## Introduction

Medical treatment cannot prevent progressive disability in patients with advanced Parkinson disease (PD) because its long-term clinical benefits are compromised by disabling adverse reactions including motor and psychiatric complications. Continuous high-frequency stimulation of the bilateral subthalamic nucleus (STN) is now widely accepted as a surgical procedure that strikingly improves motor symptoms and levodopa-induced motor complications in advanced PD patients [18, 21]. Since proper patient selection is essential for the success of STN stimulation [11, 17, 28], factors predictive of satisfactory treatment outcomes have been investigated [9, 11, 22, 28]. A review of 37 cohorts of PD patients treated by STN stimulation indicated that preoperative levodopa responsiveness was the only reliable outcome predictor [18]. The role of patient age [11, 17, 28] and disease duration [17, 28] remains controversial. Broggi et al. reported that in three of their patients with suboptimal results, preoperative magnetic resonance imaging (MRI) showed cerebral vasculopathy in the white matter (WM) [9]. Although the absence of significant abnormality on brain MRI has been used as a selection criterion for surgery [28], reports on specific neuroimaging characteristics that are positively correlated with STN stimulation outcomes [6] are scarce.

Voxel-based morphometry (VBM) is a computer-based technique designed to evaluate statistically significant brain structure differences between subject groups [3]. It has been used widely to study subtle structural changes that may be difficult to quantify by visual inspection in patients with central nervous system disorders such as PD, Parkinson plus syndrome [3, 14], schizophrenia [15], multiple sclerosis [24], focal cortical dysplasia [12], and migraine [26]. VBM yields unbiased, observer-independent data and facilitates the comprehensive assessment of anatomical characteristics throughout the brain [3].

To identify the imaging characteristics of candidates who may receive the greatest benefit and to find reliable predictors of the expected degree of improvement, we performed a retrospective cohort study on 21 patients with advanced PD treated by bilateral STN stimulation. In a comprehensive approach to the brain structure, we applied a segmentation procedure for independent volumetric analysis of gray and white matter and CSF data extracted from preoperative structural information acquired by MRI. We examined whether there was a correlation between these brain structures and the improvement of Parkinsonian symptoms after STN stimulation.

## Methods

### Patients

Between November 2006 and October 2008, 23 Japanese patients with advanced PD underwent bilateral STN-deep brain stimulation (STN-DBS) at Kumamoto University Hospital. All manifested idiopathic PD, and based on the criteria of the Core Assessment Program for Intracerebral Transplantation [20], all or some of their motor symptoms responded to levodopa. The patient selection for surgery was described previously [29]. We did not intentionally exclude patients over 70 years [19] if their general physical and psychiatric status were acceptable for surgery. Surgery was in accordance with good clinical practice, and prior informed consent was obtained from the patients and their families. We excluded two female patients from the study because one had undergone another stereotactic procedure that targeted the globus pallidus internus and the other developed gait disturbance primarily due to worsened rheumatic arthritis postoperatively. Twenty-one patients were enrolled in the study. The study was approved by the Ethics Committee of Kumamoto University Hospital.

### Surgery

Surgery was with an MRI/microelectrode-guided technique [29]. The tentative target site, determined at coordinate setting, was 2 mm posterior to the midpoint of a line drawn between the anterior and posterior commissures (AC–PC line) and 12 mm lateral and 4 mm ventral to the AC–PC line. Semi-microelectrode recordings were obtained at 1.0-mm sites along the trajectory toward the subthalamic target site to determine the relative physiologic position of the probe. The trajectory that included four positive recording sites (4.0 mm) was chosen for placement of the DBS electrode (Model 3389, Medtronic Inc., Minneapolis, MN, USA). All patients underwent bilateral procedures in a single operative session. After several days of test-stimulation, pulse generators (Soletra, Model 7426 IPG, Medtronic Inc.) were subcutaneously implanted on the subclavian region of the chest wall. Most patients were treated with unipolar stimulation using one or two contacts. The parameters were frequency, 130–160 Hz; pulse width, 60–90 μsec; and amplitude, 1.5–3.0 V.

### Evaluations

The patients were evaluated pre- and postoperatively using the Unified PD Rating Scale (UPDRS). The primary measures of the disease status on the UPDRS were the

activities of daily living (ADL; UPDRS-II) and motor function (UPDRS-III) subscores. Individual Parkinsonian motor symptoms were also scored according to the definition of Kleiner-Fisman et al. [17], i.e., bradykinesia (UPDRS-III items 23–26; 0–32), tremor (UPDRS-III items 20 and 21; 0–28), rigidity (UPDRS-III item 22; 0–20), and axial symptoms (UPDRS-II items 13–15 and UPDRS-III items 29 and 30; 0–20).

The score after a drug-free period exceeding 12 h was defined as the practical worst "off" state and the score at 1–2 h after the administration of the usual morning medications as the practical "on" state. Assessments were performed by three independent observers from our departments. They calculated the raw scores and percent improvements in each score for our comparative analysis with the neuroimaging study.

### Neuroimaging

All MRI studies were performed on a 3 T clinical MR imager (Magnetom Trio; Siemens AG, Erlangen, Germany) using an eight-channel phased array head coil. Magnetization-prepared rapid gradient-echo (MPRAGE) sequences were acquired in each subject; this yielded T1-weighted volume data. The parameters for MPRAGE imaging were repetition time, 1,900 msec; effective echo time, 4.7 msec; inversion time, 900 msec; imaging time, 4 min and 18 s. All images were acquired with a field of view of 23×23 cm, a matrix of 256×256, and one excitation.

### VBM and segmentation

Brain tissue segmentation and quantification based on VBM were according to the method of Chard et al. [10]. DICOM files of MPRAGE images were transferred to a PC running the Windows XP® (Microsoft Corporation, Redmond, WA, USA) and transformed into IMG files for further processing using MRIcro software (http://www.sph.sc.edu/comd/rorden/). All structural images were checked for artifacts, and the center point was placed on the anterior commissure. The image files were then preprocessed, segmented, and quantified with SPM5 (http://www.fil.ion.ucl.ac.uk/spm/) running on MATLAB R2008a software (MathWorks, Natick, MA, USA). Firstly, to realign brain images of the patients, each MRI data underwent rigid body registration, which preserves absolute volumes of brain structures, using the SPM5 image realign function with trilinear interpolation. The three-dimensional MPRAGE images were automatically segmented into images representing the probability of any given voxel containing gray matter (GM), WM, and cerebrospinal fluid (CSF) using SPM5 supplemented with a batch utility extension spm_segment (http://www.nmrgroup.ion.ucl.ac.uk/atrophy/index.html) [10]. SPM5 calculated the volume of each segment in milliliters. Segmentations were inspected for qualitative confirmation of the adequate extraction of the intracranial contents. The total intracranial volume (TIV) was defined as GM + WM + SF [10]. The gray matter fraction (GMF), white matter fraction (WMF), brain fraction (BrF), and CSF fraction (CSFF) were defined as GM/TIV, WM/TIV, (GM + WM)/TIV, and CSF/TIV, respectively.

### Statistical analysis

To determine which volumetric value was correlated with the postoperative state of Parkinsonian symptoms, we performed both univariate analysis (Spearman's nonparametric rank correlation) and multivariate analysis (stepwise multiple regression analysis) using SPSS 10J ® software (SPSS, Chicago, IL, USA) running on a PC. A $p$ value of $<0.05$ was considered significant.

## Results

### Patient characteristics

The characteristics of the 21 patients enrolled in this study are summarized in Tables 1 and 2. Of our 21 patients, nine (43%) exhibited drug-induced psychosis and 12 (57%) presented with levodopa-induced dyskinesia although the mean levodopa dose and levodopa equivalent drug dose (LEDD) were markedly lower than those used in western countries [19, 21, 27]. Their ethnic background might render Oriental less tolerant than Caucasians to anti-Parkinsonian medications as previously suggested [16, 23, 30].

**Table 1** Characteristics of patients enrolled in VBM study

| Characteristics | Value |
|---|---|
| Total number of patients | 21 |
| Sex (number of patients) | |
| Male | 9 |
| Female | 12 |
| Duration of disease before surgery (years) | |
| Mean±SD | 11.9±6.2 |
| Range | 3–29 |
| Patients' age at surgery (years) | |
| Mean±SD | 66.0±7.9 |
| Range | 43–74 |

**Table 2** UPDRS scores and drug dose at preoperative baseline and at 3 months after surgery

| | On/off Drug | Baseline | 3months after surgery | | |
|---|---|---|---|---|---|
| | | | Score | Change (%) | *p* value |
| Total UPDRS | On | 44.2±28.8 | 21.6±19.1[b] | −51.1 | <0.001 |
| | Off | 74.1±25.2 | 25.4±19.7[b] | −65.7 | <0.001 |
| UPDRS II (ADL) | On | 13.0±11.1 | 7.1±8.5[b] | −45.6 | 0.003 |
| | Off | 23.9±10.2 | 8.7±8.3[b] | −63.7 | <0.001 |
| UPDRS III (motor) | On | 23.9±17.6 | 11.6±10.5[b] | −51.4 | <0.001 |
| | Off | 42.4±15.0 | 13.8±11.0[b] | −67.5 | <0.001 |
| Motor subscores | | | | | |
| Axial symptom | On | 8.0±7.3 | 4.5±5.9[b] | −43.1 | 0.005 |
| | Off | 16.5±6.4 | 5.4±5.9[b] | −67.4 | <0.001 |
| Tremor | On | 2.3±2.5 | 1.2±2.0[a] | −45.8 | 0.030 |
| | Off | 4.6±5.2 | 1.6±3.2[b] | −64.6 | <0.001 |
| Rigidity | On | 4.5±5.1 | 0.4±1.2[b] | −90.4 | <0.001 |
| | Off | 6.5±5.2 | 0.5±1.2[b] | −91.9 | <0.001 |
| Bradykinesia | On | 8.1±6.7 | 4.0±3.4[b] | −50.3 | 0.001 |
| | Off | 14.1±5.9 | 4.5±4.0[b] | −67.9 | <0.001 |
| Levodopa dose | – | 392.9±116.5 | 304.8±113.9[b] | −22.4 | 0.004 |
| LEDD | – | 469.0±165.8 | 331.0±135.5[b] | −29.4 | <0.001 |

*LEDD* levodopa equivalent daily dose

[a] $p<0.05$ for difference between the baseline score and the score 3 months after surgery, paired *t* test

[b] $p<0.01$ for difference between the baseline score and the score 3 months after surgery, paired *t* test

## Subthalamic stimulation

None of the operated patients manifested permanent adverse effects such as motor weakness, sensory disturbance, oculomotor palsy, or cognitive decline. Transient deterioration of Parkinsonian symptoms was successfully treated by modifying anti-Parkinsonian medications or by changing the DBS parameters. There were no infectious complications during the study period.

Pre- and postoperative Parkinsonian symptoms and anti-Parkinsonian drug doses are summarized in Table 2. At 3 months after the implementation of STN-DBS, the mean dose of levodopa/DCI and the LEDD were significantly reduced. Compared to the preoperative baseline "off" drug status, all scores for total UPDRS, UPDRS part II, UPDRS part III, and motor subscores such as axial symptom, tremor, rigidity, and bradykinesia were significantly improved at 3 months after surgery. Compared to the preoperative baseline "on" medication status, all scores for total UPDRS, UPDRS part II, UPDRS part III, and motor subscores were also significantly improved at 3 months after surgery. Possible explanations for the high improvement rate in the "on" state (>40%) are as follows: (1) Preoperative UPDRS scores in the "on" state may not reflect the *best* obtainable scores in that state because of lower tolerance to levodopa in Japanese patients [16, 23, 30]. (2) Levodopa-unresponsive axial symptoms were improved after surgery [4, 29]. The dyskinesias (UPDRS part IV, item 32) and clinical fluctuations (UPDRS part IV, item 39) were also improved. These results are comparable to those of a larger series we reported previously [30].

## VBM

SPM5 generated three mutually exclusive masks corresponding to the gray matter (GM in Fig. 1), white matter (WM in Fig. 1), and CSF (CSF in Fig. 1) and calculated their absolute volumes. Visual inspection of the segmentation data confirmed adequate extraction of the intracranial contents in all cases. The mean absolute and fractional volumes (see Methods Section) for segmented GMF, WMF, BrF, and CSFF were presented in Table 3. The fractional data obtained in our PD patients were almost identical to those in normal subjects [10] and appeared to be distributed within a normal range. This is consistent with a previous report [3] that VBM detected no significant brain structure differences between normal controls and PD patients. In contrast, our absolute data values were smaller than those reported by Chard et al. [10] who performed an SPM-based segmentation study in normal European subjects.

## Statistics for predictive factors

Univariate analysis of the correlation between absolute GM, WM, brain parenchyma, and CSF volumes and the improvement rates on the UPDRS after STN stimulation showed that there were no significant correlations (data not

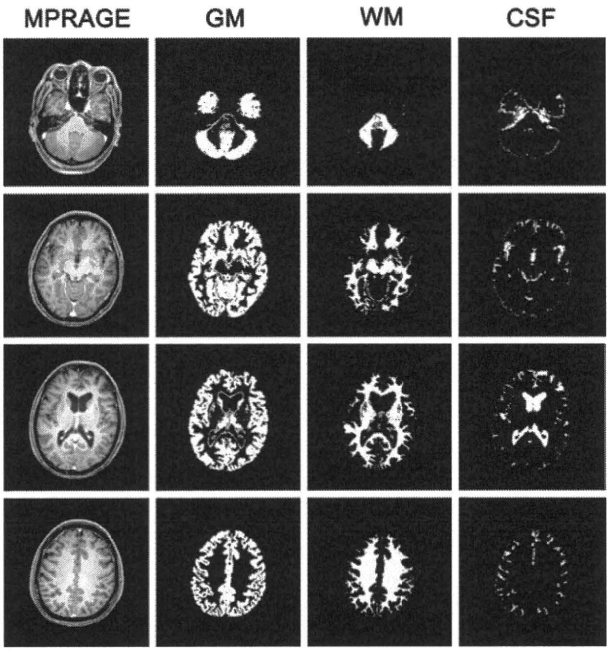


**Fig. 1** Preoperative MRI and segmented images of an illustrative case SPM5 supplemented with *spm_segment* (see Methods Section) generated three mutually exclusive masks corresponding to the gray (*second column*) and white matter (*third column*) and the CSF (*fourth column*) from 3D magnetization-prepared rapid gradient-echo (MPRAGE) images (*first column*)

shown). We then performed univariate analysis of the fractional volumes of the segmented data. We found that there was no correlation between the GMF and postoperative improvement on the total UPDRS, UPDRS part II (ADL), UPDRS part III (motor), or any of the motor subscores (Table 4 and Fig. 2). On the other hand, the WMF correlated positively with postoperative improvement of the total UPDRS score, UPDRS part II score, UPDRS part III score, axial, tremor, and bradykinesia subscores, but not with rigidity subscore (Table 4; Fig. 3). Univariate analysis also showed that there was no correlation between the BrF and postoperative improvement on any of the UPDRS scores (Table 4 and Fig. 4). Finally, our results showed that there was no correlation between the CSFF and postoperative improvement on any of the UPDRS scores (Table 4). Multivariate analysis showed similar results: The WMF was correlated with postoperative improvement rates "off" drug state on the UPDRS total score, UPDRS part II score, UPDRS part III score, axial, tremor, and bradykinesia subscores (Table 4).

To test whether the WMF can also predict the postoperative best "on" state, we performed univariate analysis on the correlation between the WMF and UPDRS scores in the "on" drug and "on" stimulation state. The results were almost similar to the improvement of the UPDRS scores: The WMF correlated negatively with postoperative "on" scores on the total UPDRS, UPDRS part II, UPDRS part III, or the axial subscore, but not with tremor, rigidity, and bradykinesia subscores (Table 5; Fig. 5).

## Discussion

We report in patients with advanced PD a factor that can predict the effect of STN stimulation based on preoperative imaging results. Our VBM study showed that the fractional volume of the white matter correlates well with postoperative improvement of both ADL (UPDRS part II) and motor (UPDRS part III) scores. The fractional volumes of the gray matter, the brain parenchyma, or the CSF manifested no significant correlation. We also document that volumetric analysis of the white matter can predict the best neurological state that STN stimulation can produce (i.e., the UPDRS scores in the "on" drug, "on" stimulation state) in individual patients. Given that the fractional volume of each structure was within the normal range, VBM detected very subtle white matter differences in our PD patients, making it possible to identify a correlation with the effect of STN stimulation.

Clinical outcome predictors for STN stimulation have been reported. Preoperative levodopa responsiveness is consistently predictive of Parkinsonian symptom improvement by STN stimulation [9, 11, 17, 28]. In 41 PD patients who underwent bilateral STN stimulation, there was no significant correlation between their age at the time of surgery (mean 56.4±8.6 years) or the duration of the disease and the clinical outcome 6 months after surgery. However, when the patients were separated into two groups, improvements in Parkinsonian motor disability

**Table 3** Results of voxel-based morphometry in 21 PD patients

| | GM (ml) | WM (ml) | Brain (ml) | CSF (ml) | TIV (ml) | GMF | WMF | BrF | CSFF |
|---|---|---|---|---|---|---|---|---|---|
| Mean | 684.1 | 370.8 | 1054.9 | 225.1 | 1280.0 | 0.53 | 0.29 | 0.82 | 0.18 |
| SD | 76.0 | 39.8 | 96.7 | 52.1 | 106.1 | 0.04 | 0.02 | 0.04 | 0.04 |

*Abbreviations*: *GM* gray matter, *WM* white matter, *Brain* GM+WM; *CSF* cerebrospinal fluid, *TIV* total intracranial volume (GM + WM + CSF), *GMF* gray matter fraction (GM/TIV), *WMF* white matter fraction (WM/TIV), *BrF* brain fraction (Br/TIV), *CSFF* cerebrospinal fluid fraction (CSF/TIV), *SD* standard deviation

**Table 4** Correlation between fractional segments obtained from voxel-based morphometry and the effect of DBS in the "off" drug state

| | GMF | WMF | BrF | CSFF |
|---|---|---|---|---|
| UPDRS total | −0.144 | 0.582[b,d] | 0.178 | −0.178 |
| UPDRS part II | −0.062 | 0.568[b,d] | 0.261 | −0.261 |
| UPDRS part III | −0.209 | 0.585[b,d] | 0.105 | −0.105 |
| Axial | 0.089 | 0.491[a,c] | 0.391 | −0.391 |
| Tremor | −0.409 | 0.522[a,c] | −0.175 | 0.175 |
| Rigidity | −0.035 | −0.062 | −0.074 | 0.074 |
| Bradykinesia | −0.139 | 0.522[a,c] | 0.151 | −0.151 |

*Abbreviations*: *BrF* brain fraction, *CSFF* cerebrospinal fluid fraction, *GMF* gray matter fraction, *UPDRS* Unified Parkinson's Disease Rating Scale, *WMF* white matter fraction

[a] $p<0.05$ after univariate analysis, Pearson linear correlation

[b] $p<0.01$ after univariate analysis, Pearson linear correlation

[c] $p<0.05$ after multivariate analysis, stepwise multiple regression analysis

[d] $p<0.01$ after multivariate analysis, stepwise multiple regression analysis

tended to be greater in patients younger than 56 years and those with a shorter disease duration (<16 years) [28]. Charles et al. [11] reported that in 54 patients whose mean age was 56.0±7.7 years, younger age was predictive of a favorable outcome 3 months after bilateral STN stimulation. Kleiner-Fisman et al. [17] who evaluated a cohort of 25 patients (mean age 57.2±11.7 years) found that no preoperative demographic variable was predictive of the outcome assessed at a median follow-up of 24 months. Regarding presurgical imaging results, Bonneville et al. quantified brain structures, such as global brain parenchyma volumes, basal ganglia volumes, and mesencephalon surfaces on MRI of patients with PD and found that the surface of the mesencephalon was correlated to the outcome after STN stimulation [6]. We suggest that it may be useful to apply VBM to preoperative MRI studies of candidates for STN stimulation.

The strong correlation between the white matter volume and the effect of STN stimulation provides insights into the mechanisms underlying STN stimulation. The motor subscore for bradykinesia was robustly correlated with WMF (Table 4). In PD patients, bradykinesia is attributable to slowness in formulating the instructions to move or to slowness in executing the instructions and is thought to be related to functional abnormality in the supplementary motor area (SMA) or dorsolateral prefrontal cortex [5]. Virtual metabolic imaging studies provided evidence for underactivity in the midline cortical motor areas (i.e., SMA) accompanied by relative overactivity in the lateral premotor areas, the so-called PD-related pattern (PDRP) [13]. Asanuma et al. [2] who used positron emission tomography

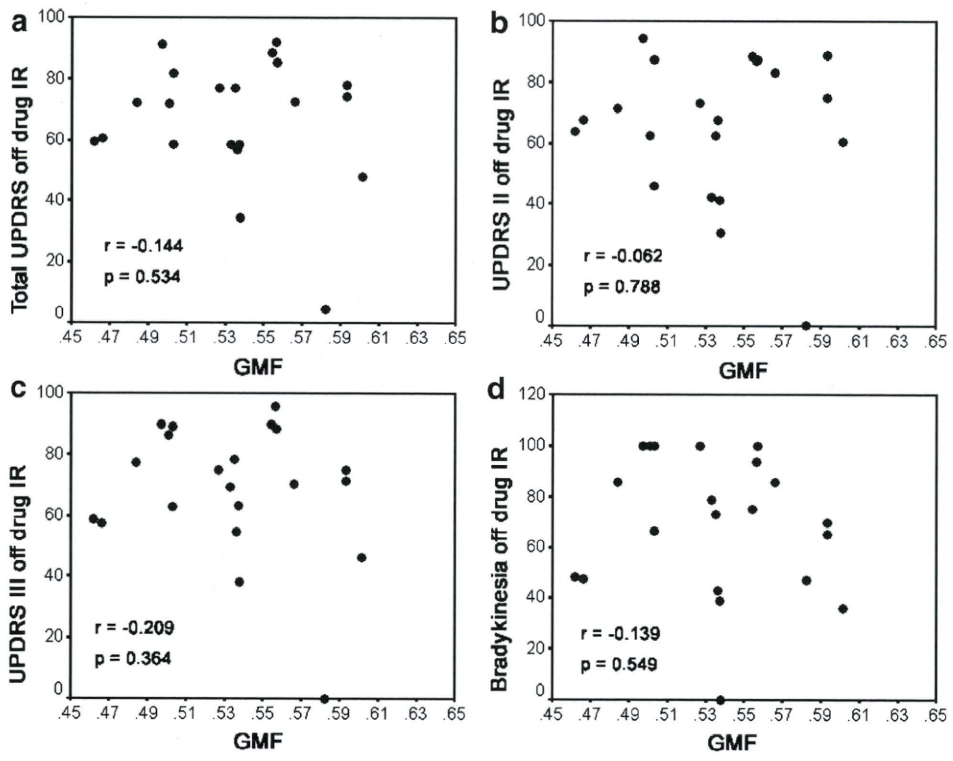


**Fig. 2** Scatter plot of postoperative improvement rates (*IR*) in the "off" medication state against the fractional gray matter volume (*GMF*). **a** Total UPDRS score, **b** UPDRS part II (ADL) score, **c** UPDRS part III (motor) score, **d** bradykinesia subscore. No linear regression curve is shown because none of the Pearson correlation coefficients ($r$) was significant at the 0.05 level

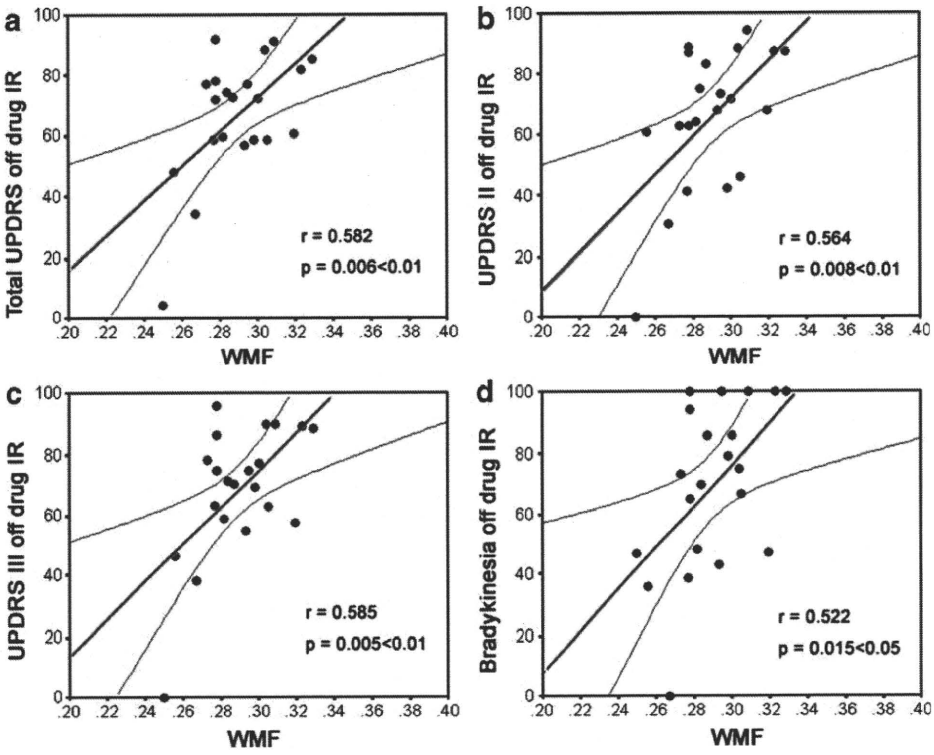


**Fig. 3** Scatter plot of postoperative improvement rates (*IR*) in the "off" medication state against the fractional white matter volume (*WMF*). **a** Total UPDRS score, **b** UPDRS part II (ADL) score, **c** UPDRS part III (motor) score, **d** bradykinesia subscore. The Pearson correlation coefficient (r) was significant at the 0.05 level in **d** and at the 0.01 level in **a**, **b**, and **c**. The best-fitting linear regression (*thick line*) with a 95% confidence interval (*thin line*) is superimposed for each plot

to investigate the effect of STN stimulation detected reductions in PDRP activity comparable to the effect generated by levodopa infusion. They proposed modulation of pathological network activity in the basal ganglia-thalamocortical circuit as the basis for the therapeutic benefit of STN stimulation in PD. Our finding that postoperative improvement is strongly correlated with the volume of the white matter may imply that preserved

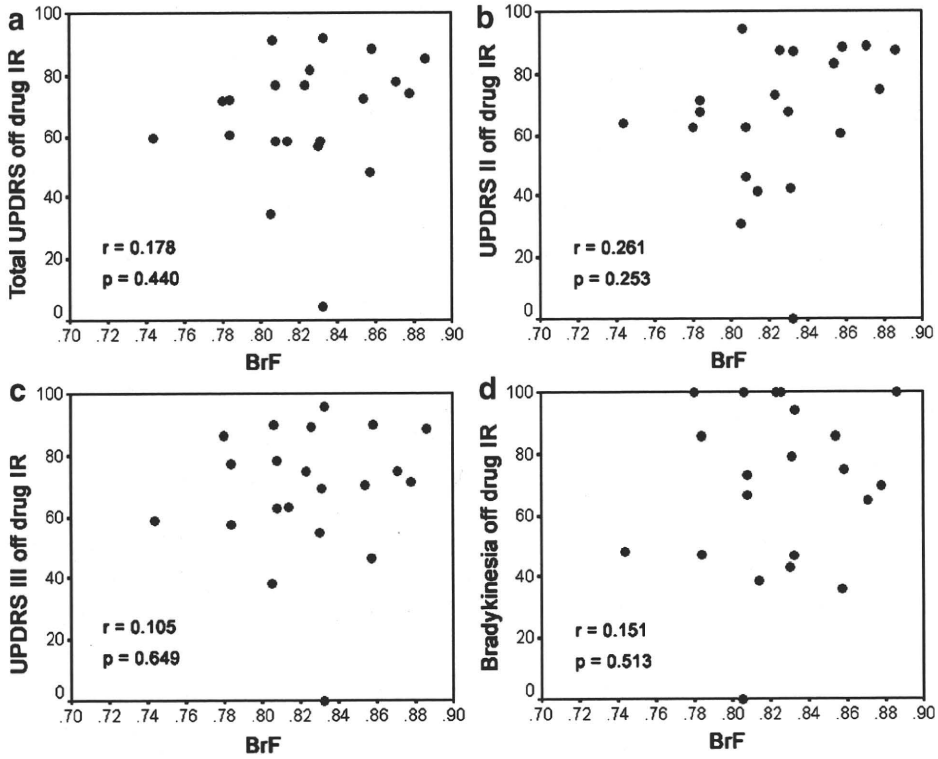


**Fig. 4** Scatter plot of postoperative improvement rates (*IR*) in the "off" medication state against the fractional brain volume (*BrF*). **a** Total UPDRS score, **b** UPDRS part II (ADL) score, **c** UPDRS part III (motor) score, **d** bradykinesia subscore. No linear regression curve is shown because none of the Pearson correlation coefficients (*r*) is significant at the 0.05 level

**Table 5** Univariate analysis of the white matter fraction (WMF) and the UPDRS scores in the "on" drug "on" STN stimulation state

| Fractional segment | Effect of STN stimulation (postoperative "on" drug) | Correlation coefficient | *p* value |
|---|---|---|---|
| WMF | UPDRS total | −0.483[a] | 0.027 |
| | UPDRS Part II | −0.506[a] | 0.019 |
| | UPDRS Part III | −0.464[a] | 0.034 |
| | Axial | −0.442[a] | 0.045 |
| | Tremor | −0.354 | 0.116 |
| | Rigidity | 0.042 | 0.857 |
| | Bradykinesia | −0.417 | 0.060 |

*UPDRS* Unified Parkinson's Disease Rating Scale, *WMF* white matter fraction

[a] $p<0.05$ after univariate analysis, Pearson linear correlation

connectivity between components of neural circuits involved in the motor function, e.g., the cortico-thalamo-basal ganglia circuit, is necessary for the beneficial effects of STN stimulation. This supports the notion that the effect of electrical STN stimulation is not confined to the site of stimulation but is transmitted via interconnections to remote components such as the SMA in the basal ganglia-thalamocortical circuit [2].

It is uncertain whether differences in the white matter volume are reflective of the pathology of the PD brain. Braak et al. [8] proposed that PD is a multisystem disorder. Based on the distribution of α-synuclein immunoreactivity in the PD brain, they suggested a pathological staging system. Accordingly, in stages 1 and 2, Lewy bodies and Lewy neurites are confined to the lower brain stem and anterior olfactory structures. In stages 3 and 4, involvement is confined to the lower and upper brain stem with initial effects on the antero-medial temporal cortex. In stages 5 to 6, Lewy bodies exhibit pathology in the neocortex [7]. We suggest VBM as a powerful tool to study comprehensive changes in the living brain affected by PD. When differences in PD severity were not considered, group analysis using VBM detected no significant differences between the brain of PD patients and age-matched normal controls [3, 14]. On

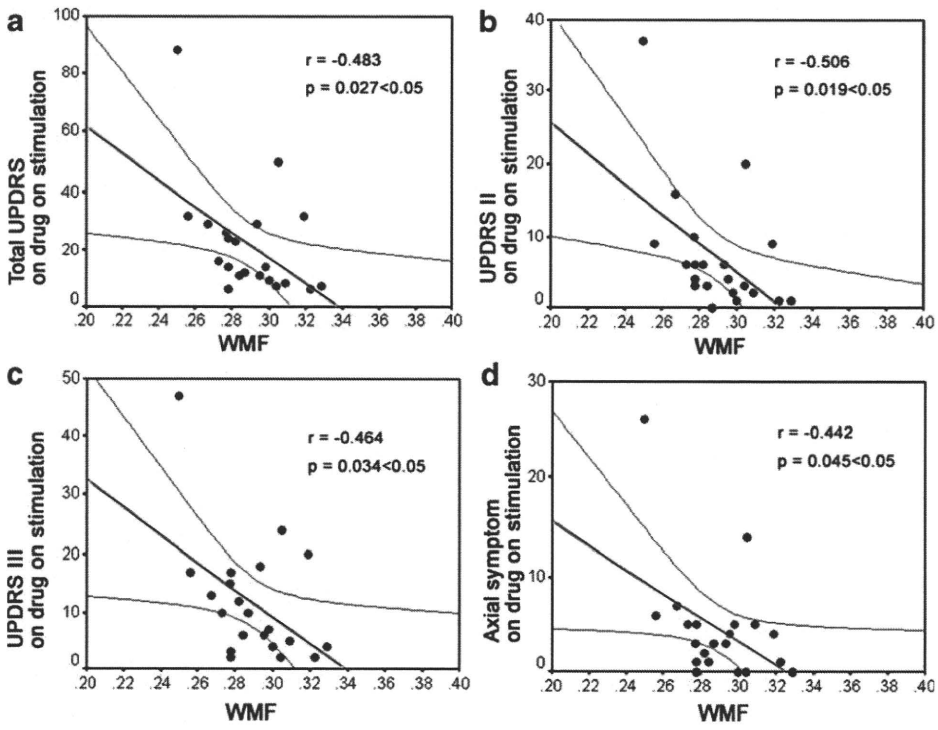


**Fig. 5** Scatter plot of postoperative UPDRS scores in the "on" medication "on" stimulation state against the fractional white matter volume (*WMF*). **a** Total UPDRS score, **b** UPDRS part II (ADL) score, **c** UPDRS part III (motor) score, **d** axial symptom subscore. The Pearson correlation coefficient (*r*) is significant at the 0.05 level in **a–d**. The best-fitting linear regression (*thick line*) with a 95% confidence interval (*thin line*) is superimposed for each plot

the other hand, some imaging studies demonstrated the relationship between brain atrophy parameters and severity of neurological symptoms of PD patients [1, 25]. We are planning to perform VBM studies that address the severity of PD in an effort to clarify whether a smaller gray or white matter volume coincides with advanced neurological or pathological stages of PD.

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**Author contributions** T. Hamasaki had the idea for the study, participated in data collection and analysis, and wrote the manuscript. KY, T. Hirai, and JK helped prepare the manuscript. All authors read and approved the final manuscript.

**Conflict of interest** We declare that none of the authors has any conflict of interest related to this work.

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## Comments

Hamasaki et al. are reporting an elegant demonstration of the negative predictive value of brain atrophy in PD receiving STN DBS. Additionally, they have shown the specific value of the white matter component atrophy. This paper is going further than the Bonneville paper (1) relying on VBM technique and may be of value for patient selection, individual results prediction, and/or series stratification.

(1) Bonneville F, Welter ML, Elie C, du Montcel ST, Hasboun D, Menuel C et al. (2005) Parkinson disease, brain volumes, and subthalamic nucleus stimulation. Neurology 64(9):1598–1604.

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CLINICAL ARTICLE

# Cardiac $^{123}$I-MIBG scintigraphy as an outcome-predicting tool for subthalamic nucleus stimulation in Parkinson's disease

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**Abstract**
*Background* $^{123}$I-meta-iodobenzylguanidine (MIBG) myocardial scintigraphy is a useful tool for differentiating idiopathic Parkinson's disease (PD) from other parkinsonian syndromes, but its prognostic value in PD has not been established. The objective of this study was to clarify the correlation between cardiac MIBG uptake parameters and the outcome in PD patients subjected to the subthalamic nucleus stimulation.
*Method* We enrolled 31 consecutive PD patients and calculated the heart-to-mediastinum ratio (H/M) and washout rate (WR) based on the activity measured at 15 min (early phase) and 3 h (delayed phase) after the intravenous injection of MIBG (111 MBq). Cardinal motor symptoms and activity of daily living (ADL) were assessed on the Unified Parkinson's Disease Rating Scale (UPDRS) and Schwab and England (S–E) ADL scale, before and 3 months after surgery.
*Findings* Neither early nor delayed H/M correlated with any of the preoperative subscores on the UPDRS or S–E, nor with postoperative outcome. On the other hand, increased WR was a positive predictor for postoperative improvement rate on S–E in medication-off state ($p$=0.00003). Also, WR showed a more faint but significant correlation with preoperative levodopa responsiveness on S–E ($p$=0.008).
*Conclusion* Our findings suggest that $^{123}$I-MIBG scintigraphy in combination with levodopa-responsiveness evaluation may represent a useful tool for prediction of outcomes in patients subjected to STN stimulation.

**Keywords** Deep-brain stimulation · 123I-MIBG · Parkinson's disease · Subthalamic nucleus

## Introduction

Continuous high-frequency stimulation of the subthalamic nucleus (STN) is a powerful surgical option for treating the motor complications of Parkinson's disease (PD) [12, 16, 20, 22]. Optimal patients selection is essential for a successful outcome of STN-stimulation [3, 27], and $^{123}$I-meta-iodobenzylguanidine (MIBG) myocardial scintigraphy may be of great help for obtaining an accurate diagnosis and for decision-making before the surgery [4, 17, 18, 21, 23, 24, 30].

$^{123}$I-MIBG scintigraphy was originally developed to evaluate cardiac sympathetic innervation and function; it is now used in a variety of cardiac diseases and disorders [24]. The prognostic value of $^{123}$I-MIBG parameters in patients with chronic heart failure [9, 15, 25] has been discussed in the field of cardiology. Aside from its utility in cardiac disease, $^{123}$I-MIBG scintigraphy detects de-

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pressed myocardial tracer uptake in patients with autonomic failure associated with various neurological diseases [1, 6] and cardiac MIBG uptake was found to be significantly depressed in patients with PD and other Lewy body disease in a disease-specific manner. The cardiac sympathetic nerve is thought to be involved in the early disease stage of PD [8, 19]. Nagayama et al. [18] demonstrated the strong negative correlation between cardiac MIBG uptake and the Hoehn-Yahr stage in PD, suggesting that Lewy body pathology may be responsible for a low MIBG uptake.

Despite the current acceptance of $^{123}$I-MIBG scintigraphy as a useful diagnostic and differentiating tool in PD, its prognostic value has not been established. We examined the correlation between cardiac $^{123}$I-MIBG parameters and the treatment outcome in PD patients subjected to STN-stimulation.

## Methods and materials

### Patients

We enrolled 31 consecutive PD patients who had undergone preoperative cardiac $^{123}$I-MIBG scintigraphy between November 2006 and December 2009 (Table 1). All manifested idiopathic PD and all or some of their motor symptoms responded to levodopa. Patients with severe dementia who scored 4 on the Unified Parkinson's Disease Rating Scale (UPDRS)-Part I item 1, patients who scored less than 20 on the Mini-Mental State Examination, had uncontrolled major psychiatric symptoms (UPDRS-I, item 2=4), or suffered from severe depression (UPDRS-I item 3=4) were considered ineligible for surgery [7, 12]. The levodopa-equivalent daily dose (LEDD) was computed for each delivered antiparkinsonian drug, including levodopa, by multiplying the total daily dose of each drug by its potency relative to a standard levodopa dose; the decarboxylase inhibitor (DCI) preparation was assigned the value of 1. The conversion factors were 100 for pergolide, 66.7 for cabergoline, 100 for pramipexole, 10 for bromocriptine, and 33.3 for ropinirole [26]. Surgery was in accordance with good clinical practice and the prior consent of the patients and/or their families was obtained.

**Table 1** Patient characteristics

| Characteristics | |
|---|---|
| Sex (number of patients) | |
| Male | 12 |
| Female | 19 |
| Age (years) | |
| Mean±SD | 64.8±8.0 |
| Range | 43–73 |
| Duration of disease (years) | |
| Mean±SD | 11.3±5.5 |
| Range | 3–29 |
| PreOP. medications (mg/day) Levodopa and DCI | |
| Mean±SD | 419.4±137.7 |
| Range | 150–650 |
| LEDD (mg) | |
| Mean±SD | 494.8±188.5 |
| Range | 150.0–849.8 |

### $^{123}$I-MIBG imaging

The $^{123}$I-MIBG was obtained from a commercial source (FUJIFILM RI Pharma Co. Ltd., Japan). Patients in the supine position were injected intravenously with $^{123}$I-MIBG (111 MBq) and 15 min (early; E) and 3 h (delayed; D) later, static data were acquired in the anterior view using a dual-head $\gamma$-camera (Millennium VG Hawkeye; GE Healthcare) equipped with a medium-energy, general-purpose (MEGP), parallel-hole collimator. Static images on a 256×256 matrix were collected for 5 min with a 20% window centered on 158 keV, corresponding to the $^{123}$I photopeak. After acquisition of the static planar images, single photon emission computed tomography images were obtained. The camera was rotated over 360° in 64 views with an acquisition time of 30 s per view. Scans were performed in a 64×64 matrix, and the images were reconstructed by ordered subsets-expectation maximization methods.

The heart-to-mediastinum ratio (H/M) was determined from the anterior planar delayed $^{123}$I-MIBG image [9, 15]. The washout rate (WR) was calculated using the formula

$$\{([H]_E - [M]_E) - ([H]_D - [H]_D)/([H]_E - [M]_E)\} \times 100(\%),$$

where $[H]$ equals the mean count per pixel in the left ventricle and $[M]$ the mean count per pixel in the upper mediastinum. We did not correct for time delay in the calculation of WR.

### Evaluations

All patients were scored on UPDRS and the Schwab-England (S–E) activity of daily living (ADL) scale. The score after a drug-free period exceeding 12 h was defined as the practical medication-off state; the score at 1–2 h after the administration of the usual morning medications as the practical medication-on state. Assessments were performed several days before and 3 months after surgery by three independent observers from our departments.

### Surgery

All patients underwent bilateral STN-deep-brain stimulation (DBS). We used a magnetic resonance images/microelectrode-guided technique [28, 29]. The tentative target site, determined at coordinate settings, was 2 mm posterior to the midpoint of a line drawn between the anterior commissure (AC)–posterior commissure (PC) line, and 12 mm lateral, and 4 mm ventral to the AC–PC line. Microelectrode recordings were obtained at 1.0-mm sites along the trajectory toward the subthalamic target site to determine the relative physiologic position of the probe. The trajectory that included more than four positive recording sites (4.0 mm) was chosen for placement of the DBS electrode (Model 3387 or 3389, Medtronic Inc., Minneapolis, MN, USA).

All patients underwent bilateral procedures in a single operative session. Implantable pulse generators (IPGs; Soletora, Model 7426, Medtronic) were subcutaneously implanted on the subclavian portion of the chest wall after several days of test-stimulation in 14 of the 31 patients. The other 17 patients underwent simultaneous implantation of DBS electrodes and IPGs.

Most patients were treated with unipolar stimulation using one or two contacts. The parameters were: frequency, 130–160 Hz; pulse width, 60–90 μs, on both sides; stimulation amplitude, 1.5–3.0 V.

### Statistics

We individually analyzed four parkinsonian motor symptoms, i.e. bradykinesia (UPDRS-III, items 23 to 26; 0 to 32), tremor (UPDRS-III, items 20 and 21; 0 to 28), rigidity (UPDRS-III, item 22; 0 to 20), and axial symptoms (UPDRS-II, items 13 to 15, UPDRS-III, items 27 to 30; 0 to 28) [3, 11].

Preoperative levodopa responsiveness was determined by measuring changes in each score when the patient was in off- and on-medication status (the difference between the on- and off-medication score divided by the off-medication score). The postoperative improvement rate was calculated by determining the difference between the pre- and postoperative score divided by the preoperative score.

We used the paired Student's *t* test to compare parametric pre- and postoperative drug dose data and the Wilcoxon signed-rank test to compare UPDRS subscores and the S–E scale before and after surgery. All data are expressed as the mean±standard deviation (SD). To determine which preoperative clinical characteristics (age, duration of disease, and neuropsychiatric, motor, complication of therapy, and ADL subscores) were related to the $^{123}$I-MIBG scintigraphy parameters we performed univariate analysis. Values of $p<0.01$ were considered as statistically significant.

## Results

### Correlation between $^{123}$I-MIBG scintigraphy parameters and preoperative clinical characteristics

None of the patients was treated with reserpine or tricyclic antidepressants. An association with chronic heart failure was excluded based on clinical symptoms and echocardiography (ejection fraction >50%).

While the normal range (mean±SD) of E- and D-H/M in our institute is 2.78±0.32 and 3.17±0.29, respectively, those of our patients were 1.53±0.31 and 1.31±0.37, respectively. WR (%) was 62.37±21.23 (normal range: 15.2–44.4). Neither E- nor D-H/M correlated with the patient age, the disease duration, or preoperative subscores on the UPDRS or S–E ($p>0.01$). However, there was a significant correlation between WR and the S–E score in the medication-off state ($p=0.0096$) and between WR and levodopa responsiveness on S–E ($p=0.0075$; Fig. 1a).

### Postoperative status

Postoperatively, none of the 31 patients exhibited permanent adverse effects such as motor weakness, sensory

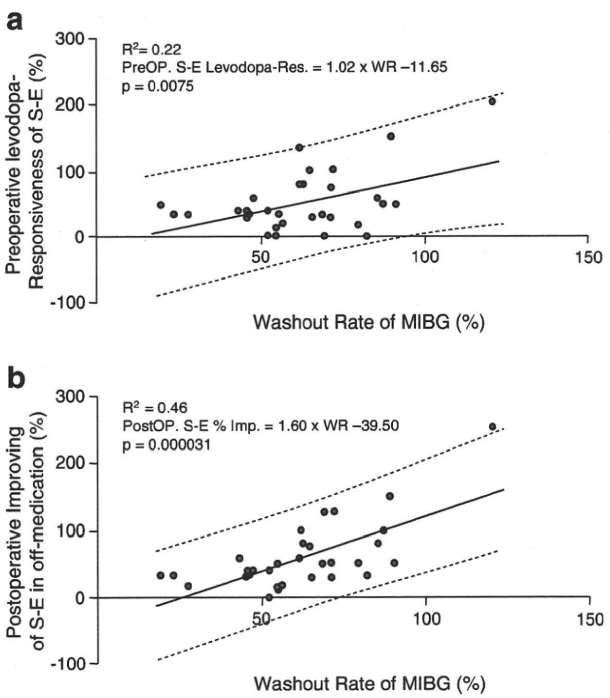


**Fig. 1** Scatter plot and linear regression analysis (95% confidence interval) showing the relationship between WR and preoperative levodopa responsiveness of S–E (**a**), and between WR and postoperative improving rate of S–E in off-medication (**b**). There is a statistically significant correlation (**a**, $p<0.01$; **b**, $p<0.0001$)

disturbance, oculomotor palsy, or cognitive decline. Transient effects were effectively treated by modifying their antiparkinsonian medications, or by changing the DBS parameters. There were no infectious complications.

The antiparkinsonian drug doses could be reduced significantly as the parkinsonian symptoms were ameliorated by chronic STN-DBS. At 3 months after the procedure, there was a significant reduction in the mean dosage of levodopa/DCI and LEDD ($p<0.001$, Table 2).

Compared to the preoperative baseline, at 3 months postoperatively, the UPDRS-I, II, III, and IV scores in both the medication-on and -off state were significantly reduced ($p<0.0001$), all aspects of motor symptoms including bradykinesia, tremor, rigidity, and axial symptoms were significantly improved as were the S–E scores in both the on- and off-medication state ($p<0.001$, Table 2).

### Correlation between $^{123}$I-MIBG scintigraphy parameters and postoperative scores

There was a significant correlation between preoperative levodopa responsiveness on S–E and the postoperative improvement rate in the off-medication state ($p<0.0000001$, data not shown).

**Table 2** Effects of STN stimulation

| | | Baseline | 3 months |
|---|---|---|---|
| UPDRS I | On | 1.8±2.1 | 1.1±1.5* |
| | Off | 2.5±2.4 | 1.1±1.5* |
| UPDRS II | On | 13.7±10.9 | 7.4±8.3* |
| | Off | 24.3±10.9 | 9.7±8.1* |
| UPDRS III | On | 26.4±19.7 | 13.7±13.1* |
| | Off | 44.9±16.3 | 16.7±13.3* |
| Bradykinesia | On | 9.6±7.4 | 5.4±5.4* |
| | Off | 15.9±6.6 | 6.3±5.6* |
| Tremor | On | 2.4±3.1 | 1.3±2.0* |
| | Off | 5.3±5.5 | 1.9±3.0* |
| Rigidity | On | 4.7±5.4 | 1.0±2.4* |
| | Off | 7.2±5.3 | 1.2±2.6* |
| Axial symptoms | On | 9.1±7.2 | 5.5±6.3* |
| | Off | 17.9±7.1 | 6.7±6.3* |
| UPDRS IV | | 6.2±3.3 | 2.7±1.8* |
| S–E ADL scale | On | 72.6±17.1 | 80.0±15.9* |
| | Off | 50.7±15.3 | 75.8±15.9* |
| Levodopa/DCI (mg) | | 419.4±137.7 | 324.2±119.0** |
| LEDD (mg) | | 494.8±188.5 | 353.7±129.5** |

*Asterisks*, significantly different from scores at preoperative baseline

*$p<0.001$, Wilcoxon signed-rank test

**$p<0.001$, Student's *t* test

While E- and D-H/M and WR were not correlated with any postoperative UPDRS subscores or S–E ($p>0.01$), increased WR was a positive predictor of the postoperative improvement rate on S–E in the medication-off state ($p=0.000031$; Fig. 1b).

## Discussion

The disease process of PD as measured by neuronal degeneration and Lewy body and neuritic pathology is widespread in the central and peripheral nervous systems [2]. As many of these non-nigral sites also produce clinical signs and symptoms, Langston [13] proposed that PD might be better viewed as a "centrosympathomyenteric neuronopathy". The Lewy body-type degeneration in the cardiac plexus is observed in almost all patients with incidental Lewy body disease as well as in patients with PD [8], and the number of sympathetic nerve fibers was markedly decreased in all the PD patients regardless of the presence or absence of orthostatic hypotension [19]. These findings suggest the involvement of the cardiac sympathetic nerve in the preclinical disease stage [8, 19], consistent with the reduction in cardiac MIBG uptake in the early stage of PD.

According to Taki et al. [24]. MIBG imaging represents an indicator of the presence of PD rather than its severity, while Nagayama et al. [18] demonstrated the negative correlation between cardiac MIBG uptake and the Hoehn-Yahr stage. We found that the relative change in MIBG uptake at the early and delayed phase (WR) was a significant predictor of the relative improvement (rate) of postoperative ADL. It has been suggested that early MIBG uptake reflects the integrity and distribution of the presynaptic sympathetic system, and that MIBG washout reflects the presynaptic functional status or tone of the sympathetic nervous system [24]. Increased MIBG washout may indicate an increase in the norepinephrine turnover. We also found that WR of MIBG significantly correlated with the levodopa responsiveness of ADL, known to predict a favorable response to bilateral STN-stimulation [3, 11]. These observations raise the hypothesis that the norepinephrine elimination rate at the myocardial sympathetic nerve endings may inversely parallel the dopamine-preserving capacity in the striatum.

Ethnic characteristics may underlie the observation that many Japanese patients treated with lower-dose antiparkinsonian drugs manifest various motor and/or non-motor side effects [10, 28, 29]. Consequently, their preoperative UPDRS subscores in the medication-on state may not reflect the best obtainable scores in that state. We therefore cannot rule out the possibility that we evaluated preoper-

ative ADL at an insufficient dose of levodopa and that STN stimulation elicited symptom improvement by acting as an "additional dopamine" [5, 14, 16]. Indeed, as demonstrated in the present study, the scores for ADL and motor function were significantly improved by STN stimulation, not only in the off-, but also in the on-medication state. In such instances, the postoperative improvement rate may often be underestimated before surgery. In combination with levodopa-responsiveness evaluation, WR of MIBG is considered to be very useful to predict postoperative outcome.

Contrary to our expectations, WR of MIBG was not correlated with the postoperative improvement rate of UPDRS subscores (data not shown). A gross myocardial sympathetic function measure based on $^{123}$I-MIBG scintigraphy may respond better to the overall daily activities expressed by S–E than individual UPDRS subscores. Furthermore, there may be some methodological limitations in conventional calculating formula that we adopted for improving rate of UPDRS. As discussed above, we speculate that reduction rate of $^{123}$I-MIBG activity may parallel to wearing-off phenomenon. If so, we should assess levodopa responsiveness (as well as postoperative improvement) by measuring the reduction rate of scores in the worse state. However, in the present analysis using the conventional formula, those were calculated by the reduction rate of UPDRS subscores in the better state on the basis of the worse state. More adequate method is needed to clarify relationship between cardiac $^{123}$I-MIBG parameters and UPDRS subscores.

## Conclusion

In PD patients who underwent STN stimulation, we found a statistically significant correlation between the WR of myocardial MIBG and the levodopa responsiveness in ADL scale. Myocardial norepinephrine turnover might parallel to preserving capacity of the basal ganglia dopamine system. The present study also demonstrated a close relationship between WR of MIBG and postoperative improvement rate of ADL, suggesting that $^{123}$I-MIBG scintigraphy in combination with levodopa-responsiveness evaluation may represent a useful tool for prediction of outcomes in patients subjected to STN stimulation.

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**Conflicts of interest** None.

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# 不随意運動症に対する定位脳手術とその治療ターゲット①

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不随意運動（IVMs）症に対する定位脳手術は，振戦・ジストニア・舞踏運動・バリズムなど，さまざまな疾患にその適応を拡大させつつある．IVMsのおもな治療ターゲットは，淡蒼球内節（GPi）と視床外側部である．GPiのなかではその機能分画の性質上，腹側部がIVMsに対して有効である．視床では，腹吻側（Vo）核はジストニアの，腹側中間（Vim）核は振戦の治療ターゲットになる．それぞれの神経核の機能解剖学的特徴と，疾患および罹患筋群に応じたターゲット選択について論述する．

*Key Words:* 大脳基底核，不随意運動症，定位脳手術

## Ⅰ．はじめに

不随意運動（involuntary movements: IVMs）とは，患者本人の意思と無関係に生じる運動の総称であるが，通常，痙攣はIVMsには含めない（表1）．このため，ほとんどのIVMsが大脳基底核の病的活動と関連していると言える．パーキンソン病（Parkinson's disease: PD）も大脳基底核疾患の一つであり，また振戦やレボドパ誘発性ジスキネジアなどもその症候に含むが，厳密にはIVMsには分類されない．紙数の都合もあるため，PDについての詳述は割愛し，IVMsに対する定位脳手術を論ずるうえで必要不可欠の事柄について触れるにとどめる．

IVMsに対する定位脳手術について2部に分け，本稿ではIVMsの治療ターゲットと手術時の座標決定法について概説し，次回はIVMs疾患各論と治療ターゲットの選択について記載する．

## Ⅱ．不随意運動に対する外科治療の歴史と大脳基底核－視床－皮質ループ

IVMsは薬物治療に抵抗するものが多いため，外科治療は比較的古くから試みられ始めた．そのさきがけは，1940年代に行われた開頭術による皮質下構造（視床や淡蒼球）の破壊術[18]であるが，同時期には運動皮質[4]や大脳脚[23]（つまり錐体路）の切除術や，前脈絡叢動脈結紮術[5]など，侵襲的な手術も行われていた．より正確で侵襲が少なく，再現性のある外科治療が可能となるには，SpiegelとWycis[19]，やや遅れてLeksell[12]による

**表1　おもな不随意運動**

| |
|---|
| ①ジストニア（dystonia） |
| 一次性ジストニア |
| 全身性ジストニア……DYT1 ジストニアなど |
| 分節性ジストニア……Meige 症候群など |
| 局所性ジストニア……書痙，痙性斜頸など |
| 二次性ジストニア |
| 遅発性ジストニア，脳性麻痺など |
| ②振戦（tremor） |
| 安静時振戦 |
| 動作時振戦 |
| 姿勢時振戦 |
| 運動時振戦 |
| その他の振戦 |
| ③舞踏運動（chorea） |
| ④バリズム（ballism） |
| ⑤発作時ジスキネジア（paroxysmal dyskinesias） |
| ⑥ミオクローヌス（myoclonus） |

定位脳手術装置の開発を待たなければならない．

レボドパの登場によって PD の外科治療が激減した 1970 ～ 1980 年代後半にかけても，振戦あるいはジストニアに対する thalamotomy および pallidotomy は，限定的であったにせよ継続されてきた[9, 13, 16]．Laitinen ら[11] が PD に対する Leksell の淡蒼球内節（globus pallidus internus: GPi）後腹側部凝固術（posteroventral pallidtomy: PVP）を改変して再導入し，さらにこれまでおもに振戦に対して試みられてきた脳深部刺激術（deep brain stimulation: DBS）[2, 3, 20] が普及し始めた 1990 年代以降，IVMs に対する外科治療が再び注目されるようになってきた．

DBS を中心とした近年の定位脳手術法が発展する基盤には，このような外科技術の発達や画像診断法の進歩が存在したが，治療ターゲットの選択に理論的根拠を与えた機能解剖学的知見として，DeLong ら[7] が提唱した大脳基底核－視床－皮質ループの並列処理システムが重要である．IVMs は運動ループのいずれかの部位の活動異常により，視床－皮質への抑制性制御が強化あるいは減弱され，結果的に過小運動や過剰運動が引き起こされるとされる（図 1）．特に PD では，このモデルによって臨床症状が説明されるだけでなく，すでに行われていた GPi 破壊術に正当性が与えられ，視床下核（subthalamic nucleus: STN）手術の可能性が理論づけられた．

DeLong らのモデルはジストニアの臨床症状を説明するのにも有用である．しかし，GPi 手術（特に破壊術）の臨床効果[9, 13, 22] を説明することができない．すなわち，神経活動が低下している GPi を破壊すると，運動の抑制性制御がさらに減弱してしまい，ジストニア症状の増悪につながるはずである．

この矛盾的解釈は，同じ hyperkinetic disorder である舞踏運動／バリズムに対する GPi 破壊術についても指摘されている．Vitek ら[21] は，ジストニアおよびバリズム患者の術中電気生理学検査において，特徴的な“intermittent grouped discharge”を見出し，GPi（および GPe）の abnormal firing pattern がジストニア症状発現に関与しており，“rate theory”に“pattern theory”を加味した新モデルを提唱した（図 1）．今後，IVMs の病態生理と機能神経外科の臨床効果をより適切に説明するために，機能解剖モデルの修正が行われていくと考えられるが，現在のモデルでは重視されていない線条体内 compartment 構造[8] や小

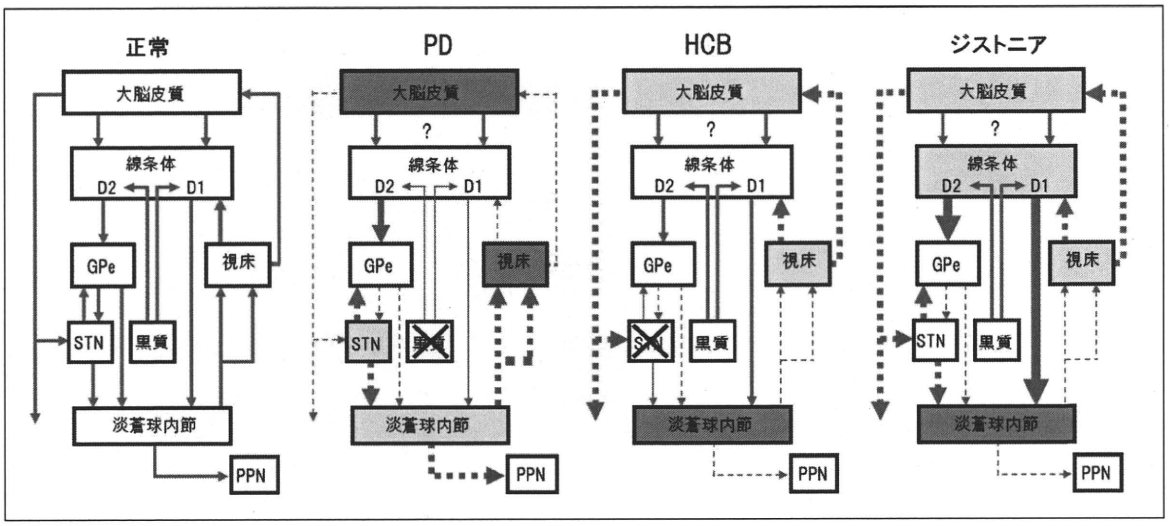


**図1　運動異常症における運動ループの活動変化を示すモデル**（文献21より改変）

赤線はグルタミン酸作動性興奮性出力，青線はGABA作動性抑制性出力を示す．ただし，黒質からの出力はいずれもドパミン作動性で，D1とD2レセプターを持つ線条体細胞に対し，それぞれ興奮性と抑制性の相反する作用を示す．それぞれの病態において，「正常」のシェーマに比してより太い線は出力の増強，より細い線は減弱を示す．DeLongら[15]の理論に従えば，PDでは黒質ドパミン作動性出力の減少により，STNと淡蒼球内節が過剰興奮に陥り，視床ー皮質系の抑制が強まって寡動を生じる．HCBおよびジストニアでは，異常活動の起源はそれぞれSTN，線条体と異なるが，いずれも淡蒼球内節活動が低下して，運動の抑制性制御が減弱（脱抑制）し，過剰運動を引き起こす．破線は活動パターンの異常を意味し，DeLongらのclassic"rate theory"だけでは矛盾の生じる現象を説明するために，Vitekら[21]の"pattern theory"が補完されている．

GPe: globus pallidus externus, HCB: hemichorea/ballismus, PD: Parkinson's disease, PPN: pedunculopontine nucleus, STN: subthalamic nucleus

脳との線維連絡[24]なども考慮されるべきであろう．

## Ⅲ．IVMsの治療ターゲット

IVMsに対するおもな治療ターゲットは，GPiと視床外側部（motor thalamus）である．視床の亜核分類については，大きくアメリカ学派とドイツ学派に分かれ，さらに緒家による微妙な呼称変容があるため，混乱を招きがちである[14]．ただし機能外科の治療ターゲットは（少なくとも筆者らの場合）Schaltenbrandのアトラスに基づいて決定されるので，必然的にHasslerら（ドイツ学派）の亜核分類が採用されることが多いと思われる．

### 1）GPi

GPiは，大脳基底核出力核であり，大脳基底核ー視床ー皮質ループの中枢的役割を担っている．GPiは，多くのhyperkinetic disordersの治療ターゲットであるが，並列処理システムのtopographical organizationから，最も効果的な部位はsensorimotor territoryに相当するGPi後腹側部である[15]．GPi内には機能分画（functional organization）が存在し，背外側と腹内側では，DBSを行った際，異なる臨床効果が発揮される（図2）[10]．すなわち，背側刺激はPDの寡動に有効だがレボ

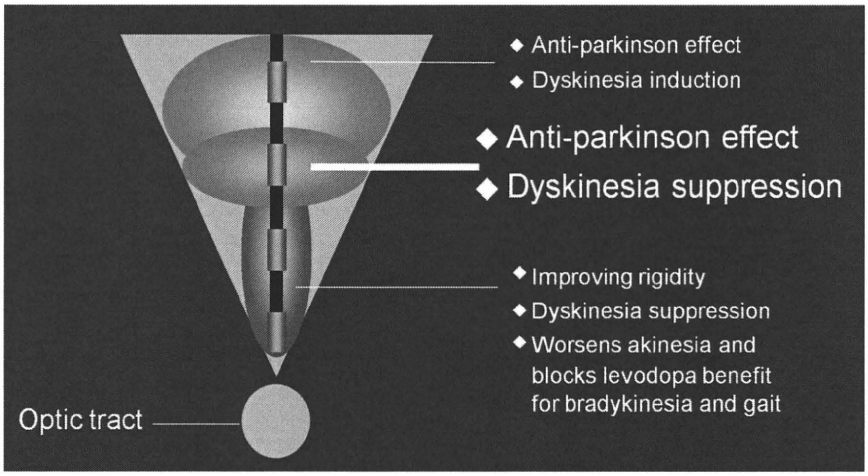


**図2　淡蒼球内節における2つの機能分画**（文献10より改変）
淡蒼球内節背側刺激は，パーキンソン病の寡動に有効だがレボドパ誘発性ジスキネジアが悪化し，腹側刺激はジスキネジアや振戦に有効だが寡動が悪化するとされる．ジストニアについても類似の現象が見られ，腹側刺激が有効である．

ドパ誘発性ジスキネジアが悪化し，腹側刺激はジスキネジアや振戦に有効だが寡動が悪化するとされる．ジストニアについても，後述するように刺激部位による類似の現象が見られることが多い．またGPi外側部（GPie）からレンズ核ワナ（ansa lenticularis: AL）が内側部（GPii）の腹側を回ってForel野にいたり，GPiiからはレンズ核束（lenticular fasciculus）が出て視床束（thalamic fasciclus）としてALと合流する．GPiの腹側部はALと接しているため，この部位を刺激すると，淡蒼球－視床路の投射線維にも影響を及ぼすため，ジストニアの改善には好都合と言える．

GPiにはfunctional organizationに加えて，他の大脳基底核との線維連絡を持つsomatotopic organization[1, 6, 17]が存在する．GPi（およびGPe）を内外，吻尾，そして背腹の3軸方向に分けた場合，下肢領域はGPiの中心部背側に位置し，上肢領域は前後に広く存在するが，より外側に位置する．顔面領域は腹尾側に同定される．しかし，ジストニアではこのsomatotopyが変容し非特異的になっているとの指摘もあり[21]，刺激電極を使い分けてsomatotopyを選択し，罹患筋群を個別に治療することは，きわめて困難であると考える．

2）視　床

IVMsの治療ターゲットになる視床の亜核群は外側に位置するmotor thalamusと呼ばれる部位で，Hasslerの腹吻側（ventralis oralis: Vo）［＝Walkerの外腹側（ventralis lateralis: VL）］核と腹側中間（ventralis intermedius: Vim）核である．Vo核はさらに前方部（Voa）と後方部（Vop）に分かれる．矢状断アトラスで見ると，これらの亜核は2 mm幅の短冊状構造で配列している（**図3**）．

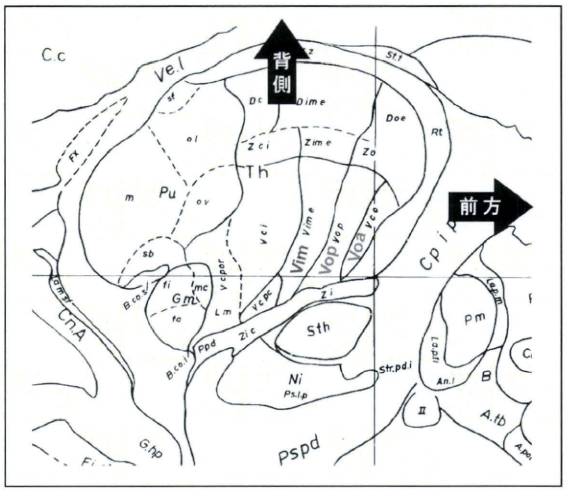


**図3　視床外側部の Schaltenbrand アトラス矢状断のシェーマ（AC-PC 線の 15 mm 外側）**

前方から Voa，Vop，Vim の亜核が約 2 mm 上下に伸びた短冊状構造に配列している．縦線は MCP を通る coronal plane を，横線は AC-PC 線を通る horizontal plane を示している．
AC: anterior commissure, MCP: mid-commissural point, PC: posterior commissure, Vim: ventralis intermedius, Voa: ventralis oralis anterior, Vop: ventralis oralis posterior

Vim 核の後方には感覚中継核である腹尾側（ventralis caudalis: VC）［= Walker の後腹側（ventralis posterior: VP）］核が存在する．Voa 核は GPi から，Vop 核は GPi と小脳歯状核から，Vim 核は小脳歯状核と筋紡錘からそれぞれ入力線維を受け，運動前野と運動野，Vim 核の一部は感覚野に投射している．Voa と Vop は合わせて Vo-complex と呼ばれ，ジストニアのターゲットになる．Vim 核は oscillatory movement 制御の中枢と考えられており，非常に効果的な振戦治療のターゲットである．

## Ⅳ．治療ターゲットの座標決定

筆者らは，FrameLink®システムを用いて仮想ターゲットの座標決定を行っている．Leksell 式フレームを頭部に固定した後，手術室設置の CT 装置を用いて 1 $mm^3$ voxel データを取得する．これと，あらかじめ撮像しておいた 3-D MRI voxel データを fusion することによって，座標決定の準備が整う．われわれの施設では，CT 設置型手術室を利用しているためこの方法をとっているが，フレーム装着後，MRI を撮像してもよい．

MRI T2 強調画像では，鉄分を多く含む STN，赤核および淡蒼球は hypointensity area として描出される．FLAIR 画像は，よりコントラストがつくため，筆者らは好んで用いている（**図 4**）．

STN の場合は直接法によって仮想目標点を決定することも可能であるが，GPi および motor thalamus の仮想目標決定は直接法では困難と考えられ，前交連（anterior commissure: AC）－後交連（posterior commissure: PC）線とその中点（mid-commissural point: MCP）を基準にした間接法を用いる．Schaltenbrand のアトラスに基づいて，例えば GPi の仮想目標点は MCP の 2 mm 前方，20 ～ 21 mm 外側，3 mm 腹側，Vim 核であれば PC の 5 ～ 6 mm 前方，13 ～ 14 mm 外側，AC-PC 線上というようになる．この際，FLAIR で明瞭に描出される STN・赤核と FramLink®アトラスのずれを参考にして仮想目標点の修正を行う（**図 4**）．

最も留意すべきは内包後脚との位置関係で，GPi では内側後方に，視床では外側に走行してい