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Globus pallidus stimulation reduces frontal hyperactivity in tardive dystonia

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Tardive dystonia (TD) is a disabling disorder induced by neuroleptics. Internal globus pallidus (GPi) stimulation can dramatically improve TD. The present positron emission tomography and H₂¹⁵O study aimed to characterize the abnormalities of brain activation of TD and the impact of GPi stimulation on these abnormalities in five TD patients treated with GPi stimulation and eight controls. Changes of regional cerebral blood flow (rCBF) were determined: (i) at rest; (ii) when moving a joystick with the right hand in three freely chosen directions in on and off bilateral GPi stimulation. A significant increase of rCBF was found in TD patients in off-stimulation condition compared to controls: (1) during motor execution in the prefrontal, premotor lateral, and anterior cingulate cortex; (2) at rest, in the prefrontal and anterior cingulate cortex and the cerebellum. Internal globus pallidus stimulation led to a reduction of rCBF (1) during motor execution, in the primary motor and prefrontal cortex and the cerebellum; (2) at rest, in the primary motor and anterior cingulate cortex and supplementary motor area. The results are as follows: (1) TD is related to an excess of brain activity notably in the prefrontal and premotor areas; (2) GPi stimulation reduces the activation of motor, premotor, and prefrontal cortex as well as cerebellum.

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Introduction

Dystonia is characterized by sustained muscle contractions leading to abnormal postures and movements (Geyer and Bressman, 2006). From an aetiological point of view, dystonias have been divided into primary dystonias, in which dystonia is the sole clinical manifestation, and secondary dystonias, which are due to degenerative disorders or acquired lesions of the basal ganglia (Geyer and Bressman, 2006). Tardive dystonia (TD) belongs to the secondary dystonias and is related to neurolep-

tic intake for at least 3 months. Tardive dystonia belongs to the so-called tardive dyskinesia, which were reported for the first time 50 years ago (Najib, 1999). Tardive dyskinesia is a heterogeneous entity that comprises dystonic and choreic abnormal movements. Usually, clinical symptoms predominantly affect the orofacial and axial muscles (Najib, 1999). Mild cases most often consist in orofacial dyskinesias, but more severe cases present generalized abnormal movements with a predominance of axial dystonia. This is the case in patients reported in this study explaining why we prefer to write about TD instead of tardive dyskinesia, which is less precise. The prevalence of tardive dyskinesia is between 15% and 20% among patients treated with neuroleptics, and despite withdrawal of dopamine blockers, more than 50% of cases are irreversible (Najib, 1999). Furthermore, severe disability is observed in approximately 2% of cases of tardive dyskinesia (Pourcher *et al.*, 1995). Medical

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treatments for tardive dyskinesia are usually of weak or short-lasting efficacy (Soares and McGrath, 1999). For these intractable cases, deep brain stimulation (DBS) of the internal globus pallidus (GPi) has been proposed, which leads to a dramatic improvement of the motor symptoms, as recently demonstrated by several case reports and in a controlled study from our group (Schrader *et al*, 2004; Eltahawy *et al*, 2004; Trottenberg *et al*, 2005; Franzini *et al*, 2005; Damier *et al*, 2007). The improvement in tardive dyskinesia with DBS of the GPi is comparable to the one observed in primary generalized dystonia (Vidailhet *et al*, 2005).

The pathophysiology of dystonia is complex and not fully understood. Electrophysiological and functional imaging studies have shown an excess of brain activation, a loss of corticocortical inhibition, and a lack of the selectivity of brain activation (Hallett, 2004). In primary generalized dystonia, functional imaging studies have shown that during the execution of a simple hand motor task there is widespread overactivation of the brain, notably in the prefrontal, premotor, parietal cortex as well as in the supplementary motor area (SMA), cerebellum, and striatum (Ceballos-Baumann *et al*, 1995a; Playford *et al*, 1998; Kumar *et al*, 1999; Detante *et al*, 2004). In secondary dystonia caused by lesions of the basal ganglia, additional overactivation of the primary motor cortex was observed (Ceballos-Baumann *et al*, 1995b). Other studies of writer's cramp and Meige's syndrome have demonstrated an altered somatotopic representation, which contributes to the loss of functional selectivity of muscle activity (Delmaire *et al*, 2005). In addition, dysfunction of the cortical sensory system with an enhanced response of the basal ganglia to sensory inputs has been shown (Butterworth *et al*, 2003). Interestingly, these abnormalities of the pattern of cerebral activation in primary dystonia can be reversed by efficient pallidal stimulation (Kumar *et al*, 1999; Detante *et al*, 2004).

The pathophysiology of TD remains debated, but the main hypothesis is that dopamine-blocking agents induce a hypersensitivity of dopaminergic receptors, leading to a dysfunction of both direct and indirect striatopallidal pathways (Silvestri *et al*, 2000; Van Kampen and Stoessl, 2000). This dysfunction would inhibit the GPi, thereby releasing the inputs from the thalamus to the cortex and leading to an excess of brain activation observed in TD. Furthermore, abnormal patterns of neuronal activity in GPi have been shown in dystonia (Vitek *et al*, 1999). Thus, GPi stimulation may act through the replacement of this abnormal firing pattern of GPi neurons by a more regular one.

Few functional imaging data are available in TD. Most of the positron emission tomography (PET) and single-photon emission computed tomography studies have looked at the modifications of the postsynaptic dopaminergic system. In patients studied after long-term neuroleptic treatment

withdrawal, an upregulation of dopaminergic D2 receptors has been observed using PET and [¹¹C]raclopride, a D2 receptor ligand. Notably, these studies concerned patients with severe TD, which is in agreement with the suspected role of dopamine receptor trafficking in the occurrence of TD (Silvestri *et al*, 2000). In contrast, other studies showed normal dopamine D2 receptor density and affinity in TD (Blin *et al*, 1989; Andersson *et al*, 1990; Adler *et al*, 2002).

To our knowledge, no functional magnetic resonance imaging or PET activation study has investigated changes of brain activation patterns in TD. Therefore, the objectives of the present PET H₂¹⁵O study were (1) to determine whether an abnormal pattern of brain activation is associated with TD; in the light of what is known about primary and secondary dystonias, we hypothesized that TD would be related to increased activation of the motor, premotor, and prefrontal regions and (2) to investigate the changes of cerebral perfusion induced by bilateral GPi stimulation in patients operated for severe TD in the French multicentric STARDYS study (Damier *et al*, 2007). Ten patients participated in the STARDYS study, which demonstrated the great efficacy of GPi stimulation in severe TD. Among them, five were included in the present PET activation study. In the light of what was observed in primary dystonia, we hypothesized that GPi stimulation would at least partly reverse the abnormalities of brain activation in TD.

Methods

Subjects

Five right-handed patients suffering from severe TD were included in the study (4 females and 1 male; mean age 51.4 ± 11.4 years; see Table 1 for clinical characteristics and stimulation parameters). All these patients had received neuroleptics in the past for severe anxiety associated with depression but none presented with psychotic disorders. For all these patients, the clinical presentation consisted of severe predominantly axial dystonia affecting the face (*n* = 5), the trunk (*n* = 4), the arms (*n* = 3), or the legs (*n* = 1). One patient also had mild choreic movements affecting the fingers on both sides. All patients participated in the French multicentre collaborative STARDYS study and had been operated on for at least 6 months with chronic bilateral stimulation of the GPi (Damier *et al*, 2007). The surgical method has been detailed elsewhere (Damier *et al*, 2007). On the day of the PET scans, the patients had been withdrawn from their usual medication for at least 12 h. On the day preceding the PET scan, the severity of the patients' abnormal movements was assessed using the Extrapyramidal Symptoms Rating Scale (ESRS) score (Chouinard and Margolise, 2005). This assessment was completed during the on stimulation condition and then 1 h after the stimulators had been switched off; at the time of the assessment, the assessor was fully aware of whether the stimulators were

Q1

Q2

Table 1 Characteristics of the patients

Patient no./sex/age (years)	Reason for treatment with neuroleptics	Disease duration (years)	ESRS off stimulation	ESRS on stimulation	Contact	Voltage (V)	Pulse width (μ secs)	Frequency (Hz)	Treatment
1/F/36	Depression	8	78	21	1-/L 5-/R	2.7 3	210 210	130 130	Amitriptyline Tetrabenazine
2/F/59	Depression	7	66	28	1-/L 5-/R	3.9 3.9	150 150	130 130	Bromazepam
3/M/56	Depression	4	35	10	1-/L 5-/R	4.5 4.5	90 90	130 130	Lorazepam Sertraline Valpromide Lormetazepam
4/F/63	Depression	12	72	26	1-/L 5-/R	3.5 3.5	90 90	130 130	Clonazepam Amitriptyline
5/F/43	Depression	6	35	22	1-/L 4-5-/R	3.9 2.9	90 90	130 130	Clonazepam Mianserine Alprazolam
Mean \pm s.d.: 51.4 (11.4)		7.4 (3)	57.2 (21)	21.4 (7)		3.6 (0.6)	126 (51)	130	

ESRS, Extrapyrimal Symptom Rating Scale.

on or off. For all patients, stimulation led to a clear improvement of the dystonia and chorea with a mean improvement of the ESRS score of 63% at the time of the PET study ($P < 0.01$). In addition, eight age-matched control subjects were recruited (3 females and 5 males; mean age \pm s.d.: 47.5 ± 13 years). All controls were right-handed and had no history of neurologic disease.

The study was approved by the local research ethics committee. All subjects participated after the aims of the study and the nature of the procedures had been fully explained. They signed an informed consent form in line with the Declaration of Helsinki Principles.

Tasks

Subjects lay on the bed of the PET scanner with their eyes closed. Two conditions were considered: execution of the task with the right hand (T) and rest condition (R). The motor task consisted of moving a joystick in three freely chosen different directions (front, back, and left or right) with the right hand, without repeating the same motor sequence and as accurately as possible (i.e., with a good amplitude of movement). The joystick was restrained by strings to enable only left-right and front-back movements. The participants were instructed to go back to the centre between two consecutive movements. The movement was externally cued by an auditory stimulus (a high tone) that was displayed regularly every 8 secs. This externally cued motor task was repeated in the same manner during 120 secs leading to a total of 15 movements. In the rest condition, subjects held the joystick in their right hand and heard the auditory cue but did not move the hand. Each task was repeated three times for a total of six scans. The order of conditions was randomized.

Patients underwent two PET scan sessions on two consecutive days (six scans each), leading to a total number of 12 scans. Each PET session was performed after GPi stimulation had either been bilaterally switched on or off for at least 3 h. The order of stimulation (i.e., DBS on first or off first) was counterbalanced. We checked that the duration after having switched the stimulator on or off was sufficient for the motor signs to reappear or disappear. In all cases, this latency was short, and most of the dystonic postures came back or were suppressed with a delay of a few minutes.

For control subjects, one PET scan was performed for a total of six scans.

Behavioural Analysis

Movement duration (time needed to perform the three different movements with the joystick) and reaction time (interval from beep to the first movement) were computed for the motor task. A between (patients, control)-by-within (experimental condition) analysis of variance design was used to identify significant differences between the experimental groups and conditions. Data from all responses were incorporated into this analysis of variance. Duncan's multiple range test was used for *post hoc* comparisons of the means. The threshold for statistical significance was set at 0.05.

Positron Emission Tomography Data Acquisition

Positron emission tomography scanning was performed at the CERMEP-Imagerie du vivant (PET Imaging Centre, Lyon, France) on a CTI HR+ Siemens tomograph (CTI/Siemens, Knoxville, TN, USA). The head was maintained in a fixed position using a molded helmet. The head

position was checked before and after each scan using a laser alignment together with reference points on Reid's line.

A 10-min transmission scan was acquired using rotating rod sources filled with $^{68}\text{Ge}/^{68}\text{Ga}$. For each emission scan, an intravenous injection of H_2^{15}O (343 ± 77 MBq) through a forearm catheter placed into the brachial vein was realized. The integrated counts were collected for 90 secs, starting 30 secs after the injection. The interval between successive H_2^{15}O administrations was 9 mins to allow for adequate radioactivity decay. Images were reconstructed by three-dimensional back-filtered projection (Hanning filter; cut-off frequency 0.5 cycles per 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.

Positron Emission Tomography Data Analysis

Using CAPP software, the original emission scans in ECAT7 file format were converted into ANALYZE file format and then processed in MATLAB 6 (MathWorks, Natick, MA, USA) using the Statistical Parametric Mapping software (SPM 2; Wellcome Department of Cognitive Neurology, MRC Cyclotron Unit, London, UK). In the first stage of analysis, the 12 images from each subject were realigned to the first scan with an automated algorithm for head movement correction and then normalized into the standard stereotactic space provided in SPM 2. The normalized images were smoothed with an isotropic Gaussian filter of 12 mm to account for variation in gyral anatomy and individual variability in structure–function relationships and to improve the signal-to-noise ratio. Variations in global flow across subjects were removed by proportionally scaling each image to have an arbitrary level of 50 mL per 100 mL per min. Regional cerebral blood flow (rCBF) changes were statistically analysed for all voxels exceeding 80% of the mean value of the scan.

- We first analysed the abnormalities of brain activation pattern observed in TD patients in the off-stimulation condition compared to controls. Increase of rCBF at rest in patients compared to controls was determined by the following contrast: $(R_{\text{patientOff}} - R_{\text{controls}})$. In addition, we determined in each group the increase of rCBF when subjects executed the motor task (T) compared to the rest (R) condition by the following contrast: T–R. In patients, this was performed in the off-stimulation condition $(T-R)_{\text{patientOff}}$. Then, between-group comparisons of rCBF were made. Increase of rCBF during the execution of the motor task in patients compared to controls was assessed by the following interaction contrast: $(T-R)_{\text{patientOff}} - (T-R)_{\text{controls}}$. Decrease of rCBF during the execution of the motor task in patients compared to controls was assessed by the following interaction contrast: $(T-R)_{\text{controls}} - (T-R)_{\text{patientOff}}$.
- We then analysed the modifications of rCBF induced by bilateral GPi stimulation. The increase of rCBF induced by GPi stimulation at rest was determined by the following contrast: $R_{\text{patientOn}} - R_{\text{patientOff}}$. The decrease of rCBF induced by GPi stimulation at rest was determined

by the following contrast: $R_{\text{patientOff}} - R_{\text{patientOn}}$. The decrease of rCBF induced by GPi stimulation during the execution of the motor task was assessed by the following interaction contrast: $(T-R)_{\text{patientOff}} - (T-R)_{\text{patientOn}}$. The increase of rCBF induced by GPi stimulation during the execution of the motor task was assessed by the following interaction contrast: $(T-R)_{\text{patientOn}} - (T-R)_{\text{patientOff}}$.

- Finally, the covariation of rCBF, with the ESRS score used as a covariate, was analysed. In a covariate-only model, the positive covariation of rCBF with this score was determined.

Global differences in cerebral blood flow were covaried for all voxels within the mask, and comparisons across conditions were made using *t*-statistics with appropriate linear contrasts and then converted to *Z*-scores. The minimal cluster size comprised at least 10 voxels. Only voxels that exceeded a threshold of a false-positive error (FWE)-corrected $P \leq 0.05$ were considered as significant. For regions with a strong *a priori* hypothesis based on previous functional imaging studies performed in dystonia (i.e., prefrontal, lateral premotor, primary motor, parietal cortex, SMA, cerebellum, basal ganglia), small volume corrections were applied if the FWE-corrected *P*-value did not reach the $P \leq 0.05$ statistical threshold (here again, a corrected *P*-value after small volume correction ≤ 0.05 is considered as significant). All coordinates reported were based on the Talairach atlas and were derived from procedures developed by M Brett (<http://www.mrc-cbu.cam.ac.uk/Imaging>; Talairach and Tournoux, 1988).

Results

Behavioural Results

In the patient group, no significant difference in movement duration between on- and off-stimulation conditions ($3,931 \pm 972$ ms on stimulation versus $3,535 \pm 1,135$ ms off stimulation; $P = 0.6$) or between patients with off-stimulation condition and control subjects ($3,535 \pm 1,135$ ms for patients versus $2,823 \pm 681$ ms for controls; $P = 0.18$) was observed.

Similarly, no difference in reaction time was observed when comparing on- and off-stimulation conditions (697 ± 152 ms on stimulation versus 692 ± 167 ms off stimulation; $P = 0.9$). In addition, there was a nonsignificant trend for patients in both on- and off-stimulation conditions to be slower than controls (558 ± 101 ms for controls versus 697 ± 152 ms for patients in on-stimulation condition; $P = 0.055$ and 558 ms for controls versus 692 ± 167 ms for patients in off-stimulation condition; $P = 0.065$).

Positron Emission Tomography Results

Patterns of brain activation in tardive dystonia

- In control subjects, a significant increase of rCBF was observed during the execution of the motor task with the right hand versus rest (T–R) in the left primary

motor cortex (Brodmann area (BA) 4, M1), superior parietal lobe (BA 7), and SMA (BA 6), and in the right lateral premotor cortex (BA 6), anterior cingulate cortex (BA 24), and cerebellar hemisphere.

- In patients, in the off-stimulation condition, a significant increase of rCBF was noted during the execution of the motor task with the right hand versus rest $(T-R)_{\text{patientOff}}$ in the left superior parietal lobe (BA 7), dorsolateral prefrontal cortex (DLPFC; BA 9), SMA (BA 6), the right lateral premotor cortex (BA 6), anterior cingulate cortex (BA 24), putamen and bilaterally in the primary motor cortex (BA 4), inferior parietal lobe (BA 40), cerebellar hemisphere, and vermis (Figure 1A).
- Comparisons were then made between patients with off stimulation and controls. Areas showing higher rCBF at rest in patients with off stimulation compared to controls were extracted from the following contrast: $(R_{\text{patientOff}} - R_{\text{controls}})$ and comprised the left DLPFC (BA 9), medial and superior frontal gyrus (BA 10), and anterior cingulate cortex (BA 24) and the right inferior and dorsal frontal gyrus (BA 10 and 44), anterior cingulate cortex (BA 32) and bilaterally in the cerebellum (Figure 2). Areas showing higher rCBF during the execution of the motor task in patients with off stimulation compared to controls were extracted from the following contrast: $(T-R)_{\text{patientOff}} - (T-R)_{\text{controls}}$ and comprised the left medial and superior frontal gyrus (BA 11 and 8) and the right anterior cingulate gyrus (BA 24) and lateral premotor cortex (BA 6). No significant increase of rCBF was found in controls compared to patients with off

stimulation during the execution of the motor task as extracted from the following comparison: $(T-R)_{\text{controls}} - (T-R)_{\text{patientOff}}$. These results are summarized in Table 2.

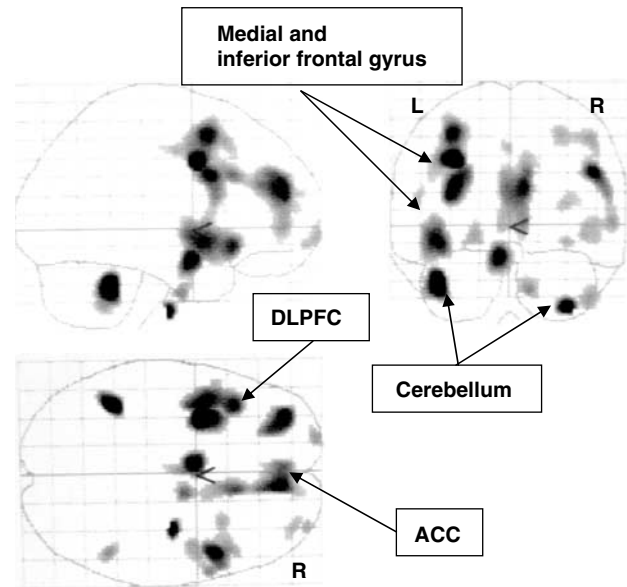


Figure 2 Areas of increase of rCBF at rest in TD patients compared to controls. These areas are displayed on sagittal, lateral, and coronal views of a 'glass' brain (FWE-corrected P -value ≤ 0.05).

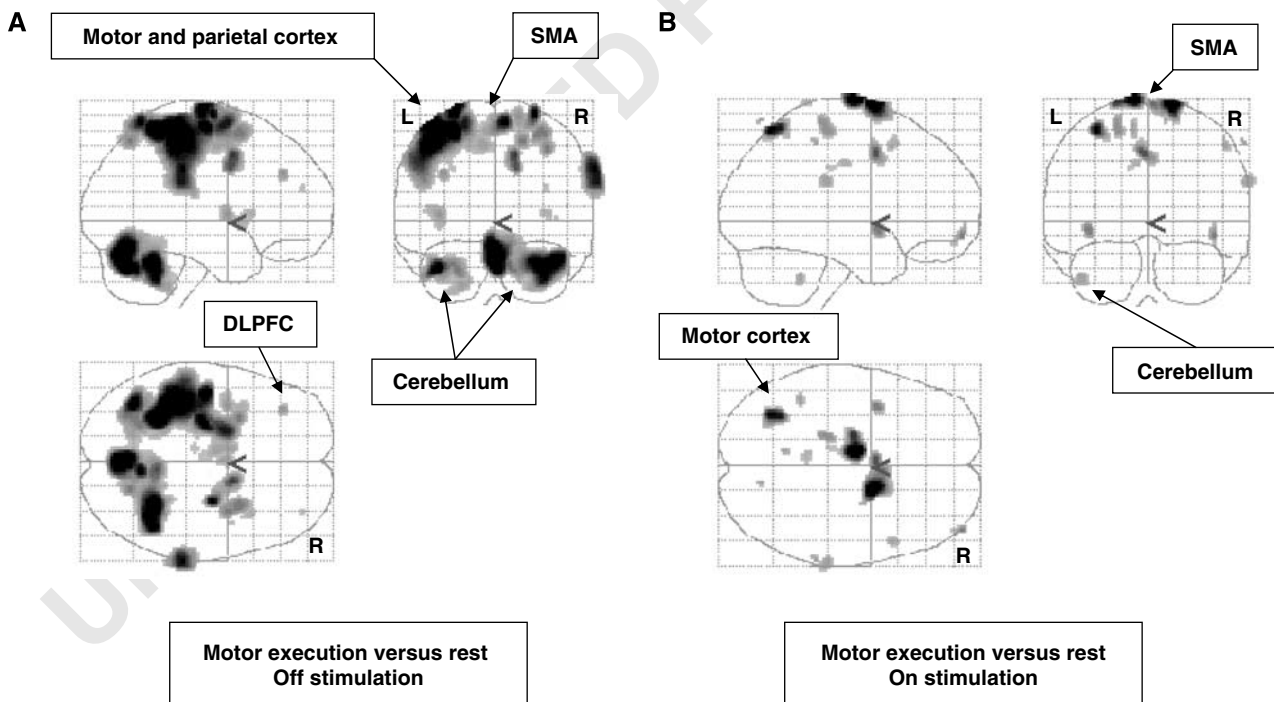


Figure 1 (A) Pattern of activation during motor execution versus rest in TD patients in the off GPI stimulation condition (FWE-corrected P -value ≤ 0.05). These areas are displayed on sagittal, lateral, and coronal views of a 'glass' brain. (B) Pattern of activation during motor execution versus rest in TD patients in the on GPI stimulation condition (FWE-corrected P -value ≤ 0.05). These areas are displayed on sagittal, lateral, and coronal views of a 'glass' brain.

Table 2 Brain activation pattern in TD patients without GPi stimulation and control subjects during motor execution

	Areas	Left/right	Stereotactic coordinates				
			x	y	z	Z-score	P-value corrected voxel
<i>Within-group analysis</i>							
Control subjects	Primary motor cortex (BA 4)	L	-36	-24	68	7.60	0.0001
	Superior parietal lobe (BA 7)	L	-10	-70	58	6.95	0.0001
	Lateral premotor cortex (BA 6)	R	64	8	24	5.81	0.0001
	Anterior cingulate cortex (BA 24)	R	18	0	50	5.25	0.005
	SMA (BA 6)	L	-1	-5	60	5.10	0.01
	Cerebellum (hemisphere)	R	32	-50	-28	6.80	0.0001
TD patients	Primary motor cortex (BA 4)	L	-41	-19	57	4.85	0.01
		R	24	-13	64	4.57	0.05
	Superior parietal lobe (BA 7)	L	-25	-50	50	5.26	0.003
	DLPFC (BA 9)	L	-31	34	30	3.67	0.03 (SVC)
	SMA (BA 6)	L	-1	-3	61	3.52	0.04 (SVC)
	Lateral premotor cortex (BA 6)	R	26	4	53	3.88	0.025 (SVC)
	Inferior parietal lobe (BA 40)	L	-38	-36	49	5.05	0.008
		R	59	-32	30	4.50	0.08
	Anterior cingulate cortex (BA 24)	R	12	1	38	4.20	0.02 (SVC)
	Putamen	R	31	12	4	3.38	0.05 (SVC)
	Cerebellum (hemisphere)	L	-34	-65	-32	4.75	0.03
		R	34	-54	-28	4.91	0.015
	Cerebellum (vermis)		-3	-71	-23	5.42	0.001
<i>Between-group analysis</i>							
Control subjects > TD patients off at rest	None						
TD patients off > control subjects at rest	DLPFC (BA 9)	L	-32	2	38	7.26	<0.0001
	Medial frontal gyrus (BA 10)	L	-32	50	22	6.07	<0.0001
	Superior frontal gyrus (BA 10)	L	-20	70	-6	5.13	0.003
	Anterior cingulate cortex (BA 24)	L	-2	-6	44	4.95	0.007
	Inferior frontal gyrus (BA 44)	R	48	10	30	6.25	<0.0001
	Dorsal frontal gyrus (BA 10)	R	8	48	22	6.07	<0.0001
	Anterior cingulate cortex (BA 32)	R	10	22	30	5.57	<0.0001
	Cerebellum	L	-40	-46	-34	7.05	<0.0001
		R	34	-14	-48	6.47	<0.0001
Control subjects > TD patients Off during motor execution	None						
TD patients Off > control subjects during motor execution	Medial frontal gyrus (BA 11)	L	-22	34	-16	4.17	0.02 (SVC)
	Superior frontal gyrus (BA 8)	L	-25	8	51	3.29	0.05 (SVC)
	Anterior cingulate cortex (BA 24)	R	12	-5	29	3.67	0.03 (SVC)
	Lateral premotor cortex (BA 6)	R	24	16	55	3.47	0.04 (SVC)

BA, Brodmann area; DLPFC, dorsolateral prefrontal cortex; GPi, internal globus pallidus; L, left; R, right; SMA, supplementary motor area; SVC, small volume correction; TD, tardive dystonia.

Changes of Brain Activation Patterns Induced by Internal Globus Pallidus Stimulation in Tardive Dystonia Patients

At rest

Bilateral GPi stimulation reduced rCBF in the left primary motor cortex (BA 4) and bilaterally in the anterior cingulate cortex (BA 24 and 32) and SMA. An increase of rCBF was induced by GPi stimulation in the right occipital cortex (BA 19), in both cerebellar hemispheres and in the left superior parietal lobe (BA 7).

During motor execution

- In patients with on stimulation, the increases in rCBF during the execution of the motor task with the right hand versus rest were more restricted than with off stimulation and concerned the left anterior cingulate cortex (BA 24), primary motor cortex (BA 4), superior parietal lobe (BA 7), cerebellum, and the right medial frontal gyrus (BA 10) and bilaterally in the SMA and the lateral premotor cortex (BA 6) (Figure 1B).

- A within-group interaction analysis ((T-R)_{patientOff}-(T-R)_{patientOn}) revealed that bilateral GPi stimulation reduced rCBF during the execution of the motor task in the left primary motor cortex (BA 4) and DLPFC (BA 9) and bilaterally in the cerebellar hemispheres. No significant increase of rCBF was induced by GPi stimulation as assessed by the following contrast: (T-R)_{patientOn}-(T-R)_{patientOff}.

These results are summarized in Table 3 and illustrated in Figure 3.

Covariation of rCBF with Severity of Dystonia

A positive covariation was observed between the ESRS score and the activation of the left anterior cingulate cortex (BA 24) and the superior frontal gyrus (BA 10) and bilaterally in the primary motor cortex (BA 4), superior parietal lobe (BA 7), SMA, and cerebellar hemispheres. These results indicate that the more severe the dystonia, the greater the rCBF in these areas. The location, coordinates, and peak Z-scores of the activated areas are detailed in Table 4.

Discussion

This study provides, for the first time, evidence of abnormal patterns of brain activation in TD. These

abnormalities mostly consist in excess of activation of the prefrontal, premotor, and anterior cingulate cortex. Furthermore, this study shows that the clinical improvement induced by GPi stimulation is mediated by a reduction of activation in the primary motor and prefrontal cortex and in the cerebellum.

Study Limitations

The rest condition was not a true rest, as an auditory cue was present and subjects had to refrain from moving the hand. This could have led to an activation of the prefrontal cortex to inhibit the movement. However, this probably did not affect our results, as this condition was similar for both groups and in on- and off-stimulation conditions.

We have to acknowledge the lack of significant differences in reaction time and movement duration between the on- and off-stimulation conditions despite the clear global improvement of the abnormal movements as assessed by the ESRS scale. The predominance of axial dystonia and the mild severity of hand dystonia made it difficult to disclose important differences in hand motor condition and thus significant differences in both reaction time and movement duration. Finally,

Table 3 Changes of brain activation induced by bilateral GPi stimulation in TD patients

Condition	Areas	Left/right	Stereotactic coordinates				
			x	y	z	Z-score	P-value correction voxel
<i>Rest</i>							
Increased activation induced by GPi stimulation	Occipital cortex (BA 19)	R	28	-78	28	4.59	0.05
	Superior parietal lobe (BA 7)	L	-28	-50	56	3.68	0.05 (SVC)
	Cerebellum (hemisphere)	R	18	-72	-30	3.89	0.04 (SVC)
		L	-38	-36	-18	4.05	0.03 (SVC)
Decreased activation induced by GPi stimulation	Primary motor cortex (BA 4)	L	-58	-4	42	4.24	0.001 (SVC)
	Anterior cingulate cortex (BA 24,32)	L	-4	-12	34	5.38	0.002
		R	2	32	22	4.41	0.001 (SVC)
	SMA (BA 6)	L	-8	-12	80	5.56	0.001
		R	10	-4	78	4.58	0.05
<i>Motor execution</i>							
Activation profile in on-stimulation condition	Primary motor cortex (BA 4)	L	-18	-32	54	3.51	0.05 (SVC)
		L	-31	-65	51	4.07	0.01 (SVC)
	Superior parietal lobe (BA 7)	R	38	55	-6	3.58	0.035 (SVC)
		L	-10	-13	71	4.46	0.001 (SVC)
	SMA (BA 6)	R	3	4	69	3.36	0.03 (SVC)
		L	13	-1	68	4.71	0.036
	Lateral premotor cortex (BA 6)	L	-17	-13	69	3.88	0.02 (SVC)
		L	-4	1	40	3.78	0.025 (SVC)
	Anterior cingulate cortex (BA 24)	L	-4	1	40	3.78	0.025 (SVC)
		L	-39	-48	-36	3.35	0.05 (SVC)
Cerebellum (hemisphere)	L	-39	-48	-36	3.35	0.05 (SVC)	
	L	-39	-48	-36	3.35	0.05 (SVC)	
Off > on	Primary motor cortex (BA 4)	L	-36	-32	49	3.57	0.035 (SVC)
		L	-31	34	31	3.20	0.05 (SVC)
	DLPFC (BA 9)	L	-17	-50	-40	3.52	0.035 (SVC)
		R	24	-54	-28	3.47	0.04 (SVC)
	Cerebellum (hemisphere)	L	-17	-50	-40	3.52	0.035 (SVC)
R		24	-54	-28	3.47	0.04 (SVC)	
On > off	None						

BA, Brodmann area; DLPFC, dorsolateral prefrontal cortex; GPi, internal globus pallidus; L, left; R, right; SMA, supplementary motor area; SVC, small volume correction; TD, tardive dystonia.

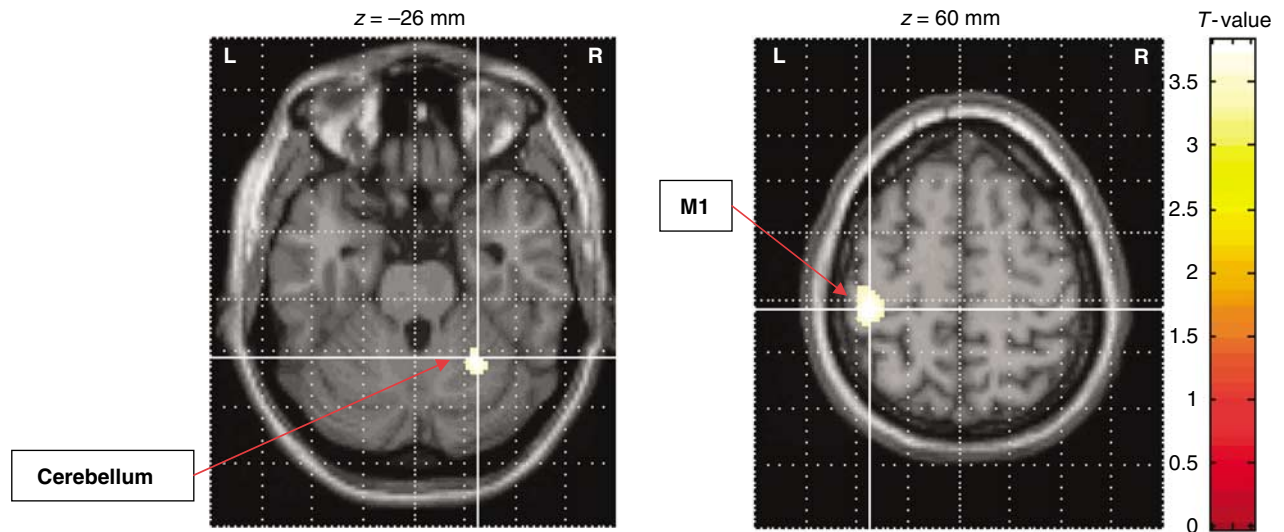


Figure 3 Areas of significant decrease of rCBF induced by GPI stimulation during motor execution in TD patients (FWE-corrected P -value ≤ 0.05). These areas mostly concern the left primary motor cortex and DLPFC and bilaterally in the cerebellum (right-sided cerebellar activation is shown). These areas have been superimposed on axial slices of a single subject brain MRI extracted from SPM 2.

Table 4 Positive covariation of rCBF with the severity of the dystonia

Areas	Left/right	Stereotactic coordinates				
		x	y	z	Z-score	P-value corrected voxel
Anterior cingulate (BA 24)	L	-1	30	24	5.84	0.0001
Superior parietal lobe (BA 7)	L	-10	-52	48	4.92	0.013
	R	36	-76	54	4.75	0.028
Primary motor cortex (BA 4)	L	-52	-10	34	4.74	0.029
	R	24	-22	65	3.79	0.05 (SVC)
SMA	L	-8	-4	65	4.51	0.03 (SVC)
	R	8	-8	65	4.51	0.03 (SVC)
Superior frontal gyrus (BA 10)	L	-16	70	8	4.38	0.04 (SVC)
Cerebellum	R	40	-94	-20	3.55	0.05 (SVC)
	L	-48	-82	-20	4.46	0.05 (SVC)

BA, Brodmann area; L, left; R, right; rCBF, regional cerebral blood flow; SMA, supplementary motor area; SVC, small volume correction.

owing to the rarity of such operated patients, the sample size in this study was small; a larger population would certainly disclose differences between DBS on and off in the basic parameters of movement, which may correlate with patterns of brain activation. Nevertheless, despite few subjects, the PET results were statistically significant. In addition, this lack of kinematic differences has the great advantage of not inducing a confounding factor related to the motor activity itself.

Abnormalities of Patterns of Brain Activation in Tardive Dystonia

A 'qualitative' (i.e., without statistical analysis) comparison of the pattern of brain activation during the execution of our motor task in controls and

patients without stimulation reveals that these patterns are similar but are more widespread in patients. For example, patients bilaterally recruit the primary motor cortex, the inferior parietal lobe, and the cerebellar hemispheres, whereas these areas are unilaterally activated in controls. Furthermore, patients recruit the left DLPFC and the right putamen, both regions that are not activated in controls. However, interaction analysis shows that the differences in the profile of brain activation are more restricted and consist of an increase in rCBF in TD patients in the left prefrontal cortex (BA 8 and 11), the anterior cingulate, and the right lateral premotor cortex. Interestingly, at rest, we also observed increases of rCBF bilaterally in the prefrontal cortex and the cerebellum as well as in the anterior cingulate cortex. These results are consistent with those reported in primary dystonia in which over-

activations were found in the DLPFC, premotor cortex, anterior cingulate cortex, cerebellum, and putamen (Ceballos-Baumann *et al*, 1995a; Playford *et al*, 1998; Kumar *et al*, 1999; Detante *et al*, 2004). On the one hand, in primary dystonia (generalized or focal), a decrease of rCBF is usually seen in the primary motor cortex, although this decrease is not constant (Ceballos-Baumann *et al*, 1995a; Playford *et al*, 1998; Odersgren *et al*, 1998; Kumar *et al*, 1999; Ibanez *et al*, 1999; Feiwell *et al*, 1999; Hutchinson *et al*, 2000; Pujol *et al*, 2000; Preibisch *et al*, 2001; Oga *et al*, 2002; Detante *et al*, 2004). However, in secondary dystonia, rCBF is often increased in the primary motor cortex (Ceballos-Baumann *et al*, 1995b; Lehericy *et al*, 2004). In this study, no decrease or increase of rCBF is observed in the primary motor cortex.

In addition, it is interesting to note that the activation of the anterior cingulate, primary motor cortex, cerebellum, and superior parietal lobe correlated with the severity of the dystonia, which means that these regions are directly involved in the genesis of the dystonia and do not reflect the underlying psychiatric disease (i.e., depression in all our cases).

Overall, this study shows that, irrespective of the cause of the dystonia and despite some differences between primary and secondary dystonias, the execution of a simple motor task is associated with an excess of brain activation in TD. This finding is in line with the suspected pathophysiological model of dystonia. Indeed, dystonia, as shown by electrophysiological experiments, would result from an excess of excitatory output from the thalamus to the cortical areas, a deficit of reciprocal inhibitory mechanisms at several levels of the central nervous system, and a loss of selectivity of brain activation with a lack of the somatotopy (Hallett, 2004). Furthermore, several lines of evidence suggest that surround inhibition (i.e., the inhibition of unwanted movements to perform the desired one) is impaired in dystonia (Hallett, 2004). This symptom could be mediated by the reduced influence of the indirect pathway as suggested by the reduction of dopaminergic D2 receptor density observed by PET in primary dystonia (Perlmutter *et al*, 1997). However, the pathophysiology is probably more complex because microrecordings performed during lead implantation in dystonic patients indicate a decrease in mean discharge rates in both the external globus pallidus (GPe) and the GPi, suggesting a hyperactivity of both the direct and indirect striatopallidal pathways (Vitek *et al*, 1999). The reduction of GPi activity would, in turn, lead to a reduction of thalamus inhibition and release thalamocortical output. This theory, however, has to be considered with caution, as the reduction of mean GPi discharge rate could in fact be explained by the anaesthetic drugs (Hutchinson *et al*, 2003). Furthermore, it appears that dystonia is related not only to changes in the mean rate of discharges in GPi/GPe,

but also to an irregular pattern of pallidal activity that disrupts cortical neuronal activity (Vitek *et al*, 1999). The role of dopaminergic blocking drugs is crucial in TD. Animal models of TD have shown a hypersensitivity of D1 dopaminergic receptors that could increase the activity of the direct striatopallidal pathway and inhibit the GPi (Van Kampen and Stoessl, 2000). However, the blockade by neuroleptics of D2 dopaminergic receptors induces a dysfunction of the indirect pathway that contributes to the hypoactivity of the GPi (Casey, 2004). Although simplistic, this finding could explain how the long-term intake of antidopaminergic drugs would lead to an increase in cortical neuronal activity and to the occurrence of dystonic movements. However, it must be acknowledged that functional imaging studies of the dopaminergic system have shown an increase or a normal density/affinity of the D2 dopaminergic receptors when dopaminergic drugs had been withdrawn (Blin *et al*, 1989; Andersson *et al*, 1990; Silvestri *et al*, 2000; Adler *et al*, 2002).

Consequences of Internal Globus Pallidus Stimulation

The second aspect of this study concerns the impact of GPi stimulation on the aforementioned abnormalities of the profile of cerebral activation in TD. Before discussing the PET data, it is important to note that GPi stimulation offers a dramatic improvement of the motor symptoms for all patients. When simply looking at the changes in rCBF, it is very clear that GPi stimulation induces a dramatic and global reduction of cerebral perfusion during motor execution. In particular, the primary motor cortex and the cerebellum activation are transformed from bilateral to unilateral with DBS on, and the DLPFC and inferior parietal lobe activations disappear. Interaction analysis shows more precisely that the positive effect of GPi stimulation on TD is mediated by a reduction of rCBF in the primary motor cortex and DLPFC contralateral to the movement and bilaterally in the cerebellum. This finding indicates that the lateral corticospinal tract and the projection of the cerebellum to the contralateral primary motor cortex as well as the hyperactivation of the prefrontal cortex are directly involved in the pathophysiology of TD, which is also supported by the existence of a positive correlation between the severity of the dystonia and the activation of these areas. It is noteworthy to see that GPi stimulation did not induce any increase of rCBF during motor execution, which is clearly consistent with the suspected pathophysiology of the dystonias (see above). It is also of great interest to note that GPi stimulation did not directly act through a reduction of rCBF in the prefrontal, lateral premotor, and anterior cingulate cortex, all regions that were shown to be hyperactive during motor execution in TD patients, but rather reduced primary motor cortex, DLPFC, and cerebellar activation. This could

suggest that the overactivation of the primary motor cortex, DLPFC, and cerebellum are directly responsible for the occurrence of dystonia, whereas other regions such as the prefrontal, anterior cingulate, and lateral premotor cortex could correspond to compensatory mechanisms playing an inhibitory action on the previously mentioned overactive areas.

Such a reduction of brain activation has also been observed when GPi stimulation was applied to primary dystonia (Kumar *et al*, 1999; Detante *et al*, 2004). However, in the study by Detante *et al* (2004), the reduction mostly involved the prefrontal cortex, whereas in Kumar *et al* (1999), the reduction concerned the primary motor, premotor, prefrontal cortex, and anterior cingulate. Differences in the subtype and aetiology of the dystonias may account for these discrepancies in the findings. Taken together, all these studies show that in dystonia, GPi stimulation acts through a massive reduction of excessive brain activation.

In addition, at rest, GPi stimulation produces both a reduction of rCBF in the left primary motor cortex, comparable to that seen during the motor task, and a reduction of rCBF in the SMA and anterior cingulate cortex. This is in line with the existence of abnormalities of brain activation pattern at rest, with an overactivation of the prefrontal and anterior cingulate cortex and cerebellum compared to controls. In addition, this result shows that GPi stimulation induces a global reduction of brain activation restricted not only to motor execution areas. It also suggests (as previously noted in other studies of Parkinson's disease) that the effects of DBS, whatever the target (subthalamic nucleus or GPi), are clearly task-dependent and different (sometimes opposite) at rest and during motor execution (Detante *et al*, 2004; Limousin *et al*, 1997; Payoux *et al*, 1997). This finding has been particularly well illustrated in a study of primary dystonia (Detante *et al*, 2004). Indeed, these authors showed that GPi stimulation increased the rCBF at rest in the DLPFC and thalamus, but reduced the rCBF in the same regions during motor execution. In this study, such a discrepancy was not present, but we did find an opposite action of GPi stimulation on the cerebellum at rest and during motor execution.

To account for these complex (and sometimes opposite) effects, it has been proposed that the changes of brain perfusion induced by DBS are task-specific and depend on the particular networks engaged in specific tasks. This theory is consistent with the results of animal studies suggesting that striatal-frontal connectivity as well as functional connectivity between different nuclei of the basal ganglia depend on brain state, such as whether the animal is at rest or active (Magill *et al*, 2004). Moreover, on the basis of a review of the evidence from a variety of sources, it has been hypothesized that the mechanism of DBS action is not simply inhibitory or excitatory but depends on more

complex modifications of activity in a pathologic network (McIntyre *et al*, 2004). In dystonia, several studies suggest that GPi stimulation could replace the abnormal and irregular electrophysiological pattern of GPi neuron discharges by a much more regular one that would, in turn, reduce the excess of cortical activation.

To conclude, this study represents one of the first conclusive attempts at a better understanding of TD pathophysiology. Consistent with other forms of dystonia, the occurrence of abnormal movements is explained by an excess of the profile of brain activation, reflecting a loss of selectivity during motor execution. Furthermore, the improvement of TD by GPi stimulation is explained by a major reduction of this brain overflow.

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Disclosure

The authors state no conflict of interest.

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