in clinical practice of neurology, medical education, neuroscience research and industrial technology.

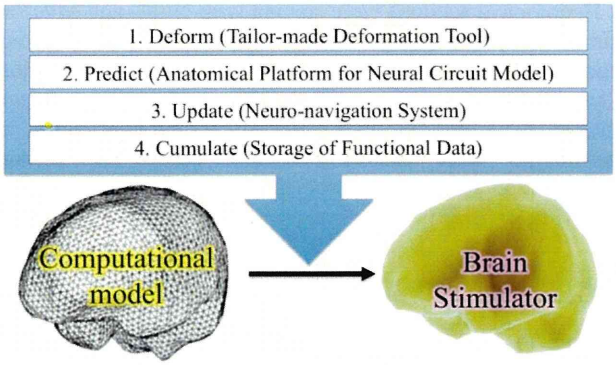

Fig. 4. Brain simulator as a computational brain model with 4 functions

IV. Achievements in 2010

A. Construction of Histological Brain Atlas

A whole brain from the cadaver, 59 year-old male who died of acute deterioration (2 days) of chronic obstructive pulmonary disease was obtained. Before its use in this study, the body was perfused with 10% formalin through femoral artery within 3 hours after death and further immersed in alcohol and used for the gross anatomy practical course of medical students in Kyushu University. After a few years of immersion, the brain was carefully extracted and used in the practical course of anatomical education and stored in 10% formalin. Gross observation in the formalin-fixed brain detected minimal senile atrophy and there was no pathological lesion in the cutting edge of every block.

The hemisphere embedded in agar was further cut into 1 cm-thick block, perpendicular to intercommissural line. The blocks were made as small as it can be mounted on the tissue holder (70x70mm) of blade-oscillation micro-slicer.

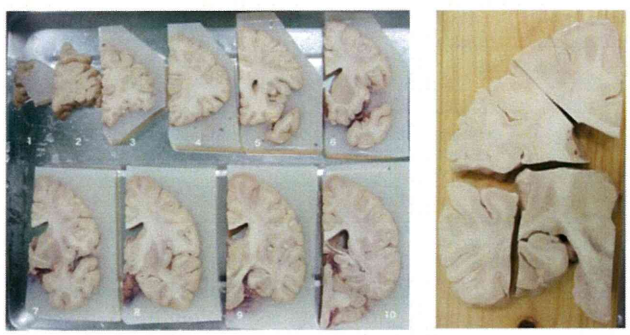

Fig. 5. Coronal block of hemisphere from cadaver

The histological sections with Nissl stain were scanned into bitmap format and the neural structures were manually traced using Neurolucida.

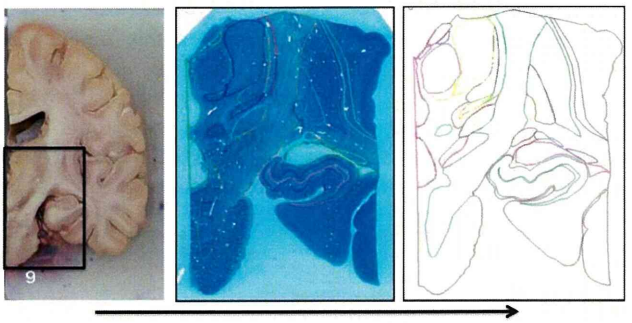

Fig. 6. Manual tracing of the neural structure

B. Digitalization of Classical Atlas

Manual tracing of the neural structures is a considerably time-consuming work; therefore, in order to promote efficiency in manual tracing of neural structures, the classical brain atlas made by Mai et al. [7] was digitalized as a reference. This digitalized model can be cut in an arbitrary section and superimposed on the histological sections, when identifying a region-specific neurons and cytoarchitecture.

C. Data collection of 3D-MRI of normal brain

High-resolution T1-weighted MR images of brain in healthy volunteers were collected. So far, 19 MR images (20-29 yr, 3 males and 1 female; 30-39 yr, 2 females; 40-49 yr, 2 males and 1 female; 50-59 yr, 5 males; 60-69 yr, 4 males and 1 female) were collected.

Using Neurolucida, visible neural structures on T1-MR images were manually traced and being reconstructed. These 3D models will be used for non-rigid deformation and collection of regional atrophy ratio for normal aging and disease population.

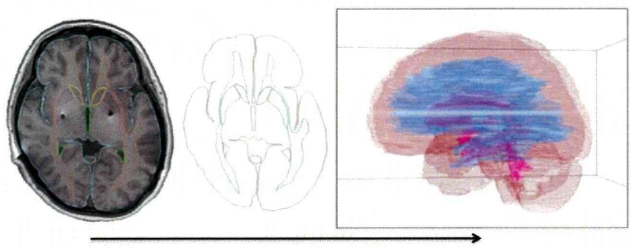

Fig. 7. Manual tracing of the boundaries of visible neural structure

D. 2D-deformation Program

By use of self-organizing deformable model by Morooka et al. [8], the programming for non-rigid deformation of brain atlas is now on-going study with 2D model (a plane including intercommissural line). Once the 2D-deformation method is established, the program will be extended in 3D-model. The histological brain atlas will be deformed to fit individual brain MR images as a tailor-made brain atlas.

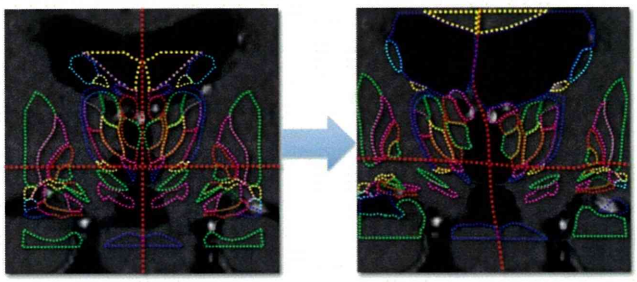

Fig. 8. A goal of non-rigid 3D-deformation for tailor-made atlas

V. Future direction in 2011

The computational brain model is now being constructed. In each step, the collection of MR images, the conversion to 3D-model and non-rigid deformation are the most time-consuming and essential determinants in this project. Further revolution to "Brain Simulator" will be achieved when 4 important functions; tailor-made brain atlas (deform), simulation of therapy (predict), intraoperative navigation (update), updatable knowledge database (cumulate).

Acknowledgment

We are grateful to Mr. T. Koya, Ms. M. Ueguchi, Ms. M. Koga, Ms. A. Ishii, Ms. S. Noda, Ms. S. Sasaki, Ms. N. Fukuyoshi, Ms. K. Fukuda for their important contributions to this project.

References

[1] G. Schaltenbrand and W. Wahren, *Atlas for stereotaxy of the human brain.* Thieme, Stuttgart, 1977.

[2] J. Talairach and P. Tournoux, *Co-planner stereotactic atlas of the human brain.* Thieme, New York, 1988.

[3] W.L. Nowinski and A. Thirunavuukarasuu: *The Cerefy Clinical Brain Atlas on CD-ROM.* New York, Thieme, 2004.

[4] K. Morooka, T. Fukuda and Y. Miyagi, T. Hayami, T. Okamoto, X. Chen, "3D Human brain modeling for constructing Japanese brain database," *Fourth International Workshop on Medical Imaging and Augmented Reality*, 2008.

[5] T. Fukuda, K. Morooka and Y. Miyagi, "A simple but accurate method for histological reconstruction of the large-sized brain tissue of the human that is applicable to construction of digitized brain database," *Neurosci Res* 67(3):260-265, 2010.

[6] A.W. Toga, P.M. Thompson, S. Mori, K. Amunts and K. Zilles, "Towards multimodal atlases of the human brain," *Nature Rev* 7:952-966, 2006.

[7] J.K. Mai, G. Paxinos and T. Voss, *Atlas of the Human Brain, Third Edition. Academic Press, 2007*

[8] K. Morooka, S. Matsui and H. Nagahashi "Self-organizing Deformable Model for mapping 3D Object Model onto Arbitrary Target Surface", *The 6th International Conference on 3-D Digital Imaging and Modeling*, pp.193-200, 2007

List of accepted and published papers since 1st April 2010

[9] Y. Miyagi, T. Fukuda, K. Morooka, K. Chen, T. Hayami, T. Okamoto, K. Sunagawa, S. Tobimatsu and T. Yoshiura, "Application of digital imaging technique for the construction of stereotactic human brain atlas," *Functional Neurosurg* 49(2):136-141, 2010.

Case Report

Stereotactic and Functional Neurosurgery

Stereotact Funct Neurosurg 2010;88:259–263
DOI: 10.1159/000315464

Received: July 30, 2009
Accepted after revision: March 14, 2010
Published online: June 8, 2010

Thalamic Deep Brain Stimulation for the Treatment of Action Myoclonus Caused by Perinatal Anoxia

Kazutaka Kobayashi[a, b] Yoichi Katayama[a, b] Toshiharu Otaka[a, b] Toshiki Obuchi[a, b] Toshikazu Kano[a, b] Takafumi Nagaoka[a, b] Masahiko Kasai[a] Hideki Oshima[a, b] Chikashi Fukaya[a, b] Takamitsu Yamamoto[a, b]

[a]Division of Neurosurgery, Department of Neurological Surgery, and [b]Division of Applied System Neuroscience, Department of Advanced Medical Science, Nihon University School of Medicine, Tokyo, Japan

Key Words
Myoclonus · Deep brain stimulation · Thalamus · Perinatal anoxia

Abstract
Background: Perinatal anoxia rarely causes myoclonus as the main neurologic abnormality. The exact neuronal mechanism underlying myoclonus induced by perinatal anoxia remains unknown. Some studies have indicated that the development of involuntary movements may be related to the maturation of the thalamus after birth. ***Objectives and Methods:*** Here, we describe the first case of a patient who developed action myoclonus after experiencing perinatal anoxia and was successfully treated by chronic deep brain stimulation (DBS) of the thalamus (thalamic DBS). ***Results and Conclusion:*** The effectiveness of chronic thalamic DBS in this patient supports the concept of involvement of the thalamus in postperinatal anoxic myoclonus.

Introduction

Myoclonus is rarely the main neurologic sequela of perinatal anoxia [1–3]; it is more commonly observed after brain anoxia in adults [1–3]. Deep brain stimulation (DBS) of the thalamus (thalamic DBS) is effective for the treatment of tremors [4–13]. Furthermore, thalamic DBS has been reported to effectively control various other involuntary movements such as hemiballismus [8, 14], writer's cramp [15] (which is a type of dystonia) and chorea associated with a case of cerebral palsy [16]. This treatment has also been found to ameliorate myoclonic symptoms in patients with inherited myoclonus dystonia syndrome [17–19]. However, the effectiveness of DBS for the treatment of myoclonus induced by perinatal anoxia has not yet been studied. We report here the case of a patient who developed action myoclonus as a result of perinatal anoxia and was successfully treated by thalamic DBS.

Case Report

Patient History

A 36-year-old right-handed man presented with marked aggravation of involuntary movements. The patient had a history of perinatal hypoxia and was diagnosed as having floppy infant syn-

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1011–6125/10/0884–0259$26.00/0

Accessible online at:
www.karger.com/sfn

Kazutaka Kobayashi, MD, PhD
Department of Neurological Surgery, Nihon University School of Medicine
30-1 Oyaguchi Kamimachi
Itabashi-ku, Tokyo 173-8610 (Japan)
Tel. +81 33 972 8111, Fax +81 33 554 0425, E-Mail kitta@med.nihon-u.ac.jp

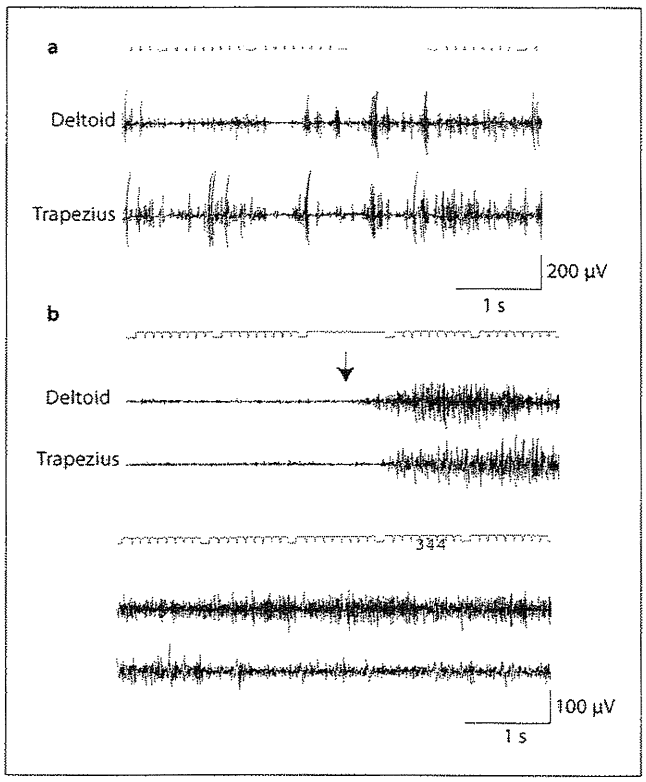

Fig. 1. Surface electromyography (EMG) of the deltoid and trapezius in the present patient. **a** Before surgery; recording of the patient attempting to hold his left arm in front of him. **b** After surgery; recording during thalamic stimulation. The arrow indicates the point at which the patient started to hold his left arm out in front of him. (Note: the EMG amplitude scale differs between **a** and **b**.)

drome at birth. He had an unsteady gait due to hypotonia of the muscles of the lower limbs and required an orthotic for walking between the ages of 12 and 18 months. He was diagnosed as having cerebral palsy at 18 months of age. He developed slight involuntary movements of both his upper limbs at 4 years of age. At 13 years of age, these involuntary movements became markedly aggravated; they subsequently progressed to jerky movements and have worsened steadily with advancing age. He has undergone treatment with several drugs, without any obvious effect. He was therefore finally referred to our hospital for DBS surgery at 36 years of age.

On examination, jerky movements of both upper limbs, mainly the proximal limbs, were observed, with no cerebellar signs such as hypotonia or hand ataxia. The involuntary movements appeared occasionally at rest. The finger-to-nose test aggravated the involuntary movements without ataxia. The involuntary movements were stereotyped. Electromyography using surface electrodes revealed irregular and repetitive burst discharges when the patient performed any action, particularly elevation of the arm or holding a cup (fig. 1a). The item of severity of myoclonus with action of the arm on the Unified Myoclonus Rating Scale (UMRS) [20] was employed to evaluate the action myoclonus. This item is scored as the product of scores for the frequency and amplitude of myoclonus with action. The frequency of myoclonus is scored as follows: no jerks per 10 s, 0; ≤1 jerk per 10 s, 1; 2 or 3 jerks per 10 s, 2; 4–9 jerks per 10 s, 3; ≥10 jerks per 10 s, 4. The amplitude of the worst myoclonus seen on finger-to-nose testing is scored using the following procedure: ask the patient to hold both arms forward with the palms down for 10 s, then ask the patient to extend both wrists for 10 s, then perform the finger-to-nose test 4 times and finally, ask the patient to finish by leaving his finger on his nose for 10 s. The movement is scored as follows: zero, 0; trace movement only, 1; small-amplitude jerks, easily visible (<25% of maximum possible movement), 2; moderate-amplitude jerks (25–75% of maximum possible movement), 3; large-amplitude jerks (near maximum movement), 4. The score for the severity of myoclonus with action of the arm on the UMRS was 12 for the left arm and 9 for the right arm.

Magnetic resonance (MR) imaging of the brain revealed slight brain atrophy, without any other abnormalities. The involuntary movements improved at rest and disappeared during sleep. There was no known family history of movement disorder or other neurological disease. We made plans to conduct surgery on the patient for implantation of a DBS electrode to treat the myoclonus, and obtained the informed consent of the patient and his family. We did not schedule the performance of bilateral surgery at one time because we needed to confirm the effectiveness of DBS for the patient. We therefore planned the introduction of an electrode in the right thalamus first, since the involuntary movements of the left hand were worse than those of the right hand.

Surgical Procedure

The surgical procedure was planned using MR images. Following the administration of a local anesthetic, a Leksell G head frame (Elekta Instruments AB) was applied to the patient's head. The anterior commissure (AC) and posterior commissure (PC) were identified using Leksell SurgiPlan® (Elekta Instruments AB), a customized software program for functional stereotaxy. An X-ray indicator (Elekta Instruments AB) was also employed to identify the AC and PC on plain X-ray films. A burr hole was made approximately 2.0 cm anterior to the coronal suture and approximately 2.5 cm lateral to the midline. Extracellular single- and multiunit recordings were obtained using a semimicroelectrode (0.4 MΩ). With the intention of identifying the anterior border of the nucleus ventrocaudalis (Vc), which constitutes the nucleus ventralis intermedius (Vim)-Vc border, we directed the first trajectory of the semimicroelectrode utilized for extracellular unit recording toward the anterior aspect of the PC in lateral view and at the level of the AC-PC line and 14.5 mm lateral to the midline. Neuronal activity was also fed into an audiospeaker. The neuronal activity was examined under various conditions such as somatic sensory stimulation and active movements. Neurons that were activated in response to somatic sensory stimulation, that is, in response to passive joint movements of the contralateral limb without a response in skin deformation caused by the stimuli, were classified as (1) deep sensory cells; and neurons that responded to light touch on the skin of the face and contralateral limbs were classified as (2) cutaneous sensory cells. The Vim-Vc border was defined physiologically as the anterior-most neurons along a trajectory which was mapped such that >50% of the neu-

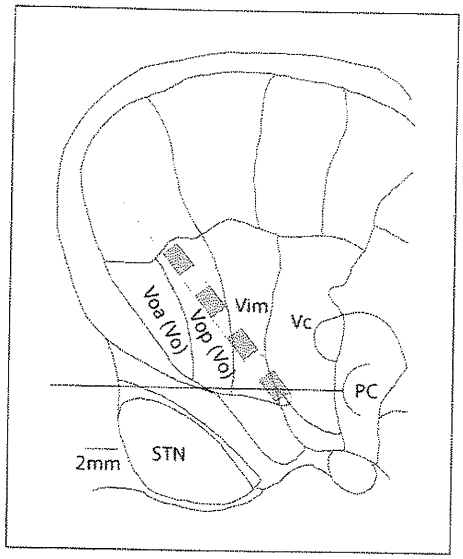

Fig. 2. Anatomical relationship between the thalamic nucleus and DBS electrode. **a** A 14.5-mm lateral section from the Schaltenbrand-Wahren human brain atlas with the AC-PC length stretched to fit the coordinates obtained from the patient's stereotactic magnetic resonance images. STN = Subthalamic nucleus; Voa = nucleus ventralis oralis anterior; Vop = nucleus ventralis oralis posterior.

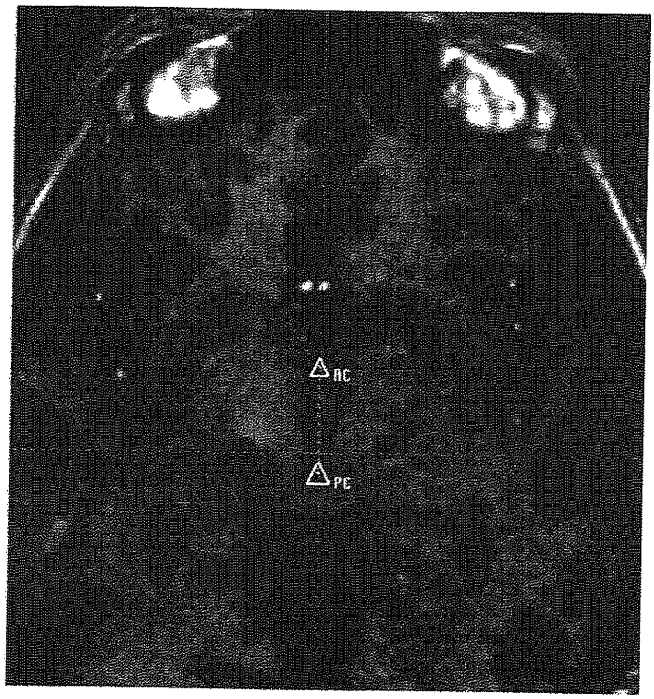

Fig. 3. Location of bilateral DBS electrodes on magnetic resonance (MR) imaging. Postoperative T_1-weighted axial MR imaging of the brain revealed the lead locations at the level of the AC-PC commissural plane. The leads are visualized as dark circular spots in the brain parenchyma.

rons located posterior to the trajectory were either deep or cutaneous sensory neurons [21]. On the basis of observations made during our initial trajectory assessment, the Vim-Vc border was identified as a vertical line approximately 3 mm anterior to the PC. This identification was consistent with the Vim-Vc border determined based on the Schaltenbrand-Wahren atlas. The second trajectory of the semimicroelectrode was directed toward a position on the Vim-Vc border at the level of the AC-PC line, 14.5 mm lateral to the midline. The target was approached through the burr hole at an angle of 52° to the horizontal plane of the AC-PC line. Subsequently, the DBS electrode (model 3387; Medtronic Inc., Minn., USA) was implanted through the second trajectory using stereotactic instruments, and a test stimulation was conducted with the DBS electrode in place. This electrode has 4 contacts that are numbered sequentially from 0 to 3, with the most distal contact being 0 and the most proximal contact being 3. Each contact is 1.5 mm long, and the contacts are spaced 1.5 mm apart. The DBS electrode was implanted to cover a wide region of the thalamus, including not only the Vim but also the nucleus ventralis oralis (Vo).

Contact 0 was located at the Vim-Vc border; contact 1 in the central part of the Vim, and contacts 2 and 3 within the Vo (fig. 2). Test stimulations were performed for 4 days after completion of the procedure to confirm myoclonus suppression (fig. 1b). The stimulations showed that satisfactory control of the involuntary movements had been achieved. Therefore, under general anesthesia, an internal pulse generator (Soletra; Medtronic) was placed in an infraclavicular pocket and connected subcutaneously to the DBS lead. After 2 weeks, another DBS electrode was implanted into the left Vo/Vim, and a pulse generator was also implanted using the method described above (fig. 3).

Postoperative Outcome

After the operations, we assessed the most effective combination of contacts of the electrode at a frequency of 135 Hz and a pulse width of 0.21 ms. The voltage of stimulation was increased to an upper limit where such adverse effects as paresthesia began to appear. The effect of stimulation was evaluated with blinded contact combinations.

The following combinations stimulated mainly the Vim (fig. 2): contact 0 as the anode (+) and contact 1 as the cathode (–), contact 1 as the cathode (–) and contact 2 as the anode (+), and monopolar stimulation using contact 1 as the cathode (–); these combinations had some effect on the myoclonus. However, the strongest effect was achieved when contact 1 was the cathode (–) and contact 3 was the anode (+); this combination activated a wide area extending from the Vo to the Vim. When contact 0 located in the Vc was used as the cathode (–), paresthesia was evoked by a low intensity of stimulation. The optimal combinations were the same on both sides. At the 24-month follow-up, the item of severity of myoclonus with action of the arm on the UMRS score was reduced from 12/16 to 2/16 for the left arm and from 9/16 to 2/16 for the right arm (table 1).

Table 1. Efficacy of thalamic DBS for myoclonus

Severity of myoclonus with action of the arm on the UMRS	Left arm		Right arm	
	before surgery	after surgery	before surgery	after surgery
Total score (frequency × amplitude)	12	2	9	2
Frequency	4	2	3	2
Amplitude	3	1	3	1

The combination of electrode contacts used was as follows: contact 1 as the cathode (–) and contact 3 as the anode (+).

Scores are between 0 (best) and 4 (worst) for frequency and amplitude and between 0 (best) and 16 (worst) for total.

Discussion

Perinatal anoxia can, on rare occasions, induce myoclonus as the main neurologic abnormality [1–3]. The detailed pathophysiology of postperinatal anoxic myoclonus remains unknown. Some reports have suggested that the symptoms of myoclonus after perinatal anoxia of the ascending efferents of the basal ganglia to the thalamus and the thalamocortical pathways are not observed in the first decade of life, despite the development of pathological lesions specific to these symptoms [22, 23]. Moreover, Sugama and Kusano [3] suggested that the development of movement disorder due to perinatal anoxia may be related to the maturation of the thalamus after birth. Our patient could thus have been in a thalamotomy-like state during the infantile period because of the immaturity of the thalamus. With advancing age, various involuntary movements develop after the maturation of the thalamus [3]. The effectiveness of chronic thalamic DBS in our patient may provide support for the concept of involvement of the thalamus in postperinatal anoxic myoclonus.

Recently, it has been reported that thalamic DBS ameliorated myoclonus in a patient with myoclonus dystonia syndrome; this patient did not have a history of perinatal anoxia [17–19]. The optimal site for thalamic DBS remains to be determined. Although the exact mechanisms underlying myoclonus are not understood, a study on monkeys has indicated that dysfunction of the Vim in the thalamus may play a role in the generation of myoclonic jerks [24]. In our patient, however, the most effective stimulation site covered a wide area that included the Vo in addition to the Vim. Tremor suppression is generally attributed to stimulation of the Vim but has been reported to follow stimulation of the Vo [25] or a wide area centered on the Vim and including the Vo [26]. In the large series of cases presented by Benabid et al. [4], the optimal tremor control site was located 4–8 mm anterior to the PC and 0–2 mm superior to the AC-PC line. From these coordinates, we infer that the areas stimulated by spread of the electrical current included not only the Vim but also the Vo [27]. Consistent with our findings, Trottenberg et al. [19] suggested that the effect of thalamic stimulation on myoclonus in myoclonus dystonia syndrome may be attributable to electrophysiological ablation of the Vo and Vim or nearby fiber systems.

Conclusions

We successfully treated a patient with severe action myoclonus due to perinatal anoxia by thalamic DBS. Such thalamic DBS may offer an effective and safe treatment modality for intractable postperinatal anoxic myoclonus.

References

1 Obeso JA, Lang AE, Rothwell JC, Marsden CD: Postanoxic symptomatic oscillatory myoclonus. Neurology 1983;33:240–243.

2 Rondot P, Said G, Ferrey G: Volitional hyperkinesia: electrological study: classification. Rev Neurol (Paris) 1972;126:415–426.

3 Sugama S, Kusano K: A case of dyskinetic cerebral palsy resembling post-anoxic action myoclonus. Brain Dev 1995;17:210–212.

4 Benabid AL, Pollak P, Gao D, Hoffmann D, Limousin P, Gay E, Payen I, Benazzouz A: Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J Neurosurg 1996;84:203–214.

5 Benabid AL, Pollak P, Gervason C, Hoffmann D, Gao DM, Hommel M, Perret JE, de Rougemont J: Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet 1991; 337:403–406.

6 Blond S, Caparros-Lefebvre D, Parker F, Assaker R, Petit H, Guieu JD, Christiaens JL: Control of tremor and involuntary movement disorders by chronic stereotactic stimulation of the ventral intermediate thalamic nucleus. J Neurosurg 1992;77:62–68.

7 Caparros-Lefebvre D, Blond S, Vermersch P, Pecheux N, Guieu JD, Petit H: Chronic thalamic stimulation improves tremor and levodopa-induced dyskinesias in Parkinson's disease. J Neurol Neurosurg Psychiatry 1993; 56:268–273.

8 Katayama Y, Fukaya C, Yamamoto T: Control of poststroke involuntary and voluntary movement disorders with deep brain or epidural cortical stimulation. Stereotact Funct Neurosurg 1997;69:73–79.
9 Koller WC, Lyons KE, Wilkinson SB, Troster AI, Pahwa R: Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor. Mov Disord 2001;16:464–468.
10 Limousin P, Speelman JD, Gielen F, Janssens M: Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. J Neurol Neurosurg Psychiatry 1999; 66:289–296.
11 Nguyen JP, Degos JD: Thalamic stimulation and proximal tremor: a specific target in the nucleus ventrointermedius thalami. Arch Neurol 1993;50:498–500.
12 Yamamoto T, Katayama Y, Kano T, Kobayashi K, Oshima H, Fukaya C: Deep brain stimulation for the treatment of parkinsonian, essential, and poststroke tremor: a suitable stimulation method and changes in effective stimulation intensity. J Neurosurg 2004;101: 201–209.
13 Yamamoto T, Katayama Y, Fukaya C, Oshima H, Kasai M, Kobayashi K: New method of deep brain stimulation therapy with two electrodes implanted in parallel and side by side. J Neurosurg 2001;95:1075–1078.
14 Katayama Y, Yamamoto T, Kobayashi K, Oshima H, Fukaya C: Deep brain and motor cortex stimulation for post-stroke movement disorders and post-stroke pain. Acta Neurochir Suppl 2003;87:121–123.
15 Fukaya C, Katayama Y, Kano T, Nagaoka T, Kobayashi K, Oshima H, Yamamoto T: Thalamic deep brain stimulation for writer's cramp. J Neurosurg 2007;107:977–982.
16 Thompson TP, Kondziołka D, Albright AL: Thalamic stimulation for choreiform movement disorders in children: report of two cases. J Neurosurg 2000;92:718–721.
17 Kuncel AM, Turner DA, Ozelius LJ, Greene PE, Grill WM, Stacy MA: Myoclonus and tremor response to thalamic deep brain stimulation parameters in a patient with inherited myoclonus-dystonia syndrome. Clin Neurol Neurosurg 2009;111:303–306.
18 Kupsch A, Trottenberg T, Meissner W, Funk T: Neurostimulation of the ventral intermediate thalamic nucleus alleviates hereditary essential myoclonus. J Neurol Neurosurg Psychiatry 1999;67:415–416.
19 Trottenberg T, Meissner W, Kabus C, Arnold G, Funk T, Einhaupl KM, Kupsch A: Neurostimulation of the ventral intermediate thalamic nucleus in inherited myoclonus-dystonia syndrome. Mov Disord 2001;16:769–771.
20 Fruchi SJ, Leurgans SE, Hallett M, Fahn S: The unified myoclonus rating scale. Adv Neurol 2002;89:361–376.
21 Hua SE, Lenz FA: Posture-related oscillations in human cerebellar thalamus in essential tremor are enabled by voluntary motor circuits. J Neurophysiol 2005;93:117–127.
22 Segawa M: Pathophysiologies of dystonia and myoclonus: consideration from the standpoint of treatment. Rinsho Shinkeigaku 1995;35:1390–1393.
23 Segawa M: Development of the nigrostriatal dopamine neuron and the pathways in the basal ganglia. Brain Dev 2000;22(suppl 1): S1–S4.
24 Guehl D, Burbaud P, Boraud T, Bioulac B: Bicuculline injections into the rostral and caudal motor thalamus of the monkey induce different types of dystonia. Eur J Neurosci 2000;12:1033–1037.
25 Hassler R, Mundinger F, Riechert T: Stereotaxis in Parkinson Syndrome. Clinical-Anatomical Contributions to Its Pathophysiology. New York, Springer, 1979.
26 Strafella A, Ashby P, Munz M, Dostrovsky JO, Lozano AM, Lang AE: Inhibition of voluntary activity by thalamic stimulation in humans: relevance for the control of tremor. Mov Disord 1997;12:727–737.
27 Starr PA, Vitek JL, Bakay RA: Ablative surgery and deep brain stimulation for Parkinson's disease. Neurosurgery 1998;43:989–1013; discussion 1013–1015.

Neurol Med Chir (Tokyo) 50, 257～259, 2010

Direct Relief of Levodopa-Induced Dyskinesia by Stimulation in the Area Above the Subthalamic Nucleus in a Patient With Parkinson's Disease

—Case Report—

Yasumasa NISHIKAWA, Kazutaka KOBAYASHI*, Hideki OSHIMA*, Chikashi FUKAYA*, Takamitu YAMAMOTO*, Yoichi KATAYAMA*, Akira OGAWA, and Kuniaki OGASAWARA

*Department of Neurosurgery, Iwate Medical University School of Medicine, Morioka, Iwate; *Division of Applied System Neuroscience, Advanced Medical Research Center, and Department of Neurological Surgery, Nihon University School of Medicine, Tokyo*

Abstract

A 71-year-old woman with a 25-year history of levodopa (LD)-responsive Parkinson's disease (PD) developed on-off motor fluctuation and severe peak dose dyskinesia. She underwent deep brain stimulation of the subthalamic nucleus (STN-DBS). STN-DBS induced attenuation of her cardinal PD symptoms and marked improvement of dyskinesia without reduction of LD dosage perioperatively. STN-DBS thus markedly attenuated the cardinal symptoms of PD. LD-induced dyskinesia can also be controlled via reduction of LD dosage as an indirect effect of STN-DBS. The present case provides evidence of the direct antidyskinetic effect of STN-DBS, and suggests that LD-induced dyskinesia can be inhibited by stimulation in the area above the STN.

Key words: deep brain stimulation of subthalamic nucleus, dyskinesia, Parkinson's disease, antidyskinetic effect, area above subthalamic nucleus

Introduction

Deep brain stimulation of the subthalamic nucleus (STN-DBS) induces attenuation of the cardinal symptoms of Parkinson's disease (PD) during off-periods as well as dopa-induced dyskinesia.[4,9,11-13] Relief of dopa-induced dyskinesia after STN-DBS is believed to depend on postoperative reduction of dopaminergic medication,[6] but STN-DBS may directly decrease dopa-induced dyskinesia.[1,5,10,14] We describe a patient with PD whose dopa-induced dyskinesia improved after STN-DBS.

Case Report

A 71-year-old woman with a 25-year history of levodopa (LD)-responsive PD developed on-off motor fluctuation and peak dose dyskinesia with an LD dose of 500 mg/day. She had suffered fracture of her left femur 11 years previously and had difficulty with ambulation due to contracture of her left lower extremity. About 30-60 minutes after each administration of LD, choreiform dyskinesia developed and persisted for 1 hour. Motor score on the United Parkinson's Disease Rating Scale (UPDRS) motor score was 38 in the off-condition and 28 in the on-condition. Dyskinesia score (six body parts, each scored 0-4, maximum score 24) was 17 in the on-condition.

Bilateral STN-DBS was performed. She continued to receive medication perioperatively, except on the day of the procedure. A tentative target was determined based on magnetic resonance (MR) imaging using human brain atlas software, single- and multi-unit extracellular recording, and microstimulation. Model 3387 DBS electrodes were implanted under microelectrode guidance without complications. The electrodes were directed from the frontal burr hole at an angle of 50° to the horizontal plane.

Postoperative MR imaging demonstrated correct placement of the electrodes (Fig. 1). Two of the four contacts (contacts 0 and 1) were within the STN. Contacts 2 and 3 were located in the area above the STN including the Forel H field and the zona incerta. While receiving the same doses of antiparkinsonian drugs as preoperatively, the patient underwent monopolar stimulation using contacts 0 to 3 as the cathode and a case as the anode. However, dysarthria was observed using all contacts under low amplitude. Then she underwent bipolar stimulation using contacts 0 to 2 as the cathode and contact 3 as the anode. The intensity and frequency of stimulation were 1.8 V and 135 Hz, respectively, and the pulse width was 150 μsec. No adverse effect was observed under these conditions. Using contact 0 or 1 as the cathode, her cardinal Parkinson sym-

Received April 14, 2009; Accepted July 29, 2009

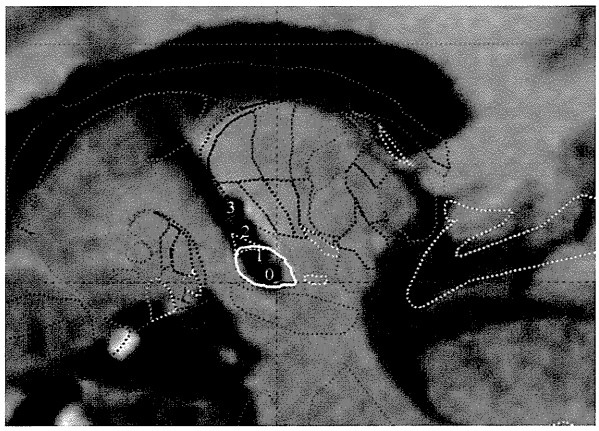

Fig. 1 Postoperative T_1-weighted magnetic resonance image showing contacts placed in the subthalamic nucleus and the area above this nucleus.

Table 1 Correlation between position of the cathode and symptoms under bipolar stimulation

Cathode contact	Rigidity	Tremor	Akinesia	Dyskinesia
0	↓	↓	↓	→
1	↓	↓	↓	→
2	↓	↓	↓	↓↓

Anode was contact 3. →: no change, ↓: decrease, ↓↓: large decrease.

ptoms were improved, although LD-induced dyskinesia remained unchanged. In contrast, using contact 2 as the cathode, both LD-induced dyskinesia and cardinal Parkinson symptoms were markedly attenuated (Table 1). The dose of LD was gradually reduced, and the patient eventually received only dopamine agonist (cabergoline, total dose 1.0 mg/day). The postoperative UPDRS motor score was 27 and the dyskinesia score was 0.

Discussion

The antidyskinetic effect of STN-DBS is due to the postoperative reduction of LD intake.[3,7,15] In contrast, DBS of the globus pallidus internus (GPi) has a direct antidyskinetic effect.[16] GPi-DBS yields significant improvement of LD-induced dyskinesia after surgery without reduction of LD dosage. In our case, bipolar stimulation for STN-DBS using contacts 0 or 1 as the cathode induced attenuation of cardinal PD symptoms but not LD-induced dyskinesia, whereas bipolar stimulation using contact 2 as the cathode induced attenuation of both cardinal PD symptoms and LD-induced dyskinesia without reduction of LD dosage. These findings suggest that stimulation in the area above the STN inhibited LD-induced dyskinesia, consistent with previous findings.[1,5,8,10,14] Pallidothalamic, pallidosubthalamic, and subthalamopallidal fibers are densely distributed in the area above the STN.[10] Furthermore, a study using tracer techniques in the squirrel monkey demonstrated that pallidothalamic fibers originating within the sensorimotor region of the GPi mainly project through the lenticular fasciculus, running through the area above the STN.[2] Stimulation of these fibers may have effects similar to GPi-DBS and thus inhibit dopa-induced dyskinesia.

References

1) Alterman RL, Shils JL, Gudesblatt M, Tagliati M: Immediate and sustained relief of levodopa-induced dyskinesia after dorsal relocation of a deep brain stimulation lead. Case report. *Neurosurg Focus* 17(1): E6, 2004
2) Baron MS, Sidibe M, Delong MR: Course of motor and associative pallidothalamic projections in monkeys. *J Comp Neurol* 429: 490–501, 2001
3) Benabid AL, Benazzouz A, Limousin P, Koudsie A, Krack P, Piallat B, Pollak P: Dyskinesias and the subthalamic nucleus. *Ann Neurol* 47: S189–192, 2000
4) Burchiel KJ, Anderson VC, Favre J, Hammerstad JP: Comparison of pallidal and subthalamic nucleus deep brain stimulation for advanced Parkinson's disease: results of a randomized, blinded pilot study. *Neurosurgery* 45: 1375–1382, 1999
5) Figueiras-Mendez R, Marin-Zarza F, Antonio Molina J, Jimenez-Jimenez FJ, Orti-Pareja M, Magarinos C, Lopez-Pino MA, Martinez V: Subthalamic nucleus stimulation improves directly levodopa induced dyskinesias in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 66: 549–550, 1999
6) Follett KA: Comparison of pallidal and subthalamic deep brain stimulation for the treatment of levodopa-induced dyskinesias. *Neurosurg Focus* 17(1): E3, 2004
7) Fraix V, Pollak P, Van Blercom N, Xie J, Krack P, Koudsie A, Benabid AL: Effect of subthalamic nucleus stimulation on levodopa-induced dyskinesia in Parkinson's disease. *Neurology* 55: 1921–1923, 2000
8) Herzog J, Pinsker M, Wasner M, Steigerwald F, Wailke S, Deuschl G, Volkmann J: Stimulation of subthalamic fibre tracts reduces dyskinesias in STN-DBS. *Mov Disord* 22: 679–684, 2007
9) Katayama Y, Kasai M, Oshima H, Fukaya C, Yamamoto T, Ogawa K, Mizutani T: Subthalamic nucleus stimulation for Parkinson disease: benefits observed in levodopa-intolerant patients. *J Neurosurg* 95: 213–221, 2001
10) Katayama Y, Oshima H, Kano T, Kobayashi K, Fukaya C, Yamamoto T: Direct effect of subthalamic nucleus stimulation on levodopa-induced peak-dose dyskinesia in patients with Parkinson's disease. *Stereotact Funct Neurosurg* 84: 176–179, 2006
11) Krack P, Pollak P, Limousin P, Hoffmann D, Xie J, Benazzouz A, Benabid AL: Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. *Brain* 121(Pt 3): 451–457, 1998
12) Kumar R, Lozano AM, Kim YJ, Hutchison WD, Sime E, Halket E, Lang AE: Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. *Neurology* 51: 850–855, 1998
13) Moro E, Scerrati M, Romito LM, Roselli R, Tonali P, Albanese A: Chronic subthalamic nucleus stimulation reduces medication requirements in Parkinson's disease. *Neurology* 53: 85–90, 1999
14) Oshima H, Kobayashi K, Kasai M, Fukaya C, Yamamoto T, Katayama Y: [Effect of subthalamic nucleus stimulation on levodopa-induced dyskinesia]. *Kinoteki No Shinkei Geka* 42: 49–52, 2003 (Jpn, with Eng abstract)

15) Russmann H, Ghika J, Combrement P, Villemure JG, Bogousslavsky J, Burkhard PR, Vingerhoets FJG: L-dopa-induced dyskinesia improvement after STN-DBS depends upon medication reduction. *Neurology* 63: 159–155, 2004
16) Volkmann J, Sturm V, Weiss P, Kappler J, Voges J, Koulousakis A, Lehrke R, Hefter H, Freund HJ: Bilateral high-frequency stimulation of the internal globus pallidus in advanced Parkinson's disease. *Ann Neurol* 44: 953–961, 1998

Address reprint requests to: Yasumasa Nishikawa, M.D., Department of Neurosurgery, Iwate Medical University School of Medicine, 19–1 Uchimaru, Morioka, Iwate 020–8505, Japan.

TABLE 1. *Characteristics of the four operated PD patients with the neck and/or the trunk lateral deviation*

	Present age	Age at PD onset	PD duration on pallidotomy	Years from pallidotomy to symptoms onset	PD duration on symptoms onset	Lesion localization based on MRI
Our pt	61	38	13	4	17	GPi/GPe
Pt 1[a]	72	44	17	8	25	GPi/GPe
Pt 2[a]	63	47	6	9	15	GPi/Internal Capsule
Pt 3[a]	69	43	17	4	21	GPi/GPe/Sella Media
Mean	66.3 ± 5	43 ± 3.7	13.3 ± 5.2	6.3 ± 2.6	19.5 ± 4.4	

[a]Patients 1, 2, and 3 are reported in Ref. 1.

The aggravation of the lateral body deviation by L-dopa could represent a motor asymmetry similar to that observed in rats following a unilateral lesion of the nigrostriatal pathway.[4] In this rotating rat model of Parkinsonism, L-dopa, given weeks after intracerebral injection of the neurotoxin 6-Hydroxydopamine, induces a contralateral body rotation associated with increased ^{3}H-spiroperidol binding in the lesioned striatum.[4] More recent studies[5] have shown that long-term administration of L-dopa to rats lesioned by 6-Hydroxydopamine alters corticostriatal bidirectional synaptic plasticity. As such, it is possible that pallidotomy has altered the local basal ganglia circuitry in our patient, resulting in the L-dopa aggravated motor asymmetry.

In light of the above, we could conclude that contralateral deviation of the head, the neck, and/or the trunk can occur as a delayed adverse event following unilateral pallidotomy. The extension of the primary medial pallidal lesion to other neighboring basal ganglia structures could be the underlying pathogenetic mechanism. In this regard, it is unclear as to why it takes so many years for the deformity to develop following the neurosurgical procedure, when in other acute basal ganglia lesions dystonia occurs immediately or shortly after the destructive event. A long-term postoperational modification of the basal ganglia physiology, perhaps similar to that occurring in the rat model of Parkinsonism in which contralateral rotation requires some time to develop following damage to the nigrostriatal pathway,[4] may be implicated. Since follow-up studies of operated PD patients extend from 1 to 5 years,[6,7] it is not surprising that dystonia is never reported as a postoperative complication of pallidotomy. Follow-up studies of longer duration are needed to reveal the long-term motor consequences of this neurosurgical procedure.

Financial Disclosures: Cleanthe Spanaki has been receiving grants from the Parkinson Disease Foundation and from the Second Operational Program for Education and Initial Vocational Training (EPEAEK II) from the Ministry of Education of Greece. Spyros Zafeiris has nothing to disclose. Andreas Plaitakis has been supported by the European Community and the Ministry of Development/General Secretariat for Research and Technology (Contract grant number: PENED 2003/03ED576) and by the Association for the Advancement of Research and Treatment of Neurologic Disorders of Crete ≪ΕΥ ΖΗΝ≫.

Authors Roles: Cleanthe Spanaki: Conception and writing of the manuscript; Spiros Zafeiris: Taking care of the patient, providing photographs; Andreas Plaitakis: Conception, review, and critique of the final manuscript.

Cleanthe Spanaki, MD, PhD*
Spiros Zafeiris, MD
Andreas Plaitakis, MD, PhD
Department of Neurology, University of Crete, Medical School, Heraklion, Crete, Greece
**E-mail: kliospanaki@yahoo.com*

References

1. van de Warrenburg BP, Bhatia KP, Quinn NP. Pisa syndrome after unilateral pallidotomy in Parkinson's disease: an unrecognised, delayed adverse event? J Neurol Neurosurg Psychiatry 2007;78: 329–30; Erattum in J Neurol Neurosurg Psychiatry 2008;79: 337.
2. Tolosa E, Compta Y. Dystonia in Parkinson's disease. J Neurol 2006;253 (Suppl 7):VII7–VII13.
3. Bhatia KP, Marsden CD. The behavioral and motor consequences of focal lesions of the basal ganglia in man. Brain 1994;117:859–876.
4. Heikkila RE, Shapiro BS, Duvoisin RC. The relationship between the loss of dopamine nerve terminals, striatal 3H-spiroperidol binding and rotational behavior in unilaterally-lesioned rats. Brain Res 1981;211:285–292.
5. Picconi B, Centonze D, Hakansson K, et al. Loss of bidirectional synaptic plasticity in L-dopa induced dyskinesias. Nat Neurosci 2003;6:501–506.
6. Fine J, Duff J, Chen R, Chir B, Hutchison W, Losano AM, Lang AE. Long-term follow-up of unilateral pallidotomy in advanced Parkinson's disease. N Engl J Med 2000;342:1708–1714.
7. Strutt AM, Lai EC, Jankovic J, et al. Five-years follow-up of unilateral posteroventral pallidotomy in Parkinson's disease. Surg Neurol 2009;71:551–558.

GPi-pallidal Stimulation to Treat Generalized Dystonia in Cockayne Syndrome

Video 

Cockayne syndrome (CS) is a rare autosomal recessive, progeroid disorder characterized by progressive multisystem degeneration.[1] While neurological impairments usually begin

Additional Supporting Information may be found in the online version of this article.

Potential conflict of interest: Nothing to report.

Published online 3 February 2010 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.22992

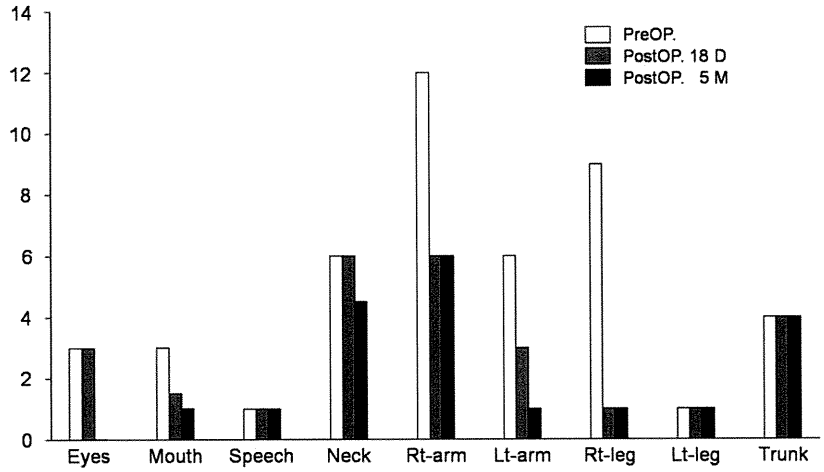

FIG. 1. Changes in the Burke-Fahn-Marsden Dystonia Rating Scale (BFM-DRS) subscores before and after surgery. During the 5 month of follow-up period, dystonic symptoms in the craniofacial region, neck, and extremities improve progressively. His total BFM-DRS score, 45 before treatment (maximum = 120) decreased to 26.5 (41.1% improvement) at 18 days and to 19.5 (56.7% improvement) at 5 months after the operation.

in early infancy,[1] CS spans a wide range of phenotypical expressions and a variable clinical course.[1,2] We describe our experience with the use of deep brain stimulation (DBS) for the bilateral globus pallidus internus (GPi) in a CS patient associated with generalized dystonia.

The patient, a 52-year-old man with growth failure manifesting cognitive disturbance (IQ = 44), microcephaly (head circumference = 48 cm), and low body height (155 cm) and weight (44 kg) also presented with retinal degeneration, cataract, and sensorineuroal hearing impairment, bilaterally. He had been born without perinatal complications as the 8th of 9 healthy siblings; however, abnormal growth and cognitive development became apparent before he entered elementary school. Around the age of 30 years, he began to manifest involuntary movements of his right arm; at the age of 33, he was placed in a nursing home. At the age of 42, he developed cervical dystonia (CD). Despite variable medical therapies, such as Clonazepam, Haloperidol, or Trihexyphenidyl combined with botulinum toxin injections, dystonia spread to his trunk and lower extremities, making walking difficult. Progressive CD severely interfered with his eating and he consequently suffered aspiration pneumonia in April 2008. On admission to our hospital, the patient received 2 mg/day of Clonazepam. He exhibited blephalospasm, oromandibular grimacing, CD with muscular pain, truncal bending and torsion, and dystonic tremor of the extremities. He was unable to hold out his hands horizontally. He could not grasp his right hand usefully, and his dystonic tremor and posture also severely interfered with eating with his left hand (Video Segment 1).

His preoperative Burke-Fahn-Marsden (BFM)-Dystonia Rating Scale (DRS) was 45/120 (Fig. 1). Neuroradiological studies showed extensive atrophy of the cortical and subcortical structures and the cerebellum without marked calcified lesions. We proceeded surgery after receiving prior informed consent from the patient and his family indicating uncertain outcome.

In June 2008, under general anesthesia, he underwent stereotactic implantation of DBS electrodes (model 3387; Medtronic) into the bilateral GPi. On the microelectrode recordings, the background activity was significantly reduced when the probe was passing through the point 2 mm anterior, 21 mm lateral, and 3 mm ventral to the midpoint of the anterior–posterior commissure line. Then, the contact 0 of the DBS electrode was placed at this target site.

His postoperative course was uneventful. Using the contacts 0 and 1, chronic unipolar stimulation (130 Hz frequency, 450 μsec pulse width) was started with pulse generators (Soletra, Medtronic) implanted in the subclavian portion. In the course of 1 month, the amplitude was gradually increased to 2.8 V. Dose of clonazepam was reduced to 1 mg/day postoperatively. During a 5-month follow-up period, his dystonic symptoms progressively improved (Fig. 1). His dystonic tremor responded promptly GPi stimulation (Video Segment 2) and his muscular neck and shoulder pain disappeared within several days. By 1 week after surgery, he could eat by himself using his left- and occasionally his right hand (Video Segment 2). The abnormal posture of his trunk did not change (Video Segments 1–3). His BFM-DRS decreased to 26.5/120 (41.1% improvement) at 18 days and to 19.5/120 (56.7% improvement) at 5 months.

The incidence of movement disorders associated with CS is not high; however, in their presence, they tend to be refractory to medical therapy.[1,3] Progressive pathologic changes in the basal ganglia-thalamocortical motor loop[4] may underlie the manifestation of abnormal movements in CS.[5]

In contrast to primary generalized dystonia, patients with secondary dystonia experienced less and more variable benefits from GPi-DBS.[6] However, it exerted considerable effects on generalized dystonia secondary to rare neurodegenerative syndromes such as pantothenate kinase-associated neurodegeneration.[7] These findings as well as ours strongly suggest

that even patients with decade-long dystonia due to progressive pathological and/or anatomical changes may derive benefits from this treatment.

As previously suggested, that is, phasic forms of dystonia may have a better improvement with DBS than tonic and fixed forms, dystonic tremor (and cervical muscular pain) responded promptly to GPi stimulation in our patient. His long-lasting spinal deformity might affected his mild but sustained abnormal posturing of the trunk.

Despite the secondary nature of dystonia, GPi-DBS exerted beneficial effects on daily living activities in our patient. Although additional case histories must be accumulated and long-term follow-up studies are needed to clarify optimal indications, our findings suggest DBS as a potential therapeutic option to treat movement disorders in CS.[3]

LEGENDS TO THE VIDEO

Segment 1. Preoperatively, the patient manifests continuous right-side dominant dystonic tremor of the extremities. He cannot hold his hands out horizontally and he is unable to grasp with his right hand. Note that his cervical and craniofacial dystonia is aggravated by actions tasked to the right hand (distant part of body). Tonic dystonia in his trunk and lower extremities interfere with his walk. There is severe interference in eating.

Segment 2. Eighteen days postoperatively, the dystonic tremor of the extremities disappeared. He can hold up both hands and use his right hand. Moderate cervical and craniofacial symptoms remain. His walk is steadier and he can eat by himself using his left- and occasionally his right hand.

Segment 3. After 5 months of continuous GPi stimulation, he can easily hold up both hands, although mild cervical dystonia is remained. He demonstrates that he can use chop sticks with his left hand and drink with either hand.

Acknowledgments: 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.

Kiyotoshi Hamasaki, MD
Kazumichi Yamada, MD, PhD*
Tadashi Hamasaki, MD, PhD
Jun-ichi Kuratsu, MD, PhD
Department of Neurosurgery
Graduate School of Medical Sciences
Kumamoto University
Kumamoto, Japan
**Email: yamadakazu@fc.kuh.kumamoto-u.ac.jp*

References

1. Nance MA, Berry SA. Cockayne syndrome: review of 140 cases. Am J Med Genet 1992;42:68–84.
2. Tan WH, Baris H, Robson CD, Kimonis VE. Cockayne syndrome: the developing phenotype. Am J Med Genet 2005;135:214–216.
3. Hebb OM, Guadet P, Mendes I. Deep brain stimulation to treat hyperkinetic symptoms of Cockayne syndrome. Mov Disord 2006;21:113–115.
4. Eltahawy HA, Saint-Cyr J, Giladi N, Lang AE, Lozano AM. Primary dystonia is more responsive than secondary dystonia to pallidal interventions: outcome after pallidotomy or pallidal deep brain stimulation. Neurosurgery 2004;54:613–619.
5. Rapin I, Weidenheim K, Lindenbaum Y, et al. Cockayne syndrome in adults: review with clinical and pathologic study of a new case. J Child Neurol 2006;21:991–1006.
6. Mink JW. The basal ganglia and involuntary movements: impaired inhibition of competing motor patterns. Arch Neurol 2003;60:1365–1368.
7. Castelnau P, Cif L, Valente EM, et al. Pallidal stimulation improves pantothenate-kinase-associated neurodegeneration. Ann Neurol 2005;57:738–740.

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

Tadashi Hamasaki · Kazumichi Yamada · Toshinori Hirai · Jun-ichi Kuratsu

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

T. Hamasaki (✉) · K. Yamada · J.-i. Kuratsu
Department of Neurosurgery, Kumamoto University Medical School,
1-1-1 Honjo,
Kumamoto 860-8556, Japan
e-mail: thamasaki-nsu@umin.ac.jp

T. Hirai
Department of Diagnostic Imaging, Kumamoto University Medical School,
1-1-1 Honjo,
Kumamoto 860-8556, Japan

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

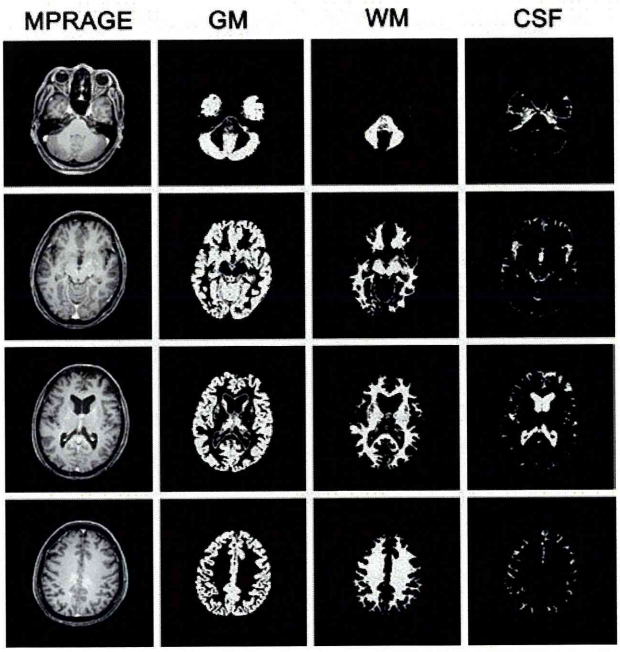

Fig. 1 Preoperative MRI and segmented images of an illustrative case SPM5 supplemented with *spm_segment* (see Methods Section) generated three mutually exclusive masks corresponding to the gray (*second column*) and white matter (*third column*) and the CSF (*fourth column*) from 3D magnetization-prepared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

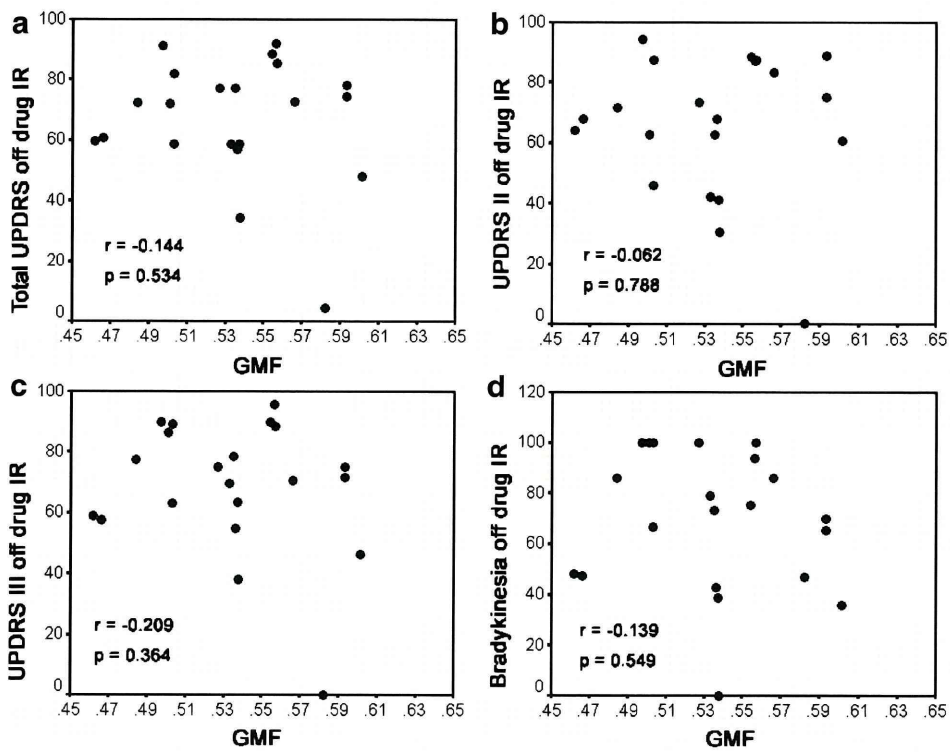

Fig. 2 Scatter plot of postoperative improvement rates (*IR*) in the "off" medication state against the fractional gray matter volume (*GMF*). **a** Total UPDRS score, **b** UPDRS part II (ADL) score, **c** UPDRS part III (motor) score, **d** bradykinesia subscore. No linear regression curve is shown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

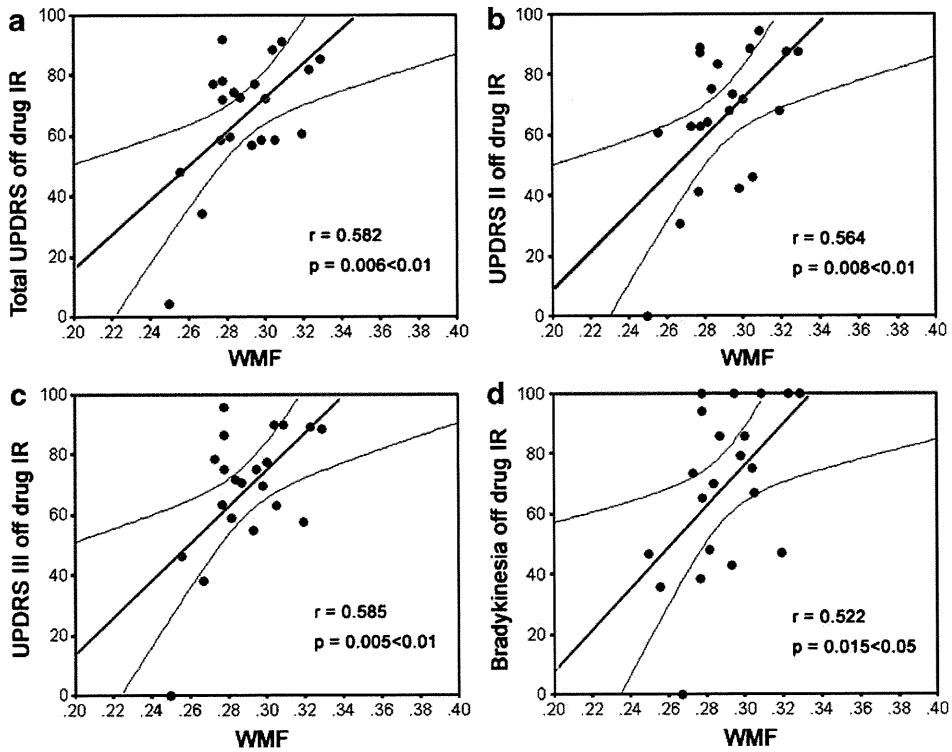

Fig. 3 Scatter plot of postoperative improvement rates (*IR*) in the "off" medication state against the fractional white matter volume (*WMF*). **a** Total UPDRS score, **b** UPDRS part II (ADL) score, **c** UPDRS part III (motor) score, **d** bradykinesia subscore. The Pearson correlation coefficient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

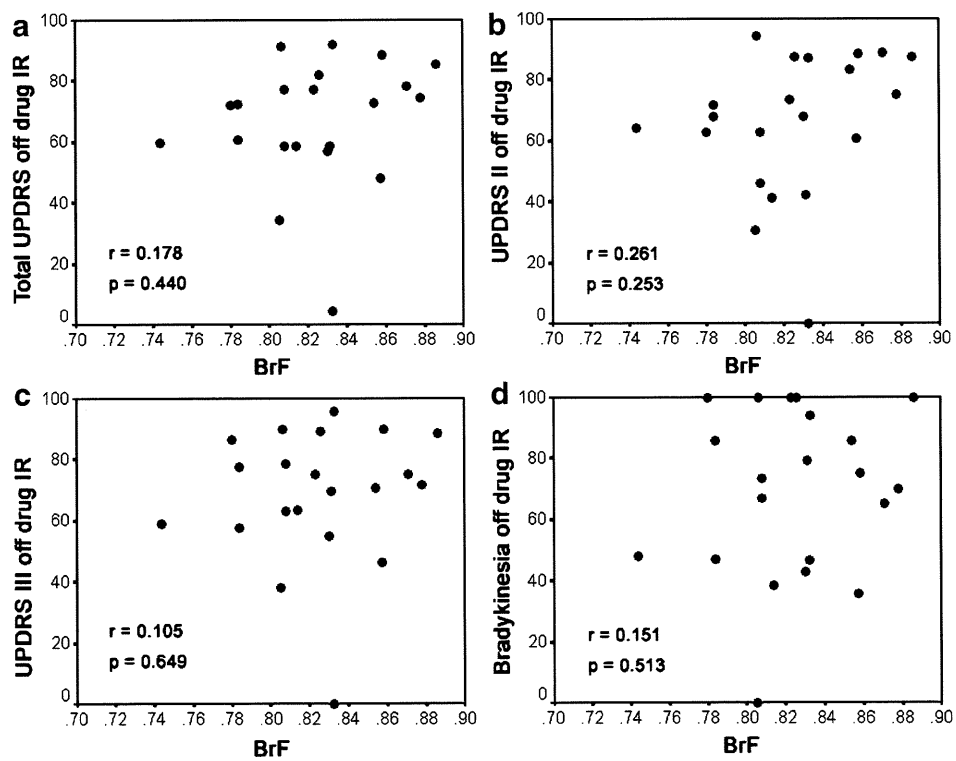

Fig. 4 Scatter plot of postoperative improvement rates (*IR*) in the "off" medication state against the fractional brain volume (*BrF*). **a** Total UPDRS score, **b** UPDRS part II (ADL) score, **c** UPDRS part III (motor) score, **d** bradykinesia subscore. No linear regression curve is shown because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