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# Chronological Changes in Astrocytes Induced by Chronic Electrical Sensorimotor Cortex Stimulation in Rats

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## Abstract

**Motor cortex stimulation (MCS) is a treatment option for various disorders such as medically refractory pain, poststroke hemiplegia, and movement disorders. However, the exact mechanisms underlying its effects remain unknown. In this study, the effects of long-term chronic MCS were investigated by observing changes in astrocytes. A quadripolar stimulation electrode was implanted on the dura over the sensorimotor cortex of adult rats, and the cortex was continuously stimulated for 3 hours, 1 week, 4 weeks, and 8 weeks. Immunohistochemical staining of microglia (ionized calcium-binding adaptor molecule 1 [Iba1] staining) and astrocytes (glial fibrillary acidic protein [GFAP] staining), and neuronal degeneration histochemistry (Fluoro-Jade B staining) were carried out to investigate the morphological changes following long-term chronic MCS. Iba1 staining and Fluoro-Jade B staining showed no evidence of Iba1-positive microglial changes or neurodegeneration. Following continuous MCS, GFAP-positive astrocytes were enlarged and their number increased in the cortex and the thalamus of the stimulated hemisphere. These findings indicate that chronic electrical stimulation can continuously activate astrocytes and result in morphological and quantitative changes. These changes may be involved in the mechanisms underlying the neuroplasticity effect induced by MCS.**

Key words: motor cortex stimulation, neural plasticity, trophic function, pain, cingulate gyrus

## Introduction

Continuous electrical stimulation of the human brain and the spinal cord is known to have therapeutic effects on various disorders. In particular, motor cortex stimulation (MCS) has been increasingly receiving attention since the first application to intractable thalamic pain.[28-30] Nowadays, MCS is applied for both thalamic and peripheral neuropathic pain, movement disorders, and neurorehabilitation.[1,3,15,20,21] Continuous electrical stimulation may induce neuroplasticity and reorganization of the neural networks.[3,14,27]

We previously investigated the neural activities in the rat brain following unilateral chronic MCS utilizing c-Fos immunopositivity as a functional marker.[27] Both astrocytes and neurons were activated as shown by the observation of c-Fos-immunopositive cells in the sensorimotor cortex (SMC) and deep brain structures.[27] On the other hand, recent studies have shown that astrocytes are important in neural networks, and that abnormalities of astrocytes are associated with various disorders.[8,13] Several studies demonstrated that electrical stimulation activates astrocytes in vitro,[12,13] and we also found unusually large astrocytes in a patient with Parkinson's disease who had long-term continuous subthalamic nucleus stimulation (manuscript in preparation). On the basis of these findings, we extended our previous investigation to evaluate the chronological changes in the astrocytes following continuous MCS.

In this study, the SMC in the left hemisphere in rats was chronically stimulated for 3 hours, 1 week, 4 weeks, and 8 weeks. The motor cortex has direct

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and indirect connections with deep brain structures such as the thalamus (TH), basal ganglia, anterior cingulate cortex, and periaqueductal gray matter.[6,22] Therefore, chronological changes in the number of c-Fos-immunopositive astrocytes in the SMC and two deep brain structures (i.e. TH and cingulate gyrus [CG]) were observed utilizing immunohistochemical techniques. In addition, the number and area of astrocytes in the CG were investigated, as the CG has crucial roles in mood and pain control.[6,7,22,23] We discuss the possible mechanisms underlying pain suppression and neuroplasticity effects induced by MCS.

## Materials and Methods

This study was carried out in accordance with the Guide for Animal Experimentation of the Faculty of Medicine, Nihon University and Guide for the Care and Use of Laboratory Animals (NIH publication No. 86-23, revised 1985), and approved by the Animal Care and Use Committee of Nihon University.

The surgical procedure and the parameters of electrical stimulation were described in detail in our previous study.[27] The experimental animals were 12 adult male Wistar rats (body weight, approximately 500 g). The animal was anesthetized by intramuscular injection of ketamine hydroxylase (100 mg/kg body weight), and a mixture of 0.5% epinephrine hydrochloride and lidocaine hydrochloride (1 ml each) was injected under the skin and external ear canals to numb the areas. Then intraperitoneal injection of sodium pentobarbital (Nembutal; Abbot Laboratories, Chicago, Illinois, USA) (20 mg/kg body weight) was carried out. The rat was positioned in a stereotactic frame (Narishige, Tokyo) and a cranial burr hole (2 mm × 5 mm) was drilled on the left coronal suture, 3.5 mm lateral to the midline. A quadripolar stimulation electrode 2 mm wide and 5 mm long (Unique Medical, Tokyo) was positioned on the dura over the SMC in the left hemisphere. The electrode with four contact points numbered 0 to 3 sequentially from the most distal contact (0) to the most proximal contact (3) was placed, so that contact 0 was located in the rostral portion of the SMC. Each contact of the electrode was 0.7 mm long and the contacts were 0.7 mm apart. The optimal location was confirmed by test stimulation that causes forelimb muscle contraction. An extension wire was then passed from the head to the back subcutaneously and connected to an implantable pulse generator (Soletora Model 7426 IPG; Medtronic Inc., Minneapolis, Minnesota, USA).

Bipolar stimulation was applied at 25 Hz with the anode on the rostral contact and the cathode on the caudal contact beginning on postoperative day 1. A stimulation voltage of approximately 2–3 V was applied with a pulse width of 0.2 msec. The voltage was determined as less than 80% of that required for forelimb muscle contraction. These parameters were lower than the threshold level that induces seizure activity.[27,32] The stimulation was applied for 3 hours, 1 week, 4 weeks, and 8 weeks, and the stimulation parameters were not changed during these periods. Following each stimulation period, it was confirmed that the SMC was continuously stimulated by test stimulation before sacrificing the rat. The same operative procedures were carried out except for electrical stimulation was not performed as controls.

Following the chronic stimulation period, the rats were sacrificed by intraperitoneal injection of pentobarbital (60 mg/kg body weight) and perfused with 4% paraformaldehyde in 0.1 M phosphate-buffered saline, pH 7.4, following perfusion of 0.15 M NaCl. The brains were removed, postfixed in the same fixative for 12 hours with constant shaking, and then immersed in 20% sucrose for approximately 48 hours at 4°C until the brains sank. Brain slices were made at 5 mm anterior to the vertical zero point, which was immediately below the stimulated part of the SMC, for determining the number, area, and density of cells in each slice. The brains were embedded in the OCT compound, frozen, and sectioned (40 $\mu$m thick) on a freezing sliding microtome (Yamato Kohki Industrial Co., Ltd., Tokyo).

Immunohistochemical analyses used fluorescent double-staining methods to identify c-Fos-immunopositive astrocytes, and an immunoenzymatic staining method to detect glial fibrillary acidic protein (GFAP)-immunopositive cells to measure the areas of astrocytes. Selected sections were pretreated with 0.3% hydrogen peroxide solution in methanol and incubated in normal goat serum and 10% fish gelatin in 0.1 M phosphate buffer, pH 7.4 (FG-PB). Then, the sections were incubated with a mixture of an anti-c-Fos goat antibody (1:100; Santa Cruz Biotechnology, Santa Cruz, California, USA) and anti-GFAP rabbit antibody (1:100; Sigma, St. Louis, Missouri, USA) diluted in FG-PB for 48 hours at 4°C. After several washes with PB, the sections were incubated with secondary antibodies. The sections were first reacted with a fluorescein isothiocyanate-labeled anti-goat immunoglobulin G (IgG) donkey antibody (1:200; Chemicon, Billerica, Massachusetts, USA), and following several washes, an Alexa Fluor-labeled anti-rabbit IgG goat antibody (1:200; Invitrogen, Carlsbad, California, USA) diluted in FG-PB was used. The sections were set on slide


**Fig. 1 Photomicrographs of double immunostaining of c-Fos (A) and glial fibrillary acidic protein (B) of cells in the lateral thalamus following 1-week stimulation. *Arrows* indicate double-immunopositive cells in the merged photograph (C). Original magnification ×400.**

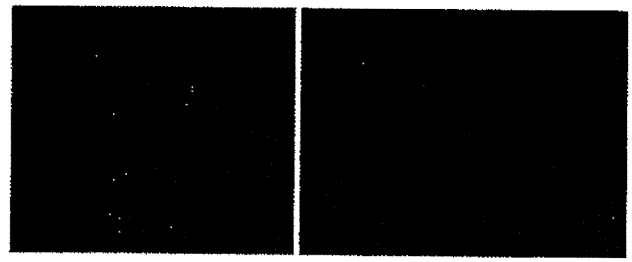

**Fig. 3 Photomicrographs of giant astrocytes in rats stimulated for 4 and 8 weeks. Glial fibrillary acidic protein immunohistochemistry showed unusually large astrocytes (*arrows*) compared with other astrocytes (*arrowheads*) in the cingulate gyrus following 4-week stimulation (A) and the thalamus following 8-week stimulation (B). Original magnification A: ×80, B: ×160.**

glasses and mounted with nonfluorescent glycerine (Merck, Darmstadt, Germany). The sections were photographed using a Coolscope CCD camera (Nikon, Tokyo) attached to an Eclipse microscope (Nikon). Then, the numbers of c-Fos/GFAP-double-immunopositive cells in the SMC, TH, and CG were counted (Fig. 1). In this process, GFAP-positive cells in the capillary walls were excluded.

Selected sections were pretreated with 0.3% hydrogen peroxide solution in methanol and normal goat serum, then incubated with only anti-GFAP rabbit antibody diluted in FG-PB for 48 hours at 4°C. Following several washes with PB, the sections were incubated with a biotinylated goat anti-rabbit IgG antibody (Vector Laboratories, Burlingame, California, USA) and reacted with avidin-biotin complex solution (Vector Laboratories). Then, the sections were reacted with 0.02% diaminobenzidine and 0.03% $H_2O_2$ for 10 minutes. Select sections were stained with Nissl for counterstaining. The sections were mounted on gelatin-coated glass slides, and air-dried, then dehydrated with ethanol, cleared in xylene, and coverslipped. The sections were examined and photographed utilizing a Coolscope CCD camera attached to an Eclipse microscope. First, the CG, TH, and SMC sections were examined to search for giant astrocytes. Then, the number of GFAP-immunopositive cells in the CG was counted and the area was also measured utilizing a Neurolucida system (MicroBrightField, Inc., Williston, Vermont, USA) installed on a personal computer attached to an AX-10 microscope (Olympus, Tokyo) and a 2400c CCD camera (Hamamatsu Photonics, Hamamatsu, Shizuoka).

Cell density (number of c-Fos/GFAP-double-immunopositive cells/0.1 mm²) was first calculated,

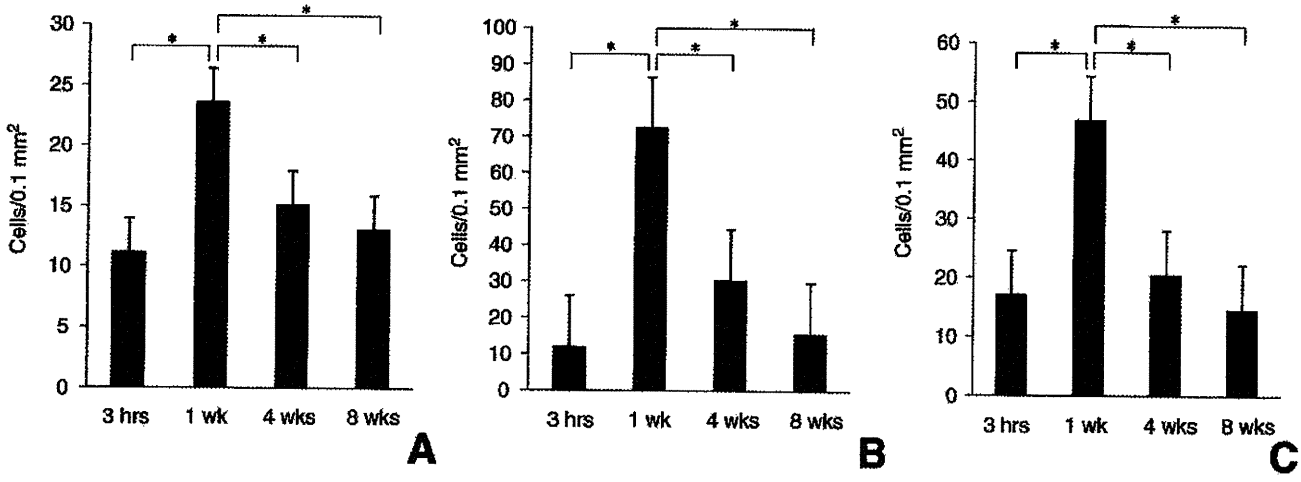


**Fig. 2 Mean number of c-Fos-immunopositive astrocytes over time. The number of activated (c-Fos-immunopositive) astrocytes peaked following 1 week of continuous stimulation in the cingulate gyrus (A), thalamus (B), and sensorimotor cortex (C). Values are mean and standard deviation. *$p < 0.01$.**

and then compared between time points utilizing the Wilcoxon signed-rank test. To investigate the chronological changes in astrocytes, differences in area were compared between time points as well as between the left and right hemispheres. Two-way analysis of variance (ANOVA) was used to test the null hypothesis of no chronological differences in the number and area. SAS Enterprise Guide 4.1 (SAS Institute, Cary, North Carolina, USA) was used for the statistical analyses.

To validate the experimental procedures, we confirmed that electrical stimulation did not cause neuronal damage by performing double staining using c-Fos and ionized calcium-binding adaptor molecule 1 (Iba1). Fluoro-Jade B (FJB) staining was also carried out to detect degenerating neurons in accordance with the method of Schmued et al.[26] Iba1 was used as a marker of microglia/macrophages, and the staining method was as for the c-Fos/GFAP double staining method except that anti-Iba1 rabbit antibody (1:250; Wako Pure Chemical Industries, Ltd., Osaka) was used instead of the anti-GFAP rabbit antibody as the primary antibody. For FJB histochemistry, the sections were incubated with 1% sodium hydroxide in 80% ethanol for 5 minutes and in 0.06% potassium permanganate for 10 minutes on a shaker. The sections were then incubated in freshly mixed 0.0004% FJB (Cosmo Bio Co., Ltd., Tokyo) in 0.1% acetic acid for 20 minutes, washed in distilled water, and air-dried at 50°C for 10 minutes. The sections were cleaned using xylene and coverslipped.

## Results

The number of c-Fos-immunopositive astrocytes was counted in one sham-operated rat (control) and two stimulated rats at each time point. Twelve high-power fields (HPFs) were examined for the CG, 4 HPFs for the TH, and 4 HPFs for the SMC in each animal. The area of each HPF was 0.1 $mm^2$. The chronological changes in the mean number of c-Fos-immunopositive astrocytes showed that the number peaked following 1 week stimulation in all areas (Fig. 2). Only a few c-Fos-immunopositive astrocytes were observed in control rats, whereas a significantly larger number of c-Fos-immunopositive astrocytes were found in stimulated rats.

Several unusually large astrocytes (larger than 50 $\mu m^2$) were observed; in particular, we observed supergiant astrocytes with areas larger than 100 $\mu m^2$ (*arrows* in Fig. 3) in the CG and TH of rats stimulated for more than 4 weeks. The mean areas and numbers of measured astrocytes are summarized in Fig. 4. Two-way ANOVA revealed that the mean area of astrocytes peaked following 4 weeks of continuous

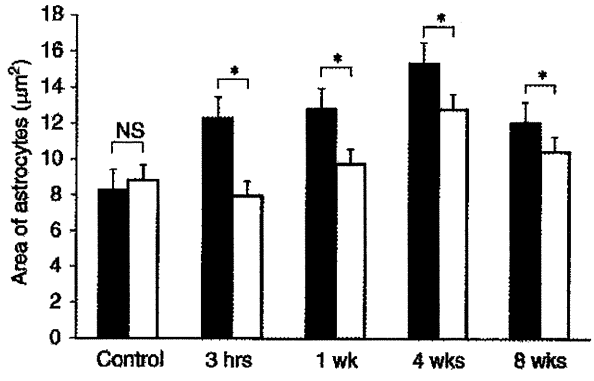


**Fig. 4 Comparison of the area of astrocytes between stimulated (left, *closed columns*) and nonstimulated (right, *open columns*) cingulate gyri. The mean area of astrocytes in the stimulated hemisphere was significantly larger than that in the nonstimulated hemisphere. NS: not significant. Values are mean and standard deviation. *p < 0.01.**

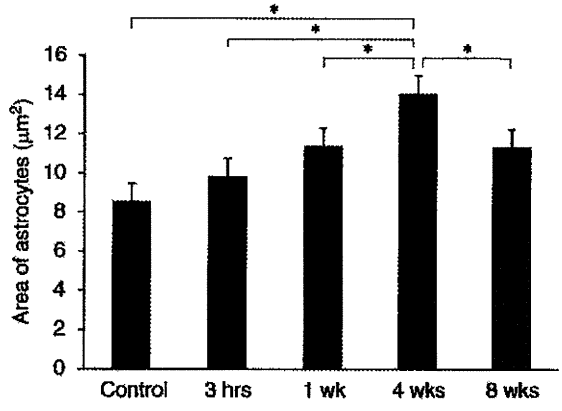


**Fig. 5 Area of astrocytes over time in the cingulate cortex. The mean area of astrocytes peaked following 4 weeks of continuous stimulation. Values are mean and standard deviation. *p < 0.01.**

stimulation (Fig. 5), and the mean area was larger in the left hemisphere (stimulated side) than in the right hemisphere (nonstimulated side) throughout the 8 weeks (Fig. 4).

No abnormal seizure movements were observed during the surgical procedure or observation periods up to 8 weeks. Perfused brains did not show obvious macroscopic hemorrhage or contusion under the electrodes. A few cells were positive for both c-Fos and Iba1 in both the control rats and stimulated rats up to 8 weeks, as observed in a previous study.[24] Moreover, there were no FJB-stained cells in the cortex, hippocampus, and TH. These findings indicate no evidence of neurodegeneration or injury

due to surgery or chronic electrical stimulation, consistent with our previous study.[27]

## Discussion

The present study showed the changes in astrocytes following continuous electrical stimulation of SMC in rats. As shown in our previous study by c-Fos histochemistry,[24] the present study found that astrocytes were activated by chronic electrical stimulation in rats without damage to the neural structures. Most previous studies showed that neurons are activated following short-term electrical stimulation ranging from 3 hours to 2 weeks,[4,10,11,16,25,31] but the present study found changes in astrocytes following chronic electrical stimulation up to 8 weeks.

Our in vivo study showed that the astrocytes were activated in a delayed manner as the activity indicated by the number of c-Fos/GFAP-double-immunopositive cells peaked following 1 week of continuous stimulation. Moreover, the astrocytes become larger following activation by continuous stimulation as the area of astrocytes peaked after 4 weeks. Other in vitro studies have also demonstrated that electrical stimulation activated and enlarged astrocytes.[10,11]

Recent studies have shown that astrocytes are important in synaptic activity, and that structures consisting of astrocytes and neurons are known as "tripartite synapses."[2,8] In this context, astrocytes and neurons may influence each other under MCS. High-frequency electrical stimulation facilitates the release of brain-derived neurotrophic factor (BDNF) from neurons,[2] and the morphology of astrocytes is regulated via a BDNF-specific receptor.[18] In addition, BDNF is derived from neurons not astrocytes, and astrocytes regulate synaptic formation via BDNF-specific receptors.[5] Together with these previous reports, the present study indicates that MCS activates both neurons and astrocytes, and then the astrocytes are morphologically changed via neurotrophic factors such as BDNF released by neurons. Furthermore, local contacts of astrocytes with neurons enhance synaptogenesis.[9] We speculate that the number of contacts of astrocytes with neurons is increased by the enlargement of astrocytes in a tripartite synapse, and that this increase may result in the enhancement of synaptogenesis in the electrically stimulated brain.

Concerning chronological changes in a clinical setting, patients with chronic pain usually experience gradual improvement in pain over hours or days following MCS.[6] In addition, some patients with thalamic pain experience functional recovery following chronic MCS,[30] and MCS may enhance the effect of rehabilitation.[3] Our findings that chronic MCS activated and enlarged astrocytes over weeks in rats may shed light on the mechanism underlying the effect of chronic MCS in practice. We speculate that MCS activates astrocytes and modulates the function of neurotransmitters, which may result in pain relief and functional recovery from stroke or movement disorders in humans. On the other hand, our results may implicate the decreased number of reactive astrocytes after electrical stimulation is continuously applied for a long period. A phenomenon called "tolerance" or "habituation" occurs in patients with pain or movement disorders following long-term neurostimulation therapy including MCS and deep brain stimulation.[17,19] The decrease in the number of c-Fos/GFAP-double-immunopositive cells and the mean area of astrocytes following 8 weeks may be related to the mechanisms of tolerance/habituation.

In our study, the CG, TH, and SMC were investigated as the motor cortex has projections to and from different brain areas such as the thalamocortical projections, corticocortical projections, and local cortical connections in parallel to the cortical layers.[12] A recent positron emission tomography study in humans has demonstrated increased cerebral blood flow following MCS in neuronal structures such as the ventrolateral nucleus of the thalamus, medial thalamus, insula, orbitofrontal area, CG, and upper brain stem.[16] In particular, the anterior cingulate cortex is considered to be important in moods: for example, the number and density of glial cells in depressed or bipolar patients are reduced in the anterior cingulate cortex, which is associated with the affective components of pain.[21] Our study showed that the astrocytes in the CG were both activated and enlarged, suggesting that these changes may contribute to the pain relief mechanism induced by MCS in human patients.

In this study, the chronological changes in astrocytes were observed up to 8 weeks. Further study will be necessary to determine the more detailed reciprocal relationship between neurons and astrocytes, and the mechanism of modulation of the clinical symptoms in humans.

Changes in GFAP-immunopositive astrocytes were observed over time in this study. Activation and morphological changes of astrocytes may contribute to the mechanisms underlying pain relief or functional recovery from stroke or movement disorders. MCS may induce neuroplasticity through the activation of astrocytes.

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# DBS Candidates That Fall Short on a Levodopa Challenge Test

## *Alternative and Important Indications*

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**Introduction:** Candidacy for deep brain stimulation (DBS) in Parkinson disease (PD) is typically assessed by the preoperative motor response to levodopa along with an interdisciplinary evaluation. However, recent cases treated at our institution have achieved good outcomes with DBS despite a sub-30% improvement in motor scores. The aim of this study was to examine the outcomes of DBS in a subset of patients who failed to reach the 30% motor improvement threshold.

**Methods:** A review of all DBS patients treated at the University of Florida Movement Disorders Center between 2002 and 2009 was performed utilizing a DBS database. All patients with sub-30% improvement in Unified Parkinson Disease Rating Scale Part III after dopaminergic medication administration were included.

**Results:** Nine patients were identified; DBS was performed for severe dyskinesia (n = 5), "on/off motor" fluctuations (n = 1) and medication-refractory tremor (n = 3). The target symptoms were improved in all patients. Postoperatively, scores on the Unified Parkinson Disease Rating Scale Part II and III and subscores on Parkinson disease questionnaire-39 improved ($P < 0.05$).

**Conclusions:** Although motor response to levodopa remains the primary selection criteria for DBS candidacy in Parkinson disease, patients who do not meet the 30% threshold and have disabling symptoms may still benefit from DBS. Select patients with severe dyskinesia, "on/off" motor fluctuations, and/or medication-refractory tremor may experience significant benefits from DBS and should be considered on a case by case basis through an interdisciplinary team evaluation.

**Key Words:** deep brain stimulation, Parkinson disease, levodopa challenge test, dyskinesia, on-off motor fluctuations, tremor, quality of life

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Deep brain stimulation (DBS) is commonly employed for the treatment of medication-refractory symptoms in Parkinson disease (PD). Recent studies have revealed the efficacy of DBS for both subthalamic nucleus (STN) and globus pallidus interna (GPi) targets in well-selected patients.[1–7] Institutions with expertise in DBS commonly employ neurocognitive and psychiatric testing along with a levodopa/dopaminergic challenge test to screen potential candidates. In the latter, potential DBS candidates report to their neurologist's office 12 hours off their dopaminergic medications, and are then evaluated with the Unified Parkinson Disease Rating Scale (UPDRS) in the "off" state. Afterwards, they are challenged with a suprathreshold dose of dopaminergic medication and reevaluated at their best "on" state. Optimal surgical candidates typically demonstrate at least a 30% improvement in the motor portion (Part III) of the UPDRS,[4,8–12] as levodopa response has been considered to be one of the strongest indicators of a positive outcome in DBS for PD.[8,9,12] There may, however, be patients who do not achieve a 30% improvement with levodopa or dopaminergic medications but have alternative and potentially responsive indications for DBS (dyskinesia, "on/off" motor fluctuation, and medication-refractory tremor).[12] The aim of this study was to examine alternative indications and the surgical outcomes of a tailored unilateral DBS approach for a cohort of PD patients with a sub-30% improvement on a levodopa/dopaminergic challenge test.

## METHODS

### Study Design

A database query of the University of Florida Movement Disorders Center DBS database (approved by the Institutional

Review Board) containing all patients treated by DBS at our institution from July 2002 to March 2009, was performed. Inclusion criteria included all patients treated with DBS for a primary diagnosis of PD who demonstrated a UPDRS Part III sub-30% improvement on levodopa/dopaminergic challenge testing. After patients were identified, retrospective chart reviews were performed and history, performance scores, operative information, and other information were obtained for each patient.

A levodopa/dopaminergic challenge test was performed on all potential DBS candidates, and definitive diagnosis of PD was confirmed by a movement disorders fellowship trained specialist at our institution. Patients reported to the clinic after being "off" levodopa/dopaminergic therapy for a minimum of 12 hours. A suprathreshold dose of their usual PD medications (1.5 times the dose) was then administered. The UPDRS Part III was collected in the "off" and then "on" medication states and the percentage improvement noted. Patients with dose failures, 45 minutes after ingesting dopaminergics received an additional dose of carbidopa/levodopa 25/100 mg, in an attempt to document the best "on" response. Patients with a sub-30% improvement, but with disabling dyskinesia, "on/off" motor fluctuations, or medication-refractory tremor resulting in subjective impairment in quality of life (QOL) were further considered for DBS by our interdisciplinary DBS team (neurologist, neurosurgeon, neuropsychologist, psychiatrist). In addition, previous history of successful lesional surgery (eg, pallidotomy) was also considered as an indication for DBS despite a sub-30% response. Excluded were patients with a sub-30% improvement on a levodopa/dopaminergic challenge test without disabling tremor, dyskinesia, and/or on-off fluctuations. We did not specifically track those excluded.

## Performance Testing

UPDRS Part III (motor) scores were obtained preoperatively in both "on" and "off" dopaminergic states and then repeated at 4 months, 1 year, and last follow-up in an "off medication/on DBS" state. In addition, the UPDRS Part II (activities of daily living), Part IV (motor fluctuations and dyskinesia), and dyskinesia rating scale contralateral to the side of DBS implantation were documented (range 0 to 5 with 5 being the worst).[13] Parkinson disease questionnaire (PDQ-39) QOL scores were also assessed at baseline and at 6 months and last follow-up. The PDQ-39 is a validated measure of QOL in PD[14] and the scale has 8 subscores (mobility, activities of daily living, emotional, stigma, social, cognition, community, and discomfort). Scores range from 0 to 100 with 100 representing the worst possible function. The Patient Global Impression Scale (PGIS) and the Clinician Global Impression Scale (CGIS) scores (1—very much improved; 2—much improved; 3—minimally improved; 4—no change; 5—minimally worse; 6—much worse; 7—very much worse) were also obtained 6 months after DBS. Annual cognitive evaluations [ie, Mini Mental Status Examination (MMSE) and dementia rating scale (DRS)] were also performed.

## Surgical Procedure

A high-resolution, volumetric brain magnetic resonance imaging (MRI) was obtained 1 day before surgery followed by a stereotactic head computed tomography (CT) the morning of surgery. CT and MRI image fusion was then performed to map out the neuronal brain structures in coordinate space by software developed at our institution. The brain target point was selected utilizing a combination of direct and indirect targeting. For this series although STN was a target of choice in patients without cognitive issues, GPi was selected when patients had severe "on/off" fluctuations/dyskinesia and testing revealed mild cognitive impairment (dementia rating scale score <130). The anterior commissure, the posterior commissure, and a midline plane were identified to anchor the coordinate system. Multiple-pass microelectrode mapping was employed followed by intraoperative test stimulation to verify lead placement. Moreover, a postoperative CT scan was performed and fused to the MRI to assess lead location. An implantable pulse generator (IPG) was placed approximately 4 weeks after the procedure and DBS programming/medication adjustment was performed by protocol once a month for the first 6 months and then every 3 to 6 months.

## Statistical Analysis

Comparisons were made between preoperative and postoperative UPDRS Part III scores in "off" medication states, levodopa equivalent dose, UPDRS Part II, and PDQ-39 values. The Wilcoxon signed rank tests were calculated to assess statistical significance. Statistical analyses were performed utilizing PASW statistics 16.0 (SPSS, Chicago, IL). For patients in the dyskinesia subgroup, the UPDRS Part IV item 32 (duration of dyskinesia) and the preoperative and postoperative dyskinesia rating scale scores[13] were included for comparison. For the medication-refractory tremor subgroup, the UPDRS Part II item 16 (tremor) and Part III item 20 (resting tremor) were compared preoperatively and postoperatively.

# RESULTS

## Clinical Outcomes

The database search revealed 153 PD DBS patients of which 9 (8 men and 1 woman) with average age of 64.2 met inclusion criteria and had a sub-30% improvement on levodopa/dopaminergic challenge testing. These patients were followed up for at least for 6 months and for an average of 2.5 years. Staged bilateral GPi DBS was performed on the 2 patients with severe dyskinesia who also had mild cognitive impairment (DRS < 130). STN DBS was performed on the remaining patients for dyskinesia (n = 3), "on/off" motor fluctuations (n = 1) and medication-refractory tremor (n = 3). Of 9 patients, 7 patients had staged bilateral DBS. In addition, 2 patients were revealed to have a previous history of pallidotomy, and these patients had unilateral DBS (contralateral to the pallidotomy). The patient characteristics are summarized in Table 1.

DBS surgery led to a significant improvement in the UPDRS Part III scores at 4 months and 1 year (16% and 12.5% changes, respectively; $P < 0.05$) (Table 2). When followed to last clinical follow-up, statistical significance for change in motor overall motor score was lost, however, target symptoms remained improved. Furthermore, significant improvements ($P < 0.05$) were observed in the UPDRS Part II and PDQ-39 subscores (ie, activities of daily living, emotional, and stigma) with medium to large effect sizes (Table 3). Interestingly, the cognition subscore of the PDQ-39 improved in patients who underwent GPi DBS (cases 1 and 2), and no significant deteriorations were observed in MMSE and DRS scores 1 year after the first surgery. Overall improvements were demonstrated by the PGIS and CGIS scores; 5 patients had "very much improved" (score of 1) on both scales, whereas the other 4 had "much improved" (score of 2) on both scales (Table 4). Conversely, the statistical analyses failed to detect a significant

TABLE 1. Preoperative Patient Demographics

| Case | Age | Gender | Duration (y) | F/U (y) | Handedness | Target | DBS Side | MMSE | DRS | LED (mg) | H&Y | Preoperative UPDRS motor scores Off Med | On Med | % Change |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dyskinesia patients | | | | | | | | | | | | | | |
| 1 | 65 | Male | 17 | 1 | Right | GPi | Bilateral | 25 | 120 | 1200 | 3 | 35 | 27 | −22.9 |
| 2 | 68 | Male | 19 | 3 | Right | GPi | Bilateral | 26 | 121 | 684.5 | 3 | 48 | 42 | −12.5 |
| 3 | 48 | Female | 7 | 5 | Right | STN | Bilateral | 29 | N/A* | 500 | 2.5 | 49 | 35 | −28.6 |
| 4 | 71 | Male | 8 | 2.5 | Left | STN | Bilateral | 30 | 138 | 1133.4 | 2 | 41 | 32 | −22.0 |
| 5† | 66 | Male | 16 | 0.5 | Right | STN | Right | 28 | 135 | 987.5 | 3 | 51 | 40 | −21.6 |
| Motor fluctuation patients | | | | | | | | | | | | | | |
| 6 | 67 | Male | 11 | 0.5 | Right | STN | Right | 29 | 134 | 1100 | 3 | 37 | 28 | −24.3 |
| Medication-refractory tremor patients | | | | | | | | | | | | | | |
| 7 | 59 | Male | 4 | 1.5 | Right | STN | Bilateral | 29 | 138 | 301.5 | 1.5 | 11 | 16 | 45.5 |
| 8 | 64 | Male | 5 | 3.5 | Right | STN | Bilateral | 30 | 132 | 600 | 2 | 25 | 20 | −20.0 |
| 9† | 70 | Male | 13 | 5.5 | Right | STN | Right | 30 | 138 | 350 | 3 | 41 | 33 | −19.5 |
| Mean (SD) | 64.2 (7.03) | | 11.1 (5.46) | 2.5 (0.6) | | | | 28.4 (1.81) | 132 (7.43) | 761.9 (349.6) | 2.56 (0.58) | 37.6 (12.8) | 30.3 (8.6) | −14.0 (22.7) |

*Unable to do, due to a language barrier as Spanish was her first language.
†Previous history of a contralateral pallidotomy.
DBS indicates deep brain stimulation; DRS, dementia rating scale; F/U, follow-up; GPi, globus pallidus interna; H&Y, modified Hoen and Yahr staging; LED, levodopa equivalent dose; MMSE, Mini Mental Status Examination; N/A, not available; SD, standard deviation; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale.

change in preoperative and postoperative levodopa equivalent dose dosages at 1 year and the last follow-up ($P$-value > 0.05).

In the dyskinesia subgroup, duration of dyskinesia in waking time decreased in all 5 patients, as did scores on the dyskinesia rating scale (Table 4). The motor fluctuation patient (case 6) preoperatively complained of "off" periods during 50% of a day, however, these periods had completely resolved at 6 months after STN DBS. In the medication-refractory tremor patients, improvements were seen in both items 16 and 20 (Table 4).

## Complications

Transient mental status change on postoperative day #1 was noted in 2 patients who underwent STN DBS (cases 5 and 7). A transient IPG seroma was encountered in a single patient (case 7). An intracerebral hemorrhage around the STN (12 $mm^3$) resulted in a transient hemiparesis in 1 patient (case 9) that had resolved when the patient returned for the IPG implantation 4 weeks later.

## DISCUSSION

The levodopa/dopaminergic challenge test is frequently utilized as the primary first-line screening method to select appropriate DBS candidates with PD.[8–10,12] The test has proven particularly useful for excluding parkinsonian syndromes (syndromes deemed not to meet the criteria for idiopathic PD, but may have prominent parkinsonian features), for defining levodopa unresponsive symptoms (eg, gait, balance, speech), and for predicting surgical outcomes.[15] The ability to exclude parkinsonian syndromes has been a particularly important use of the test and a recent study revealed that 5 of 41 referred patients with DBS failure had misdiagnosis due to lack of appropriate challenge testing.[15] Most authorities have promoted that >30% improvement after dopaminergic administration (UPDRS-III testing) may identify the optimal candidates for DBS and those who should move on to a complete interdisciplinary evaluation. Our data however, revealed that at least 3 scenarios exist where alternative indications for DBS might be useful: severe dyskinesia, "on/off" motor fluctuations, and medication-refractory tremor.[3,5,6,16] Anecdotally, many expert centers have observed similar positive results to those reported here (author personal communications with National Parkinson Foundation and other Centers of Excellence for DBS therapy).

There are several important issues that emerge upon closer inspection of the levodopa/dopaminergic challenge test when utilized for screening potential DBS candidates. First, some patients may not tolerate clinically effective doses of levodopa due to complications such as nausea, sedation, and/or dyskinesia, and thus it may be difficult to glean clean data from a levodopa/dopaminergic challenge test.[17,18] In some cases, severe dyskinesias can impair the performance on select items of the UPDRS such as finger tapping, hand movement, and rapid alternating movements, giving the impression of minimal improvements in these items as highlighted in case 7. In these patients, select examples of successful improvement of symptoms as a result of DBS have been previously reported.[17,18] In addition, delayed gastric emptying may profoundly impact the measured response of a levodopa/dopaminergic challenge test,[19] and some authors advocate apomorphine as a reasonable alternative in this scenario.[11] Further, another scenario that must be considered is a history of successful lesioning therapy (pallidotomy, thalamotomy, subthalamotomy) that may reduce the measured responsiveness of levodopa and other dopaminergics

**TABLE 2.** UPDRS Part III (Motor) Scores and LED

| | UPDRS Total Motor Scores | | | | LED | | |
|---|---|---|---|---|---|---|---|
| | Preoperative | 4 mo | 1 y | Last F/U | | | |
| Case | Off medication | Off medication/ On stim | Off medication/ On stim | Off medication/ On stim | Preoperative | 1 y | Last F/U |
| 1 | 35 | 26 | 30 | 30 | 1200 | 816.7 | 816.7 |
| 2 | 48 | 54 | 49 | 63 | 684.5 | 25.1 | 33.5 |
| 3 | 49 | 38 | 45 | 7 | 500 | 683.4 | 1000 |
| 4 | 41 | 21 | 37 | 41 | 1133.4 | 750 | 900 |
| 5 | 51 | 42 | NA | 42 | 987.5 | NA | 300 |
| 6 | 37 | 28 | NA | 28 | 1100 | NA | 1033.4 |
| 7 | 11 | 14 | 14 | 31 | 301.5 | 0 | 450 |
| 8 | 25 | 23 | 21 | 33 | 600.0 | 400 | 600 |
| 9 | 41 | 38 | 34 | 56 | 350.0 | 400 | 300 |
| Mean (±SE) | 37.6±4.3 | 31.6±4.1 | 32.9±12.5 | 36.8±16.4 | 761.9±116.5 | 439.3±125.9 | 603.7±118.3 |
| % change | | −16% | −12.5% | −2.1% | | −42.3% | −20.8% |
| *P*-value* | | 0.03* | 0.04* | 0.42 | | 0.08 | 0.13 |

*Statistically significant values. *P*-values were calculated by comparing the motor score from baseline to each follow-up period.

F/U indicates follow-up; LED, levodopa equivalent dose; NA, not available; PD, Parkinson disease; SE, standard error; UPDRS, Unified Parkinson Disease Rating Scale.

and ultimately reset the UPDRS off score to a lower (better) baseline. This particular scenario is highlighted in 2 of our reported cases (5 and 9), where previous pallidotomy may have contributed to the sub-30% responsiveness to levodopa/dopaminergic challenge testing. Moreover, clinicians should be aware that a UPDRS "on/off" test does not reveal the extent or severity of "on/off" motor fluctuations which ultimately require careful history taking and/or formal documentation by a diary.[20–22] Finally, the threshold values for the levodopa/dopaminergic challenge test have not been standardized for DBS; values vary in the literature from 25% to 50% in published surgical series.[4,8,9,11,23,24] Clinicians should be aware that higher threshold levels on levodopa/dopaminergic challenge testing may lead to excluding potentially reasonable DBS candidates, especially those with dyskinesias, fluctuations, and tremor.

In our series, significant improvements were evidenced in the UPDRS Part II (activity of daily living) and in the PDQ-39 QOL subscores despite only subtle improvement in total motor scores, highlighting the importance of not overvaluing UPDRS motor scores. These findings further support the argument that DBS teams should remain vigilant for potential candidates that may not meet the 30% motoric improvement criteria. A recent meta-analysis of STN DBS outcomes revealed 52% improvement in the UPDRS Part III motor section after surgery.[4] The UPDRS motor scores improved by only 16% and 12.5% at 4-month follow-up, respectively, in our series. These improvements may on the surface seem disappointing; however, these improvements failed to measure changes important for an individual patient, as the target symptoms were successfully addressed in each case (Table 4) and the improvement contributed to enhanced activity of daily living and QOL scores. The low motor improvement seen in several of our cases is in direct support of the notion that DBS has its effects on levodopa responsive motor symptoms, but that UPDRS III may not tell the whole story. PGIS and CGIS scores also support the observed improvements in our cohort.

**TABLE 3.** Comparison of UPDRS Part II (ADL) and PDQ-39 Scores From Baseline to 6 Months and Last Follow-up

| | Preoperative | 6 mo | 1 y | Last F/U |
|---|---|---|---|---|
| UPDRS | | | | |
| PDQ-39 | | | | |
| Part II | 19.4±2.4 | 13.7±1.6* | 15.0±2.4 | 21.6±2.6 |
| Mobility | 42.2±9.3 | 34.7±8.4 | 25.4±5.3 | 43.6±7.5 |
| ADL | 44.0±7.0 | 22.7±4.5* | 26.8±3.0 | 36.1±5.3 |
| Emotional | 32.0±5.0 | 12.5±4.8* | 17.3±4.7 | 16.2±3.8* |
| Stigma | 35.4±9.8 | 8.4±3.9* | 9.8±5.1* | 19.4±6.9* |
| Social | 7.4±2.9 | 9.2±4.9 | 7.1±3.8 | 13.0±4.0 |
| Cognition | 39.6±10.1 | 20.9±5.7 | 16.1±5.1 | 31.9±4.1 |
| Community | 35.2±9.5 | 21.3±5.4 | 28.6±6.8 | 38.0±5.4 |
| Discomfort | 46.3±9.4 | 36.1±7.5 | 28.6±6.0 | 30.6±7.7 |

*Statistically significant ($P < 0.05$); mean and standard error shown.

ADL indicates activity of daily living; F/U, follow-up; UPDRS, Unified Parkinson Disease Rating Scale; PDQ, Parkinson disease questionnaire.

Dyskinesia and "on/off" motor fluctuations represent most of the motor complications encountered with long-term levodopa therapy; however, these issues are potentially amenable to DBS therapy. Levodopa dosage and DBS unresponsive PD features (eg, gait, balance, speech) have been demonstrated in recent studies to progress over time, whereas improvements in dyskinesia and "on/off" motor fluctuations seem to persist up to 5 years after STN DBS.[5,25] Further, a meta-analysis of available studies in the literature revealed 69.1% and 68.2% reduction in dyskinesia and daily off periods after DBS.[4] Thus, those patients with a chief complaint of severe dyskinesia or "on/off" motor fluctuations may have the potential to experience symptomatic improvement from DBS and this improvement may translate into improved activities of daily living, QOL, and global outcome scores. This improvement may be evident even when significant improvement in UPDRS motor scores is absent.

The issue of preexisting cognitive dysfunction has led many groups to shy away from DBS implantation primarily because of fear of worsening deficits.[26] Typically DRS scores of 130 or above are considered to be the minimal cut-off for DBS surgery.[8] Some groups have also alternatively used a MMSE score >24 as a selection criteria to exclude frank dementia.[6] Interestingly, in our series, 2 patients had temporary

**TABLE 4.** UPDRS Subscores, Dyskinesia Rating Scale Scores, PGIS, and CGIS

| | Dyskinesia Rating Scale | | UPDRS Part IV | | | | UPDRS Part II | | UPDRS Part III | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total Scores | | Item 32 (Dyskinesia) | | Item 39 (Off Periods) | | Item 16 (Tremor) | | Item 20 (Resting Tremor) | | | |
| Case | Preoperative | Postoperative | Preoperative | Postoperative | Preoperative | Postoperative | Preoperative | Postoperative | Preoperative (UE/LE) | Postoperative (UE/LE) | PGIS | CGIS |
| Dyskinesia patients | | | | | | | | | | | | |
| 1 | 3 | 0 | 2 | 1 | — | — | — | — | — | — | 1 | 1 |
| 2 | 3.5 | 1 | 2 | 1 | — | — | — | — | — | — | 1 | 1 |
| 3 | 3.5 | 0 | 2 | 0 | — | — | — | — | — | — | 2 | 2 |
| 4 | 2 | 0 | 2 | 1 | — | — | — | — | — | — | 1 | 1 |
| 5 | 2 | 0 | 2 | 0 | — | — | — | — | — | — | 1 | 1 |
| Motor fluctuation patients | | | | | | | | | | | | |
| 6 | — | — | — | — | 2 | 0 | — | — | — | — | 2 | 2 |
| Medication-refractory tremor patients | | | | | | | | | | | | |
| 7 | — | — | — | — | — | — | 3 | 0 | 2/0 | 0/0 | 2 | 2 |
| 8 | — | — | — | — | — | — | 4 | 1 | 3/0 | 1/0 | 1 | 1 |
| 9 | — | — | — | — | — | — | 2 | 1 | 3/1 | 0/0 | 2 | 2 |

CGIS indicates Clinician Global Impression Scale; Item 32, duration of dyskinesia; Item 39, duration of off periods; LE, contralateral lower extremity; PGIS, Patient Global Impression Scale; Preoperative, Baseline off medication state; UE, contralateral upper extremity; UPDRS, Unified Parkinson's Disease Rating Scale. Dyskinesia rating scale ranges 0 to 5 with 5 being the worst.

mental status change after STN DBS, whereas the 2 patients with preexisting mild cognitive impairment seemed to tolerate the GPi target without worsening of the cognitive status. Although clearly more data are needed, recent studies have revealed the possibility that the incidence of cognitive adverse events may be lower with GPi DBS when compared with STN DBS.[1,7,27,28] GPi DBS has been shown to be a powerful direct suppressor of dyskinesia and also is effective against "on/off" motor fluctuations.[1,3,27] In this small series, we utilized the GPi option for preexisting cognitive dysfunction. It should be noted, however, that we did not attempt STN DBS, and thus we cannot comment on the superiority of one approach over another.

DBS has been recommended for advanced PD patients by the Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease. This committee also recommended selecting patients with at least a 5-year disease duration.[8] However, in our cohort 2 patients had disabling tremor despite relatively short disease durations (cases 7 and 8) and both benefitted from STN DBS. STN DBS may thus be a reasonable treatment option for medication-refractory tremor in earlier stage PD. Although ventral intermediate thalamic nucleus (Vim) is also a viable target for medically-refractory tremor, Vim DBS does not as effectively address other cardinal symptoms of PD or address the development of lower extremity tremor.[29] Fraix et al[29] reported favorable results when utilizing bilateral or contralateral STN DBS after thalamic surgery for tremor dominant PD patients. The relative roles of STN, GPi, and thalamic DBS in medication-refractory tremor have not been carefully analyzed in randomized controlled trials and currently most groups are choosing the STN as the target unless cognitive dysfunction is present. Further study is needed in this area.

The data from our cohort demonstrates benefit in well-selected PD patients with a preoperative sub-30% UPDRS motor change if the diagnosis of PD is a reasonable certainty. We would and therefore do argue that DBS indications should be tailored to the individual patient, and that the indications for surgery should be given strong weight in an interdisciplinary evaluation for selection of appropriate patients. Patients with severe dyskinesia, "on/off" fluctuations, and/or medication-refractory tremor may thus be reasonable DBS candidates even if they fail a classic levodopa/dopaminergic challenge test. Although this case series suffers from biases introduced by its retrospective and unblinded nature and the limited number of observations, we feel the data tell an important story. Further studies should be pursued to confirm these findings. In the meantime, we would encourage groups to employ an interdisciplinary screening process for DBS indications that tailors decisions to the individual patient, even if the results of a levodopa/dopaminergic challenge test fall short of widely accepted criteria.

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# 難治性疼痛に対するneuromodulation
## ―神経障害性疼痛に対する治療を中心に―

大島秀規[1-3]，山本隆充[2]，片山容一[1]

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神経障害性疼痛に対する薬物治療を，そのガイドラインを中心に解説するとともに，神経障害性疼痛を中心とした難治性疼痛に対するニューロモデュレーション（末梢神経，脊髄，視床に代表される脳深部および大脳皮質運動野の電気刺激療法やドラッグポンプによる薬物の髄腔内投与）の現状を紹介する．

*Key Words:* ニューロモデュレーション，神経障害性疼痛，脊髄，視床，刺激

## Ⅰ．はじめに

難治性疼痛とは，その原因にかかわらず既存の除痛法では治癒させることが困難な疼痛の総称であり，その病態は侵害受容性疼痛（nociceptive pain），神経障害性疼痛（neuropathic pain），および心因性疼痛（psychogenic pain）の3つに分類することができる．

侵害受容性疼痛は，末梢の痛み受容器が持続的かつ過剰に刺激されるために発生する疼痛であり，がん性疼痛，疾患や外傷の急性期の痛みの多くがこれにあたる．神経障害性疼痛は，神経組織そのものの損傷や機能異常に伴い発生する慢性の難治性の疼痛であり，末梢から中枢神経のさまざまな疾患・病態により生じる．最後の心因性疼痛は，何らかの精神疾患や非疼痛性疾患などが引き金となり生じる心身症としての痛みや，慢性疼痛に伴う抑うつなどの心因的要因による痛みへの負の修飾などが含まれる．慢性難治性疼痛ではこれらの病態が複合的に存在しており，各病態に対する多面的な治療のアプローチを要することが少なくない．

われわれ脳神経外科医が日常的に診療にあたる難治性疼痛の多くは，脳卒中後の中枢性疼痛を筆頭に，さまざまな神経疾患を基礎とする慢性の神経障害性疼痛であるといってよい．近年，神経障害性疼痛に対する薬物治療ガイドラインが国際疼痛学会（(International Association for the Study of Pain：IASP）から示されるとともに，本国の医療状況を踏まえた日本版のガイドラインが日本ペ

インクリニック学会から発刊され，試行錯誤の多い神経障害性疼痛の薬物治療に一つの道筋ができた．このガイドラインを踏まえ，本稿では，脳神経外科医がその治療に際して抑えておくべき神経障害性疼痛に対する薬物治療の現状を解説するとともに，テーマである neuromodulation（ニューロモデュレーション）を中心とした外科治療とその神経障害性疼痛治療全体のなかの位置付けに関して解説する．

## Ⅱ．神経障害性疼痛の定義とその原因疾患

神経障害性疼痛は，国際疼痛学会では 'Pain caused by a lesion or disease of the somatosensory nervous system' と定義されており，中枢神経および末梢神経系の体性感覚系の障害に起因するすべての痛みが含まれる．神経障害性疼痛を主訴とするさまざまな疼痛性疾患が報告されている（表 1）[1]．それらの多くはニューロモデュレーション療法の対象となりうる痛みである．

## Ⅲ．神経障害性疼痛の治療

### 1）治療目標の設定

今日，EBM に基づいた神経障害性疼痛に対する薬物治療ガイドラインが示され，それに従い，低侵襲かつ有効性が高いと考えられる薬物治療から試みられるようになってきている．それでも個々の症例において有効な薬剤をあらかじめ予測

**表 1　神経障害性疼痛を主因とする疼痛性疾患**（文献 1 より一部改変のうえ引用）

| 末梢性 | 中枢性 |
|---|---|
| 複合性局所疼痛症候群（CRPS） | 脳卒中後疼痛（視床痛ほか） |
| 三叉神経痛 | 多発性硬化症に伴う疼痛 |
| 幻肢痛 | パーキンソン病に関係した疼痛 |
| 腫瘍による圧迫・浸潤による神経障害 | 脊髄損傷後疼痛 |
| 神経根障害 | 脊髄空洞症 |
| 外傷性末梢神経障害 | 脊柱管狭窄症による脊髄症 |
| 拘約性神経障害（手根管症候群など） | 虚血後脊髄症 |
| 医原性神経痛（乳房切除後，開胸手術後など） | 放射線照射後脊髄症 |
| 放射線照射後神経叢障害 | HIV 脊髄症 |
| 化学療法誘発性多発性神経障害 | |
| 急性・慢性炎症性脱髄性多発性根神経障害 | |
| 突発性感覚障害 | |
| 帯状疱疹後神経痛（PHN） | |
| HIV 感覚神経障害 | |
| 有痛性糖尿病性神経障害 | |
| アルコール性多発性神経障害 | |
| 中毒性神経障害 | |
| 栄養障害による神経障害 | |

することは困難であり，試行錯誤となることも少なくない．また，単剤では効果が明確でなくても，作用の異なる薬剤を併用することにより疼痛の軽減が得られる場合も少なくない．残存する痛みに対しては，さらに改善させたいとの患者の要求に応じて，薬物治療に加えて各種ブロック療法，外科的治療（ニューロモデュレーション），および精神・心理学的療法などのさまざまな治療が試みられる．

しかしながら，薬物療法以外の治療も確実な効果を期待できるものではなく，集学的に治療を行っても，なお疼痛を完全に消失させることは困難であることがほとんどである．また，患者の残存する痛みを完全に克服したいという過度の欲求は，かえって自己の疼痛への注意・関心を高め，疼痛増悪の一因である不快な情動経験の重畳となり心因性要素を増悪させる原因となる．痛みと戦わず，うまく共存できている患者は生活の質（quality of life：QOL）が良い傾向にある．このような現状を踏まえれば，医師はもとより患者自身にも治療の目標を疼痛の完全制圧ではなく，QOLの向上する程度の疼痛軽快にまずは置くべきことを理解してもらう必要がある．

**2）薬物治療**

国際疼痛学会による神経障害性疼痛の治療ガイドライン（**表2**）[2]では，神経障害性疼痛の治療の第一選択薬は三環系抗うつ薬，セロトニン・ノルアドレナリン再取り込み阻害薬（SNRI），カルシウムチャネルα2-δリガンドが挙げられている．少ない神経障害性疼痛に有効な薬剤のなかでも，アミトリプチンやノルトリプチリンといった三環系抗うつ薬は以前から使用されることの多い薬剤であり，薬剤の有効性の一つの指標であるNNT（疼痛が50％改善する患者1人を得るために何人の患者に同一の薬剤を投与する必要があるかという数値）からみても最も有効率の高い（NNT: 2.1-4.0）薬剤であることが報告されている（**表3**）[3,4]．一方で，近年日本でも発売されたα2-δリガンド（ガバペンチンおよびプレガバリン）は，使用経験上の印象とは異なりNNT（3.9-7.1）と三環系抗うつ薬には及ばない．SNRIはガイドラインでは第一選択薬として推奨されているが，有痛性多発ニューロパチー以外の疼痛に関するエビデンスはほとんどない．わが国においても，日本ペインクリニック学会の神経障害性疼痛薬物療法ガイドライン作成ワーキンググループより，本邦の医療環境に即した神経障害性疼痛治療のアルゴリズムが提唱されている（**表2**）[5]．同アルゴリズムに記載されている薬剤であっても，神経障害性疼痛に対する使用が保険適用外のものが含まれていることに留意する必要がある．

**3）難治性疼痛に対するニューロモデュレーション**

**A：ニューロモデュレーションとは**

国際ニューロモデュレーション学会では，'Neuromodulation is technology that acts directly upon nerves. It is the alteration or modulation of nerve activity by delivering electrical or pharmaceutical agents directly to a target area' と定めている．治療の対象とする神経組織に直接薬物や電気刺激を加えて神経機能の調節を行う治療技術としては，デバイスを用いたドラッグポンプによる薬物の持続髄腔内投与や電気刺激療法が

**表2　神経障害性疼痛治療のガイドライン**（文献2，5を参考に筆者作製）

| | 国際疼痛学会（IASP） | 日本ペインクリニック学会*<br>（神経障害性疼痛薬物療法ガイドライン作成ワーキンググループ） |
|---|---|---|
| 第一選択薬 | 三環系抗うつ薬（二級アミン）<br>ノルトリプチリン，desipramine<br>三環系抗うつ薬（四級アミン）<br>（二級アミンが使用できない時）<br>セロトニン・ノルアドレナリン再取り込み阻害薬（SNRI）<br>デュロキセチン，Venlafaxine<br>Caチャネルα2-δリガンド<br>ガバペンチン，プレガバリン<br>リドカイン外用<br>（表在性，局所性の神経障害性疼痛に対して） | 三環系抗うつ薬<br>ノルトリプチリン，アミトリプチン，イミプラミン<br>Caチャネルα2-δリガンド<br>ガバペンチン，プレガバリン<br>ー下記の病態に限り上記薬剤とともに第一選択薬として考慮ー<br>・帯状疱疹後神経痛（PHN）<br>ワクシニアウイルス接種家兎炎症皮膚抽出液含有製剤<br>（ノイロトロピン®）<br>・有痛性糖尿病性ニューロパチー<br>SNRI（デュロキセチン）<br>抗不整脈薬（メキシレチン）<br>アルドース還元酵素阻害薬（エパルレスタット） |
| 第二選択薬 | オピオイド鎮痛薬（状況に応じて第一選択薬として使用）<br>モルヒネ，オキシコドン，トラマドール，methadone，levorphanol | ワクシニアウイルス接種家兎炎症皮膚抽出液含有製剤<br>（ノイロトロピン®）<br>SNRI（デュロキセチン）<br>抗不整脈薬（メキシレチン） |
| 第三選択薬 | 抗てんかん薬<br>バルプロ酸，カルバマゼピン，ラモトリギン，トピラマート，oxcarbazepine<br>抗うつ薬<br>パロキセチン，bupropion，citalopram<br>メキシレチン<br>NMDA受容体拮抗薬<br>カプサイシン外用 | 麻薬性鎮痛薬<br>フェンタニル，モルヒネ，オキシコドン，トラマドール，ブプレノルフィン |

（*三叉神経痛を除く）

**表3　神経障害性疼痛に対する各種治療薬のNNT**（文献3，4を参考に筆者作製）

| | 三環系抗うつ薬 | ガバペンチン/プレガバリン | バルプロ酸 | カルバマゼピン | ラモトリギン | オピオイド |
|---|---|---|---|---|---|---|
| 中枢性疼痛 | 4.0（1.6-8.5） | 7.1（3.9-40） | — | 3.4（1.7-105） | — | — |
| 帯状疱疹後神経痛 | 2.8（2.2-3.8） | 4.6（4.3-5.4） | 2.1（1.4-4.2） | — | — | 2.6（2.0-3.8） |
| 有痛性多発ニューロパチー | 2.1（1.9-2.6） | 3.9（3.3-4.7） | — | 2.3（1.6-3.9） | 4.0（2.1-42） | 2.6（1.7-6.0） |
| 末梢神経損傷後疼痛 | 2.5（1.4-11） | — | — | — | — | 3.0（1.5-74） |

現在では最も広く行われているニューロモデュレーションと言える．難治性疼痛に対して今日行われているおもなニューロモデュレーションを表4に記した．将来的には，治療技術やデバイスの革新により，その範疇に含まれる治療法はさらに増加すると予想される．

**表4　難治性疼痛に対するニューロモデュレーション**

| 治療部位 | 治療法 | 適　応 |
|---|---|---|
| 末梢神経 | 末梢神経刺激 | 比較的局所の慢性疼痛全般：頭部・顔面のPHN，後頭神経痛，特発性顔面痛など |
| | 経皮的電気神経刺激療法 | 局所の慢性疼痛全般：慢性腰痛，末梢性神経障害性疼痛など |
| 脊　髄 | 脊髄（電気）刺激療法 | さまざまな神経障害性疼痛 |
| | 脊髄後根進入部破壊術 | 幻肢痛や神経叢引き抜き損傷後疼痛で選択されることが多い |
| | ドラッグポンプによる薬物の持続髄腔内投与* | おもにがん性疼痛に対するオピオイドの投与<br>（＊日本においては疼痛に対する適用が未承認） |
| 間　脳 | 脳深部刺激療法（視床知覚中継核刺激など） | おもに脊髄・末梢性の神経障害性疼痛 |
| 大脳皮質 | 運動野（電気）刺激療法 | さまざまな神経障害性疼痛<br>特に脳卒中後の中枢性疼痛で選択されることが多い |

PHN：帯状疱疹後神経痛

B：末梢神経刺激（peripheral nerve stimulation: PNS）/ 経皮的電気神経刺激療法（transcutaneous electrical nerve stimulation: TENS）

PNSは，頭部・顔面のPHN，後頭神経痛，特発性顔面痛などのような限局した狭い領域の疼痛に対して選択されることが多い．末梢神経障害に起因する疼痛に有効なことが多く，同じ顔面痛でも中枢性（脳卒中後の疼痛など）の痛みに対しては無効であることが多い．

TENSの臨床応用には30年以上の長い歴史があり，胸・腹部手術後の創部痛（急性痛）の有効性に関する報告は多数あるが，慢性痛の特に長期効果に関する報告はあまり多くない．上肢領域の末梢神経障害に起因する神経障害性疼痛19症例に対する初期治療効果は，未治療対象群に比べてVisual Analogue Scale（VAS）スコアが有意に低かった（50%以下）ことをChainingら[6]は報告している．初期に治療が奏効しても，長期にわたって本治療を使用する頻度は10%程度であるため長期効果はあまり期待できないが，本治療は簡便であるために疼痛の治療初期から試みる価値があることが報告されている[7]．

C：脊髄刺激療法（spinal cord stimulation: SCS）

SCSを受けた疼痛患者（3,679例）の文献レビュー[8]によれば，奏効率はCRPS（84%）で最も高く，次いで帯状疱疹後神経痛（82%），末梢性のニューロパチー（67%），脊椎手術後疼痛：FBSS（62%），幻肢痛および断端痛（62%），脊髄損傷後の疼痛（57%）の順であった．Kumarらにより長期的な有効性も報告されている（**表5**）[9]．症例数（8～53例）は少ないながらも，RCTにより末梢血管障害に伴う痛み，難治性の狭心痛，FBSS，CRPSなどに対するSCSの有効性が高いエビデンスレベルで報告されている．これらのエビデンスを反映して英国疼痛学会（The British Pain Society）よりSCSの適応が示されている（**表6**）[10]．

**表5　脊髄刺激療法の長期成績**（文献9より一部改変のうえ引用）

| 疼痛の原因 | 症例数 | 治療成績（初期） 有効数（%） | 治療成績（長期） 有効数（%） |
|---|---|---|---|
| FBSS | 220 | 184 (84) | 132 (60) |
| Peripheral vascular disease | 52 | 42 (81) | 31 (60) |
| CRPS I and II | 32 | 28 (88) | 23 (72) |
| Peripheral neuropathy | 17 | 14 (82) | 12 (71) |
| Phantom limb pain/stump pain | 5 | 1 (20) | 1 (20) |
| Multiple sclerosis | 19 | 17 (90) | 15 (79) |
| Angina | 9 | 9 (100) | 9 (100) |
| Bone and joint pain syndromes | 8 | 8 (100) | 4 (50) |
| Spinal cord injury/lesion/ cauda equina syndrome | 15 | 7 (47) | 5 (33) |
| Perirectal pain | 6 | 4 (67) | 3 (50) |
| Postherpetic/intercostals neuralgia | 19 | 10 (53) | 4 (21) |
| Upper limb pain secondary to disc surgery and Miscellaneous pain syndromes | 8 | 4 (50) | 4 (50) |
| Total | 410 | 328 (80) | 243 (59) |

平均 follow-up 期間：97.6 カ月（1 ～ 22 年）

傾向として，①障害部位が中枢より末梢（神経）にあり，②SCS の治療ターゲットである脊髄後索の障害がないかあっても軽度で，③痛みのある身体部位が四肢（体幹でない）にあるものが SCS に奏効することが多い．SCS の適応が広いことに加えて，X 線透視下で胸・腹部手術における周術期の疼痛管理のための脊髄硬膜外カテーテルの挿入に類似した手法で局所麻酔下に電極挿入が行うことができるため，その施行の簡便さや侵襲の低さからニューロモデュレーション治療のファーストラインとして位置付けられるようになってきた．

D：脳深部刺激療法（deep brain stimulation: DBS）

脳深部の間脳およびその周辺構造をターゲットとする DBS は，定位脳手術法を用いて行われる．今日までにさまざまな部位に対する DBS 治療が試みられてきた．なかでも，神経障害性疼痛に対して最も選択されることの多い治療部位は視床 Vc（VPM /VPL）核である．その適応となるおもな病態に，幻肢痛や神経叢引き抜き損傷後疼痛に代表される末梢から脊髄レベルの神経障害性疼痛がある．疼痛に対する DBS 治療は，その適応疾患の多くが SCS の適応疾患と重複するため，今日では SCS が無効であった症例や SCS の効果があまり期待できない神経叢引き抜き損傷後疼痛などに行われることが多い．

神経障害性疼痛に対する Vc-DBS の刺激開始初期の有効率は，61 ～ 78% と報告されており[11-14]，この有効性は一年以上の期間にわたってある程度（有効率 30 ～ 72%）維持されている[11-14]．これらの報告に含まれる患者には，SCS が無効であ

**表 6　脊髄刺激療法の適応**（文献 10 より一部改変のうえ引用）

| | |
|---|---|
| Good indication (likely to respond) | ・頚部・腰部の脊椎手術後の四肢の神経障害性疼痛（FNSS / FBSS）<br>・複合性局所疼痛症候群（CRPS）<br>・末梢神経損傷後の神経障害性疼痛<br>・末梢血管障害（ASO など）に伴う疼痛<br>・難治性の狭心痛<br>・外傷性（神経根引き抜き損傷を除く）および放射線療法後の腕神経叢損傷 |
| Intermediate indication (may respond) | ・四肢切断に伴う痛み（幻肢痛に比べて断端痛のほうが奏効しやすい）<br>・脊椎手術後の体幹の痛み<br>・肋間神経痛（開胸術後，帯状疱疹後神経痛）<br>・脊髄障害に伴う痛み<br>・その他の末梢性神経障害性疼痛 |
| Poor indication (rarely respond) | ・中枢性疼痛（脊髄障害でない）<br>・脊髄損傷（脊髄後索機能の完全な脱出を伴う）<br>・会陰部および肛門直腸部の痛み |
| Unresponsive to SCS | ・完全脊髄横断損傷<br>・侵害受容性疼痛（虚血性疼痛を除く）<br>・神経根引き抜き損傷 |

った症例が多く含まれている．幻肢痛に対する効果は，Levy ら[11]の報告（有効率 20%）を除くと，50 ～ 98%[15-19]と高い有効性が報告されている．

E：大脳皮質運動野刺激療法（motor cortex stimulation: MCS）

MCS は，視床痛などの脳卒中後の中枢性疼痛に対して選択されることが多い．MCS を受けた疼痛患者（327 例）の系統的レビュー[20]によれば，奏効率は 72.9%と報告されている．

F：ドラッグポンプによる薬物の持続髄腔内投与

現在，日本においてはドラッグポンプで使用可能な薬剤は痙縮に対して用いられるバクロフェンのみであり，疼痛に対する適用がない．欧米においてはオピオイドの髄腔内投与を筆頭に，多くの薬剤の臨床応用が試みられている．特にがん性疼痛（侵害受容性疼痛が主体）に対するオピオイド系鎮痛薬の髄腔内投与は，経口投与に比較して除痛効果が高く，またオピオイドの使用量の大幅な減量ならびに副作用の軽減といった点で優れているようである[21]．

## Ⅳ．おわりに

デバイスの著しい進歩とそれに伴う脊髄刺激療法の治療成績の向上や適応疾患の拡大をきっかけに，脊髄刺激療法を中心とするニューロモデュレーション（療法）の慢性疼痛治療における位置付けが大きく変わりつつある．ニューロモデュレーション療法を薬物治療やその他の治療と並行して行うことは，個々の治療を独立して行うことより疼痛改善に効果的であることから，従来考えられ