

Epidural Premotor Cortical Stimulation in Primary Focal Dystonia: Clinical and ^{18}F -Fluoro Deoxyglucose Positron Emission Tomography Open Study

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ABSTRACT: The aim of this study was to evaluate the efficacy and safety of epidural premotor stimulation in patients with primary focal dystonia. Seven patients were selected: 6 had cervical dystonia and 1 had right upper limb dystonia. In 2 patients, sustained muscle contractions led to a prevalently fixed head posture. Patients with cervical dystonia received a bilateral implant, whereas the patient with hand dystonia received a unilateral implant. Neurological and neuropsychological evaluations were performed before surgery (baseline), and 1, 3, 6, and 12 months afterward. The Burke-Fahn-Marsden scale (BFMS) and the Toronto Western spasmodic torticollis rating scale (TWSTRS)

were administered at the same time points. Patients underwent resting ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET) scans, before and 12 months after surgery. No adverse events occurred. An overall improvement was observed on the BFMS and TWSTRS after surgery. Patients with prevalently fixed cervical dystonia had a reduced benefit. Presurgical neuroimaging revealed a significant bilateral metabolic increase in the sensorimotor areas, which was reduced after surgery. © 2012 Movement Disorder Society

Key Words: dystonia; Parkinson's disease; tremor; DaTscan

Recent observations have prospected the efficacy of surgical interventions in patients with dystonia syndromes. Deep brain stimulation (DBS) of the globus pallidum has proven efficacious for primary generalized dystonias¹ and for segmental primary forms such as spasmodic torticollis.^{2–4} More recently, it has been postulated that premotor cortex stimulation may have a symptomatic effect on dystonia. The rationale for this approach is based on clinical and neurophysiological evidence. A number of studies have claimed that inhibitory repetitive transcranial magnetic stimulation

(rTMS) applied over the dorsal premotor cortex can reduce symptoms of dystonia. rTMS delivered over the premotor cortex at slow rates (≤ 1 Hz) can ameliorate defective reciprocal inhibition, a hallmark of dystonia.⁵ Moreover, subthreshold 0.2-Hz rTMS applied to the premotor cortex, but not to M1, improved handwriting in patients with upper limb dystonia.⁶ Recently, it has also been shown that continuous theta burst TMS to the premotor cortex partially reverses the short-interval intracortical inhibition abnormalities that occur in dystonia,⁷ opening the way to new potential therapeutic approaches.^{8,9} In a previous study, we observed that epidural motor cortex stimulation can improve primary fixed dystonia¹⁰; based on this result we designed an explorative study on the efficacy of premotor cortical stimulation in patients with primary focal dystonia syndromes.

Patients and Methods

Six patients affected by primary cervical dystonia and 1 patient with primary upper limb dystonia were selected for epidural cortical stimulation and

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

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prospectively recruited. Inclusion criteria were as follows: age between 20 and 65 years; no neurologically active oral medication (such as anticholinergics, benzodiazepines, or neuroleptics); withdrawal of botulinum neurotoxin treatment for at least 3 months before enrollment; and no previous brain surgery. These patients did not respond satisfactorily to previous treatments with botulinum neurotoxins and had a primary pure form of dystonia¹¹; known secondary or primary plus forms were excluded. In 2 cervical dystonia patients, sustained muscle contractions had led to prevalently fixed cervical postures with trunk involvement. They had no psychiatric disorders or cognitive impairment (Mini-Mental State Examination Score > 24). The patients' demographic and clinical features are reported in the Supporting Information, Table S1.

Cervical dystonia patients received a bilateral epidural cortical electrode implant; their mean age at surgery was 45 ± 7 (range, 37–55) years, with a mean disease duration of 11 ± 7 years. The patient with right upper limb focal dystonia was implanted unilaterally on the contralateral hemisphere. The study was approved by the Besta Institute internal review board (registered at the Office for Human Research Protections as IORG0006168). Each patient signed an informed consent on the protocol.

Electrode placements were performed under general anesthesia. The cortical target was the motor-premotor cortex, set 2 cm anterior to the hand area. This was identified using coordinates according to a computerized neuronavigation system, based on the patient's neuroimaging (brain computed tomography [CT] and magnetic resonance imaging [MRI]). A tetrapolar electrode strip (RESUME; Medtronic, Inc., Fridley, MN) with 4 contacts in line was positioned in the extradural space. The correct localization of the electrode was verified by identifying, before surgery, the phase reversal of N20-P20 by means of somatosensory evoked potentials obtained from contralateral median nerve stimulation. In all cases, the contacts were oriented along the anterior-posterior axis, perpendicular to the precentral gyrus. A pulse generator (SOLETRA; Medtronic, Inc.) was connected to the tetrapolar lead and positioned in the subclavicular region under local anesthesia. Figure 1 illustrates the premotor-motor cortex region stimulated and the location of the active contacts on an MRI reconstruction of the region. All patients underwent a postoperative CT scan to confirm the electrode positioning.

Patients were assessed at the baseline, at 2 weeks, and at 1, 3, 6, and 12 months after implant. The Burke-Fahn-Marsden scale (BFMS)¹² was used in all patients; the Toronto Western spasmodic torticollis rating scale (TWSTRS)¹³ was additionally used in patients with cervical involvement. Cognitive and psychological evaluations were performed at the baseline and 6 and 12 months after implant according to a

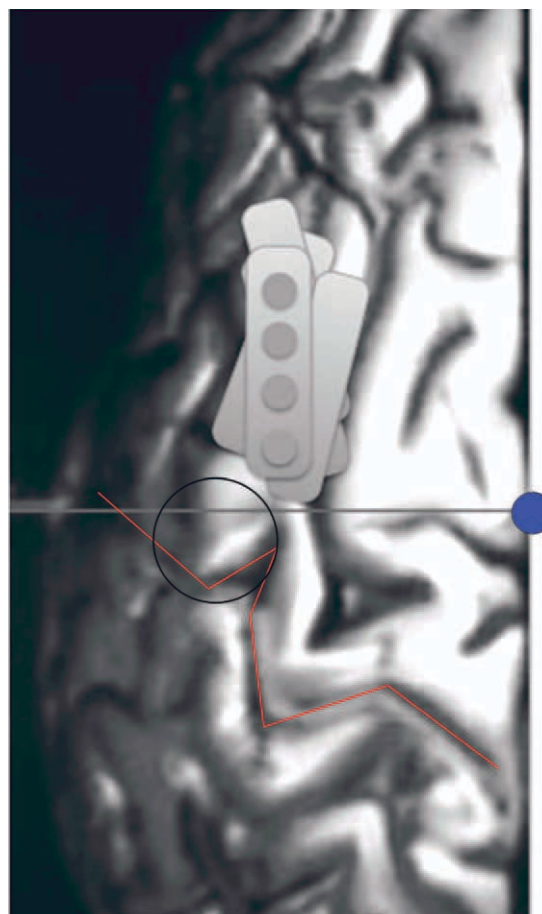


FIG. 1. Projection of all the implanted RESUME plate quadripolar electrodes on the premotor cortical surface of the left hemisphere referred to the intercommissural midpoint (blue dot). The black circle indicates the cortical hand knob area; red lines show the central sulcus. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

standardized procedure. Neuropsychological assessment included tests for global cognition, memory, executive functions, verbal fluency, and attention. Affective disorders were assessed with the Zung self-rating anxiety and depression scales.^{14,15} Furthermore, the Brief Psychiatric Rating Scale¹⁶ was administered to detect the occurrence of psychiatric features. Quality of life was evaluated before and after surgery with the Sickness Impact Profile (SIP).¹⁷

In cervical dystonia patients, monopolar stimulation was performed with 2 active contacts on the premotor cortex (0 –, 1 –, case +); in the upper limb dystonia patient there were 3 active contacts (0 –, 1 –, 2 –, case +). Based on previous reports,^{8,10} stimulation ranges used in this study were as follows: amplitude from 2.5 to 3.0 V; pulse width from 60 to 90 μ sec; frequency from 50 to 120 Hz. At each visit, the stimulation settings were reprogrammed so as to minimize side effects and maximize motor improvement. Cortical stimulation was delivered continuously for 24 hours, using the best settings for each patient. Statistical analysis was performed using the nonparametric Wilcoxon signed-rank test to compare changes of

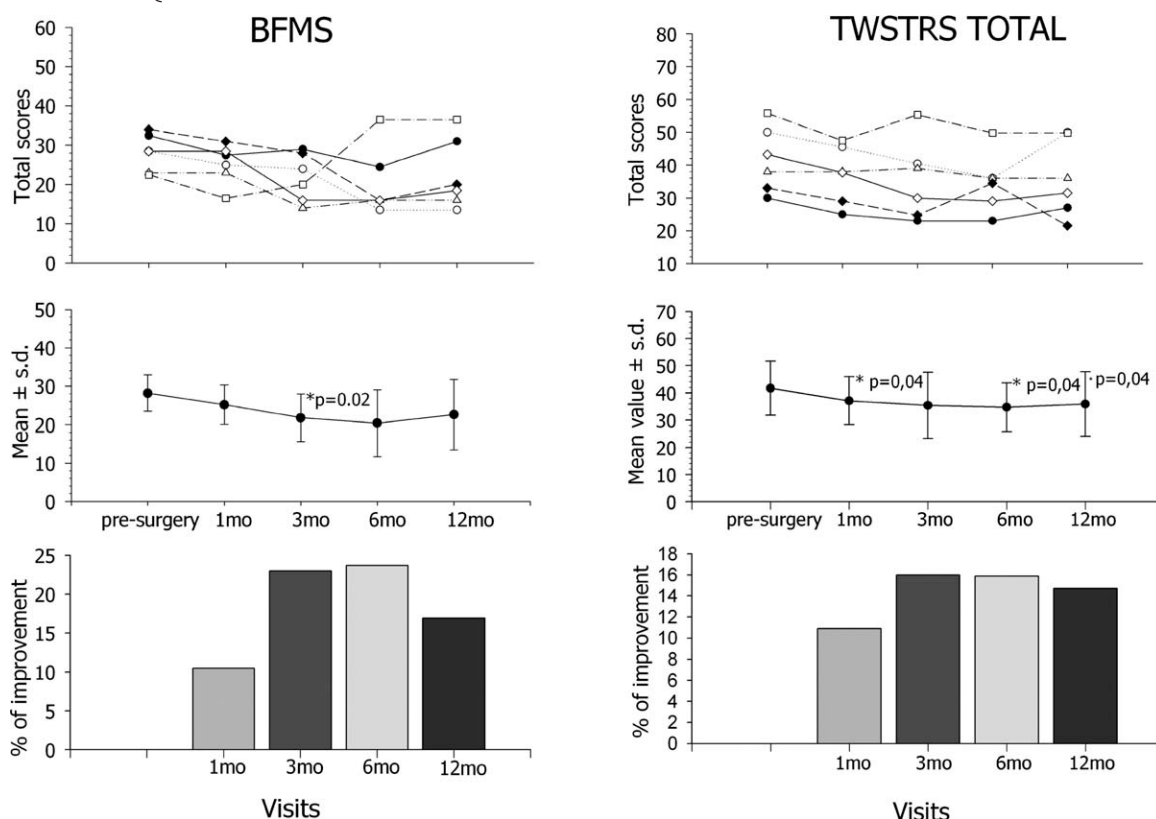


FIG. 2. Outcome for patients with cervical dystonia according to the BFMS (left side) and the TWSTRS (right side). Individual total scores are reported in the top panels; mean scores are shown in the middle panels; percent average improvement compared to baseline is reported in the bottom panels. BFMS, Burke-Fahn-Marsden scale; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

outcome measures (BFMS and TWSTRS) between baseline and follow-up visits. A P value $< .05$ was considered as statistically significant.

Five cervical dystonia patients underwent an ^{18}F -fluoro deoxyglucose PET (FDG-PET) scan before surgery (T_0) and 12 months after implant (T_{12}), using a Discovery STE (GE Medical Systems, Milwaukee, WI) multi-ring PET tomography (PET-CT) system. Image preprocessing and statistical analysis were performed using SPM8 statistical parametric mapping (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8>) running under Matlab v7.6 (MathWorks, Sherborn, MA). Statistical parametric maps for each contrast of the t -statistic were calculated on a voxel-by-voxel basis including age as a “nuisance” variable. Proportional scaling was used to remove intersubject global variation in PET intensities, the mean count being set to 6.5 in all scalp-free brain. In order to define regional cerebral metabolism differences, patients were compared to healthy controls at presurgery (T_0) and post-surgery (T_{12}) conditions, using a 2-sample t test. The threshold was settled at $P < .001$ uncorrected ($Z = 3.527$).

The voxel-wise group analysis was further explored by a region-of-interest (ROI) analysis on specific territories (precentral and postcentral cortex, supplementary motor area, basal ganglia, cerebellum

hemispheres, and vermis), defined on the a priori hypothesis of a selective involvement of brain sensorimotor system structures in dystonia.¹⁸ This analysis was performed using SPM-toolboxes WFU PickAtlas (<http://fmri.wfubmc.edu/software/PickAtlas>) and Marsbar region of interest (<http://marsbar.sourceforge.net>). Anatomical ROIs were identified from the Automated Anatomical Labelling (ALA) of WFU PickAtlas (<http://fmri.wfubmc.edu/software/PickAtlas>), imported and extracted with the Marsbar toolbox for each control subject and each patient (both in presurgical and post-surgical condition). The threshold was settled at $P < .001$ uncorrected ($Z = 3.527$).

Results

The procedure was well tolerated in all patients. No adverse events were reported. No immediate beneficial clinical changes were obtained while stimulation parameters were being adjusted (settings are listed in the Supporting Information, Table S2). No side effects were observed. The stimulation settings were changed, whenever necessary, at the same time points. No specific amplitude, pulse duration, and frequency combinations could be identified as the most effective on dystonia.

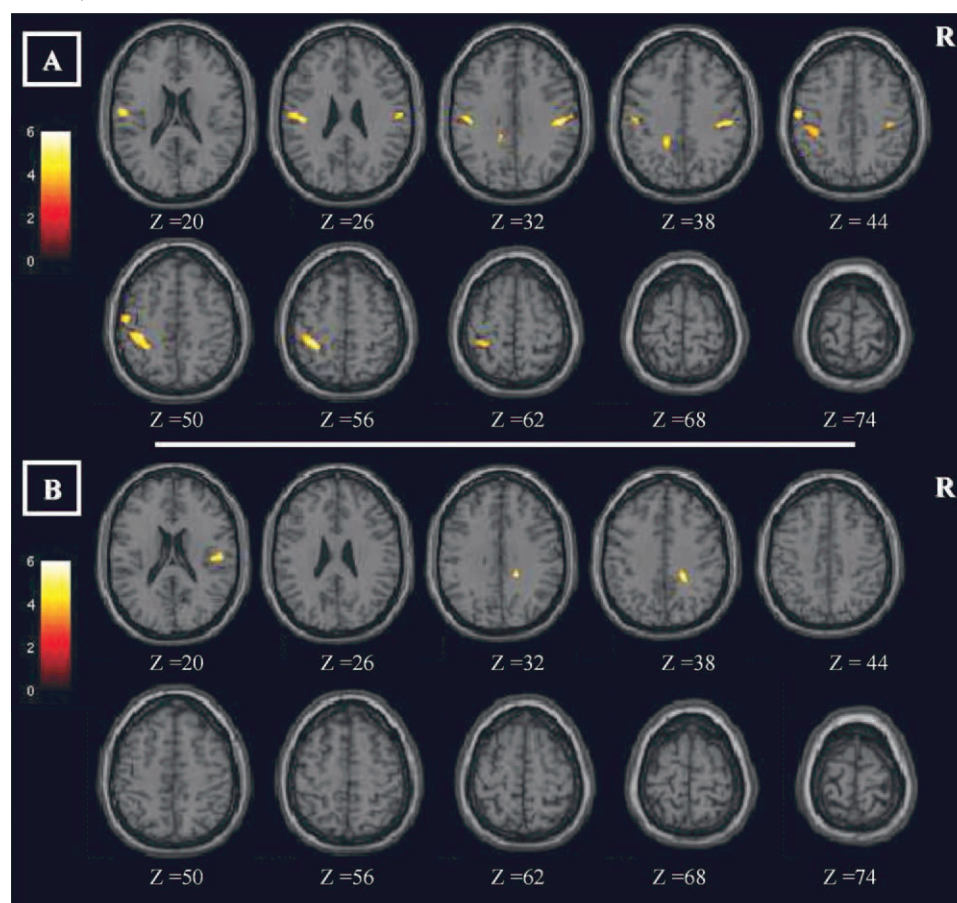


FIG. 3. Results of SPM8 group analysis showing increased metabolism in the patient group at (A) presurgery and (B) postsurgery conditions compared to normal controls (quantitative representation superimposed to a standard template; see text in the results section for details). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

In cervical dystonia patients there was an overall tendency to improvement in both scales from the baseline evaluation up to the 12-month follow-up visit (Fig. 2). The mean BFMS values showed a progressive improvement at 1, 3, and 6 months compared to the presurgery condition. TWSTRS scores showed a similar improvement at 1 and 3 months. At the 12-month evaluation, the benefit measured by the BFMS was still consistent, but did not further improve compared to the 6-month evaluation. The increase of frequencies, mainly during the last visit, was motivated by a lack of improvement progression.

In the 2 patients with a prevalently fixed attitude, a substantial inefficacy of premotor cortical stimulation emerged through the 12-month observation period. Comparison of the improvements of the BFMS and TWSTRS between mobile and fixed dystonia (see Supporting Information, Table S3) revealed a substantial inefficacy of premotor cortical stimulation in fixed dystonia patients starting 3 months postimplantation.

The patient with upper limb dystonia had a BFMS of 16.5 at baseline, which was reduced to 8 (51% improvement) after 12 months of continuous stimulation.

There were no neuropsychological deficits or affective disorders before surgery. A statistically nonsignifi-

cant progressive slight improvement in working visual memory and phonemic fluency occurred at 12-month follow-up. Zung's self-rating anxiety and depression scales also improved nonsignificantly. Quality of life improved by 50% on the SIP scale.

SPM8 analysis revealed a significant metabolic bilateral increase in the sensorimotor regions of dystonia patients at baseline compared to healthy controls; this was more pronounced on the left hemisphere. The stereotactic coordinates and statistical significance of each cluster are reported online (Supporting Information, Table S4). This local metabolic increase was attenuated after surgery (Fig. 3). No cerebral hypometabolism was observed at baseline or after surgery. No significant differences were found in the basal ganglia or in the cerebellum at either time point.

ROI analysis was consistent with results of the voxel-wise analysis, showing a local specific sensorimotor increase of glucose metabolism and its reduction in the postsurgery condition. Notably, compared to controls we found that dystonia patients at baseline had a significantly higher metabolism in the regions of the precentral and postcentral gyri, wider on the left hemisphere, and no significant differences postsurgery.

Discussion

This study reports clinical outcomes from bilateral epidural premotor cortex stimulation in patients with primary focal dystonia. Patients tolerated both the surgical procedure and the chronic stimulation. All patients were stimulated in continuous mode. Cervical dystonia improved after 1 month of bilateral epidural premotor cortex stimulation, reached the highest rating after 6 months, and slightly lessened at 12 months. Our results are in line with open data on transcranial stimulation showing motor improvement after rTMS over the premotor cortex.⁶ It has recently been shown that continuous theta burst TMS to the premotor cortex increased short-interval intracortical inhibition and the third phase of spinal reciprocal inhibition, which are typically reduced in dystonia, bringing them back toward the normal range.⁷ The duration of the therapeutic effects of premotor stimulation in dystonia remains an open issue. In our results, the improvement of BFMS and TWSTRS scores reached a plateau after 3 to 6 months of stimulation. Afterward, no additional benefit, but a slight reduction of improvement was detected, hinting to a possible loss of benefit from cortical stimulation or, alternatively, the disappearance of a transient placebo effect. A further follow-up of this patient series is ongoing.

The role played by frequency and other stimulation settings on clinical outcome following premotor or motor cortex stimulation is still largely unknown and warrants further investigation. The delay of symptomatic improvement following the start of stimulation is noteworthy. Significant differences occurred 3 months after implantation, in contrast to the effects of globus pallidus interna (GPi) DBS that are observed from a few hours up to a few days after implantation.¹⁹ This different time course is likely related to the different points of stimulation along basal ganglia outflow pathways. Premotor cortex stimulation can activate axons of inhibitory interneurons surrounding the electrode or efferent fibers connected with several cortical and subcortical structures.⁸ The delay of improvement following premotor cortex stimulation may be related to the involvement of multiple cortical areas in the pathophysiology of primary dystonia. In keeping with this, continuous theta burst TMS on the premotor cortex has no effect on M1 cortical excitability, likely due to the interaction of other interconnected areas.⁷

Neuropsychological evaluation showed a modest, not statistically significant, improvement in executive functions and a slight improvement of anxiety and depression.

The observed benefit of premotor cortex stimulation was consistent among patients with mobile, cervical, or hand dystonia. By contrast, 2 patients with preva-

lently fixed dystonia had a reduced symptomatic improvement. Our findings are in line with earlier data showing that, following GPi DBS, patients with mobile dystonia had greater improvement than patients with fixed postures following GPi DBS.³ This is in line with studies reporting that fixed dystonia patients have a poorer prognosis compared to those with mobile dystonia.²⁰

Our functional imaging results are in keeping with a previous work reporting a significantly increased metabolism in the basal ganglia, thalamus, premotor-motor cortex, and cerebellum of patients with sporadic dystonia compared to normal controls.^{10,21} Here we consistently show that the sensorimotor cortex is specifically involved with increased metabolism at baseline. At 12 months postsurgery there was a reduction of sensorimotor cortex hypermetabolism, a finding suggesting a modulatory, possibly inhibitory, effect of epidural stimulation on the hyperactive cortex. Nevertheless, at 12 months postsurgery, the clinical benefit was attenuated despite the reduction of sensorimotor cortex hypermetabolism, suggesting that additional factors, other than cortical inhibition, are to be considered.

In conclusion, the absence of safety issues with premotor cortex stimulation is encouraging although not definitive evidence, and larger numbers of patients must be followed over extended periods of time. A sham-controlled trial with premotor cortex stimulation may be warranted, above all to rule out placebo effects. The present data indicate that appropriate selection of patients for cortical stimulation is a crucial issue to be taken into account for future study design. The identification of patients specifically responding to motor or premotor cortex stimulation may contribute to increased knowledge concerning the pathophysiological mechanisms that underlie dystonia.

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