. The quality of visualization of the STN on routine pre-operative MRI scans is, however, quite variable, making the targeting procedure sometimes challenging. Three- and 7-tesla MRIs have been utilized for better visualization [1–3], although this is not a universal practice and these strategies have their own limitations. Various MRI sequences have

Fig. 1. Pre-operative MRI images. The figure shows fast spin echo inversion recovery axial sequences at the level of the STN and red nucleus in PD patients who underwent STN DBS to show representative STN rating. **a** STN rating “0.” **b** STN rating “1.” **c** STN rating “2.” **d** STN rating “3.” The excellent visualized STN rating “3” (**d**) is marked as white outline. The STN rating “2” (**c**) has a good outline and is marked as white dotted line. The borders of STN ratings “0” and “1” are visualized poorly.

also been tried and are still evolving to optimize STN visualization [4, 5]. Performing imaging under general anaesthesia may reduce movement artefacts and could also possibly lead to better visualization. As the outcome of STN DBS is dependent on accurate placement of electrodes, there is a need to assess the quality of routinely used MRI methods for targeting to determine whether they are adequate.

While MRI field strength and the MRI parameters obviously influence STN visualization, whether the patient’s clinical attributes or intrinsic brain volumetric status affect STN visualization is not known. This becomes even more relevant, as earlier studies have shown that brain volumetric changes correlate with clinical state, baseline L-dopa response and L-dopa equivalent doses [6]. Here, we assess the quality of STN visualization using routine pre-operative MRI and correlate this with measures of clinical and brain volumetric factors.

Material and Methods

Patients who underwent STN DBS for PD were screened, and we included consecutive patients who were operated prior to July 2016 and who were scanned under standard clinical MRI parameters (1.5-T GE Scanner, TR = 6,000 ms, TE = 43.15 ms, slice thickness = 2 mm, slice gap = 0 mm, FOV = 270 × 270 mm, matrix = 256 × 192 pixels, FA = 90, and inversion time = 150 ms). Patients with significant variation from the standard MRI protocol and patients with previous surgery (DBS or lesioning) were excluded. Clinical and demographic information and surgical details were collected. T1-weighted images were routinely acquired and used for stereotactic image registration and image fusion. However, as T1-weighted images were not utilized for the STN visualization and/or direct targeting, T1-weighted images were not assessed for the STN visualization. The STN was rated by 3 independent observers (2 neurosurgeons and 1 neuroradiologist) as per previous publications [4, 7]. Briefly, pre-operative 1.5-T MRI was acquired on the day of surgery with the Leksell G stereotactic frame, applied under local anaesthesia only. The STN was rated on a 4-point scale (3, excellent: the STN boundary vis-

ible and definitely clear; 2, good: the STN boundary clearly visible; 1, fair: the STN boundary visible but poorly delineated; 0, poor: not visible). Examples of STN visualization scores are shown in Figure 1. The pre-operative planning T1-weighted MRI was used to segment the brain volumes using the volBrain software platform [8].

Basic descriptive statistics including mean and standard deviation were calculated. The relationship of demographic, clinical data, therapeutic response including L-dopa equivalence [9], and brain volumetric data with the STN rating was assessed. The mean STN rating on each side was treated as a dependent ordinal variable and analysed with categorical or ordinal data by the Kruskal-Wallis test, and with continuous data by the Spearman correlation. Statistical significance was set for p values below a 0.05 threshold. Statistical analyses were performed using the SPSS v22.0 software platform and R project where appropriate. The STN rating among the observers was evaluated for interindividual variation. To assess the interobserver reliability, an intraclass correlation analysis was performed on the average reviewer rating of the STN using a 2-way mixed effects model [10]. The utility of the rating was assessed by Cronbach's alpha at the level of an individual observer and the average of 3 observers with a threshold of utility set at 0.75 [11]. Further, the variation and probability of the overall rating in the cohort were assessed, and the conditional probability of similar or different ratings for each STN rating was calculated. Briefly, to calculate the probability of various ratings for each rating score, the ratings given by observers were rearranged to give all instances where any observer had given a particular rating (for each rating 0, 1, 2, and 3). The conditional probabilities of corresponding ratings given each rating were estimated by fitting a categorical distribution with JAGS using R package "rjags" [12–14]. The variation or distribution of ratings for a given score was calculated and plotted for each STN rating.

Results

During the study period, 103 patients underwent STN DBS surgery. The earlier 16 patients were scanned with a different MRI protocol and 5 patients had prior DBS/lesioning surgery, hence were excluded from the study. There were 82 patients included in the study as per inclusion/exclusion criteria. The mean age of the patients was 58.7 years and three quarters ($n = 62$) of patients were male. The demographic and clinical information is summarized in Table 1.

STN Visualization Scores

The STN visualization was asymmetric; hence, right and left sides were rated separately (Table 2). The distribution of scores across the entire data set of 492 STN ratings (right and left STNs rated in 82 patients by 3 raters) was 10.36, 32.31, 38, and 19% for ratings 0, 1, 2, and 3, respectively. The overall incidences of the STN rating scores of 0, 1, 2, 3 were 8.5, 33.3, 39.0, and 19.1%, respec-

Table 1. Clinical and brain volumetric characteristics (means $\pm$ SD) of the cohort of 82 patients who underwent STN DBS surgery for PD

Patient clinical profile	
Age, years	58.7 $\pm$ 7.6
Duration of disease, years	10.9 $\pm$ 4.3
UPDRS III score "off"	33.7 $\pm$ 12.0
L-Dopa equivalents, mg [9]	1,218.2 $\pm$ 583.7
Brain volumetric variables, mm ³ (%)	
Grey matter	701.14 $\pm$ 67.78 (46.7 $\pm$ 2.1)
White matter	530.11 $\pm$ 68.46 (35.3 $\pm$ 2.9)
Total intracranial volume	1,501 $\pm$ 130

Table 2. STN visualization scores (means $\pm$ SD) of 82 patients

Observer	Right STN	Left STN
Observer 1	1.82 $\pm$ 0.80	1.83 $\pm$ 0.76
Observer 2	1.85 $\pm$ 0.78	1.84 $\pm$ 0.86
Observer 3	1.39 $\pm$ 0.96	1.24 $\pm$ 1.02
Average	1.69 $\pm$ 0.88	1.64 $\pm$ 0.93

Scores were rated on pre-operative fast spin echo inversion recovery stereotactic MRI utilized for STN DBS targeting.

tively, on the right ($n = 246$), and 12.1, 31.3, 36.99, and 19.5% on the left ($n = 246$).

The chance that all 3 reviewers gave the same score for any STN was 13.4%. The chance that 2 of 3 reviewers gave the same score was 63.4%, and the chance that no other reviewer gave the same score for any given STN was 23.1%. The intraclass correlation coefficient for the average rating among reviewers was found to be 0.74 with a 95% confidence interval of 0.43–0.82. The strength of correlation was found to be statistically significant by the F test ($p < 0.005$). The most common rating was 2 in the series, closely followed by 1, and most of the non-concordant ratings were overlapping with rating 1 and 2 and vice versa. The probability of similar ratings (i.e., the same score being given by any other observer) was comparable with STN ratings being 1, 2, and 3, which was in range from 34 to 42%. This probability was lost when the STN was scored as "0" by any observer and the ratings varied widely (Fig. 2). However, the extreme discordant rating was negligible (i.e., one observer rating 3 in case others rated as 0 or vice versa) (Fig. 2).

Fig. 2. Concordance in STN visualization rating scores. The graph shows the concordance in assigned scores when any rater gives a specified score of either 0, 1, 2, or 3 (4 various lines). The graph shows the probability of rating an STN "0" by another observer in a case of where the STN was rated "0" by any observer as is 15.2%, while the probabilities for the same STN rating in case of STN rating of 1, 2, and 3 are 42.3, 37.3, and 33.7%, respectively.

The mean STN rating on the right side ranged from 1.39 to 1.85 among the 3 observers. The average mean of the STN on the right side was 1.69. On the left side, the STN rating varied between 1.24 and 1.84 among the observers with an average STN rating of 1.64. Though the STN visualization was asymmetric, there was a strong correlation of visualization on the contralateral side (non-parametric correlation Spearman $\rho = 0.815$, $p < 0.005$). The mean STN rating on the right side was 1.69 in male patients and 1.77 for female patients, while the mean STN ratings on the left side for male and females were 1.63 and 1.67, respectively. The gender differences were not statistically significant (Table 3). Among other demographic parameters correlated with the STN ratings, age was inversely correlated with the visualization of the STN ($p < 0.05$). Ethnic origin information was available for 76 patients, and there was no correlation with STN visualization. Among the clinical variables, the presence of dyskinesia was associated with lower visualization of the STN. The mean STN visualization rating on the right side with dyskinesia was 1.33 while the mean STN visualization rating in patients without dyskinesia was 1.80 ($p = 0.012$). The mean STN visualization score on the left side in patients with dyskinesia was lower than in patients without dyskinesia (1.37 vs. 1.73). However, this difference was statistically significant only on the right side ($p = 0.012$),

although there was a trend towards significance ($p = 0.075$) on the left side (Table 3). The L-dopa equivalence and UPDRS III on and off scores were not correlated with the STN visualization rating on either side of the STN.

Correlations between brain volumetrics and the STN visualization were assessed. White matter volume correlated with STN visualization ($p < 0.05$). The lesser the volume of white matter, the poorer the visualization of the STN. The intracranial volume was found to correlate with the STN visualization on the right side ($p = 0.040$) but not on the left ($p = 0.217$). The grey matter volume and the brainstem volume were not found to correlate with STN visualization (Table 4).

Discussion

The visualization of STN borders on routine 1.5-T MRI has been variable [15]. We performed 3 independent evaluations of STN visualization scores in 82 PD patients undergoing STN DBS surgery. The data we present here suggest that STN visualization is good or excellent (scores of 2 or 3) in approximately 60% cases and suboptimal in 40%. Other studies have obtained similar STN ratings in the range of 1.25–2.94 varying with the MRI parameters used, the highest being for quantitative susceptibility mapping pulse sequences [4, 7].

We found that the interobserver reliability of the STN visualization ratings was high (0.744), suggesting a moderate to good reliability among recommended guidelines [11]. As an assessment of the reliability of ratings in a given case, we found a reasonably good probability of similar or minor variations in the rating of STN among observers. The probability of extreme non-concordance rating (1 observer score 0 and others score 3 or vice versa) was 5–11% (Fig. 2), which is considered low. There was however a wide variation in rating when the STN is not visualized (rating of 0). Possible observer speculation about the STN borders could account for the wider variation in ratings.

The STN is known to have heterogeneity in terms of size, shape, and distribution [15, 16]. In one of the previous studies in 18 PD patients from our centre [15], the positions of the borders of the STN were highly variable and noted in all patients studied. Within constant MRI parameters, the variation in the STN visualization could be related to the intrinsic STN anatomy, iron content [17, 18] and/or patient-specific clinicoradiological parameters. However, there is scarcity of literature assessing the correlation of these factors with STN visualization.

Table 3. Correlation of categorical clinic-demographic profile and STN score (means $\pm$ SD)

Categorical variables	<i>n</i> (%)	Right STN rating	Right <i>p</i> value	Left STN rating	Left <i>p</i> value
Gender					
Female	20 (24.4)	1.77 $\pm$ 0.48	0.85	1.67 $\pm$ 0.56	0.97
Male	62 (75.6%)	1.69 $\pm$ 0.65		1.63 $\pm$ 0.63	
Ethnicity					
Caucasian	60 (78.9)	1.71 $\pm$ 0.56	0.95	1.67 $\pm$ 0.59	0.47
Asian	15 (19.7)	1.73 $\pm$ 0.84		1.60 $\pm$ 0.70	
Other	1 (1.3)	1.67 $\pm$ 0		1.00 $\pm$ 0	
Dyskinesia					
Yes	62 (75.6)	1.33 $\pm$ 0.45	<i>0.012</i>	1.37 $\pm$ 0.46	0.075
No	20 (24.4)	1.80 $\pm$ 0.61		1.73 $\pm$ 0.63	

The statistically significantly different *p* value is italicized.

Table 4. Spearman ρ non-parametric correlation of continuous clinicoradiological parameters and STN visualization (correlation and *p* value)

Continuous/ordinal variable	Right STN	<i>p</i>	Left STN	<i>p</i>
Age	−0.399	<i><0.005</i>	−0.432	<i><0.005</i>
Duration of disease	−0.189	0.088	−0.165	0.138
UPDRS III “off” score	−0.045	0.695	−0.070	0.542
L-Dopa equivalence	0.053	0.635	0.060	0.595
White matter volume	0.394	<i><0.005</i>	0.335	<i>0.002</i>
Grey matter volume	0.006	0.956	0.048	0.669
Brainstem volume	0.196	0.78	0.054	0.632
Total intracranial volume	0.227	<i>0.040</i>	0.138	<i>0.217</i>

Statistically significantly different results are italicized.

Because of specific brain changes [19, 20] and clinical attributes in PD that have been correlated with clinical response to L-dopa [6], we sought to determine whether the same factors could influence STN visualization on clinical MRI. Here we show that patient age was negatively correlated with the visualization of the STN. This could be related to age-related changes in iron content within the STN and surrounding iron-containing structures, specifically the substantia nigra. We also noted that the presence of dyskinesia seemed to correlate with STN visualization. This was significant on the right side ($p = 0.012$) but not the left ($p = 0.075$). Dyskinesia is one of the L-dopa-induced motor side effects that increases with advancing PD. However, we did not find that disease duration and UPDRS motor scores (both off and on) correlated with STN visualization. In contrast, we found that

reduced brain white matter volume was associated with poor STN visualization ratings. This may be related to the negative correlation of age and STN visualization, as advancing age is an obvious factor associated with loss of brain volume. The progression of brain atrophy is reported to be faster in PD, and white matter volume is also reported to be reduced in PD patients compared to healthy controls [6, 21]. Our result is further supported by the fact that dyskinesia has been associated with faster brain atrophy, particularly of frontal lobes [22], which again supports the notion that STN visualization is better in patients with younger age and lesser brain atrophy.

Many improvements in STN imaging are possible. One of the strategies is to improve the signal-to-noise ratio image using higher magnetic field strength – with the caveat that this may introduce geometrical distortion,

Table 5. Common MRI parameters from different centres/publications

MRI parameters	Present series, TWH, 1.5-T GE (FSE-IR)	Starr et al. [26], Siemens (IR)	Starr et al. [26], Phillips (IR)	Starr et al. [26], 1.5-T GE (T2W FSE)	Starr et al. [27] 1.5-T Phillips (T2W FSE)	Thani et al. [24], Siemens (T2W TSE)	Ishimori et al. [28], 1.5-T Toshiba (PSIR)	Hariz et al. [29], GE (T2W FSE)	Cho et al. [3], 1.5-T Siemens (2D gradient echo)
TR, ms	6,000	3,000	3,000	3,000	2,500	4,000	4,000	3,500	750
TE, ms	43.5	40	40	87	110	119	10 (effective)	90.9	30
Slice thickness, mm	2	2	2	2	1.5	1	2	2	2
Gap, mm	none	overlapping	overlapping	overlapping	-0.5 (overlapping)	none	-	0.2	-
Field of view, mm	270×270	-	-	-	260	260×260	230×230	250×250	192×192
Matrix	256×192	230×256	256×512	384×256	230×256	256×320	230×230	-	384×384

TR, repetition time; TE, echo time; TWH, Toronto Western Hospital; GE, General Electric; FSE, fast spin echo; IR, inversion recovery; T2W, T2-weighted; TSE, turbo spin echo; PSIR, phase-sensitive inversion recovery; 2D, 2-dimensional.

which may be exaggerated by the stereotactic frame. In one study on STN targeting with 1.5-T MRI, the authors found the spatial error could be up to 2.4 mm [23]. Many centres are utilizing pre-operative 3-T MRI fused with operative day CT scans with the stereotactic frame for better visualization and targeting. However, MRI/CT fusion itself introduces geometrical error [24] and requires more imaging and greater costs. Other options for improving visualizations include performing imaging under general anaesthesia to reduce movement artefacts and optimizing MRI parameters. Various sequences have been used across centres (Table 5). Hamani et al. [25] reported a relatively good concordance of micro-electrode recording and STN boundary visualized on MRI. Visualization of the STN is becoming increasingly important, as many centres are now implanting STN electrodes purely based on anatomical targeting without micro-electrode recording.

Limitations

This study is a retrospective review of the available information from charts and archived MR images. The univariate analysis revealed limited factors as significant in the study, and furthermore it was not felt to be an optimum model for multivariate analysis. This may limit the significance of correlation. The images were clinical MRI, and there were no specific sequences to individually optimize STN visualization.

Conclusion

STN visualization is relatively fair to good with a high degree of consistency among observers on routine 1.5-T clinical MRI used to plan DBS surgery. Although STN visualization is highly dependent on the MRI and the sequences used, patient-specific factors also influence the visualization. Advancing age and reduced white matter volume are associated with poor STN visualization, possibly reflecting local iron content distribution and the contrast from the surrounding structure. Knowing the factors associated with poor visualization will prompt neurosurgeons to strengthen the surgical targeting combined with other targeting methods to optimize the final selection of target coordinates, in particular for those who rely heavily on direct targeting without micro-electrode recording or intra-operative imaging. Better visualization of the STN in younger patients and in patients with dyskinesia might be a ground for further supporting earlier STN DBS surgery in PD patients.

Acknowledgements

This work was supported by Tier 1 Canada Research Chair in Neuroscience (to A.M.L.) and the R.R. Tasker Chair in Functional Neurosurgery, Toronto Western Hospital, University Health Network (to A.M.L.).

The authors wish to acknowledge Dr. Vivek Gupta, Assistant Professor, Community Ophthalmology, All India Institute of Medical Sciences, New Delhi, India, for his valuable assistance in statistical analysis.

References

- Abosch A, Yacoub E, Ugurbil K, Harel N: An assessment of current brain targets for deep brain stimulation surgery with susceptibility-weighted imaging at 7 tesla. *Neurosurgery* 2010;67:1745–1756; discussion 1756.
- Slavin KV, Thulborn KR, Wess C, Nersesyan H: Direct visualization of the human subthalamic nucleus with 3T MR imaging. *AJNR Am J Neuroradiol* 2006;27:80–84.
- Cho ZH, Min HK, Oh SH, Han JY, Park CW, Chi JG, Kim YB, Paek SH, Lozano AM, Lee KH: Direct visualization of deep brain stimulation targets in Parkinson disease with the use of 7-tesla magnetic resonance imaging. *J Neurosurg* 2010;113:639–647.
- Liu T, Eskreis-Winkler S, Schweitzer AD, Chen W, Kaplitt MG, Tsiouris AJ, Wang Y: Improved subthalamic nucleus depiction with quantitative susceptibility mapping. *Radiology* 2013;269:216–223.
- Chandran AS, Bynevelt M, Lind CR: Magnetic resonance imaging of the subthalamic nucleus for deep brain stimulation. *J Neurosurg* 2016;124:96–105.
- Bonneville F, Welter ML, Elie C, du Montcel ST, Hasboun D, Menuel C, Houeto JL, Bonnet AM, Mesnage V, Pidoux B, Navarro S, Cornu P, Agid Y, Dormont D: Parkinson disease, brain volumes, and subthalamic nucleus stimulation. *Neurology* 2005;64:1598–1604.
- Nagahama H, Suzuki K, Shonai T, Aratani K, Sakurai Y, Nakamura M, Sakata M: Comparison of magnetic resonance imaging sequences for depicting the subthalamic nucleus for deep brain stimulation. *Radiol Phys Technol* 2015;8:30–35.
- Manjon JV, Coupe P: volBrain: an online MRI brain volumetry system. *Front Neuroinform* 2016;10:30.
- Lozano AM, Lang AE, Galvez-Jimenez N, Miyasaki J, Duff J, Hutchinson WD, Dostrovsky JO: Effect of GPi pallidotomy on motor function in Parkinson's disease. *Lancet* 1995;346:1383–1387.
- Shrout PE, Fleiss JL: Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 1979;86:420–428.
- Cicchetti DV: Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. *Psychol Assess* 1994;6:284–290.
- Plummer M: rjags: Bayesian graphical models using MCMC. R package version 2.2.0-3. 2011. <http://CRAN.R-project.org/package=rjags>.
- Plummer M: JAGS: a program for analysis of Bayesian graphical models using Gibbs sampling. *Proceedings of the 3rd International Workshop on Distributed Statistical Computing (DSC 2003)*, Vienna, March 20–22, 2003.
- R Core Team: R: a language and environment for statistical computing. Vienna, R Foundation for Statistical Computing, 2017. <https://www.R-project.org/>.
- 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.
- Daniluk S, Davies K, Elias SA, Novak P, Nazaro 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;152:201–210; discussion 210.
- Brass SD, Chen NK, Mulkern RV, Bakshi R: Magnetic resonance imaging of iron deposition in neurological disorders. *Topics Magn Reson Imag* 2006;17:31–40.
- Dormont D, Ricciardi KG, Tande D, Parain K, Menuel C, Galanaud D, Navarro S, Cornu P, Agid Y, Yelnik J: 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.
- Durif F, Pollak P, Hommel M, Ardouin C, Le Bas JF, Crouzet G, Perret J: Relationship between levodopa-independent symptoms and central atrophy evaluated by magnetic resonance imaging in Parkinson's disease. *Eur Neurol* 1992;32:32–36.
- Alegret M, Junque C, Pueyo R, Valdeoriola F, Vendrell P, Tolosa E, Mercader JM: MRI atrophy parameters related to cognitive and motor impairment in Parkinson's disease. *Neurologia* 2001;16:63–69.
- Lee SH, Kim SS, Tae WS, Lee SY, Choi JW, Koh SB, Kwon DY: Regional volume analysis of the Parkinson disease brain in early disease stage: gray matter, white matter, striatum, and thalamus. *AJNR Am J Neuroradiol* 2011;32:682–687.
- Cerasa A, Fasano A, Morgante F, Koch G, Quattrone A: Maladaptive plasticity in levodopa-induced dyskinesias and tardive dyskinesias: old and new insights on the effects of dopamine receptor pharmacology. *Front Neurol* 2014;5:49.
- Zonenshayn M, Rezai AR, Mogilner AY, BERIC A, Sterio D, Kelly PJ: Comparison of anatomic and neurophysiological methods for subthalamic nucleus targeting. *Neurosurgery* 2000;47:282–292; discussion 292–284.
- Thani NB, Bala A, Swann GB, Lind CR: Accuracy of postoperative computed tomography and magnetic resonance image fusion for assessing deep brain stimulation electrodes. *Neurosurgery* 2011;69:207–214; discussion 214.
- Hamani C, Richter EO, Andrade-Souza Y, Hutchison W, Saint-Cyr JA, Lozano AM: Correspondence of microelectrode mapping with magnetic resonance imaging for subthalamic nucleus procedures. *Surg Neurol* 2005;63:249–253; discussion 253.
- Starr PA: Placement of deep brain stimulators into the subthalamic nucleus or globus pallidus internus: technical approach. *Stereotact Funct Neurosurg* 2002;79:118–145.
- Starr PA, Vitek JL, DeLong M, Bakay RA: Magnetic resonance imaging-based stereotactic localization of the globus pallidus and subthalamic nucleus. *Neurosurgery* 1999;44:303–313; discussion 313–304.
- Ishimori T, Nakano S, Mori Y, Seo R, Togami T, Masada T, Kusuhara T, Ohkawa M, Nagao S, Yamashita Y, Sugiura S: Preoperative identification of subthalamic nucleus for deep brain stimulation using three-dimensional phase sensitive inversion recovery technique. *Magn Reson Med* 2007;6:225–229.
- Hariz MI, Krack P, Melvill R, Jorgensen JV, Hamel W, Hirabayashi H, Lenders M, Wesslen N, Tengvar M, Yousry TA: A quick and universal method for stereotactic visualization of the subthalamic nucleus before and after implantation of deep brain stimulation electrodes. *Stereotact Funct Neurosurg* 2003;80:96–101.