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Globus pallidus internus stimulation in primary generalized dystonia: a $H_2{}^{15}O$ PET study

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Summary

Globus pallidus internus (GPi) deep brain stimulation (DBS) increasingly shows promising efficacy in the treatment of severe primary generalized dystonia. Functional imaging studies have shown previously that dystonia could be related to abnormal cortical activation during voluntary movement. In the present study, the effects of GPi DBS on regional cerebral blood flow (rCBF) during a motor task were studied in patients with primary generalized dystonia. rCBF was measured using $H_2{}^{15}O$ and PET in eight control subjects and six patients with dystonia treated with bilateral GPi DBS. Subjects were scanned at rest and while performing joystick movements. Dystonic patients were tested in two conditions: 'OFF' (stimulator bilaterally switched off) and 'ON' (unilateral stimulation). In the 'OFF' condition, compared with rest, motor activation of the most dystonic hand was associated with overactivity in the contralateral dorsolateral prefrontal cortex, gyrus frontalis medialis, superior frontal gyrus (area 10), fronto-orbital cortex and thalamus. In the 'ON' condition, GPi DBS contralaterally to the most dystonic hand induced a decrease of the overactivation in the same areas, as well as the putamen. According to the present study, generalized dystonia is associated with prefrontal overactivation which can be reversed by effective GPi DBS.

Keywords: dystonia; globus pallidus; deep brain stimulation; PET

Abbreviations: BA = Brodmann area; BFMS = Burke–Fahn–Marsden scale; DBS = deep brain stimulation; DLPFC = dorsolateral prefrontal cortex; DSS = dystonia severity score; GPi = globus pallidus internus; rCBF = regional cerebral blood flow; SMA = supplementary motor area; SPM = statistical parametric mapping.

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Introduction

Dystonia is defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, and/or abnormal postures (Fahn *et al*., 1998). Primary generalized dystonia describes patients in whom dystonia is the sole phenotypic manifestation and involves a combination of segmental crural dystonia which spreads to any other segment (Fahn, 1988; Fahn *et al*., 1998). Most cases of early-onset primary generalized dystonia are related to *DYT1* mutations located on chromosome 9q34.1. The *DYT1* gene (also known as torsin A gene) is transmitted as an autosomal dominant trait with a penetrance of 30–40% (Kramer *et al*., 1994; Lenz *et al*., 1999).

Primary dystonia classically appears in middle to late childhood and progresses to generalized dystonia in a few years, leading to debilitating states (Bressman *et al*., 2000). Because medical treatment efficacy is limited, functional brain surgery has been considered as a potentially effective alternative treatment (Krack and Vercueil, 2001). Historically, brain surgery for dystonia followed the development of surgery for idiopathic Parkinson's disease and the observation of an

improvement of dystonic symptoms in parkinsonian subjects (Krack and Vercueil, 2001). Initially, ablative procedures, especially thalamotomy, were used for generalized dystonia and produced a substantial benefit (Cooper, 1976; Andrew *et al*., 1983; Tasker *et al*., 1988; Cardoso *et al*., 1995). More recently, with the renewal of posteroventral pallidotomy in Parkinson's disease (Lozano *et al*., 1995; Lang *et al*., 1997; Fine *et al*., 2000), pallidotomy was rediscovered as a treatment for generalized dystonia and provided a substantial improvement in dystonic movements and motor function (Lozano *et al*., 1997; Ondo *et al*., 1998; Lin *et al*., 1999). Deep brain stimulation (DBS) has been investigated more recently, and, unlike ablative surgery, DBS is reversible and adjustable. The globus pallidus internus (GPi) is now the commonly preferred target for DBS in generalized dystonia (Coubes *et al*., 1999, 2000, 2002; Krack *et al*., 1999; Tronnier *et al*., 2000; Vercueil *et al*., 2001). In primary dystonia, no degenerative or structural neuropathological abnormalities are elicited, and several reviews suggest that there is a functional disturbance within the basal ganglia system (Brooks, 1995; Berardelli *et al*., 1998; Nemeth, 2002). Accordingly, a highly irregular activity within the GPi with grouped discharges separated by periods of pauses has been recorded intraoperatively (Vitek *et al*., 1999).

The exact mechanism of DBS remains unclear, and the pathophysiological basis of dystonia is still poorly understood. Using PET and [^{18}F]fluorodeoxyglucose (FDG), Eidelberg *et al*. (1998) observed an increased metabolic activity in the lentiform nuclei, cerebellum and supplementary motor areas (SMAs) in DYT1 dystonia. They also showed, in an analysis of affected gene carriers with sustained contractions at rest, an increased metabolic activity in the midbrain, cerebellum and thalamus. Few studies have examined the modifications of regional cerebral blood flow (rCBF) in generalized dystonia with PET and $H_2{}^{15}O$. Vibrotactile stimulation of the hand showed an attenuation of the rCBF increase in the contralateral sensorimotor cortex (Tempel and Perlmutter, 1990, 1993) and in the SMA (Tempel and Perlmutter, 1993) in comparison with control subjects. During freely selected joystick movements, three studies reported enhanced activation (increase of rCBF) of the premotor cortex, dorsolateral prefrontal cortex (DLPFC) (Ceballos-Baumann *et al*., 1995*a*,*b*; Playford *et al*., 1998), SMA (Ceballos-Baumann *et al*., 1995*a*; Playford *et al*., 1998), lenticulate nucleus (Ceballos-Baumann *et al*., 1995*a*) or putamen and cerebellum (Playford *et al*., 1998). Concerning the primary sensorimotor cortex, one of these studies reported increased activation during the motor task in acquired hemidystonia (Ceballos-Baumann *et al*., 1995*b*), while two reported a reduced activation (Ceballos-Baumann *et al*., 1995*a*; Playford *et al*., 1998). At rest, Ceballos-Baumann *et al*. (1995*b*), studying patients with acquired hemidystonia, observed an increased activation in the frontoorbital cortex, thalamus and lenticulate nucleus.

Only one $H_2{}^{15}O$ PET study assessed the effects of GPi DBS in a single patient suffering from generalized dystonia (Kumar *et al*., 1999). This study showed that, during freely selected joystick movements, GPi stimulation reduced activation in the primary sensorimotor cortex, lateral premotor, SMA and prefrontal cortex, including DLPFC, corresponding to Brodmann areas (BAs) 9 and 46.

In an attempt to extend and clarify the results of the previous studies, we studied dystonic patients treated with GPi DBS using $H_2{}^{15}O$ PET performing freely selected joystick movements. The aim of the present study was to analyse the functional effects of GPi stimulation on rCBF during this motor task in primary generalized dystonia and to compare the activation profile in dystonic patients with those of control subjects.

Material and methods

Subjects

We studied six patients with primary generalized dystonia treated with bilateral high- frequency GPi DBS (three women and three men; mean age = 26 years; range = 18–36) and eight control subjects (eight men; seven right-handed, one left-handed; mean age = 25 years; range = 21–28). All control subjects were healthy without neurological or psychiatric disorders and without medical treatment. Out of a series of 25 consecutive patients treated by GPi DBS for primary dystonia, six patients were included according to the following criteria: (i) dystonia without additional neurological abnormalities (Fahn, 1988; Fahn *et al*., 1998); (ii) generalized dystonia requiring surgery by stimulation of the GPi because of a vital risk or a severe disability; (iii) failure of medical treatment; (iv) clinical improvement superior to 30% on the Burke–Fahn–Marsden scale (BFMS) after 3 months of bilateral GPi DBS; (v) tolerable recurrence of dystonia in the tested hand when the stimulator is switched off; and (vi) minimal cervical dystonia compatible with head immobilization required for the PET procedure. All patients were taking their regular medication during the study (anticholinergics, three patients; benzodiazepines, two patients; tetrabenazine, one patient). The three women were taking oral contraceptives. Five of the six patients had a mutation of the *DYT1* gene. The patients' general characteristics and stimulation parameters for GPi DBS are shown in Table 1.

The quadripolar electrodes (Model 3389; Medtronic, Minneapolis, MN) were inserted in the postero-lateral GPi under stereotactic guidance and connected to a telemetrically controllable pulse generator (Kinetra; Medtronic) placed in the subclavicular area. The accuracy of electrode placement was checked by imaging techniques and intraoperative electrophysiology as previously described for stimulation in Parkinson's disease (Limousin *et al*., 1998) and dystonia (Vercueil *et al*., 2001). The target (postero-lateral GPi) was visualized by preoperative stereotactic MRI, then drawn on the intraoperative teleradiographs. The superimposition of the tip of the electrode and the target position was checked at the end of surgery and the precise location was confirmed, after surgery, by MRI. All patients underwent surgery in Grenoble.

Written informed consent was obtained from each subject according to the Declaration of Helsinki. The present study was approved by the Lyon University Hospital Ethics Committee.

Clinical assessment

The patients and control subjects were videotaped during the scanning procedure to check the accuracy of the task execution and rest, and the appearance of dystonic postures. Based on these videotape recordings, we evaluated the six patients' severity of dystonia in the tested hand by using a dystonia severity score (DSS) developed by our group to

Table 1 *General characteristics of the six patients with primary generalized dystonia and electrical variables of bilateral deep brain stimulation (DBS) of the globus pallidus internus (GPi)*

Patient no.	Sex	Age at study (years)	Age at onset (years)	*DYT1*	Duration of DBS (months)	Voltage (V) R/L	Pulse width (μs) R/L	Clinical improvement (%)*	Disability score**	Tested hand
1	M	36	8	+	3	3.5/3.5	60/60	45	13	L
2	M	18	8	+	32	4.0/3.0	60/60	78	5	L
3	F	18	9	+	3	4.2/4.2	90/90	96	6	R
4	M	25	7	−	13	3.8/4.2	90/90	30	10	R
5	F	32	7	+	21	3.3/3.5	90/90	86	6	R
6	F	26	8	+	5	4.4./5.0	120/120	35	5	R

*All patients were treated with a high-frequency stimulation of 130 Hz. M = male; F = female; *DYT1* = presence (+) or absence (−) of the mutation of the *DYT1* gene; L = left; R = right. Clinical improvement induced by chronic bilateral GPi DBS. Comparison between the movement score according to Burke–Fahn–Marsden scale (BFMS; maximum score = 116) before surgery and at the maximal follow-up. **Disability score according to the BFMS (maximum score = 30).

score off-period dystonia in Parkinson's disease patients (Krack *et al*., 1999) and already used in another clinical study with dystonic patients (Detante *et al*., 2004): 0, no dystonia; 1, minimal dystonia or abnormal posture; 2, moderate dystonia; 3, severe dystonia with a moderate interference with movement; and 4, severe dystonia with an intense interference with movement. Moreover, the patients were videotaped before and after each scan and scored with the BFMS (Burke *et al*., 1985).

Activation tasks

PET scanning was performed at the CERMEP medical cyclotron in Lyon.

Subjects were scanned while executing a motor task with the dominant hand for control subjects and with the more dystonic hand for patients (Table 1). Subjects lay down with their eyes closed.

The conditions were the following: (i) for control subjects, rest (Rest control) and execution of a motor task (Exe control); and (ii) for patients, rest without stimulation (Rest OFF), execution of a motor task without stimulation (Exe OFF), rest with unilateral effective GPi DBS (Rest ON) and execution with unilateral effective GPi DBS (Exe ON). Each condition was carried out in triplicate, lasted for 90 s and began a few seconds before $H_2{}^{15}O$ injection. The motor task conditions were randomized.

During the rest condition, subjects were asked to relax their arms and hands keeping the joystick in a central position. They heard tones every 3 s (30 tones) and were instructed to not react. During the free selection task, subjects had to move a joystick after each tone in a single direction (either left, right, forward or back). Subjects freely chose one direction. They were asked to move the joystick as randomly as possible and to avoid repetitive sequences. The completion of the joystick movement was recorded for each subject and the errors were counted automatically when the subject failed to complete the movement because of a reduced amplitude or an absence of movement.

The control subjects underwent six scans (1.5 h): three at rest and three during movement execution. The patients underwent six scans in the OFF stimulation condition and six in the ON condition. In the OFF stimulation condition, the stimulator was bilaterally switched off (OFF/OFF) with a recurrence of dystonia in the tested hand. In the ON stimulation condition, only the stimulator contralateral to the tested hand was switched on (ON/OFF) with a maximal clinical benefit on the hand tested. Unilateral stimulation was chosen as the ON condition to not confound ipsilateral and contralateral effects of this stimulation. The stimulator had been switched on or off for 3.40 h (range = 0.25–6.50) on average before the PET scanning, depending on the tolerable recurrence of dystonia. Because of the latency between turning on the stimulator and the clinically induced effects, PET scans in the ON stimulation condition were performed on one day and PET scans in the OFF stimulation condition another day within the same week. The order of stimulation conditions for each patient was randomized.

Scanning procedure

Subjects' heads were maintained in a fixed position using a thermoformed mask. Confirmation of head position throughout the examination was made by laser alignment along with reference points on Reid's line before and after each session. PET scans were acquired using a Siemens CTi HR+ tomograph (CTi/Siemens, Knoxville, TN) in three-dimensional mode. Transmission data were acquired using rotating sources filled with $^{68}Ge/^{68}Ga$. Images were reconstructed by 3D back-filtered projection (Hanning filter; cut-off frequency, 0.5 cycles/pixel), giving a transaxial resolution of 6.5 mm full width at half maximum, and displayed in a 128×128 pixel format with 63 planes creating 2 mm cubic voxels. rCBF was estimated by recording the distribution of radioactivity following an intravenous injection of 370 MBq of $H_2{}^{15}O$ through a forearm catheter placed into the brachial vein. The integrated counts were collected for 90 s. For data analysis, we only considered the 60 s corresponding to the maximum radioactivity. The interval between successive $H_2{}^{15}O$ administrations was 10 min to allow for adequate radioactivity decay.

Statistical analysis and PET data

For clinical data, we compared the BFMS scores and DSS obtained in the OFF and ON stimulation conditions with a Wilcoxon signed rank test. A P value <0.05 was considered significant. We also compared the number of errors made by control subjects and patients in the ON and OFF stimulation conditions with a Mann–Whitney U test. A P value <0.05 was considered significant.

Image and statistical analyses were performed using MATLAB 5.3 (MathWorks, Natick, MA) for statistical parametric mapping (SPM 99, Wellcome Department of Cognitive Neurology, MRC Cyclotron Unit, London). First, the images corresponding to one control subject and the two patients who used their left hand to perform the tasks were inverted along the x-axis, making it appear that all subjects had performed the task using their right hand. Briefly, series of scans were

aligned to the first scan with an automated algorithm for head movement correction and then normalized into a standard stereotactic space. The images were smoothed with an isotropic Gaussian filter of $10 \times 10 \times 10$ mm to allow for interindividual gyral variation and to improve the signal to noise ratio. Global differences in rCBF were covaried out for all voxels, and comparisons across conditions were made using *t* statistics with appropriate linear contrasts, and then converted to *Z*-scores. Coordinates of the activated foci obtained from SPM 99 were then converted into Talairach coordinates (Talairach and Tournoux, 1988). Only regional activation significant at $P < 0.001$ at each pixel, uncorrected for multiple comparisons, and with *Z*-scores >3.30 were retained. Uncorrected *P* values were accepted because of an *a priori* strong hypothesis on the primary and prefrontal cortex.

We carried out statistical analyses both within groups and between groups. For the within-group analysis, we calculated statistical parametric mappings (SPM) comparing the motor task with rest in control subjects (Exe control versus Rest control), in patients without stimulation (Exe OFF versus Rest OFF) and in patients using unilateral GPi stimulation (Exe ON versus Rest ON). We also compared the ON and OFF stimulation conditions to evaluate the effect of GPi DBS at rest (Rest OFF versus Rest ON) and during the motor task [(Exe OFF versus Rest OFF) − (Exe ON versus Rest ON) and (Exe ON versus Rest ON) − (Exe OFF versus Rest OFF)].

For the between-group analysis, we calculated SPM during resting and active conditions. The following comparisons were made for the motor task: (i) control subjects versus patients in the OFF stimulation condition to evaluate rCBF changes due to primary generalized dystonia [(Exe OFF versus Rest OFF) − (Exe control versus Rest control)]; and (ii) control subjects versus patients in the ON stimulation condition to appreciate the effects of GPi DBS [(Exe ON versus Rest ON) − (Exe control versus Rest control)].

Results

Task performance

At the time of PET scanning, all patients had dystonia in the task-performing hand during the OFF stimulation condition. The ON stimulation condition improved dystonia in the performing hand during the motor task, and two patients (2 and 6) had complete amelioration of dystonia (Table 2). Dystonia severity in the performing hand was significantly higher ($P < 0.05$) during the OFF stimulation condition (mean DSS = 2.7; range = 2.0–4.0) than during the ON stimulation condition (mean DSS = 1.2; range = 0–3.0). Moreover, the mean value of the BFMS was 44.6 (range = 24.5–77.0) in the OFF stimulation condition, and 34.4 (range = 17.5–69.5) in ON stimulation condition (Table 2). This improvement of 23% on BFMS by acute unilateral GPi DBS was significant ($P = 0.002$).

During the OFF stimulation condition, we recorded 25 (range = 12–43) errors per 90 movements on average and 27 (range = 15–45) errors during the ON stimulation condition. Control subjects made 17 (range = 11–22) errors on average. Thus, patients made more errors in both conditions compared with controls. However, regardless of the stimulation condition, the difference between patients and controls did not reach statistical significance (in the ON and OFF stimulation condition $P = 0.06$ and $P = 0.14$, respectively).

PET results

Within-group comparison: control subjects (Table 3)

When motor execution of the right hand was compared with rest (Exe control versus Rest control), we observed significant activations in the left primary motor cortex, left and right premotor cortex (lateral BA 6), left thalamus and cerebellar hemispheres. The right parietal cortex (BA 7) was also activated by the motor task. No significant activation was observed in the DLPFC.

Within-group comparison: patients

Motor task without GPi DBS (OFF stimulation condition) (Table 4). When the motor task was compared with rest (Exe OFF versus Rest OFF), we observed significant activations in the left primary sensorimotor cortex, right and left caudal SMA, left DLPFC (BA 9), left parietal (BA 7 and 40), right anterior cingulate cortex (BA 24), in the left thalamus, vermis and cerebellar hemispheres. Contrary to that observed in the control group, activation was not elicited in the premotor cortex.

Motor task with effective unilateral GPi DBS (ON stimulation condition) (Table 5). When the motor task was compared with rest (Exe ON versus Rest ON), there was significant activation in the left primary sensorimotor cortex, left caudal SMA, left parietal cortex (BA 40), cerebellar vermis and right cerebellar

Table 2 *Clinical features at the time of PET for the six patients with primary generalized dystonia*

Patient no.	Movement score OFF stimulation*	Movement score ON stimulation*	DSS during PET OFF stimulation	DSS during PET ON stimulation
1	77.0	69.5	4	3
2	31.5	17.5	2	0
3	24.5	20.0	3	1
4	49.5	40.5	3	2
5	34.0	22.0	2	1
6	51.0	37.0	2	0

*Mean movement scores were calculated with scores obtained before and after the PET procedures in OFF and ON stimulation conditions. Within each condition, the two scores were identical on average. During the PET procedure, we evaluated the dystonia severity score (DSS, 0–4) for the performing hand. Movement score according to Burke–Fahn–Marsden scale (BFMS; maximum score = 116).

Table 3 *Areas activated in the normal subjects during freely selected joystick movements when compared with the rest condition (Exe–Rest control)*

Areas	Side (L/R)	Talairach coordinates (*x*, *y*, *z* mm)	*Z*-score	*P* uncorrected (voxel-level)
Primary MC (BA 4)	L	−38, −24, 58	6.74	0.0001
Premotor cortex (lateral BA 6)	R	24, −6, 62	5.38	0.0001
Premotor cortex (lateral BA 6)	L	−30, −10, 64	5.24	0.0001
Parietal cortex (BA 7)	R	10, −62, 62	4.58	0.0001
Thalamus	L	−18, −20, 2	4.30	0.0001
Cerebellum	R	4, −64, −30	5.79	0.0001
Cerebellum	L	−32, −60, −28	5.26	0.0001

L = left; R = right; BA = Brodmann area; MC = motor cortex.

Table 4 *Areas of increased activation in the primary generalized dystonia group without stimulation during freely selected joystick movements when compared with the rest condition (Exe OFF versus Rest OFF)*

Areas	Side (L/R)	Talairach coordinates (*x*, *y*, *z* mm)	*Z*-score	*P* uncorrected (voxel-level)
Primary MC (BA 4)	L	−28, −24, 66	4.92	0.0001
Primary SC (BA 2)	L	−34, −36, 60	5.20	0.0001
Caudal SMA (BA 6)	R	12, −2, 74	4.24	0.0001
Caudal SMA (BA 6)	L	−12, −12, 76	3.84	0.0001
DLPFC (GFm, BA 9)	L	−32, 32, 20	3.85	0.0001
Parietal cortex (BA 40)	L	−48, −28, 24	4.13	0.0001
Parietal cortex (BA 7)	L	−30, −50, 72	4.47	0.0001
Cingulate cortex (BA 24)	R	10, 14, 32	3.79	0.0001
Thalamus	L	−8, −16, 16	4.47	0.0001
Cerebellar vermis	R	2, −64, −28	5.49	0.0001
Cerebellum	L	−34, −60, −32	4.96	0.0001
Cerebellum	R	32, −52, −32	4.11	0.0001

L = left; R = right; BA = Brodmann area; MC = motor cortex; SC = sensory cortex; SMA = supplementary motor area; DLPFC = dorsolateral prefrontal cortex; GFm = gyrus frontalis medius.

Table 5 *Areas of increased activation in the primary generalized dystonia group with effective stimulation of the left internal globus pallidus (GPi) during freely selected joystick movements when compared with the rest condition (Exe ON versus Rest ON)*

Areas	Side (L/R)	Talairach coordinates (*x*, *y*, *z* mm)	*Z*-score	*P* uncorrected (voxel-level)
Primary MC (BA 4)	L	−32, −20, 62	5.82	0.0001
Primary SC (BA 2)	L	−38, −38, 60	5.72	0.0001
Caudal SMA (BA 6)	L	−8, −10, 62	3.76	0.0001
Parietal cortex (BA 40)	L	−50, −30, 48	5.02	0.0001
Cerebellar vermis	R	2, −62, −26	4.21	0.0001
Cerebellum	R	34, −54, −32	3.63	0.0001

L = left; R = right; BA = Brodmann area; MC = motor cortex; SC = sensory cortex; SMA = supplementary motor area.

hemisphere. Contrary to the results obtained in the OFF stimulation condition, we did not observe rCBF changes in the thalamus, DLPFC or right SMA.

Modifications of rCBF induced by effective unilateral GPi DBS at rest (Table 6; Fig 1). Left GPi stimulation during the rest condition in dystonic patients was associated with increased activation (Rest ON versus Rest OFF) in the right DLPFC (BA 9), right inferior frontal gyrus (BA 47), left gyrus frontalis medius (BA 11), parietal cortex bilaterally (right BA 7, 40 and left BA 31), right temporal cortex (BA 38), left cingulate cortex (BA 23) and in the right cerebellar hemisphere. Increased activation in the right caudate nucleus, left thalamus and left GPi (site of stimulation) was also noted. Moreover, left GPi DBS decreased activation (Rest OFF versus Rest ON) of the left primary motor cortex at rest.

Modifications of rCBF induced by effective unilateral GPi DBS during the motor task (Table 7). During freely selected joystick movements of the right hand, unilateral GPi stimulation did not increase cerebral activation. Instead, left GPi stimulation produced a decrease in activation of the left superior frontal

Table 6 *Modifications of regional cerebral blood flow (rCBF) induced by effective stimulation of the left globus pallidus internus (GPi) during the rest condition in the dystonic patients (Rest ON versus Rest OFF)*

Areas	Side (L/R)	Talairach coordinates (*x*, *y*, *z* mm)	*Z*-score	*P* uncorrected (voxel-level)
Increased activation				
DLPFC (GFm, BA 9)	R	28, 36, 20	5.71	0.0001
GFd (BA 8)	R	4, 30, 58	4.06	0.0001
Inferior frontal gyrus (BA 47)	R	28, 28, −12	4.05	0.0001
GFm (BA 11)	L	−22, 40, −26	3.94	0.0001
Parietal cortex (BA 7)	R	28, −36, 26	4.09	0.0001
Parietal cortex (BA 40)	R	54, −40, 28	4.23	0.0001
Parietal cortex (BA 31)	L	−22, −66, 28	3.98	0.0001
Temporal cortex (BA 38)	R	42, −14, −10	4.60	0.0001
Cingulate cortex (BA 31)	L	−6, −52, 36	4.75	0.0001
Caudate	R	10, 8, 20	5.15	0.0001
Thalamus	L	−8, −14, 10	4.58	0.0001
GPi	L	−14, −2, −4	4.63	0.0001
Cerebellum	R	32, −82, −28	6.00	0.0001
Decreased activation				
Primary MC (BA 4)	L	−24, −20, 58	3.63	0.0001

L = left; R = right; BA = Brodmann area; MC = motor cortex; DLPFC = dorsolateral prefrontal cortex; GFm = gyrus frontalis medius; GFd: = gyrus frontalis medialis.

gyrus (BA 10), right temporal cortex (BA 38), left putamen and left thalamus.

Between-group comparison

In the OFF stimulation condition (Fig. 2). During freely selected movements, there was significantly greater activation during the OFF stimulation state for dystonic patients in the left superior frontal gyrus (BA 10), right inferior frontal gyrus, left gyrus orbitale (BA 11), a large part of the left DLPFC (BA 8, 46), gyrus frontalis medialis (BA 9, 10) and parietal cortex (BA 40). No lesser degree of activation was seen in dystonic patients during the OFF stimulation condition compared with control subjects.

In the ON stimulation condition (Fig. 3). For freely selected movements, we observed significantly increased activation of a small segment of the left DLPFC (BA 8/9, 46) (Fig. 3), left gyrus rectus (BA 11), left premotor cortex and left temporal cortex (BA 37). Contrary to that observed when comparing the control group with patients during the OFF stimulation state (Fig. 2), no differences in rCBF were noted in the left orbital gyrus and left middle frontal gyrus (BA 45). No lesser degree of activation was seen in dystonic patients in the ON stimulation condition compared with control subjects.

Discussion

The three main results of this study involving a homogeneous population of dystonic patients (five out of six *DYT1* carriers) are: (i) hand movements hampered by dystonia in primary generalized dystonia are characterized by prefrontal overactivation including the DLPFC and frontoorbital cortex; (ii) in contrast to the pattern displayed by the control group, caudal SMA activation, but no lateral premotor activation, was observed during task performance in dystonic patients; and (iii) GPi DBS decreases the overactivation in the contralateral thalamus, putamen, DLPFC and frontoorbital cortex, thus restoring a more physiological activation pattern.

Of particular interest is the pattern of activation at rest in dystonic patients receiving unilateral GPi DBS. Contralateral to the side of stimulation, a significant increase of rCBF is seen in the prefrontal cortex including the DLPFC, inferior frontal gyrus, parietal cortex, posterior cingulate cortex and caudate nucleus. Ipsilateral to the side of stimulation, a similar augmentation of activity is seen in the GPi and thalamus. Moreover, unilateral GPi DBS reduces activation in the primary motor cortex on the ipsilateral side at rest.

Clinical improvement of dystonia by GPi stimulation during the PET study

The stimulator was switched on or off for an average of 3.40 h (0.25–6.50 h) prior to PET scan acquisition. For each patient, we assessed the time between the stimulation onset and the appearance of clinical effects with a preliminary study of tolerance. Acute clinical effects normally began after a few minutes and this remained stable for hours (notably during the duration of the PET scan). As a result, it was possible to analyse a true recurrence of hand dystonia in the OFF condition, and subsequently demonstrate a real improvement of dystonia in the ON condition for each patient prior to the PET scan. Thus, we were able to elicit a tolerable recurrence of hand-tested dystonia in the OFF stimulation condition.

On PET scan, unilateral GPi DBS produced a 23% improvement in BFMS for all body parts and a 56% reduction in DSS for dystonia in each tested limb. However, these findings cannot be extrapolated to the long-term effects of bilateral GPi stimulation as the stimulator was switched on or off only for several hours before scoring and the stimulation was unilateral.

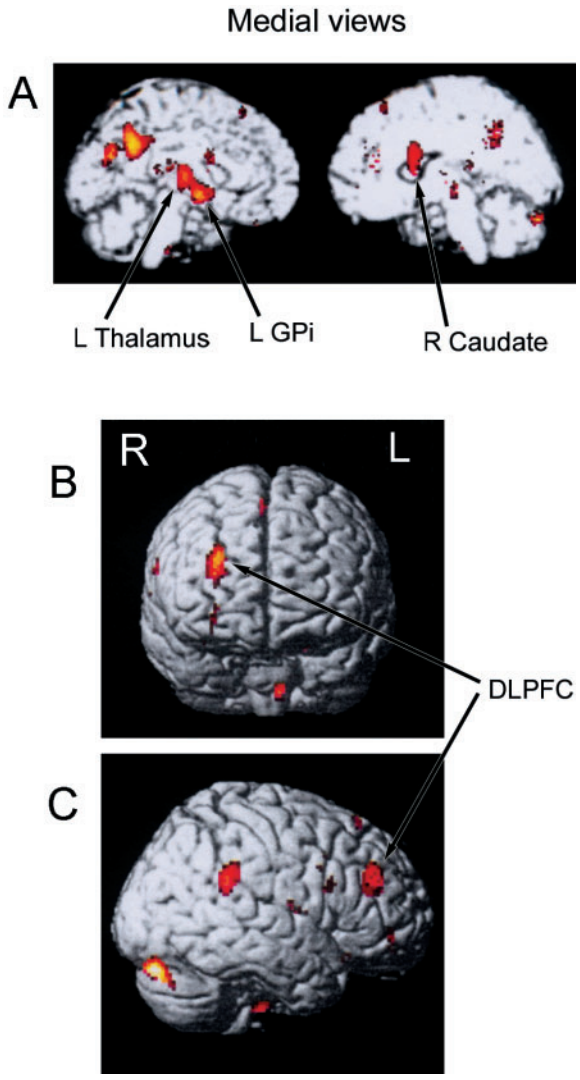

Fig. 1 Relative activations induced by left globus pallidus internus (GPi) stimulation during the rest condition in the six patients with primary generalized dystonia. Comparison of the difference in activation between effective left GPi stimulation versus no GPi stimulation during the rest condition (Rest ON versus Rest OFF). The statistical parametric maps are displayed in the anatomical space of Talairach and Tournoux as a maximum intensity projection superimposed onto medial views (**A**) of SPM 96, anterior (**B**) and right lateral (**C**) views of the single-subject brain MRI of SPM 99. Height threshold T = 3.95. R, right; L, left; DLPFC, dorsolateral prefrontal cortex.

Additionally, the present study demonstrated that GPi DBS is a fully reversible treatment providing a clear clinical benefit in generalized dystonia, notably in patients carrying the *DYT1* mutation (Coubes *et al*., 1999, 2000, 2002; Tronnier *et al*., 2000; Vercueil *et al*., 2001).

OFF stimulation: abnormal cerebral activation pattern of dystonia during hand movements

Dystonic patients during the OFF stimulation periods can be considered representative of primary generalized dystonia patients without treatment. Assuming this hypothesis is true, it is possible to evaluate modifications of cerebral activation during a motor task in primary generalized dystonia. The contralateral primary sensory cortex, DLPFC and parietal cortex (BA 40) are activated in dystonic patients but not in healthy subjects (Table 4). In contrast to control subjects, the premotor cortex was not activated during task execution in dystonic patients. Whereas the caudal SMA was bilaterally activated in dystonic patients, it was not activated in the control group. This pattern of prefrontal overactivation was confirmed by the between-group comparisons (Fig. 2). The rCBF in the contralateral prefrontal cortex of dystonic patients was higher than that found in control subjects during task execution compared with the resting state. These overactivated prefrontal areas included the DLPFC, frontoorbital cortex and the middle frontal gyrus. The overactivation of the parietal cortex, primary sensory cortex or caudal SMA was not confirmed by the between-group comparison.

Our findings confirm previous studies showing an abnormal pattern of cerebral activation during hand movements in primary generalized dystonia (Ceballos-Baumann *et al*., 1995*a*, *b*; Playford *et al*., 1998). This pattern is characterized by an enhanced activation (increase of rCBF) mainly in the DLPFC and SMA. Contrary to other studies, we noted no overactivation in the lenticulate nucleus, cerebellum or premotor cortex (Ceballos-Baumann, 1995*a*; Playford *et al*., 1998).

This abnormal pattern in dystonia involves the lateral prefrontal areas implicated in movement preparation. This is consistent with the idea that there is a disorder of movement preparation and selection in dystonia. During our simple externally cued task, patients used prefrontal areas normally involved in more complex motor tasks, notably in self-initiated tasks used by Jenkins *et al*. (2000). This enhanced activity of the prefrontal cortex, including the DLPFC, may be a result of overactivity of the basal ganglia via increased output through the thalamo-cortical pathway.

Table 7 *Modifications of regional cerebral blood flow (rCBF) induced by effective stimulation of the left globus pallidus internus (GPi) during freely selected joystick movements in dystonic patients when compared with the rest condition*

Areas	Side (L/R)	Talairach coordinates (*x*, *y*, *z* mm)	*Z*-score	*P* uncorrected (voxel-level)
Increased activation				
None				
Decreased activation				
Superior frontal gyrus (BA 10)	L	−4, 68, 24	3.49	0.0001
Temporal cortex (BA 38)	R	32, 10, −18	3.39	0.0001
Putamen	L	−20, 10, 14	3.31	0.0001
Thalamus	L	−8, −16, 16	3.24	0.001

L = left; R = right; BA = Brodmann area.

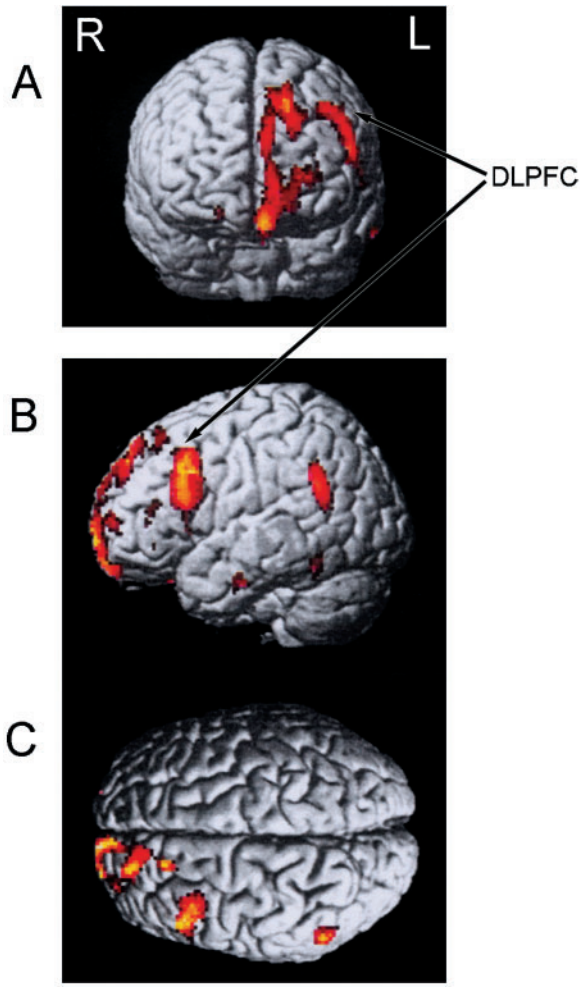

Fig. 2 OFF stimulation condition: between-group analysis of activated areas during motor tasks. Comparison between the six patients with primary generalized dystonia (without stimulation) and the eight normal control subjects during joystick movements in a freely selected direction with the right hand ([Exe OFF versus Rest OFF] − [Exe control versus − Rest control]). The statistical parametric maps are displayed in the anatomical space of Talairach and Tournoux as a maximum intensity projection superimposed onto anterior (**A**), left lateral (**B**) and superior (**C**) views of the single-subject brain MRI of SPM 99. Height threshold T = 3.17. R, right; L, left; DLPFC, dorsolateral prefrontal cortex.

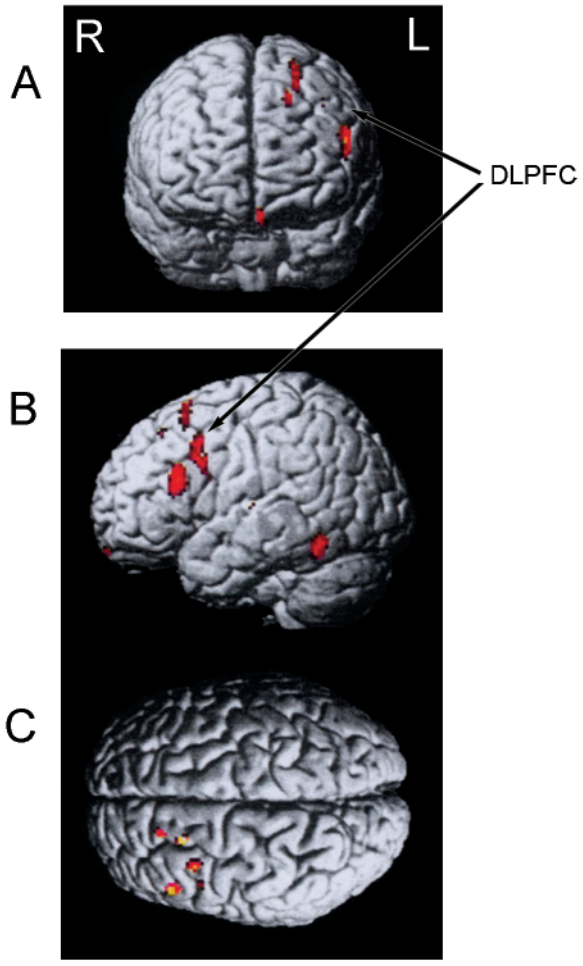

Fig. 3 ON stimulation condition: between-group analysis of activated areas during motor tasks. Comparison between the six patients with primary generalized dystonia with stimulation of the left GPi and the eight normal control subjects during joystick movements in a freely selected direction with the right hand ([Exe ON versus Rest ON] − [Exe control versus Rest control]). The statistical parametric maps are displayed in the anatomical space of Talairach and Tournoux as a maximum intensity projection superimposed onto anterior (**A**), left lateral (**B**) and superior (**C**) views of the single-subject brain MRI of SPM 99. Height threshold T = 3.17. R, right; L, left; DLPFC, dorsolateral prefrontal cortex.

It is interesting to note that our findings in primary dystonia contrast with those reported in patients with Parkinson's disease undertaking the same task in which the activity of the SMA and DLPFC is decreased (Playford *et al*., 1992; Samuel *et al*., 1997).

ON stimulation: GPi stimulation corrects the abnormal activation pattern of dystonia during hand movements

The present study provides important insights into the effects of GPi DBS in primary generalized dystonia. Contrary to the OFF stimulation condition (Table 4), during the ON stimulation state (Table 5), no rCBF increase is displayed in the DLPFC and thalamus during the motor task. Moreover, unilateral GPi DBS reduces activation in the ipsilateral superior frontal gyrus (BA 10), thalamus and putamen (Table 7). No increase of cerebral activation was induced by the GPi stimulation during hand movements. When comparing patients in the ON stimulation condition with controls, we showed that GPi DBS reduces the prefrontal overactivation (Fig. 3), thus restoring a more physiological activation pattern. Thus, GPi DBS corrects the abnormal prefrontal overactivation in primary dystonia, as suggested in a previous study of one patient. However, we did not observe an activation of the primary cortex by GPi stimulation (Kumar *et al*., 1999).

In contrast to Ceballos-Baumann *et al*. (1997) who found that botulinum toxin does not reverse the cortical dysfunction associated with writer's cramp (focal dystonia), we observe in our study that modifications of basal ganglia dysfunction with GPi stimulation in generalized dystonia can reverse the abnormal activation pattern. This finding supports the view that the primary pathophysiological disorder in dystonia is associated with abnormal neuronal activity in the basal ganglia system and possibly in the GPi.

GPi DBS effects at rest

At rest, GPi DBS increases activation in the contralateral DLPFC and the ipsilateral thalamus and GPi (Table 6; Fig. 1). This finding is another argument to consider that GPi DBS modifies basal ganglia function.

However, contrary to the motor task condition, the results at rest show a paradoxical effect with an increased rCBF within several cortical and subcortical areas which seems to aggravate the abnormal dystonic activity pattern. A similar paradoxical effect at rest was also observed in other imaging studies addressing the effects of DBS in Parkinson's disease (Limousin *et al*., 1997; Ceballos-Baumann *et al*., 1999).

More generally, this finding raises the question of the DBS proper effect which remains unclear. Emerging data (Garcia *et al*., 2003; Hashimoto *et al*., 2003) suggest that stimulation feeds thalamo-cortical pathways with high frequencies. The abnormal neuronal activity pattern would be masked by this high-frequency feeding. This might explain the overactivity at rest of the GPi, thalamus and cortical projections, especially prefrontal cortex. This is in keeping with the anatomical projection from the somatomotor GPi to cortical areas other than the primary motor cortex via the thalamus (Hoover and Strick, 1999).

This apparent paradoxical effect of GPi DBS at rest does not preclude that, during movement, GPi stimulation restores, at least in part, the regular cortex function. During a motor task, high-frequency stimulation of the postero-lateral GPi seems to improve the abnormal dystonic activity pattern (Ceballos-Baumann *et al*., 1995*a*; Playford *et al*., 1998). Therefore, the effect of GPi stimulation seems to be task dependent as suggested in other functional imaging studies using DBS (Limousin *et al*., 1997; Ceballos-Baumann *et al*., 1999).

Such a hypothesis accounts for the GPi DBS-induced clinical improvement of primary dystonia both at rest and during voluntary movement.

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