Brain Networks Underlying the Clinical Effects of Long-Term Subthalamic Stimulation for Parkinson's Disease: A 4-Year Follow-up Study with rCBF SPECT

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The motor improvement derived from high-frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) in Parkinson's disease (PD) is maintained over time after surgery. The aim of the present prospective follow-up study was to assess regional cerebral blood flow (rCBF) changes related to such improvement in the long term. **Methods:** Ten PD patients with STN-DBS underwent 3 rCBF SPECT studies at rest—once preoperatively in the off-drug condition and the other 2 postoperatively in the off-drug/on-stimulation conditions at 5 ± 2 and 42 ± 7 mo. Patients were administered with Unified Parkinson Disease Rating Scale (UPDRS), Hoehn and Yahr (H&Y) scale, and Schwab and England (S&E) scale. Statistical parametric mapping was used to investigate rCBF changes during long-term STN stimulation in comparison with preoperative rCBF and the relationship between rCBF and UPDRS scores was used as a covariate of interest. **Results:** All patients showed a maximum clinical improvement during the first months after surgery and remained rather stable during further follow-up. The effect of STN-DBS from the pre- to the postoperative condition at 5 mo was to produce rCBF increases in the presupplementary motor area (pre-SMA), premotor (PMC), and dorsolateral prefrontal cortices. From the postoperative condition at 5 mo to that at 42 mo, the STN stimulation produced further rCBF increases in these frontal areas, and also in the primary motor/sensory cortices, globus pallidi, ventral lateral thalamic nuclei, cerebellum, pons, and midbrain entailing the substantia nigra ($P < 0.0001$). A correlation was detected between the improvement in motor scores and the rCBF increase in the pre-SMA and PMC ($P < 0.0001$). No correlation was present between the daily consumption of levodopa and the rCBF. **Conclusion:** Our study suggests that the long-term STN stimulation leads to improvement in neural activity in the frontal motor/associative areas. After an rCBF increase during the first months of stimulation, these regions showed a further increment in the later phase, which was accompanied by an increased activity in subcortical structures. The correlation between motor improvement and rCBF increase in higher order motor cortical areas suggests that even in the long term, as well as in the short term, the STN-DBS achieves its therapeutic benefit by restoring the activity within these cortical regions.

Key Words: Parkinson's disease; deep brain stimulation; subthalamic nucleus; SPECT

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During the last 10 y, chronic high-frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become an established therapeutic approach for the management of patients with late-stage idiopathic Parkinson's disease (PD). Results of clinical follow-up studies have shown that STN-DBS produces a robust improvement in a wide variety of motor symptoms (*1*) and that this beneficial effect is maintained for several years after surgery (*2–5*).

Despite the fact that these therapeutic benefits are produced over a long period of time, considerable debate relating to the underlying neural mechanisms still remains. Beginning with the current models of the function of the basal ganglia motor circuit (*6–8*) and the changes that occur in PD (*9,10*), the effect of STN-DBS has been currently associated with a reduction of the excessive drive of the STN to the globus pallidus pars interna (GPi) and the pars reticulata of the substantia nigra (SNr) (*11*). This reduction should decrease the tonic inhibitory influence of these structures on the thalamic nuclei, with subsequent activation of the motor cortex (*12–14*). However, due to the crucial position of the STN nucleus and its widespread connections, a more complex network has been hypothetized to be involved during long-term stimulation (*15*).

The combination of functional neuroimaging and DBS offers a powerful technique to examine the discrete effects of long-term STN stimulation on the neural system. This

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technique has been used to investigate the mechanisms underlying the clinical benefit of STN-DBS during short-term treatment. In their pioneering PET study, Limousin et al. (*16*) found that clinically effective levels of stimulation in the STN led to a greater movement-related rCBF increase in the rostral part of the presupplementary motor area (pre-SMA). In a PET study performed by Ceballos-Baumann et al. (*17*), significant movement-associated regional cerebral blood flow (rCBF) increases coupled with improvement in akinesia during STN stimulation were found in the pre-SMA and premotor cortex (PMC). Similarly, results of a PET study performed by Turner et al. (*15*) showed that the therapeutic stimulation of the STN during tracking movements increased rCBF in the primary sensorimotor, supplementary motor area (SMA), and dorsal premotor cortices. Further confirmation in another SPECT study showed that the effect of the stimulation on the entire brain volume was to significantly change rCBF in the right pre-SMA, anterior cingulate cortex, premotor cortex, and dorsolateral prefrontal cortex (DLPFC) and that the motor improvement was mainly related to changes in the function of the pre-SMA (*18*).

Although several efforts have been made to investigate the brain areas related to motor improvement during short-term treatment with STN-DBS, to our knowledge, no study has been performed to date investigating the neural mechanisms underlying the therapeutic effects in the long term. The present prospective follow-up study was designed to investigate the mechanisms underlying the beneficial effect of bilateral long-term STN-DBS. Functional neuroimaging with high-resolution SPECT and statistical parametric mapping (SPM) were used to address this issue. First, we evaluated the effects produced by the chronic bilateral STN stimulation throughout the entire brain volume from the pre- to the postoperative conditions at a mean of 5 and 42 mo follow-up. Second, we investigated which of the brain areas showing an rCBF increase during long-term STN-DBS related significantly to the improvement in motor function. Finally, the effect of daily levodopa intake on rCBF was considered.

MATERIALS AND METHODS

Patients and DBS

Ten consecutive patients with medically intractable PD who underwent DBS implantation in 1999 at our hospital were included in the study (4 women, 6 men; mean age, 64 ± 8 y; mean disease duration, 15 ± 5 y; range of disease duration, 6–22 y). The side prevalence of motor symptoms was left in 1 patient, bilateral in 2 patients, and right in 7 patients. Bilateral implantation of electrodes in the STN was performed only in the presence of clinically diagnosed idiopathic PD, as defined by the diagnostic criteria of the U.K. Parkinson's Disease Society Brain Bank (*19*), disabling motor fluctuations despite all drug therapies, an age of <70 y, normal cerebral MRI findings, and no severe dementia (as revealed by scores on the Mini-Mental State Examination). The exclusion criteria were neurologic signs suggestive of secondary forms of parkinsonism and the presence of other significant medical illnesses. Patients were evaluated only after all antiparkinsonian medications had been completely withdrawn for at least >12 h. Before scanning and while unmedicated, motor performance was assessed in all patients by means of the motor Unified Parkinson Disease Rating Scale (UPDRS). Patients were also graded according to the Hoehn and Yahr (H&Y) staging system and the Schwab and England (S&E) scale. At the time of surgery, the mean motor UPDRS, H&Y, and S&E scores were 69 ± 9.8, 3.65 ± 0.7, and 24 ± 11.7, respectively. The mean administered dose of levodopa before DBS was 1,440 ± 465 mg/d. Six patients also received dopamine receptor agonist therapy (pergolide mesylate). The procedure for bilateral implantation of STN electrodes conformed with the previously published procedure (*20*). There were no serious complications due to surgery. In all patients, continuous monopolar stimulation was applied bilaterally. Stimulator settings remained substantially stable during the course of the study. The mean values of voltage intensity, frequency stimulation, and the pulse width used at 5 and 42 mo after surgery were as follows: 2.8 ± 0.4 V (range, 2.3–3.7 V) and 2.9 ± 0.5 V (range, 2–3.7 V); 140 ± 12 Hz (range, 135–185 Hz) and 144 ± 16 Hz (range, 130–185 Hz); 85 ± 34.5 μs (range, 60–210 μs) and 93 ± 44 μs (range, 60–210 μs). Written informed consent was obtained from all subjects according to the Declaration of Helsinki. The study was approved by the Ethics Committee of our institution.

Study Design

Subjects underwent rCBF SPECT 3 times at rest: once preoperatively (T_0) in the off-drug condition at 1 d before surgery; once postoperatively in the off-drug/on-stimulation condition at 5 ± 2 mo (T_1) after surgery; and once later, in the off-drug/on-stimulation condition at 42 ± 7 mo (T_2), respectively.

SPECT Data Acquisition and Reconstruction

Each patient received an intravenous dose of ^{99m}Tc-ethyl cysteinate dimer ([ECD] bicisate, Neurolite; DuPont Merck Pharmaceutical Co.). The administered dose was 740 MBq for all scanning conditions. SPECT data were acquired 30 min after radioligand injection using a triple-head rotating γ-camera (PRISM 3000; Picker International Inc.) equipped with ultra-high-resolution fanbeam collimators. A polycarbonate head holder was used to reduce head movement during the scan. Acquisition consisted of 180 projections recorded in step-and-shoot mode over a 360° rotation arch (60 projections were acquired for each head). The angular step was 2°, and the frame time was 22.50 s per step. Acquisition was completed in 26 min. The acquisition matrix was 128 × 128, with 3.5-mm sampling. An iterative algorithm based on the ordered-subset expectation maximization method was used for data reconstruction compensating for the spatial response of the collimator (*21*). This reconstruction method allowed for an in-plane and axial resolution of 5.5–5.7 mm in full width at half maximum. Attenuation correction using Chang's method was performed for each slice by means of an attenuation coefficient of 0.11 (*22*).

Image Transformation and Data Analysis

Images were analyzed for regionally specific effects using SPM99 developed at the Wellcome Functional Imaging Laboratory (http://www.fil.ion.ucl.ac.uk/spm/) implemented in MATLAB, version 5.3 (The Mathworks, Inc.) (*23*). After conversion from Interfile into Analyze format using the ImageJ software (http://rsb.info.nih.gov./ij/), all images were spatially realigned to the first one of the series to compensate for position changes. All

brain images were then spatially transformed into the standard stereotactic space (*24*). The default spatial normalization procedure used was based on a bilinear interpolation method, involving a 12-parameter linear affine transformation and a nonlinear 3-dimensional deformation to match each scan to a generic SPECT template (*25*). A resulting voxel size of $2 \times 2 \times 2$ mm was used. The normalized images were smoothed with an isotropic 13-mm kernel.

Three sets of statistical analyses were performed. First, we examined the pattern of brain areas with rCBF changes induced by the long-term STN stimulation (main effect of condition). To address this issue, categoric comparisons between the adjusted rCBF voxel values at T_0 and T_1 and between the values at T_1 and T_2 were performed by using the "one scan per subject, 2-sample *t* test" option in SPM99. Appropriate linear contrasts were used within a single paradigm to extract regions in which the rCBF increased or decreased from the preoperative condition to the postoperative conditions at 5 and 42 mo, respectively, due to the bilateral STN stimulation. Then, a covariance analysis was performed to extract regions whose changes in rCBF correlated significantly with changes in motor function. To assess specific effects of this covariate on rCBF, individual motor UPDRS scores during each scanning condition were introduced into the design paradigm. Finally, the effect of daily levodopa intake on time-dependent changes in rCBF from the pre- to the postoperative conditions was considered by computing a separate covariate analysis using the daily levodopa dosage as the covariate of interest.

After specifying the appropriate design matrix, image intensity was normalized between subjects to prevent intersubject variability in tracer uptake from masking regional changes. To this end, the proportional scaling technique was performed. Global blood flow was normalized by scaling across the entire dataset to a grand mean of 50 mL/100 mL per minute. The gray matter threshold was set to the default value 0.8. These analyses produced a *t* statistic for each voxel, which constituted the statistical parametric map $SPM_{\{t\}}$. The $SPM_{\{t\}}$ map was then transformed to the unit normal distribution to give a gaussian field or $SPM_{\{Z\}}$. The level of significance of areas of rCBF changes was assessed by the spatial extent (*k*) and peak height (u) of their foci using estimations based on the theory of gaussian fields. The whole-brain analyses were designed to confirm participation of several cortical and subcortical regions relevant for PD that were identified a priori on the basis of current model basal ganglia motor circuits (*6–15,26–29*) and results of previous neuroimaging studies concerning the mechanisms underlying the recovery of motor function in PD patients treated with STN-DBS (*16–18*). Thus, with an anatomically constrained hypothesis about effects in particular brain regions, the statistical parametric maps were thresholded at a probability of $P < 0.0001$ uncorrected for multiple comparisons. For all analyses we accepted only clusters comprised of ≥100 adiacent voxels because this could also demonstrate a consistent effect in a particular neuroanatomic distribution. Talairach brain coordinates were given by a nonlinear transform to Talairach space (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html). Talairach Daemon software was used for conversion into Brodmann localization (http://ric.uthscsa.edu/projects/talairachdaemon.html) (*30*).

Comparisons of motor UPDRS, H&Y, and S&E scores and daily consumption of levodopa for each patient pre- and postoperatively with stimulators on were tested using an ANOVA. Post hoc comparisons were performed with the Scheffé test. The correlations between clinical parameters were assessed by the Pearson rank correlation coefficient. Conventional statistics were performed using SPSS, version 11.5, for Windows (SPSS). A level of $P < 0.05$ was considered significant. Results are presented as mean ± SD.

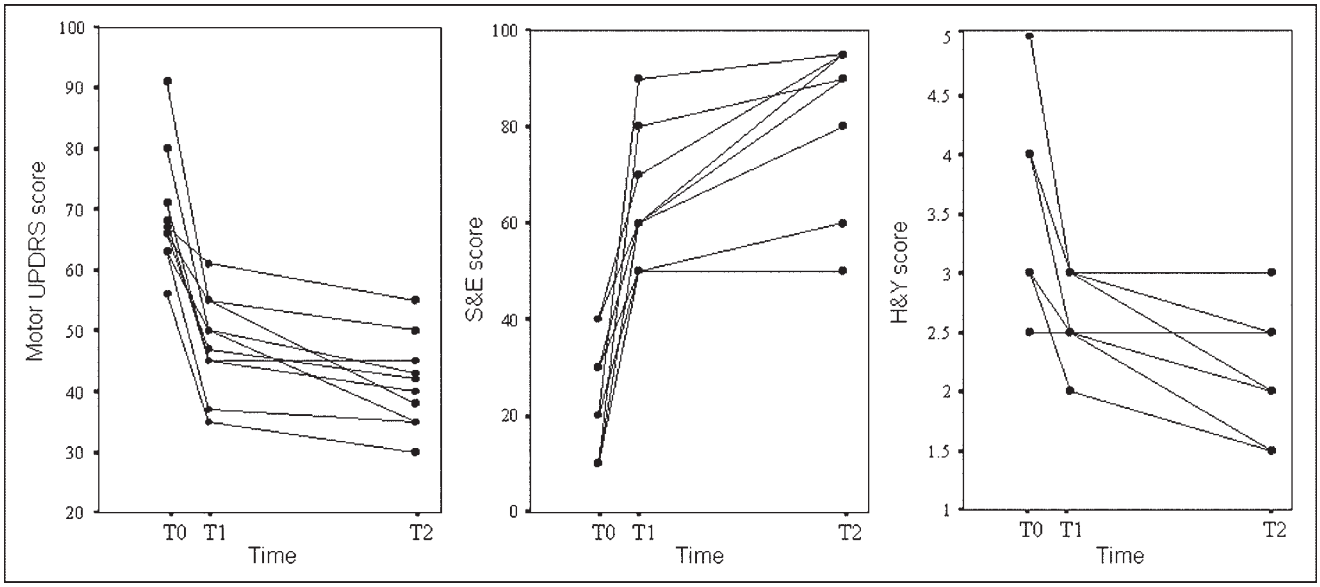

FIGURE 1. Plots of individual clinical scores for motor UPDRS, H&Y, and S&E for preoperative (T_0) and postoperative on-stimulation conditions at 5 mo (T_1) and 42 mo (T_2). Clinical scores were assessed in unmedicated patients. Reduction in motor UPDRS and H&Y scores and increase in S&E score indicate improvement in motor function, global stage disease, and performance of activities of daily living, respectively. Differences between mean scores for UPDRS, H&Y, and S&E at T_0 and T_1 and at T_0 and T_2 were significant. No significant differences were present between mean scores at T_1 and T_2.

TABLE 1
Effects of Long-Term STN-DBS on Clinical Parameters and Medication

Parameter	Clinical score and medication (mg/d)			Clinical improvement and L-Dopa reduction (%)					
	T_0	T_1	T_2	T_0 vs. T_1	*P*	T_1 vs. T_2	*P*	T_0 vs. T_2	*P*
UPDRS	69 ± 10	48 ± 8	41.3 ± 7	30	0.0001	14.5	ns	40.5	0.0001
H&Y	3.65 ± 1	2.7 ± 0.3	2.3 ± 0.5	26	0.003	15	ns	37	0.0001
S&E	24 ± 12	62 ± 14	75.5 ± 20	158	0.0001	21	ns	212.5	0.0001
Levodopa	1,440 ± 465	897 ± 189	655 ± 155	38	0.002	27	ns	54.5	0.0001

UPDRS = UPDRS section III (motor); H&Y = Hoehn and Yahr staging system; S&E = Schwab and England scale; ns = not significant. Clinical scores and medication are expressed as mean ± SD.

RESULTS

Effects of Long-Term STN-DBS on Motor Function and Medication

All patients showed a maximum clinical improvement during the first months after surgery and remained rather stable during further follow-up. While off-medication, the mean improvements for motor UPDRS were 30.4% (T_0–T_1 interval), 14.5% (T_1–T_2 interval), and 40.5% (T_0–T_2 interval). The mean improvements for H&Y and S&E were 26%, 14.8%, 36.9%, and 158.3%, 20.9%, 212.5%, respectively (Fig. 1; Table 1). The mean administered dose of levodopa (mg/d) decreased by 37.7% (T_0–T_1 interval), 26.9% (T_1–T_2 interval), and 54.5% (T_0–T_2 interval) (Table 1). At T_2, some patients received dopaminergic medications of pergolide ($n = 4$), pramipexole ($n = 2$), and cabergoline ($n = 1$).

rCBF

Effect of Bilateral STN Stimulation at 5 Months After DBS Implants. Improvement in regional neural activity as indexed by rCBF from the preoperative off-drug condition to the postoperative off drug/on-stimulation condition at 5-mo follow-up was found in a cluster located in frontal lobes ($P < 0.0001$) (Fig. 2). As listed in Table 2, rCBF increases were bilateral and included the superior, middle, and inferior frontal gyri, corresponding to the PMC (lateral BA6/BA8, where BA is Broadmann area) and DLPFC (BA9/BA10); and the medial frontal gyrus, corresponding to the rostral part of SMA (pre-SMA, medial BA6). These regions formed a spatially contiguous cluster containing 3,297 voxels, with a peak of enhanced rCBF in the PMC. No regions with significant rCBF decreases were evident.

Effect of Bilateral STN Stimulation at 42 Months After DBS Implants. From the postoperative off-drug/on-stimulation condition at 5 mo to the postoperative off-drug/on-stimulation condition at 42 mo we found rCBF increases in 5 clusters located in the frontal lobes, basal ganglia, thalami, cerebellum, and brainstem ($P < 0.0001$) (Fig. 3; Table 3). The rCBF increases in frontal lobes included the pre-SMA, PMC, DLPFC, and precentral and postcentral gyri, corresponding to the primary motor (MI, BA4) and primary sensory (SI; BA1/BA3) cortices, respectively. These regions formed 2 spatially contiguous clusters containing 868 and 465 voxels each, with a peak of enhanced rCBF in the PMC. All rCBF increases were bilateral with the exception of the MI, SI, and lateral BA6, which presented a left rCBF increase.

At the subcortical level, rCBF increases were found bilaterally in the globus pallidus pars externa (GPe) and thalami, entailing the left pulvinar, right ventral posterior medial nucleus (VPM), and bilateral ventral lateral nucleus (VL) nuclei. These regions formed 2 different clusters of 604 and 377 voxels each, with a peak of enhanced rCBF in the thalami. The analysis also showed a significant rCBF increase in the bilateral anterior lobes of cerebellum and in the brainstem, entailing the bilateral pons and the right midbrain. The rCBF increase in midbrain included the substantia nigra (SN) bilaterally. These regions formed a continuous cluster of 803 voxels with a peak of enhanced rCBF

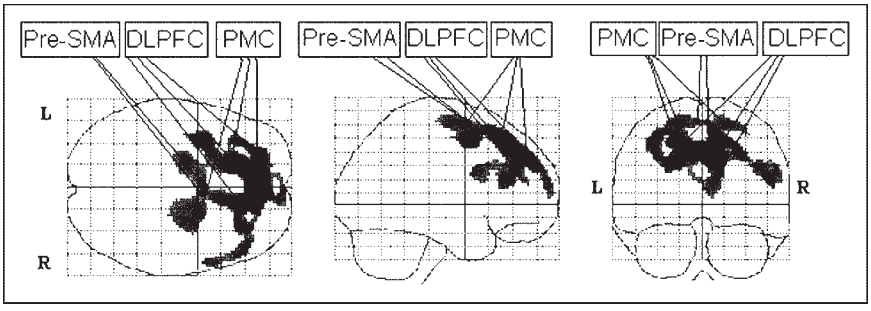

FIGURE 2. Brain areas showing significant rCBF increase from pre- to postoperative on-stimulation condition at 5-mo follow-up (main effect of condition). Results are displayed as SPM projections in 3 orthogonal views ($P < 0.0001$, uncorrected). Pre-SMA = rostral part of the supplementary motor area.

TABLE 2
Location and Peak Z Scores of Areas with rCBF Increase During First 5 Months of STN Stimulation

K_E	Location (functional area, Broadmann area)	Coordinate			Z score
		x	*y*	*z*	
3,297	Bilateral medial frontal gyrus (PMC, 8; DLPFC, 9)	−6	48	38	5.37
		5	44	40	4.51
		4	50	36	5.10
		15	38	25	3.53
	Bilateral superior frontal gyrus (PMC, 8; DLPFC, 9)	−24	45	34	4.30
		44	35	30	3.38
		−18	30	48	4.07
		25	30	45	3.65
		8	62	18	3.36
	Bilateral middle frontal gyrus (PMC, 8; DLPFC, 9, 10)	−28	44	34	4.01
		32	38	36	3.65
		36	28	40	3.52
		−35	28	42	3.43
	Right inferior frontal gyrus (DLPFC, 9)	56	6	26	3.38
	Right middle frontal gyrus (PMC, 6)	24	0	60	3.35
	Left superior frontal gyrus (PMC, 6)	−18	−10	64	3.35
	Bilateral medial frontal gyrus (pre-SMA, 6)	−4	0	62	3.34
		6	4	62	3.33

Z scores ($P < 0.0001$, uncorrected), spatial extent of clusters in voxels (K_E), Talairach coordinates in millimeters together with their anatomic location, and corresponding functional and Broadmann areas are given.

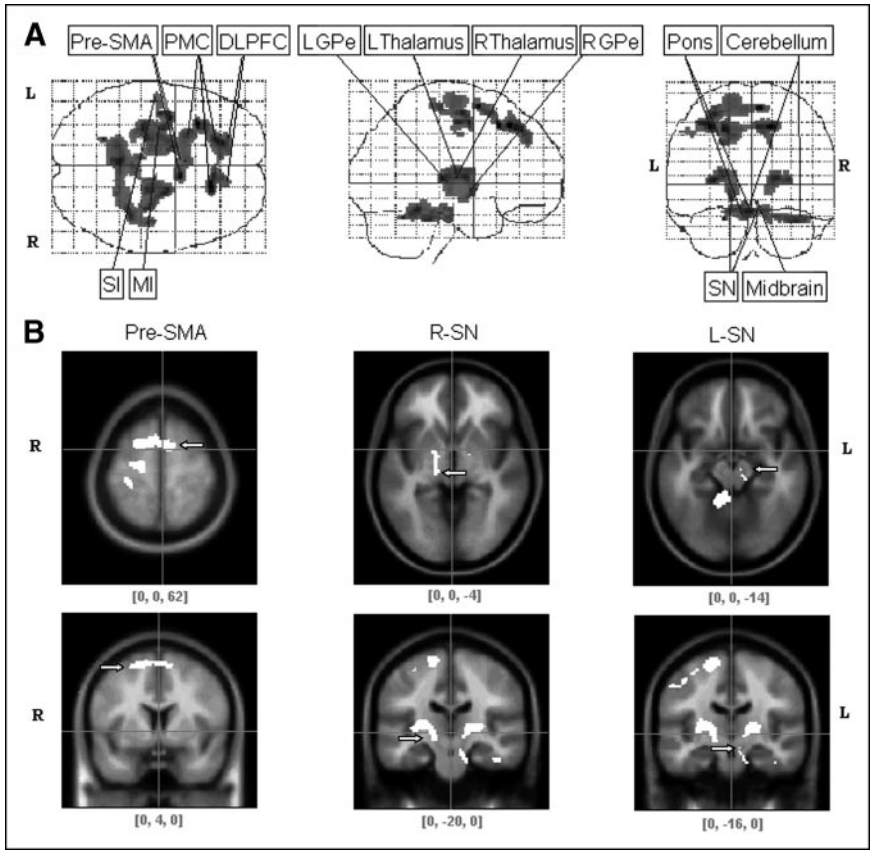

FIGURE 3. (A) Brain areas show significant rCBF increase from postoperative on-stimulation condition at 5 mo to postoperative on-stimulation condition at 42-mo follow-up. Results are displayed as SPM projections in 3 orthogonal views ($P < 0.0001$, uncorrected). MI = primary motor cortex; pre-SMA = rostral part of supplementary motor area; SI: primary sensory cortex; Gpe = globus pallidus pars externa; SN = substantia nigra. (B) rCBF increases in pre-SMA and SN were superimposed on normalized T1-weighted MR images to increase clarity.

TABLE 3
Location and Peak Z Scores of Areas with rCBF Increase During Long-Term DBS of STN from Postoperative Condition at 5 Months to Postoperative Condition at 4 Years

K_E	Location (functional area, Broadmann area)	Coordinate			Z score
		x	*y*	*z*	
868	Bilateral medial frontal gyrus (pre-SMA, 6)	6	4	62	4.57
		−4	4	62	3.70
	Bilateral superior frontal gyrus (PMC, 8)	16	28	48	5.05
		−34	20	48	4.98
		−22	32	46	4.50
		−18	38	44	4.39
		10	38	44	3.95
	Left middle frontal gyrus (PMC, 6)	−24	10	60	3.94
		−28	12	58	3.94
	Bilateral superior frontal gyrus (DLPFC, 9)	−20	42	36	3.91
		16	42	36	3.56
803	Bilateral cerebellum, anterior lobe	−4	−46	−18	4.44
		38	−36	−26	4.21
	Bilateral brainstem, pons	−8	−28	−20	4.03
		0	−34	−20	3.89
	Right brainstem, midbrain	10	−18	−18	3.88
		12	−24	−16	3.80
	Bilateral brainstem, midbrain, SN	8	−16	−14	3.75
		−14	−20	−4	3.63
465	Left middle frontal/precentral gyrus (PMC, 6)	−38	−4	50	4.39
		−30	−10	58	4.27
	Left precentral gyrus (MI, 4)	−42	−12	50	4.20
		−42	−6	52	4.11
		−30	−28	62	3.95
		−48	−14	42	3.32
	Left postcentral gyrus (SI, 1, 3)	−52	−14	44	3.31
		−54	−18	46	3.30
604	Left thalamus	−22	−22	8	4.17
		−16	−12	8	4.10
	Left lentiform nucleus, GPe	−16	−2	−6	4.09
377	Right thalamus	18	−22	6	4.17
		18	−14	8	4.12
	Right lentiform nucleus, GPe	26	−18	4	3.84

Z scores ($P < 0.0001$, uncorrected), spatial extent of clusters in voxels (K_E), Talairach coordinates in millimeters together with their anatomic location, and corresponding functional and Broadmann areas are given.

in the left anterior lobe of cerebellum. No regions with significant rCBF decreases were evident.

Cerebral Perfusion Correlates of Motor Improvement and Daily Consumption of Levodopa. When we examined the correlation between individual motor UPDRS scores and rCBF, a significant relationship ($P < 0.0001$) was found in the right pre-SMA and in the left PMC (Figs. 4A–4C; Table 4). These regions formed 2 different clusters of 141 and 268 voxels, respectively. According to clinical scores, the rCBF in these cortical regions presented with an initial rapid increase from the pre- to the postoperative condition at 5-mo follow-up followed by a second less rapid increase from this condition to the postoperative condition at 4 y (Figs. 4D and 4E). The rCBF in the pre-SMA increased by 39.2% (interval T_0–T_1), 10.2% (interval T_1–T_2), and 53.5% (interval T_0–T_2), respectively (rCBF at T_0: 0.168 ± 0.03 vs. at T_1: 0.234 ± 0.03, $P = 0.001$; rCBF at T_1 vs. at T_2: 0.258 ± 0.03, P = not significant [ns]; rCBF at T_0 vs. at T_2, $P = 0.0001$). With regard to the PMC, the rCBF increased by 57% (interval T_0–T_1), 12.5% (interval T_1–T_2), and 76% (interval T_0–T_2), respectively (rCBF at T_0: 0.214 ± 0.03 vs. at T_1: 0.336 ± 0.05, $P = 0.0001$; rCBF at T_1 vs. at T_2: 0.378 ± 0.04, P = ns; rCBF at T_0 vs. at T_2, $P = 0.0001$). Covariance analysis that uses the daily consumption of levodopa as the covariate of interest did not show any significant relationship between this parameter and the rCBF.

DISCUSSION

In the current follow-up study we investigated the brain areas underlying the clinical effects of long-term treatment with STN-DBS by means of perfusion SPECT. After about 4 y of chronic STN-DBS, all parkinsonian patients

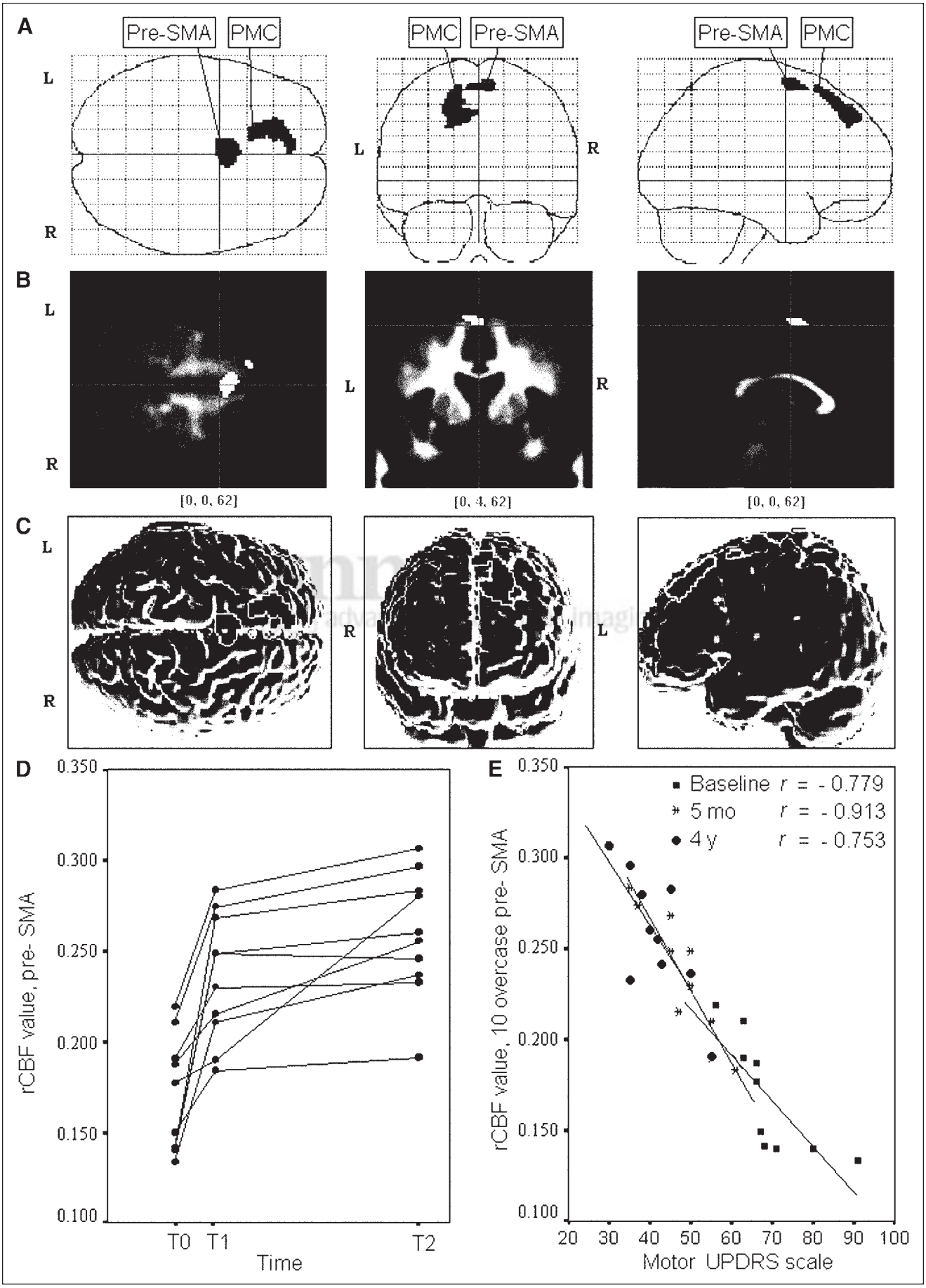

TABLE 4
Location and Peak Z Scores of Areas Whose Increases in rCBF Significantly Correlated with Improvement in Motor Symptoms from Preoperative to Postoperative Conditions at 5 Months and 4 Years

		Coordinate			
K_E	Location (functional area, Broadmann area)	*x*	*y*	*z*	Z score
268	Left superior frontal gyrus (PMC, 6)	−16	28	58	4.11
		−20	38	46	4.02
141	Right medial frontal gyrus (pre-SMA, 6)	6	4	62	3.68

Z scores ($P < 0.0001$, uncorrected), spatial extent of clusters in voxels (K_E), Talairach coordinates in millimeters together with their anatomic location, and corresponding functional and Broadmann areas are given.

presented with significant improvements in motor ratings (UPDRS, H&Y, S&E) while they were in a medication-off state. In accord with findings in a larger series (*2–5*), the improvement was maximum during the first months after surgery and remained rather stable during further follow-up (Fig. 1). Moreover, medication for PD was significantly lowered.

As far as rCBF changes are concerned, the main effect of STN stimulation in the long term was to produce rCBF changes in several components of the motor hierarchy that are not activated after the first months of treatment. Indeed, according to previous findings (*16–18*), STN stimulation during the first months after surgery produced rCBF increases mainly in cortical areas of frontal lobes, including the pre-SMA, PMC, and DLPFC. Thereafter, along with further rCBF increases in these cortical areas, chronic stimulation of the STN also produced a significant increment in neural activity in other cortical regions, such as the MI/SI, and in several subcortical structures, including the basal ganglia, thalami, cerebellum, pons, and midbrain.

When we investigated the brain areas in which the rCBF changes correlated with the motor UPDRS, significance was found only in only a few of the above regions—specifically, for the right pre-SMA and the left premotor cortex. Results of the covariate-only analysis with the daily levodopa dosage as the confounding covariate confirmed that the observed changes in rCBF were related to the effect of long-term STN-DBS rather than to differences in acute response of the brain to discontinuation of levodopa therapy.

The finding that STN stimulation in the long term produces a significant rCBF increase in motor (pre-SMA, PMC) and associative (DLPFC) areas in the frontal cortex is consistent with the current view of the topographic organization of the primate STN and basal ganglia–thalamocortical motor circuits (*26*). Such topography was shown to reflect the large-scale organization of the basal ganglia, a family of reentrant subloops arising from several separate but functionally related cortical areas in the frontal lobes (pre-SMA, SMA, MI/SI, DLPFC) and returning to the original cortical areas by way of motor and associative portions of the basal ganglia and thalami (*7,26*). Accordingly, we found rCBF increases in the GPe and VL nuclei, which are known to represent important relays within the basal ganglia motor circuit.

Chronic bilateral STN stimulation was found to induce rCBF increases in both cerebellar hemispheres and brainstem, entailing the pons and midbrain. These findings are consistent with results of neuroimaging studies showing that the brainstem and cerebellum could be severely affected in PD (*15*) and that activity within these subcortical regions can be restored by means of therapeutic procedures (*31,32*). In agreement with the organization of basal ganglia–cerebellothalamocortical circuitry for motor control (*31*), activation in brainstem locomotor areas during STN stimulation has been reported to be a consequence of the reduced inhibitory pallidal output to this structure and to induce an increment of neural activity in the cerebellum (*27,28*). In turn, efferent synaptic activity from the cerebellum has been shown to converge in the MI, pre-SMA, PMC, and DLPFC via specific thalamic relay nuclei (*15,31*). Thus, along with the basal ganglia–thalamocortical motor circuits, our data seem to suggest that STN stimulation could produce rCBF increases in motor cortical areas by enhancing activation responses within the cerebellothalamocortical circuit and that it could happen mainly in the later phase of stimulation.

Among the several rCBF changes found at the subcortical level, the finding of an rCBF increase in the bilateral substantia nigra (SN) may require additional comments. First, considering that the SN reticulata (SNr) neurons are largely hypoactive during chronic DBS-STN (*11,33*), it is reasonable to assume that this result may be explained in terms of an increased activity of the SN pars compacta (SNc) rather

FIGURE 4. (A) Brain regions in which rCBF increases significantly in association with improvement in motor function (motor UPDRS) from pre- to postoperative on-stimulation conditions at 5- and 42-mo follow-up ($P < 0.0001$, uncorrected). Pre-SMA = rostral part of the supplementary motor area. (B and C) rCBF increases superimposed on normalized T1-weighted MR images and on 3-dimensional brain. (D) Plot of individual rCBF values related to motor improvement for pre-SMA from pre- to postoperative conditions. (E) Relationship between rCBF values in pre-SMA and motor UPDRS scores during course of the study.

than the SNr. Accordingly, results of electrophysiologic studies have shown that STN-DBS is followed by an increase in firing activity of nigral dopaminergic neurons via deactivation of SNr neurons (*34*), which are known to provide a large inhibitory effect on the SNc (*35*). Furthermore, recent investigations in rats have shown that STN-DBS induces an increase in the globus pallidus neural activity (*36*), that we found activated, which was proven to form, along with the STN, an important pace-maker for the inhibitory control of SNr neurons (*37*). Second, in agreement with results of previous studies investigating the effect of the STN stimulation on the nigrostriatal system (*38*), our percentage results confirm that the increased activity of a few surviving dopaminergic neurons did not produce any significant rCBF change in the striatum. As reported earlier (*38*), these data seem to support the evidence that modulation of the remaining dopaminergic activity does not play a crucial role for stimulation of the mechanisms of action in humans with PD.

When we investigated which brain areas showing an rCBF increase during the time course of the study presented a significant relationship with the observed improvement in motor function, we found an rCBF increase in the pre-SMA and PMC. According to clinical scores, the rCBF in the pre-SMA and PMC presented with an initial rapid increase from the pre- to the postoperative condition at 5-mo follow-up followed by a second less rapid increase from this condition to the postoperative condition at 4 y. This finding is consistent with results of previous neuroimaging studies showing that the PMC and pre-SMA are functionally underactive in the dopamine deficiency state (*39*) and that recovery of motor function after STN-DBS is associated with restoration of the function of these areas. The present results suggest that the mechanism by which STN-DBS continues to achieve its therapeutic response over time could be mainly related to the restored activity within higher order motor cortical areas. Particularly, as well as in the short term, the beneficial effect of long-term STN stimulation seems to be related to the function of the pre-SMA.

When considering follow-up data, the rCBF changes showed somewhat of a relationship with the duration of STN stimulation. First, as previously demonstrated, the stimulation during the first months after surgery induced rCBF changes mainly at the cortical level. Second, we found that the effect of stimulation on the cerebral cortex continued for several years after DBS implants. Analysis of time–activity curves for the cortical regions related to motor improvement showed that the functional recovery was rapid during the first months of stimulation and very slow during the following years. Third, the further increase in cortical activity during long-term stimulation was accompanied by a significant effect on several structures located at the subcortical level. Taken together these data may suggest a potential role of STN-DBS in a time-dependent strengthen-

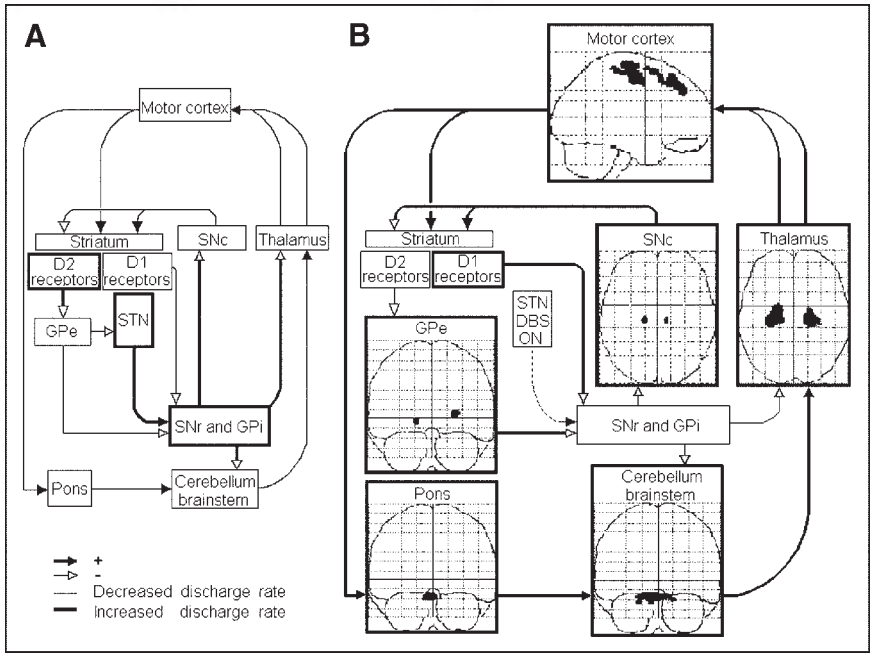

FIGURE 5. Proposed functional model of basal ganglia in patients with parkinsonism (A) and hypothetic schematic diagram of mechanisms by which STN-DBS produces its clinical benefit in the long term (B). For clarity, the neuroanatomy and interconnections shown are incomplete. Excitatory connections are indicated by solid arrowheads and inhibitory connections are indicated by open arrowheads. Relative increases and decreases in tonic discharge rates associated with parkinsonism and DBS are denoted by wider and thinner lines and outlining of each box, respectively. Dashed line indicates the inhibitory effect of long-term DBS on overactive STN. Cortical and subcortical regions resulting in activation in our study are displayed on a glass brain. (A) Parkinsonism arises from loss of dopaminergic neurons in the pars compacta segments of the substantia nigra (SNc). Reduced inhibition via the direct pathway (striatum to the globus pallidus pars interna [Gpi] and the pars reticulata of the substantia nigra [SNr]) combined with increased excitation from the STN via the indirect pathway (striatum to the globus pallidus pars externa [Gpe]) leads to overactivity of GPi and SNr. This abnormal activity may determine motor impairment by suppressing thalamocortical and cerebellocortical facilitation and by altering brainstem locomotor areas. (B) Reduction of excessive excitatory activity of the STN would partially reverse this state by eliminating excessive inhibition of both components of the output of basal ganglia. This may lead to enhanced activation responses in motor/associative areas of frontal lobes, possibly involving elements within the basal ganglia–thalamocortical motor circuits during the first months of stimulation as well as within the cerebellothalamocortical motor loop, the nigral dopaminergic system, and the brainstem during subsequent years of therapy.

ing of cortical transmission. According to clinical results, the reinforcement of motor areas of frontal lobes, and particularly those associated with higher order aspects of motor control, is likely to occur mainly during the first months after surgery and is maintained over time by the cooperation of elements within the basal ganglia and the cerebellothalamocortical motor circuits, the nigral dopaminergic system, and the brainstem (Fig. 5). Accordingly, recent work has shown that use-dependent potentiation by continuous repetitive activation by medication or stimulation can occur in the long term within the basal ganglia–thalamocortical connections through an increase in synaptic efficacy and postsynaptic intrinsic excitability (*29*).

Limitations of this study must be mentioned. Further investigations of a larger series and with instrumentation characterized by a higher spatial resolution are needed to confirm the present findings. Furthermore, although some confounding variables have been managed in the present study, some factors are difficult to control and should be considered carefully, such as the possible plastic changes induced by long-term STN-DBS or the effects of PD progression. Indeed, despite motor improvement by STN-DBS, the cortical abnormalities may progress gradually over the course of 4 y. Therefore, the functional improvement observed in our SPM analysis could be partially masked by the global progressive functional impairment in PD. In this respect, it could be useful to reproduce the study using quantitative SPECT or PET. Finally, we did not have a control group of PD patients (e.g., patient candidates for DBS but without STN stimulation) for comparison in parallel with the patients with STN stimulation to determine whether their long-term evolution of rCBF will be different.

CONCLUSION

Results of this preliminary investigation suggest that the long-term stimulation of the STN may induce bilateral rCBF increases in motor/associative areas of frontal lobes. After an expected rCBF increase during the first months of STN stimulation, these cortical regions showed a further rCBF increase in the later phase, which was accompanied by an increased activity in several subcortical structures within the basal ganglia and cerebellothalamocortical motor circuits, nigral dopaminergic system, and brainstem. Second, the results of covariance analysis showed that a significant correlation between motor improvement and rCBF increase was present only in higher order motor areas of frontal lobes, thus suggesting that, even in the long term, as well as the short term, the STN-DBS achieves its therapeutic benefit in PD patients mainly by restoring the activity within these cortical regions.

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