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

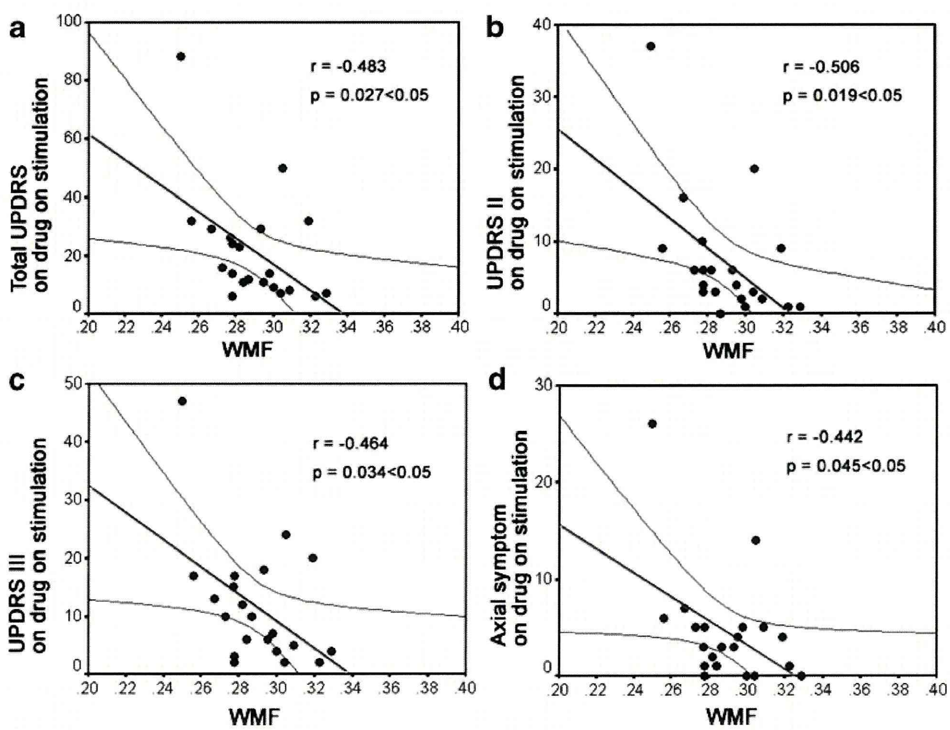

Fig. 5 Scatter plot of postoperative UPDRS scores in the "on" medication "on" stimulation state against the fractional white matter volume (*WMF*). **a** Total UPDRS score, **b** UPDRS part II (ADL) score, **c** UPDRS part III (motor) score, **d** axial symptom subscore. The Pearson correlation coefficient (*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.

Acknowledgments This work was supported in part by a Grant-in-Aid for Scientific Research (KAKENHI; C20591714) to T.H. from the Japan Society for the Promotion of Science (JSPS).

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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Acta Neurochir (2010) 152:997–1006
DOI 10.1007/s00701-010-0609-6

CLINICAL ARTICLE

A positive correlation between fractional white matter volume and the response of Parkinson disease patients to subthalamic stimulation

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Received: 29 August 2009 / Accepted: 1 February 2010 / Published online: 20 February 2010

Abstract
Background Since optimal patient selection is essential for the success of subthalamic nucleus (STN) stimulation, the identification of reliable outcome predictors is important. The purpose of this study was to identify new imaging characteristics sufficiently reliable to predict treatment results.
Method Using preoperative magnetic resonance imaging studies of 21 Parkinson disease (PD) patients treated by STN stimulation, we performed whole brain-based analysis of voxel-based morphometry (VBM) data. Intracranial structures segmented into the gray matter fraction (GMF), white matter fraction (WMF), and cerebrospinal fluid fraction (CSFF) were subjected to univariate and multivariate analysis of the correlation between fractional volumes and postoperative improvement rates using the Unified PD Rating Scale (UPDRS).
Findings At 3 months after surgery, the WMF was significantly correlated with improvement rated on the total UPDRS (p=0.006), UPDRS part II (activities of daily living; p=0.008), UPDRS part III (motor; p=0.005). In contrast, there was no significant correlation between the effect of STN stimulation and GMF or the effect of stimulation and CSFF. The WMF also showed a significant correlation with postoperative scores in the "on" drug and "on" stimulation state (total UPDRS, p=0.027; UPDRS part II, p=0.019; UPDRS part III, p=0.034).
Conclusions Our data indicate that patients with a larger white matter volume benefited from STN stimulation whereas the volume of other brain structures was not correlated with its effect. We posit that preserved connectivity between components of the basal ganglia-thalamocortical circuit may be required for the effectiveness of electrical stimulation. VBM may represent a powerful tool to predict the response of patients with advanced PD to STN stimulation.

Keywords Parkinson disease · Subthalamic stimulation · Voxel-based morphometry · White matter

Abbreviations

AC–PC	Anterior commissure–posterior commissure
ADL	Activities of daily living
BrF	Brain fraction
CNS	Central nervous system
CSFF	Cerebrospinal fluid fraction
DBS	Deep brain stimulation
GMF	Gray matter fraction
LEDD	Levodopa equivalent drug dose
MPRAGE	Three-dimensional magnetization-prepared rapid gradient-echo
MRI	Magnetic resonance imaging
PD	Parkinson disease
PDRP	Parkinson disease-related pattern
PET	Positron emission tomography
SMA	Supplementary motor area
STN	Subthalamic nucleus
UPDRS	Unified Parkinson's Disease Rating Scale
VBM	Voxel-based morphometry
WMF	White matter fraction

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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

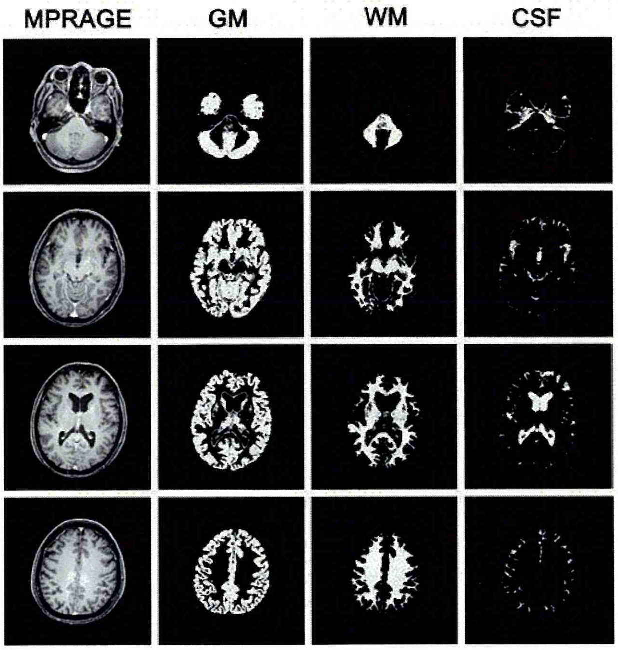

Fig. 1 Preoperative MRI and segmented images of an illustrative case SPM5 supplemented with *spm_segment* (see Methods Section) generated three mutually exclusive masks corresponding to the gray (*second column*) and white matter (*third column*) and the CSF (*fourth column*) from 3D magnetization-prepared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

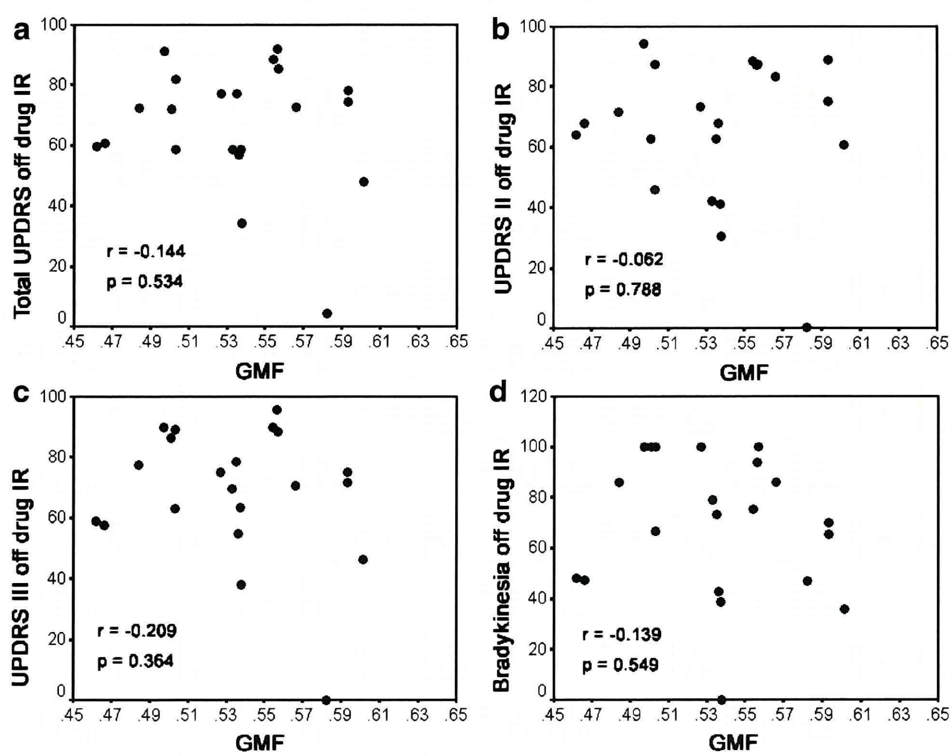

Fig. 2 Scatter plot of postoperative improvement rates (*IR*) in the "off" medication state against the fractional gray matter volume (*GMF*). **a** Total UPDRS score, **b** UPDRS part II (ADL) score, **c** UPDRS part III (motor) score, **d** bradykinesia subscore. No linear regression curve is shown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

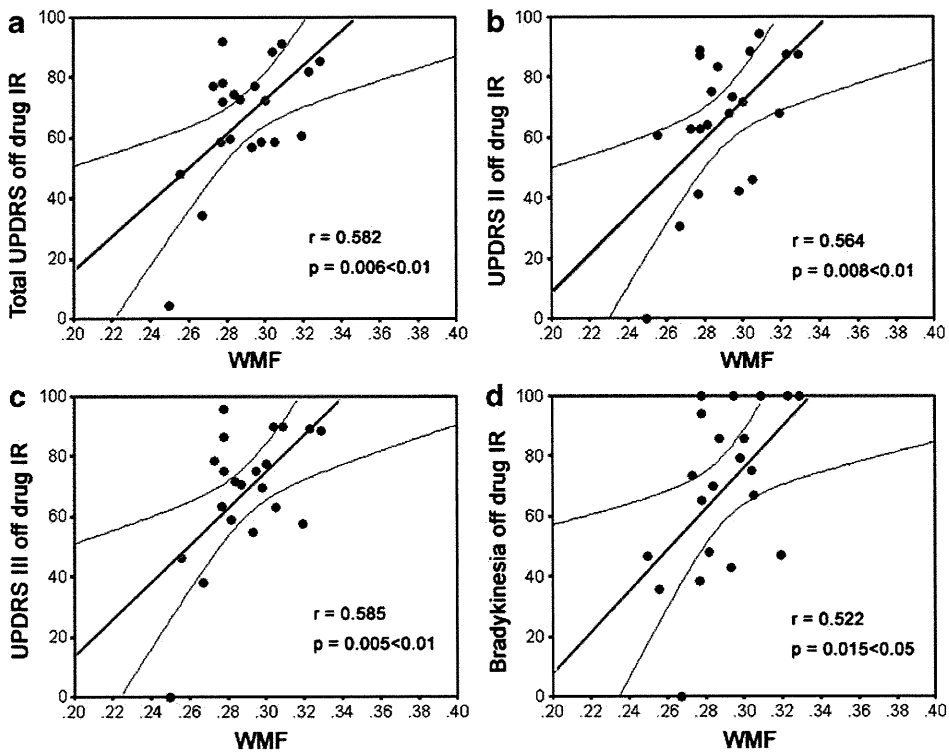

Fig. 3 Scatter plot of postoperative improvement rates (*IR*) in the "off" medication state against the fractional white matter volume (*WMF*). **a** Total UPDRS score, **b** UPDRS part II (ADL) score, **c** UPDRS part III (motor) score, **d** bradykinesia subscore. The Pearson correlation coefficient (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

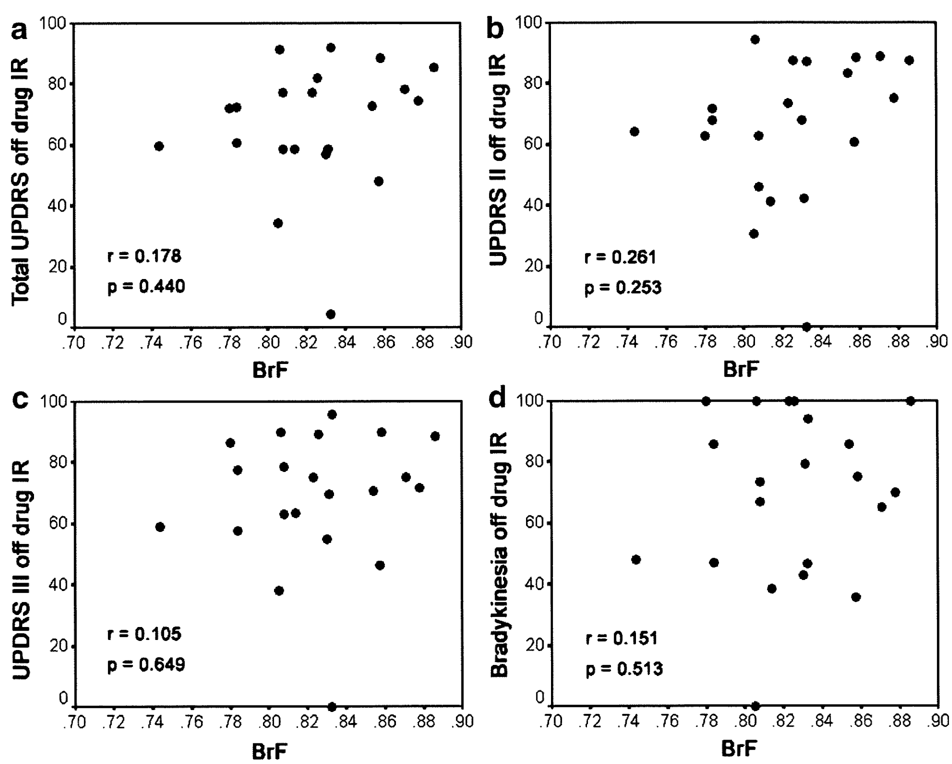

Fig. 4 Scatter plot of postoperative improvement rates (*IR*) in the "off" medication state against the fractional brain volume (*BrF*). **a** Total UPDRS score, **b** UPDRS part II (ADL) score, **c** UPDRS part III (motor) score, **d** bradykinesia subscore. No linear regression curve is shown because 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

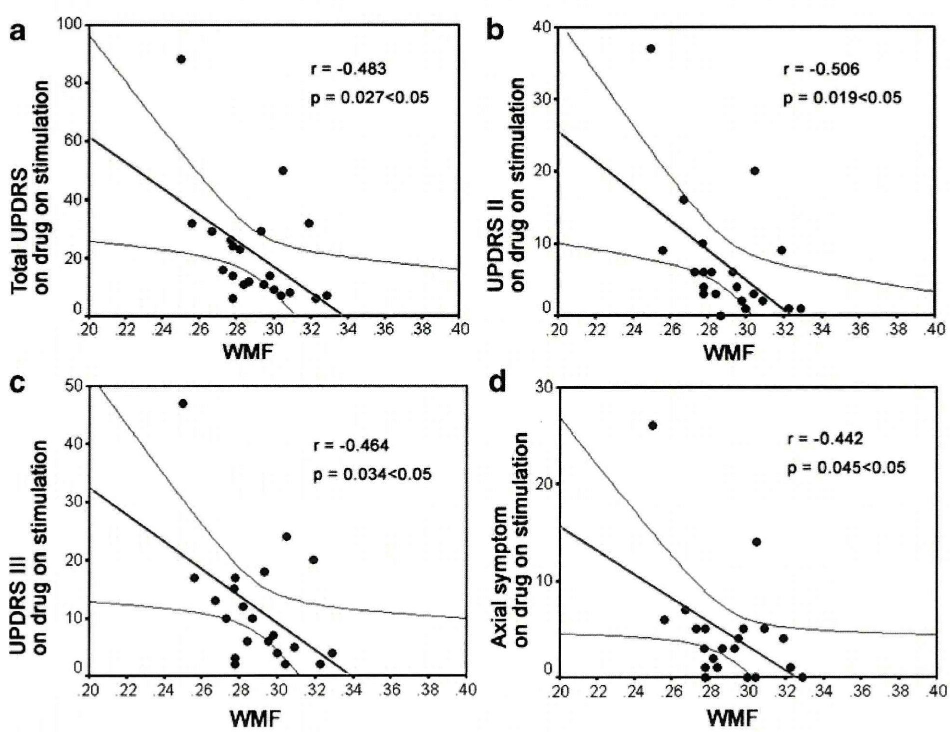

Fig. 5 Scatter plot of postoperative UPDRS scores in the "on" medication "on" stimulation state against the fractional white matter volume (*WMF*). **a** Total UPDRS score, **b** UPDRS part II (ADL) score, **c** UPDRS part III (motor) score, **d** axial symptom subscore. The Pearson correlation coefficient (*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.

Acknowledgments This work was supported in part by a Grant-in-Aid for Scientific Research (KAKENHI; C20591714) to T.H. from the Japan Society for the Promotion of Science (JSPS).

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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Acta Neurochir (2010) 152:2063–2068
DOI 10.1007/s00701-010-0825-0

CLINICAL ARTICLE

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

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Received: 13 May 2010 / Accepted: 24 September 2010 / Published online: 7 October 2010

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

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and a foundation subscribed by Hokuto Hospital, Obihiro, Hokkaido, Japan.

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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 depressed 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 γ-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

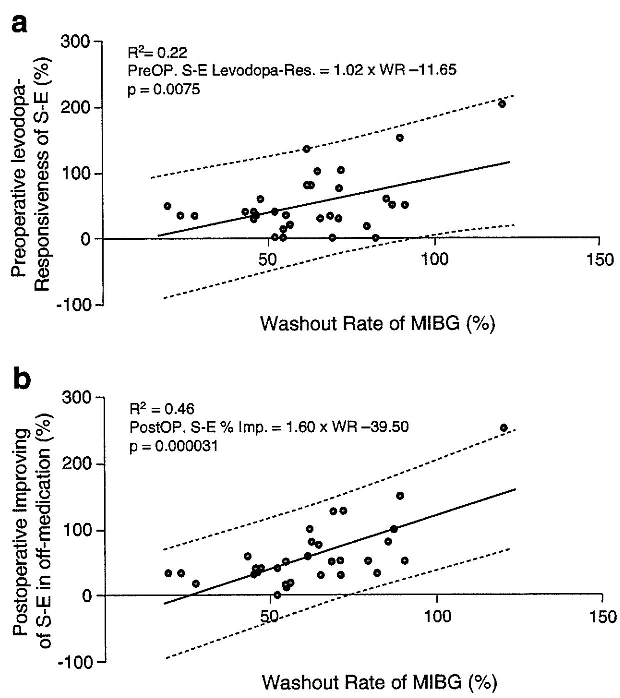

Fig. 1 Scatter plot and linear regression analysis (95% confidence interval) showing the relationship between WR and preoperative levodopa responsiveness of S–E (**a**), and between WR and postoperative improving rate of S–E in off-medication (**b**). There is a statistically significant correlation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

Acknowledgement This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and a foundation subscribed by Hokuto Hospital, Obihiro, Hokkaido, Japan.

Conflicts of interest None.

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脳神経外科速報 vol.20 no.12 1405～1411, 2010

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