

Subthalamic nucleus stimulation and dysarthria in Parkinson's disease: a PET study

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Summary

In Parkinson's disease, functional imaging studies during limb motor tasks reveal cerebral activation abnormalities that can be reversed by subthalamic nucleus (STN) stimulation. The effect of STN stimulation on parkinsonian dysarthria has not, however, been investigated using PET. The aim of the present study was to evaluate the effect of STN stimulation on regional cerebral blood flow (rCBF) during speech production and silent articulation in patients with Parkinson's disease. Ten Parkinson's disease patients surgically implanted bilaterally in the STN and with significant improvement of their dysarthria induced by STN stimulation were included. Ten healthy control subjects also participated in this study. Control subjects performed six sessions of [¹⁵O]H₂O–PET scanning corresponding to three duplicated conditions externally cued by an auditory signal. The conditions were: (i) rest; (ii) production of a short, simple sentence; and (iii) silent articulation of the same sentence. Parkinson's disease patients carried out the six PET sessions twice, i.e., in the ON and OFF STN stimulation states. PET data analysis was performed using statistical parametric mapping (SPM99). In control subjects, speech production (SP) compared with rest was associated with increased rCBF bilaterally in the primary motor cortex (M1) corresponding to the orofacial somatotopy, the supplementary motor area (SMA), the associative auditory cortex and the cere-

bellar hemispheres. Silent articulation (SA) compared with rest induced a bilateral rCBF increase restricted to the orofacial M1 and cerebellar hemispheres. In Parkinson's disease patients in the OFF stimulation condition, during both SP and SA there was a lack of activation in the right orofacial M1 and in the cerebellum, abnormal increased rCBF in the right superior premotor cortex, and overactivation of the SMA. There was also an abnormal, increased rCBF in the dorsolateral prefrontal cortex (DLPFC) only during SP and increased rCBF in the left insula only during SA. In Parkinson's disease patients ON stimulation, for both SP and SA the activation pattern appeared similar to that in control subjects. In conclusion, our results suggest that parkinsonian dysarthria is associated with altered recruitment of the main motor cerebral regions (orofacial M1, cerebellum), and increased involvement of the premotor and prefrontal cortices (DLPFC, SMA, superior premotor cortex). These abnormal activations are different from those reported during hand motor tasks. They could be a compensatory mechanism, but might also arise directly as part of the pathophysiology of Parkinson's disease. STN stimulation tends to reverse these abnormal activations, which is consistent with the observed improvement of Parkinson's disease dysarthria.

Keywords: Parkinson's disease; subthalamic nucleus stimulation; speech production; [¹⁵O]H₂O; PET

Abbreviations: BA = Brodmann area; DLPFC = dorsolateral prefrontal cortex; MT = movement time; R = rest; rCBF = regional cerebral blood flow; RI = relative intensity; RT = reaction time; SA = silent articulation; SMA = supplementary motor area; SP = speech production; STN = subthalamic nucleus

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Introduction

One of the frequent signs of Parkinson's disease is the appearance of dysarthric speech in the later stages of the disease; approximately 70% of Parkinson's disease patients have speech difficulties (Mutch *et al.*, 1986; Milcoch, 1987; Ramig *et al.*, 1994). The classic description of parkinsonian dysarthria, given by Darley and colleagues, is 'monotony of pitch, monotony of loudness, reduced stress, short phrases, variable rate, short rushes of speech, and imprecise consonants' (Darley *et al.*, 1975). Pharmacological and surgical treatments of Parkinson's disease, generally effective for the limb motor dysfunctions, have variable effects on dysarthria (Klawans, 1986; Laitinen *et al.*, 1992; Stracciari *et al.*, 1993; Gross *et al.*, 1997; Gentil *et al.*, 1998; Schulz *et al.*, 2000). It has already been shown that stimulation of the subthalamic nucleus (STN) has a beneficial impact on parkinsonian dysarthria, even if this effect is less pronounced than that on limb movements (Limousin *et al.*, 1998; Pinto *et al.*, 2003). Indeed, phonatory (Dromey *et al.*, 2000; Gentil *et al.*, 2001, 2003) and articulatory (Gentil *et al.*, 1999, 2003; Pinto *et al.*, 2003) parameters of speech are improved by STN stimulation.

In normal subjects, speech articulation and vocalization were investigated separately during different conditions using PET and [¹⁵O]H₂O (Murphy *et al.*, 1997). Regions implicated specifically in the motor component of speech were the inferior part of the primary sensorimotor cortex (M1) bilaterally, the left and right cerebellum and the right thalamus and caudate nucleus. In another PET study, the activated regions associated with articulation were the left anterior insula, lateral premotor cortex and basal ganglia (Wise *et al.*, 1999). The authors suggested that the left anterior insula plays a major role in the planning and accuracy of speech movements. In addition, speech articulation in stroke patients specifically affected by a disorder of the motor planning of articulatory movements, speech apraxia, was studied by MRI and CT scans (Dronkers, 1996). All the patients had brain lesions that included a discrete region of the left precentral gyrus of the insula, which suggests the role of this area in the motor planning of speech (Donnan *et al.*, 1997). However, few functional imaging studies have addressed dysarthric speech resulting from cerebral lesions (Selnes *et al.*, 1996; Okuda *et al.*, 1999) or Parkinson's disease (Liotti *et al.*, 2003).

Numerous PET activation studies have analysed the effect of STN stimulation during limb motor tasks (Limousin *et al.*, 1997; Ceballos-Baumann *et al.*, 1999; Thobois *et al.*, 2002). To our knowledge, no PET study has explored, in Parkinson's disease patients treated by bilateral STN stimulation, the anatomical brain areas associated with dysarthria. Therefore, by means of PET and [¹⁵O]H₂O, we measured the regional cerebral blood flow (rCBF) profiles associated with speech production (SP) and silent articulation (SA) in normal subjects and in Parkinson's disease patients treated with bilateral STN stimulation. The reason we investigated both SP and SA was to delineate the pure articulatory component

(SA) from global speech (SP). The aim of the study was: (i) to assess the rCBF changes induced by the disease by comparing the results obtained in Parkinson's disease patients during the OFF stimulation condition with that of control subjects; and (ii) to identify the rCBF modifications related to electrical stimulation of the STN. We hypothesized that: (i) brain activation changes induced by dysarthria in Parkinson's disease should essentially involve the most important areas implicated in the motor component of speech, i.e. the orofacial M1, insula, basal ganglia and cerebellum; accordingly, the major rCBF alterations found in SP should also be displayed in SA; and (ii) part of these changes should be reversed by STN stimulation.

Patients, subjects and methods

Parkinson's disease patients and control subjects

Ten Parkinson's disease patients (mean age 53.7 ± 4.7 years; mean duration of Parkinson's disease 16.8 ± 3.3 years; eight males and two females) and 10 voluntary control subjects (mean age 53.6 ± 5.3 years; seven males and three females) participated in this study. They were all right-handed (Edinburgh test, $\geq 80\%$) and native speakers of French.

The control subjects had no history of current or past neurological disease. The Parkinson's disease patients fulfilled the UK Parkinson's Disease Brain Bank criteria for idiopathic Parkinson's disease (Gibb and Lees, 1988). They suffered from akinetic-rigid symptoms and were treated by bilateral STN stimulation for at least 1 year (range 13–47 months). The surgical procedure was performed as previously described (Limousin *et al.*, 1995; Limousin *et al.*, 1998). The electrical stimulation parameters used one contact of the electrodes as the cathode, a pulse width of 60 μ s, a voltage range from 2.2 to 3.4 volts and a frequency range from 130 to 145 Hz. Without medication, Parkinson's disease patients' dysarthria was significantly improved by STN stimulation. The mean score \pm SD of item 18 of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn *et al.*, 1987) was 1.9 ± 0.6 without stimulation and 0.7 ± 0.7 with stimulation.

The study was performed after approval by the Grenoble University Hospital Ethics Committee (Grenoble, France). All control subjects and patients participated after the nature of the procedure had been fully explained. They signed an informed consent form according to the Declaration of Helsinki.

Peripheral evaluations

Clinical and biomechanical evaluations were carried out prior to the PET session, generally the day before, in order to assess the effect of STN stimulation on parkinsonian signs and some aspects of the motor component of speech production. While patients were off medication for at least 12 h, the two

investigations were performed with (ON) and without (OFF) STN stimulation; this latter condition was carried out 30 min after stopping the stimulators. Control subjects were also asked to participate in the biomechanical investigation.

Clinical evaluation

Assessment of motor signs was carried out by means of Part III (items 18–31) of the UPDRS. On this scale, the perceptual estimation of speech corresponded to item 18 with the following scoring: 0 for normal; 1 for slight loss of expression, diction and/or volume; 2 for monotone speech, slurred but understandable, moderately impaired; 3 for a marked impairment and difficulty in understanding the patient; and 4 for unintelligible.

Biomechanical evaluation

To estimate the effect of STN stimulation on the articulatory component of speech, we measured forces of the articulatory organs following a procedure described previously (Pinto *et al.*, 2003). Force transducers (Neuro Logic, Bloomington, IN, USA) were used to measure compression forces generated by the upper lip, lower lip and tongue (Barlow and Abbs, 1983). Control subjects and Parkinson's disease patients were asked to generate forces from a baseline as rapidly and as accurately as possible to reach different force targets (0.25 and 2 N). Two maximal voluntary forces (MVF) were also measured for each articulatory organ. We considered three parameters associated with parkinsonian signs: impairment of reaction time (RT) for akinesia, impairment of movement time (MT) for bradykinesia, and alteration of the MVF for hypokinesia.

Statistical analysis

For the clinical evaluation, a parametric paired Student's *t* test ($P < 0.05$) was used to compare the scores obtained in the ON and OFF stimulation conditions. Concerning the force measurements, we used a non-parametric Mann–Whitney *U* test ($P < 0.05$) to compare the Parkinson's disease patients in the ON and OFF stimulation conditions and the control subjects.

PET scanning procedure

Subjects were positioned supine on the PET scanner bed, with the eyes closed. The head was maintained in a fixed position using a thermoformed mask. Control of the 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 obtained using a Siemens CTI HR+ tomograph (CTI/Siemens, Knoxville, TN, USA) in 3D mode. Transmission data were acquired using rotating sources filled with $^{68}\text{Ge}/^{68}\text{Ga}$. Images were reconstructed by 3D-filtered back-projection (Hannig 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 333 MBq of ^{15}O through a forearm catheter placed into the brachial vein. The integrated counts were collected for 90 s, starting 20 s after the injection. For data analysis, we only considered the 60 s corresponding to the maximum radioactivity. A 10-min interval was necessary between each experimental condition to achieve adequate radioactivity decay.

Activation tasks

In Parkinson's disease patients, STN stimulation was turned OFF or maintained ON 30 min before the beginning of the first PET sessions. Half of the patients began the examination in the ON stimulation condition, and the other half in the OFF stimulation condition. When the stimulation was modified for the second PET sessions, we waited 30 min before beginning the new series of PET sessions. All control subjects and Parkinson's disease patients were scanned while executing predefined tasks. They had been trained in the speech production tasks by performing them several times the day before the PET session, to achieve automatic generation of the task, and thus minimize other aspects of speech, such as language processing beyond articulation.

Three randomized conditions of 70 s each were performed: (i) rest (R): subjects remained still, silently listening to an auditory signal (frequency 1000 Hz, length 100 ms) occurring every 7 s; (ii) speech production (SP): subjects had to pronounce the French sentence 'Bébé donne ta poupée' ('Baby, give [me] your doll') after each auditory signal, i.e. 10 times; (iii) silent articulation (SA): subjects were asked to produce the articulatory movements corresponding to the sentence 'Bébé donne ta poupée' after each auditory signal, i.e. 10 times. Each condition was duplicated and performed by Parkinson's disease patients either in the ON or the OFF stimulation condition. Thus, six PET scans corresponding to six ^{15}O injections were carried out in control subjects and 12 in Parkinson's disease patients who performed the session in ON and in OFF stimulation conditions. The conditions corresponded to different speech tasks that allowed separation of articulatory movements from global speech production. The sentence 'Bébé donne ta poupée' was chosen to represent a variety of segmental combinations, bilabial and dental occlusives, voiced and soundless, associated with different vowels. We analysed SP in condition (ii) and SA in condition (iii), in which the task focused on labial and mandibular movements (speech articulation).

Acoustical recordings during the PET sessions

To ensure all experimental conditions were performed satisfactorily, a video recording was made. An acoustic recording was also carried out during each PET session to

Table 1 Motor and speech assessments for the 10 Parkinson's disease patients in UPDRS Part III

Patient	Total motor score, items 18–31 (max. score 108)		Akinesia, items 21–26 (max. score 32)		Axial score, items 18, 22 (neck), 27–30 (max. score 24)		Speech, item 18 (max. score 4)	
	ON	OFF	ON	OFF	ON	OFF	ON	OFF
1	4	55	1	25	2	11	0	1
2	7	24	1	6	3	8		2
3	14	36	4	10	6	13	1	2
4	13	41	1	14	6	9	1	2
5	12	60	3	22	1	10	1	2
6	5	42	0	16	0	8	0	1
7	21	46	11	21	3	12	2	3
8	11	48	4	26	3	12	2	3
9	14	59	3	21	2	9	0	2
10	8	49	2	14	1	10	0	2
Mean ± SD	10.9 ± 5.1	46.0 ± 11.0	3.0 ± 3.1	17.5 ± 6.6	2.7 ± 2.0	9.7 ± 1.9	0.7 ± 0.7	1.9 ± 0.6
Improvement between OFF and ON stimulation (%)		76*		83*		72*		63*

All data are off-medication UPDRS scores. * $P < 0.001$ (paired Student's t test), ON versus OFF stimulation.

monitor speech production and to confirm that no sound was produced during conditions (i) (R) and (iii) (SA). Recordings were made using a head-worn microphone (ATM 71; Audio Technica, Stow, OH, USA), and the voices of the control subjects and the Parkinson's disease patients were recorded at a sampling frequency of 16 kHz using the software program Phonédit (SQ Lab, Aix-en-Provence, France).

These acoustical recordings allowed the analysis of the RT between the auditory signal and the beginning of the sentence production, the completion time (CT) that was needed to produce the sentence, the relative intensity (RI) of speech produced during pronunciation of the sentence, and the pause/sound ratio, which corresponded to the proportion of silence during sentence production. A parametric paired Student's t test ($P < 0.001$) was used to compare the measurements of these parameters between the Parkinson's disease patients in the ON and OFF stimulation conditions and the control subjects.

PET data and statistical analysis

Image analysis was performed in MATLAB 5.3 (MathWorks, Natick, MA, USA) using the software SPM99 (Wellcome Department of Cognitive Neurology, London, UK) for statistical parametric mapping (Friston *et al.*, 1995). Individual PET scans were oriented parallel along the intercommissural line using an averaged image from each subject, and then normalized into a standard stereotactic space (Talairach and Tournoux, 1988). Images were smoothed using an isotropic 16-mm kernel to account for variation in gyral anatomy and individual variability in structure–function relationships, and to improve the signal/noise ratio. Global differences in cerebral blood flow 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. Only regions which exceeded a threshold of $P_{\text{uncorrected}} < 0.05$ (Z score > 3.1) were considered significant.

Intra-group analysis

Contrasts $(SP - R)_{\text{control}}$, $(SP - R)_{\text{OFF stimulation}}$ and $(SP - R)_{\text{ON stimulation}}$ assessed the rCBF profiles of speech production compared with rest in, respectively, control subjects and Parkinson's disease patients in the OFF and ON stimulation conditions of the STN [Z scores > 4.0 ; minimum cluster size (k) = 20 voxels]. Accordingly, contrasts $(SA - R)_{\text{control}}$, $(SA - R)_{\text{OFF stimulation}}$ and $(SA - R)_{\text{ON stimulation}}$ assessed the rCBF profiles of silent articulation compared with rest (Z scores > 4.0 ; $k \geq 20$). We assessed the main effect of STN stimulation on speech production and silent articulation in Parkinson's disease patients by the following interactions (Z scores > 3.1 ; $k \geq 20$): $[(SP - R)_{\text{ON stimulation}} - (SP - R)_{\text{OFF stimulation}}]$, $[(SP - R)_{\text{OFF stimulation}} - (SP - R)_{\text{ON stimulation}}]$, $[(SA - R)_{\text{ON stimulation}} - (SA - R)_{\text{OFF stimulation}}]$ and $[(SA - R)_{\text{OFF stimulation}} - (SA - R)_{\text{ON stimulation}}]$.

Between-group analysis

To compare the changes in the rCBF profiles associated with speech production and silent articulation induced by Parkinson's disease, we carried out the following interactions (Z scores > 3.1 ; $k \geq 10$): $[(SP - R)_{\text{OFF stimulation}} - (SP - R)_{\text{control}}]$, $[(SP - R)_{\text{control}} - (SP - R)_{\text{OFF stimulation}}]$, $[(SA - R)_{\text{OFF stimulation}} - (SA - R)_{\text{control}}]$ and $[(SA - R)_{\text{control}} - (SA - R)_{\text{OFF stimulation}}]$.

Table 2 Force parameters of the articulatory organs for all control subjects and Parkinson's disease patients

Subject group	Upper lip			Lower lip			Tongue					
	RT (ms)	MT, 0.25 N (ms)	MT, 1 N (ms)	MVF (N)	RT (ms)	MT, 0.25 N (ms)	MT, 1 N (ms)	MVF (N)	RT (ms)	MT, 0.25 N (ms)	MT, 1 N (ms)	MVF (N)
Controls	339 ± 211	559 ± 264	483 ± 235	5.9 ± 2.4	435 ± 239	527 ± 295	524 ± 233	15.4 ± 7	402 ± 163	561 ± 373	486 ± 252	6.5 ± 3.6
PD, ON	359 ± 176	636 ± 362	528 ± 258	5.6 ± 1.5	430 ± 180	656 ± 355	558 ± 274	12.3 ± 3.2	405 ± 212	586 ± 212	423 ± 216	8.4 ± 3.7
PD, OFF	480 ± 243*	762 ± 358	618 ± 256*	3.3 ± 2.0*	518 ± 290*	640 ± 420	772 ± 442*	6.2 ± 3.5*	477 ± 295	631 ± 415	593 ± 299*	4.8 ± 2.2*

All data are off-medication measurements (mean ± SD). * $P < 0.001$ (Mann-Whitney U test), ON versus OFF stimulation and control subjects versus Parkinson's disease patients OFF stimulation. MT, 0.25 N and MT, 1 N = movement times at 0.25 and 1 N; MVF = maximum voluntary force; RT = reaction time; PD = Parkinson's disease; ON = ON stimulation; OFF = OFF stimulation.

Results

Peripheral evaluations of STN stimulation effect on parkinsonian signs and speech

The UPDRS motor scores were significantly improved by more than 72% with STN stimulation. Item 18 of the UPDRS related to dysarthria was also improved, but to a lesser extent (Table 1).

Significant differences for all articulatory organ force parameters were noted both between control subjects and Parkinson's disease patients in the OFF stimulation condition, and between the ON and OFF stimulation conditions, except for the MT at 0.25 N for all the articulatory organs and the RT for the tongue. There was no significant difference between control subjects and Parkinson's disease patients ON stimulation in force parameters, except for the RT of the upper lip and the MT at 0.25 N of the lower lip (Table 2).

Analysis of the acoustic recordings revealed a significant reduction of the RI in Parkinson's disease patients OFF stimulation when compared with the ON stimulation condition and control subjects. However, for temporal parameters (RT and CT) and the pause/sound ratio, we did not observe any significant difference between Parkinson's disease patients and control subjects or between the ON and OFF stimulation conditions (Table 3).

Brain activation profiles in control subjects

SP displayed a significant rCBF increase bilaterally in the inferior primary motor cortex (M1), corresponding to the orofacial somatotopy [Brodmann area (BA) 4], SMA (BA 6), associative (BA 21/22) auditory cortex and cerebellar hemispheres (Fig. 1A and Table 4A). For SA, bilateral rCBF increase was restricted to the orofacial M1 cortex and cerebellar hemispheres (Fig. 2A and Table 5A).

Brain activation profiles in Parkinson's disease patients without STN stimulation

For SP, increased rCBF was displayed in the left orofacial M1, but the activation volume was less than that observed in control subjects. Moreover, no activation was found in the right orofacial M1 or in the cerebellum. In addition, increased rCBF was observed in the right superior premotor cortex (BA 6), SMA, and bilateral primary (BA 42) and associative auditory cortex (Fig. 1B and Table 4B). For SA, the pattern of activation was slightly different, with increased rCBF in the left orofacial M1 cortex, right superior premotor cortex, SMA and left insula (Fig. 2B and Table 5B).

Brain activation profiles in Parkinson's disease patients with STN stimulation

For SP, there was bilateral increased rCBF in the orofacial M1, SMA, primary and associative auditory cortex, and cerebellar hemispheres (Fig. 1C and Table 4C). During SA,

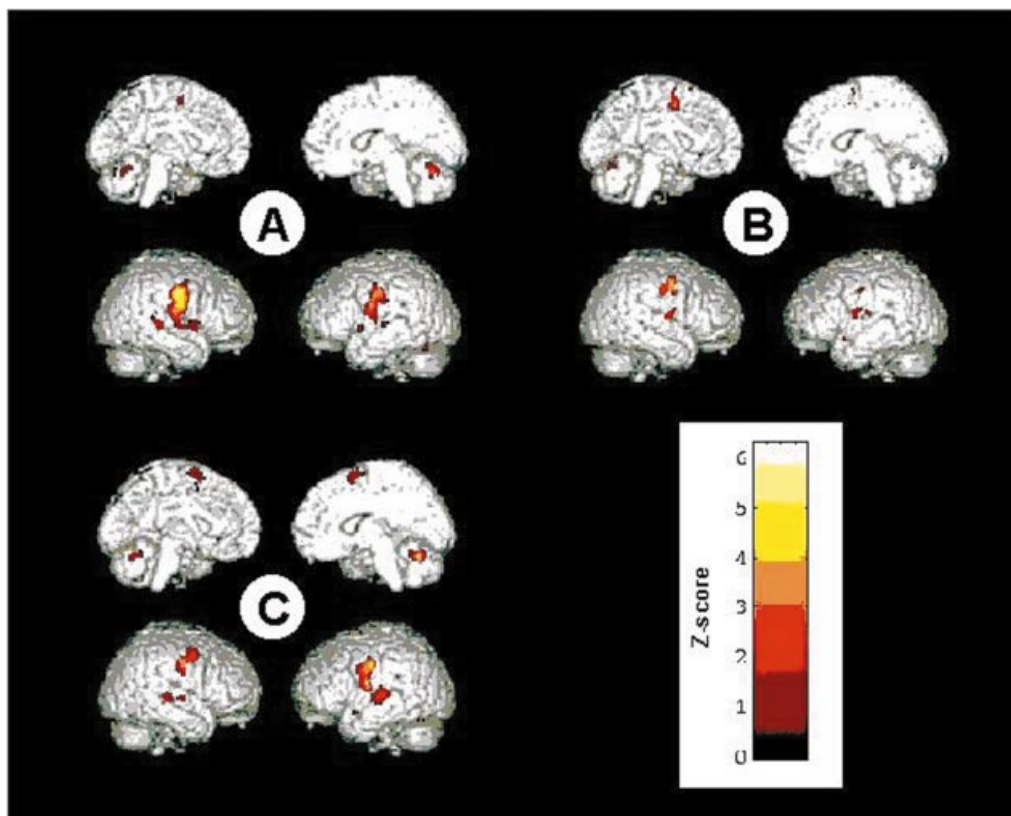


Fig. 1 Brain activation profiles associated with speech production in control subjects (A) and in Parkinson's disease patients in the OFF (B) and ON (C) bilateral STN stimulation conditions. Z scores > 4.0 correspond to corrected *P* values < 0.05.

Table 3 Parameters of the acoustic recordings for all the control subjects and Parkinson's disease patients

	RT (ms)	CT (ms)	RI (dB)	P/S ratio (%)
Control subjects	616 ± 109	1713 ± 403	67.5 ± 3.9	79.9 ± 3.1
PD patients, OFF stimulation	632 ± 206	1665 ± 446	65.5 ± 2.9*	79.0 ± 4.9
PD patients, ON stimulation	616 ± 109	1728 ± 491	67.0 ± 2.7	79.2 ± 4.3

All data are off-medication measurements (mean ± SD). * *P* < 0.001 (paired Student's *t* test), ON versus OFF stimulation conditions and control subjects versus Parkinson's disease patients in OFF stimulation condition. CT = completion time; PD = Parkinson's disease; MT, 0.25 N and MT, 1 N = movement times at 0.25 and 1 N; MVF = maximal voluntary force; P/S ratio = pause/sound ratio; RI = relative intensity; RT = reaction time.

rCBF increased bilaterally in the orofacial M1 cortex, SMA and cerebellar hemispheres (Fig. 2C and Table 5C). As mentioned above, the differences in terms of activation volume exemplify the rCBF changes observed in the present STN stimulation condition.

Comparison between control subjects and Parkinson's disease patients in OFF stimulation condition

Compared with control subjects, the main changes in rCBF in Parkinson's disease patients were: (i) overactivation of the dorsolateral prefrontal cortex (DLPFC; BA 8/9/10) during SP (Table 6A); (ii) overactivation of the rostral SMA during both SP and SA (Table 6A); (iii) underactivation of the right postcentral gyrus (BA 40) and inferior temporal gyrus (BA

21) during SP (Table 6B); and (iv) underactivation of the right orofacial M1, BA 37 and BA 19 during SA (Table 6B).

Effect of STN stimulation in Parkinson's disease patients

The main rCBF changes induced by STN stimulation were, for SP, increased activation in the left inferior temporal gyrus (BA 20/38) and decreased activation in left medial SMA (Table 7A and B). For SA, increased activation was noted in the parietal (BA 40), mid-temporal (BA 37) and hippocampal regions (Table 7A).

Discussion

The main findings of this study during SP and SA in patients with Parkinson's disease compared with normal subjects are: (i) in the OFF stimulation condition, a lack of activation of the

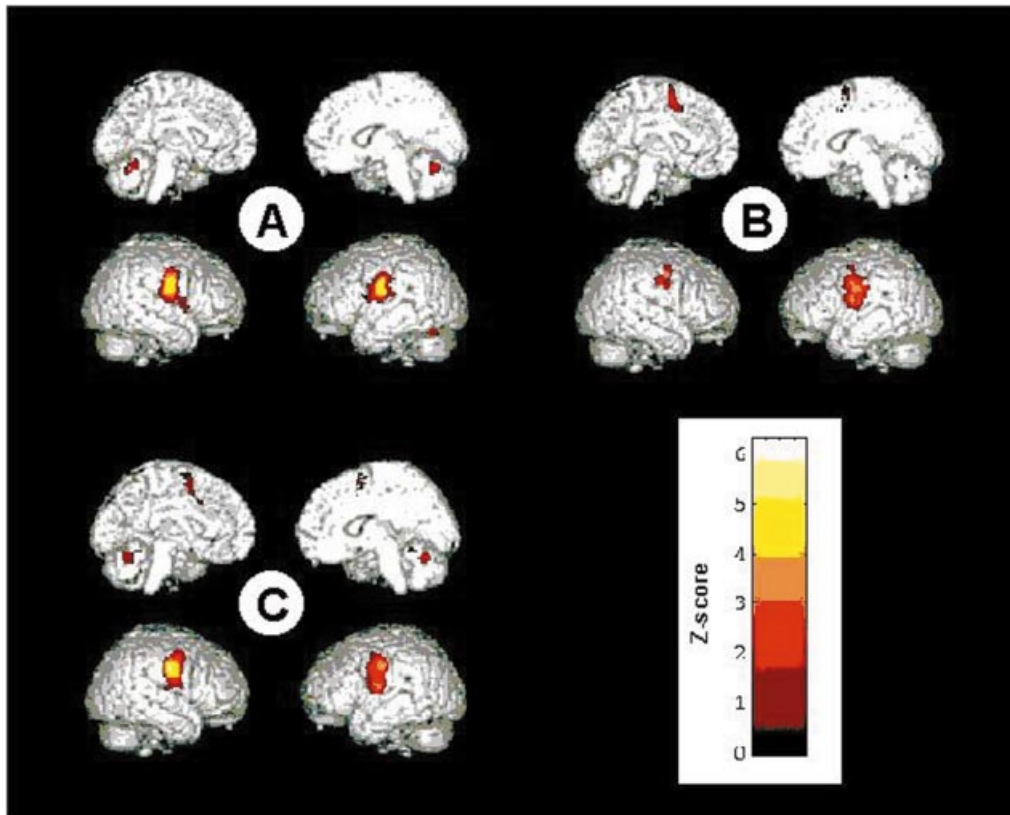


Fig. 2 Brain activation profiles associated with silent articulation in control subjects (A) and in Parkinson's disease patients in the OFF (B) and ON (C) bilateral STN stimulation conditions. Z scores > 4.0 correspond to corrected *P* values < 0.05.

right orofacial M1 cortex and the cerebellum, and enhanced activation of the SMA, DLPFC, the right superior premotor cortex and the left insula; (ii) in the ON stimulation condition, an activation pattern similar to that of control subjects, notably for the orofacial M1, cerebellum, and SMA. The speech score of the UPDRS and measurements of articulatory organ forces were improved by STN stimulation, as previously reported (Gentil *et al.*, 1999, 2003; Pinto *et al.*, 2003). Analysis of the relative intensity during the PET sessions showed a substantial hypophonia of the Parkinson's disease patients' dysarthric speech in the OFF stimulation condition, significantly improved by STN stimulation. In order to provide some physiological interpretations of regional functions altered by Parkinson's disease and restored by STN stimulation, the main aspects of the discussion will be organized by brain areas.

Primary motor cortex

This study confirms the major role of the right and left orofacial M1 cortex in both SP and SA in normal subjects (Murphy *et al.*, 1997; Wise *et al.*, 1999). This is in keeping with the bilateral recruitment of the orofacial musculature (Lotze *et al.*, 2000), clearly described by Penfield and Rasmussen in the early fifties (Penfield and Rasmussen, 1950). The activation area was quite large and also involved a somatotopic region corresponding to the trunk which is

associated with the voluntary control of breathing (Murphy *et al.*, 1997). In contrast, Broca's area was not activated, as previously observed (Murphy *et al.*, 1997; Wise *et al.*, 1999). This lack of activation was not surprising considering the automatic nature of the experimental paradigm we introduced through prelearning of the task, as well as the relative simplicity of the speech task completion. Our findings confirm that the experimental paradigm we used in this work was adequately designed to study SP and SA, and not other aspects of speech, such as language. Conversely, more complex language tasks are required in order to display activation of Broca's area (Price *et al.*, 1996; Bookheimer *et al.*, 2000; Lotze *et al.*, 2000).

In both SP and SA conditions, there was diminished activation of the orofacial primary cortex in Parkinson's disease patients in the OFF stimulation condition, particularly on the right, compared with the normal pattern displayed in control subjects. This is in keeping with a reduction of orofacial movements and the patients' speech impairment. Interestingly, this activation pattern contrasts with that reported during hand joystick movements, where bilateral overactivation of the primary motor cortex and lateral premotor cortex is found (Rascoll *et al.*, 1997; Samuel *et al.*, 1997; Sabatini *et al.*, 2000; Thobois *et al.*, 2000; Haslinger *et al.*, 2001). These findings suggest that speech tasks require a motor programme different from that employed in lateralized and freely selected hand movements, and indicates

Table 4 Sites of activation during speech production in control subjects (A) and in Parkinson's disease patients in the OFF (B) and ON (C) bilateral STN stimulation conditions

Cerebral areas	Laterality	BA	(A) Control subjects			(B) PD patients, OFF stimulation			(C) PD patients, ON stimulation		
			x, y, z	Z score	k	x, y, z	Z score	k	x, y, z	Z score	k
Orofacial M1	R	4	56, -12, 22	6.22	1543	-	-	-	62, -10, 30	5.80	293
	L	4	-50, -14, 34	5.78	777	-62, -6, 16	5.07	181	-56, -12, 28	5.54	825
Superior premotor cortex	R	6	-	-	-	58, -2, 52	5.48	100	-	-	-
	L	6	-	-	-	-	-	-	-	-	-
SMA	Medial	6	-8, -2, 54	5.38	57	-8, 0, 56	5.37	154	0, 2, 70	5.00	213
Cerebellum	R	Hemisphere	16, -66, -20	5.49	210	-	-	-	12, -62, -24	5.70	315
	L	Hemisphere	-18, -64, -24	4.75	130	-	-	-	-16, -64, -22	4.81	103
Auditory cortex	R	21/22	54, -32, 2	4.67	135	52, -26, 6	4.41	60	56, -28, 4	5.09	198
		42	-	-	-	68, -6, 14	4.87	72	62, -18, -2	4.12	-
	L	21/22	-54, 4, -2	4.37	21	-54, 8, -14	4.21	22	-70, -24, 6	5.78	231
		42	-	-	-	-54, -12, 6	4.41	24	-54, -12, 12	4.45	-

Z scores > 4.0 correspond to corrected *P* values < 0.05. PD = Parkinson's disease; BA = Brodmann area; *k* = cluster size (number of voxels); *x*, *y*, *z* = mediolateral, rostrocaudal and dorsoventral Talairach coordinates.

Table 5 Sites of activation during silent articulation in control subjects (A) and in Parkinson's disease patients in the OFF (B) and ON (C) bilateral STN stimulation conditions

Cerebral areas	Laterality	BA	(A) Control subjects			(B) PD patients, OFF stimulation			(C) PD patients, ON stimulation		
			x, y, z	Z score	k	x, y, z	Z score	k	x, y, z	Z score	k
Orofacial M1	R	4	56, -12, 22	5.91	1260	-	-	-	60, -6, 30	5.50	985
	L	4	-60, -8, 24	5.59	1122	-62, -6, 18	5.71	1057	-54, -14, 40	5.41	877
Superior premotor cortex	R	6	-	-	-	58, -2, 52	5.57	328	-	-	-
	L	6	-	-	-	-	-	-	-	-	-
SMA	medial	6	-	-	-	8, 2, 54	5.77	241	-4, 6, 54	4.13	34
Cerebellum	R	hemisphere	18, -68, -22	5.57	139	-	-	-	12, -62, -24	4.69	176
	L	hemisphere	-18, -64, -24	5.13	231	-	-	-	-14, -62, -22	5.40	134
Insula	L	-	-	-	-	-32, 24, 6	4.45	26	-	-	-

Z scores > 4.0 correspond to corrected *P* values < 0.05. PD = parkinson's disease; BA = Brodmann area; *k* = cluster size (number of voxels); *x*, *y*, *z* = mediolateral, rostrocaudal and dorsoventral Talairach coordinates.

Table 6 Comparison of activation profile between control subjects and Parkinson's disease patients in OFF stimulation condition during speech production and silent articulation

Localization	Laterality	Brodmann area	<i>x, y, z</i> coordinates	Z score	<i>k</i>
(A) Increased activation in Parkinson's disease patients compared with control subjects					
Speech production					
Superior frontal gyrus (DLPFC)	R	8	22, 46, 48	3.86	16
Middle frontal gyrus (DLPFC)	L	10	-40, 54, -8	3.73	36
Rostral SMA	L	6	-4, 18, 68	3.52	13
Superior temporal gyrus	R	22	72, -34, 16	3.51	19
Middle frontal gyrus (DLPFC)	R	9	42, 18, 30	3.45	31
Silent articulation					
Rostral SMA	L	6	-6, 36, 58	4.06	75
Fusiform gyrus	L	36	-32, -42, -8	3.74	32
Rostral SMA	L	6	-8, 6, 52	3.71	37
(B) Decreased activation in Parkinson's disease patients compared with control subjects					
Speech production					
Postcentral gyrus	R	40	64, -18, 16	3.73	38
Inferior temporal gyrus	R	21	46, -20, -18	3.65	23
Precuneus	L	7	-6, -54, 42	3.38	12
Silent articulation					
Fusiform gyrus	R	37	42, -48, -14	3.91	41
Precuneus	L	7	-8, -66, 46	3.45	16
Middle occipital gyrus	R	19	58, -66, -4	3.44	48
Inferior temporal gyrus	R	37	58, -56, -6	3.42	18
Primary M1	R	4	70, -8, 22	3.41	18

Z scores > 3.1 correspond to uncorrected *P* values < 0.05. *k* = cluster size (number of voxels); *x, y, z* = mediolateral, rostrocaudal and dorsoventral Talairach coordinates.

that these programmes seem to be differently altered in Parkinson's disease.

In Parkinson's disease patients, STN stimulation produces bilateral increased activation of the orofacial M1 cortex in both SP and SA conditions. Thus the clinical, acoustic and biomechanical improvements observed in Parkinson's disease patients' dysarthria are associated with the restored activation of one of the major areas involved in speech. These findings contrast with the reduction of ipsilateral M1 activation induced by STN stimulation during unilateral hand movement (Thobois *et al.*, 2002). This provides further arguments for the existence of two separate motor programmes involved in speech and limb movements, differentially influenced by STN stimulation.

Cerebellum

In control subjects, the bilateral activation of the cerebellar hemispheres observed in our study during SP and SA is concordant with previous reports (Price *et al.*, 1996; Murphy *et al.*, 1997; Wise *et al.*, 1999; Bookheimer *et al.*, 2000). Indeed, the cerebellum plays an important role in the motor organization of speech production (Ackermann *et al.*, 1997), particularly in the spatial and temporal adjustment of the different articulatory organs (Gentil, 1990). Based on clinical and experimental findings, its role in the control of speech has been well established, as has its possible involvement in some cognitive aspects of speech (Ackermann *et al.*, 1998). The crucial role of the cerebellum in speech production is

supported by experimental animal findings which show the relationship between thalamic afferents arising from the cerebellum and the globus pallidus, forming projections to M1 cortex and SMA (Rouiller *et al.*, 1994; Sakai *et al.*, 2000, 2002).

In a recent study performed in stuttering patients, a transient increase in cerebellar activation was observed during oral and silent reading after an intensive fluency treatment programme (De Nil *et al.*, 2001). This activation returned to normal 1 year after treatment. The authors hypothesized that, shortly after treatment, stuttering patients generated a substantial speech effort, leading to an increase in cerebellar activation. After a 1-year follow-up, speech production became more automatic, resulting in a less cerebellar activation. In our study, the cerebellar under-activation we observed for Parkinson's disease patients in the OFF stimulation condition seems to be more likely associated with the hypokinetic movements of the dysarthric speech. The cerebellar activation was restored in Parkinson's disease patients by STN stimulation, in parallel with an improvement in speech production and a reduction in the effort needed to complete the task.

Superior premotor cortex

Activation of the right superior premotor cortex was observed only in the Parkinson's disease patient group in the OFF stimulation condition, for both SP and SA. This abnormal activation is in contrast with the absence of right orofacial M1

Table 7 rCBF changes in Parkinson's disease patients induced by STN stimulation during both speech production and silent articulation

Localization	Laterality	Brodmann area	x, y, z coordinates	Z score	k
(A) Increased activation induced by STN stimulation					
Speech production					
Inferior temporal gyrus	L	20/38	-50, 0, -42	3.66	21
Silent articulation					
Supramarginal gyrus	R	40	42, -60, 32	3.58	22
Hippocampus	R	-	26, -14, -12	3.55	37
Mid-temporal gyrus	R	37	60, -58, 0	3.50	21
(B) Decreased activation induced by STN stimulation					
Speech production					
Medial frontal gyrus (SMA)	L	6	-10, -2, 48	3.84	27
Silent articulation					
None					

Z scores > 3.1 correspond to uncorrected *P* values < 0.05; *k* = cluster size (number of voxels); x, y, z = mediolateral, rostrocaudal and dorsoventral Talairach coordinates.

involvement, normally present in the control subjects. Other studies, for example in stutterers, have reported abnormal superior premotor cortex activation during speech motor tasks, which is reverted by treatment (Fox *et al.*, 1996). In addition, the superior premotor cortex has been associated with speech arrests during transcranial magnetic stimulation, indicating a potential role in speech production (Stewart *et al.*, 2001). A possible interpretation was proposed by Creutzfeldt, considering that 'speech production is subserved by several essential areas in addition to which there may exist neuronal circuits, which are widely dispersed, even to the non-dominant hemisphere' (Creutzfeldt *et al.*, 1989). Recruitment of the superior premotor cortex may reflect compensation for the reduced activation of M1. As an example, such reorganization of speech production in the motor cortex and the cerebellum has already been observed. In an fMRI study, a selective shift of the cortical representation of speech motor control to the right Rolandic cortex and the left cerebellum was found in a case of transient dysarthria following infarction of the left internal capsule (Riecker *et al.*, 2002). Interestingly, in a PET study of hand-movement tasks in Parkinson's disease, a dysfunction of the striato-mesial-frontal circuit has been suggested, which could induce the compensatory recruitment of a cerebellar-parietal-premotor circuit (Samuel *et al.*, 1997). Conversely, in our study we showed that the abnormal recruitment of the right superior premotor cortex is reverted by STN stimulation, which also normalizes the bilateral activation of the primary motor cortex. Such STN stimulation-induced disappearance of accessory motor pathways has previously been found during limb-motor tasks (Thobois *et al.*, 2002).

SMA

The motor control of speech production has been assigned to two premotor cortical areas. The pre-SMA is rostrally located, with extensive connections to the associative frontal

and parietal regions. The SMA proper is more caudal, involved in spontaneous activity of speech production, and intimately connected to the anterior cingulate gyrus (MacNeilage and Davis, 2001). These two regions are classically separated by the vertical line passing through the anterior commissure, orthogonal to the bicommissural line (Picard and Strick, 1996). Electrical stimulation mapping of the somatotopic organization of the human SMA has shown the lower part of the body represented posteriorly, head and face anteriorly, and the upper limbs between these two regions (Fried *et al.*, 1991). The authors concluded that vocalization and speech arrest, or slowing of speech, were evoked anterior to the SMA representation of the face, namely in the pre-SMA.

In our study, SMA activation was found for both control subjects and Parkinson's disease patients during SP. This activation involved both the pre-SMA and the SMA proper, and thus was not restricted to the orofacial somatotopy of the SMA. Since dysfunction or lesions of the SMA induce speech deficits (Petersen *et al.*, 1988; Baumgartner *et al.*, 1996; Krainik *et al.*, 2003), it is considered that this area is involved, at least in part, in the initiation of voluntary speech production (Murphy *et al.*, 1997).

In Parkinson's disease patients in the OFF stimulation condition, overactivation of the rostral SMA compared with control subjects was observed for both SP and SA. This is in accordance with recent studies which have shown overactivation of the SMA in Parkinson's disease patients compared with normal subjects during complex sequential motor tasks (Catalan *et al.*, 1999; Sabatini *et al.*, 2000). However, other studies concerning simple limb movement tasks in patients with Parkinson's disease have suggested underactivation of the SMA (Jenkins *et al.*, 1992; Playford *et al.*, 1992). In our study, rostral SMA overactivation in Parkinson's disease during speech could be a consequence of compensatory recruitment of that region in order to perform the complex SP tasks. Therefore, our data raise again the

question of the involvement of different motor circuits between limb (Boecker *et al.*, 1998; Remy *et al.*, 1994) and speech movements in Parkinson's disease and emphasizes the crucial role of the SMA in generating speech.

In several PET studies, STN stimulation induced increased SMA activation (Limousin *et al.*, 1997; Ceballos-Baumann *et al.*, 1999). However, decreased activation of this area in similar limb motor tasks has also been found (Thobois *et al.*, 2002). Such conflicting findings may result from the varying types of motor task used (automatic versus self-generated). In the present study, STN stimulation tended to reduce SMA activation during both SP and SA, whereas a persistent SMA activation during SA was noted. We suggest that this result could be part of a reduction of cortical recruitment induced by the stimulation, concomitantly with the improvement of dysarthria. Few functional imaging studies have investigated parkinsonian dysarthria and the effects of therapeutic intervention on this disabling symptom. To our knowledge, this is the first PET study investigating the neural correlates of the effects of STN stimulation on speech in Parkinson's disease patients. One recent report using PET explored the ability of a speech therapy, the Lee Silverman Voice Treatment (Ramig *et al.*, 2001), to modify the rCBF pattern associated with speech production in Parkinson's disease (Liotti *et al.*, 2003). One of the most important findings reported in this study was a reduction of SMA activation during the reading of a paragraph. This is in accordance with our results, although the experimental paradigm cannot be directly compared.

Dorsolateral prefrontal cortex

Abnormal DLPFC overactivation (Brodmann areas 8, 9 and 10) was found in Parkinson's disease patients in the OFF stimulation condition compared with control subjects. It is known that Parkinson's disease patients require an important involvement of frontal areas to generate automatic sequences (Schlosser *et al.*, 1998). This is also in line with the crucial role of the DLPFC in motor planning (Owen *et al.*, 1990), especially on the right (Deiber *et al.*, 1991), which implicates that its activation depends on the complexity of the tasks (Miller, 1999). This suggests that Parkinson's disease patients need more attentional resources to perform SP, due to the complexity of this function. Furthermore, the DLPFC is connected anatomically to the rostral SMA (Bates and Goldman-Rakic, 1993). This is of great interest as overactivation of the DLPFC is associated with SMA overactivation. This result is clearly different from the decreased DLPFC activation reported frequently in Parkinson's disease during limb motor tasks (Jenkins *et al.*, 1992; Playford *et al.*, 1993), and suggests that Parkinson's disease patients need a higher recruitment of the SMA/DLPFC complex than control subjects during speech production.

As previously described for the SMA, STN stimulation tends to decrease DLPFC activation during SP, concomitantly with the improvement of dysarthria. During both SP and limb motor tasks, STN stimulation restores normal DLPFC

activation. However, in the case of hand movements, STN stimulation increases the DLPFC activation (Limousin *et al.*, 1997; Ceballos-Baumann *et al.*, 1999; Thobois *et al.*, 2002), whereas during SP, STN stimulation reduces the DLPFC overactivation.

Insula

In Parkinson's disease patients in the OFF stimulation condition, the left anterior insula is activated during SA, which is not the case during the ON stimulation condition and in control subjects. During SP, we observed only a trend towards activation of the anterior insula, but this did not reach statistical significance. This finding is in accordance with the important participation of a restricted anterior region of the left insula in speech. This was demonstrated by the occurrence of speech impairment after lesion or dysfunction of this area in stroke and epileptic patients (Dronkers, 1996; Isnard *et al.*, 2000). It has been suggested that the anterior insula is associated with the motor planning aspects of speech articulatory movements (Dronkers, 1996). This hypothesis is corroborated by the present study and another report (Wise *et al.*, 1999), especially concerning the SA task. This insular activation, together with the DLPFC and SMA, reflects additional recruitments needed by the Parkinson's disease patients in order to compensate for the M1 and cerebellar underactivations previously mentioned. STN stimulation decreased this additional activation and restored a normal activation pattern.

Primary and associative auditory cortex

The observed bilateral activation of the superior temporal gyrus, especially the left one, suggests that Wernicke's area is involved in the SP task. The hypothesis is that the superior temporal gyrus is implicated in both speech perception and production. The same 'auditory representation' of words may be used for their perception and production (Hickok *et al.*, 2000; Buchsbaum *et al.*, 2001). Parkinson's disease patients in both OFF and ON stimulation conditions show additional primary auditory cortex activation bilaterally. This activation must be associated with the auditory feedback perception corresponding to speech production (McGuire *et al.*, 1996; Price *et al.*, 1996). In keeping with this interpretation, no temporal activation was noted in our study during the SA condition.

In control subjects, the lack of primary auditory cortex activation is probably due to the fact that perception of their speech production involves primarily the associative component of the auditory area. For Parkinson's disease patients, temporal activation is modulated: speech perception seems to require more auditory attention. STN stimulation does not seem to influence this additional temporal activation.

Basal ganglia

One of the unexpected results of our study was the absence of basal ganglia activation in both groups and both STN stimulation conditions. However, such activations were present in some groups and experimental conditions, but they did not reach the high statistical significance threshold we selected (data not shown). As basal ganglia activations were present in both groups and were not modified by STN stimulation, this suggests that activation of the basal ganglia may have been suppressed during between-group comparisons. It is therefore not possible to draw any conclusion about the effect of STN stimulation on basal ganglia activation during both SP and SA tasks. In future studies, a larger number of Parkinson's disease patients would be required to answer this question.

Methodological issues

Several limitations of our protocol should be addressed. First, on-line behavioural measures of speech during PET scanning were difficult to assess because of technical constraints, particularly the requirement that subjects lie supine with their eyes closed and head maintained fixed with a thermoformed mask. For this reason, we chose to carry out clinical and biomechanical evaluations of speech the day before the PET examination. To provide the on-line assessment of STN stimulation on SP and SA during the PET sessions, a simple acoustic recording was performed. Unfortunately, the gender heterogeneity, the relatively small number of subjects and the shortness of the sentence produced did not allow complete acoustical analysis, especially for the fundamental frequency.

Secondly, the interval between the STN stimulation switch-off and the PET acquisition was 30 min. This delay was enough to provide a practical off-state with the return of the main limb akinetic-rigid symptoms, but did not exclude a residual long-lasting effect of STN stimulation, especially on axial signs such as dysarthria. Temperli *et al.* (2003) recently showed that a 3–4 h delay is required to reach a baseline for axial signs. However, during PET studies it is not possible to wait for such a long time with Parkinson's disease patients. In future studies it could be interesting to compare Parkinson's disease patients chronically treated by STN stimulation with non-operated Parkinson's disease patients. This would be helpful to assess the STN stimulation effects compared with the off-state condition completely unlinked to the surgery.

Conclusions

The present study shows that speech production in Parkinson's disease is associated with specific alterations of the brain activation pattern, with underactivation of the orofacial M1 and cerebellum and overactivation of the SMA, superior premotor cortex, DLPFC and insula. The latter abnormal activations may reflect some compensatory cortical recruitment. STN stimulation reverses these activation

abnormalities, concomitantly with an improvement of dysarthria based on clinical, acoustical and biomechanical measures. Our study provides strong evidence for the existence of two different patterns of abnormal cerebral activation during limb and speech tasks in Parkinson's disease. Furthermore, the effect of STN stimulation seems also to be dependent on the nature of the motor task employed. In future studies, more complex language tasks should be considered in order to differentiate the effects of STN stimulation on the motor and cognitive components of speech.

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