A Positron Emission Tomographic Study of Subthalamic Nucleus Stimulation in Parkinson Disease

Enhanced Movement-Related Activity of Motor-Association Cortex and Decreased Motor Cortex Resting Activity

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Background: Long-term high-frequency stimulation of the subthalamic nucleus (STN) improves akinesia in Parkinson disease. The neural correlates of STN stimulation are not well understood. Positron emission tomography can be applied to the in vivo study of the mechanisms of deep brain stimulation.

Objective: To study changes in regional cerebral blood flow as an index of synaptic activity in patients with Parkinson disease with effective STN stimulation on and off during rest and movement.

Methods: Eight patients with Parkinson disease who had electrodes implanted in the STN underwent 12 measurements of regional cerebral blood flow with water O 15 positron emission tomography at rest and during performance of paced freely selected joystick movements, both with and without STN stimulation (3 scans per experimental condition). Motor performance and reaction and movement times were monitored. Statistical parametric mapping was used to compare changes in regional cerebral blood flow between conditions and differences in activation.

Results: All patients showed improvement in reaction and movement times during scans with the stimulator on. As predicted, increases in activation of rostral supplementary motor area and premotor cortex ipsilateral to stimulation were observed when stimulation was on during contralateral movement (P<.001). Unpredicted observations included decreases in regional cerebral blood flow in primary motor cortex at rest induced by STN stimulation.

Conclusion: Stimulation of the STN reduces the movement-related impairment of frontal motor association areas and the inappropriate motor cortex resting activity in Parkinson disease.

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STEREOTAXIC procedures in Parkinson disease (PD) are currently undergoing a renaissance. Medial pallidotomy has the ability to relieve levodopa-associated dyskinesias as well as akinesia, tremor, and rigidity. Overactivity of excitatory neurons from subthalamic nucleus (STN) to the GPi has been shown in monkeys rendered parkinsonian by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Lesions and high-frequency stimulation of the STN in this animal model reduce akinesia, rigidity, and tremor. Surgery aiming at the STN was then suggested as a treatment for PD in humans, as hyperactivity of STN projections to the GPi seems to represent a crucial feature of parkinsonism in animal models of PD. Eventually, STN stimulation was shown to be safe and effective for the treatment of akinesia and rigidity.

The combination of deep brain stimulation and positron emission tomography (PET) activation studies offers a powerful technique for assessing the effects of discrete perturbations at different target structures throughout the basal ganglia-thalamocortical circuitries on regional cerebral blood flow (rCBF), an index of local synaptic activity. Patients can undergo repetitive scans with stimulation off and on in a single PET study, and the task-specific effects of stimulation on segregated neuronal systems can be studied throughout the brain.

We hypothesized that increases in activation of motor association cortex coupled with improvement of akinesia would occur in patients with PD during STN stimulation. Like surgery targeting the GPi, STN stimulation aims to reduce the overactivity of the GPi by decreasing overactive excitatory STN projections that oth-
**PATIENTS AND METHODS**

**PATIENTS**

Nine patients with medically intractable PD, all levodopa responsive (7 men and 2 women; mean age, 53.8 ± 8.2 years; range, 42-72 years), were selected for this study. The patients had suffered from parkinsonian symptoms for 11 ± 6 years (range, 4-20 years). All had initially experienced onset of symptoms on one side, and this side was more affected than the other when stimulators were off. Assessment on the Unified Parkinson’s Disease Rating Scale was blinded and performed at the PET center independently from the neurosurgical teams at least 4 months after implantation of the electrodes. Patients were assessed with the stimulator on and off by means of the motor Unified Parkinson’s Disease Rating Scale at different days in randomized order in the “practically defined off period” (after a drug withdrawal of more than 12 hours). Three patients (patients 3, 6, and 9) stopped taking dopaminergic medication after implantation of the STN electrodes. Two patients (patients 4 and 7) could be weaned from their apomorphine hydrochloride pumps and be treated with moderate doses of dopaminergics after effective stimulation. The clinical details of the patients, their Unified Parkinson’s Disease Rating Scale scores, and medication are detailed in Table 1 and their stimulation variables during the PET study in Table 2.

The study was approved by the ethics committee. All subjects gave written informed consent before the PET study. Permission to administer radioactive substances was obtained from the radiation protection authorities.

Neurosurgery was performed in Homburg, Germany (2 patients), and Vienna, Austria (7 patients). All subjects gave written informed consent before implantation of the stimulating systems. The electrode implantation took place under stereotaxic conditions, with the patient under local anesthesia, with the use of computed tomography and/or magnetic resonance imaging as well as ventriculography.

**RESULTS**

**CLINICAL EFFECTS OF STIMULATION ON TASK PERFORMANCE**

Motor performance improved with STN stimulation (Table 1). Individual task performance measures with the contralateral STN stimulation switched on during PET scanning are shown in Table 3. The error rate in joystick movements was not significantly different between STN stimulation on and off conditions. The mean reaction and movement times were, on average, 24.6% and 28.9% longer when the contralateral STN stimulators were off (reaction time, $P<.005$, and movement time, $P<.001$, paired $t$ test).

**REGIONAL CEREBRAL BLOOD FLOW**

Relative increases of movement-associated activation ipsilateral to the STN electrode and contralateral to movement were observed in mesial frontal cortex (2 adjacent clusters totaling 147 voxels) and premotor cortex (106 voxels) (Table 4; Figure 1). The peak of enhanced activation in the mesial frontal cortex was in Brodmann area 6 bordering to Brodmann area 8 in the Talairach atlas (rostro supplementary motor area [SMA]). When the threshold was lowered to $P<.01$ (not included in Table 4 and Figure 1), the 2 adjacent clusters merged and extended posteriorly into the area just anterior to the vertical line erwise reinforce the inhibitory GPi overactivity directed toward the thalamus. Therefore, reduction of STN overactivity would be expected to reduce inhibitory GPi output to thalamic relay nuclei and, in turn, disinhibit the ventral thalamus and facilitate thalamic excitation of premotor and prefrontal cortical areas.

The motor paradigm used in the present study has been previously used to demonstrate impaired activation of the striatum and mesial frontal cortex in PD20,21 and increased activation of prefrontal and premotor regions in acquired and idiopathic dystonia.12,13 Herein, we report the changes in rCBF occurring in patients with PD associated with STN stimulation during resting and movement-related brain activity.

The primary anatomical target was the center of the STN, based on the Talairach diagram at a laterality of 10 to 12 mm. A computer program using both ventriculographic and magnetic resonance imaging data was used to calculate this target.14 The neurophysiological exploration of the target was done in a standard way with specially designed semiconductive electrodes (PLS; Inomed, Teningen, Germany) at intervals of 2 mm. Intraoperative test stimulation was done at a rate of 130 Hz and a pulse rate of 50 microseconds, with a variable current flow (0-5 mA). The effect of stimulation was checked by finger tapping and pronation-supination for bradykinesia, and active and passive flexion-extension of the hand for rigidity. After final identification of the target, the testing electrode was removed and replaced by a permanent quadripolar (Medtronic 338X; Medtronic Inc, Minneapolis, Minn). The electrodes were first externalized via an extension cable. This step was followed by a postoperative screening phase of several days for test stimulation. After successful test stimulation, a pulse generator was implanted. The externalized extension cable was removed and the electrode was connected to the pulse generator, which was located in a surgically prepared pocket in the pectoral region.

MOTOR ACTIVATION PARADIGM

All patients with PD underwent 12 sequential rCBF scans with water oxygen 15 ($H_2^{15}O$) PET. The light was dimmed. The stimulator contralateral to the side of initial akinetic symptoms in the course of the disease was switched on and off. The 4 experimental conditions were arranged as 6 pairs (AB and CD) of scans, randomized to ABCDABCDABCDAB. The conditions were as follows: (A) rest with STN stimulators off; the stimulators were switched off 10 minutes before the scan and left off for scan B; (B) joystick movements in freely selected directions paced by a tone at 3.0- to 3.5-second intervals of 2 mm. Intraoperative test stimulation was done at a rate of 130 Hz and a pulse rate of 50 microseconds, with a variable current flow (0-5 mA). The effect of stimulation was checked by finger tapping and pronation-supination for bradykinesia, and active and passive flexion-extension of the hand for rigidity. After final identification of the target, the testing electrode was removed and replaced by a permanent quadripolar (Medtronic 338X; Medtronic Inc, Minneapolis, Minn). The electrodes were first externalized via an extension cable. This step was followed by a postoperative screening phase of several days for test stimulation. After successful test stimulation, a pulse generator was implanted. The externalized extension cable was removed and the electrode was connected to the pulse generator, which was located in a surgically prepared pocket in the pectoral region.
scan D; and (D) joystick movements with STN stimulator on, otherwise same as B.

Patients were instructed to make 1 joystick movement for each pacing tone, to choose a different direction (forward, back, left, or right) of movement on each occasion, and to avoid repetitive patterns of movements. Patients practiced the movement task beforehand to ensure correct performance with eyes closed. We computed mean reaction time and movement time during the scans with the stimulator on and off and compared the data by means of a paired 2-tailed t test. During the rest condition, subjects were asked to relax with their arms and hands in the most comfortable position possible with eyes closed. They were told beforehand that they would be hearing tones as during the activation scans. All subjects were closely observed and videotaped during the scans to detect head movement or dyskinesias.

DATA ACQUISITION

The PET measurements were performed with a PET scanner (Siemens 931R/31; Siemens CTI, Knoxville, Tenn) in 3-dimensional mode with a total axial field of view of 10.5 cm and no interplane dead space. To measure rCBF, 277.5 MBq of H15O was administered intravenously over 30 seconds with a semibolus injection by means of an infusion pump. Single frames were acquired for 60 seconds starting with the appearance of the tracer in the brain. The pacing tones commenced 10 seconds before actual scanning both for the resting and the activated state. The interval between successive H15O administrations was 10 minutes. A 20-minute transmission scan that used rotating rods of germanium 68–gallium 68 was performed for attenuation correction with the septa in place. Two-dimensional blank and transmission scans (septa extended) were used to reconstruct a 3-dimensional attenuation map. Oblique lines of coincidence for which the attenuation correction factor had not been measured were obtained by forward projection through the 3-dimensional map. After corrections for randoms, dead time, and scatter, images were reconstructed by filtered back-projection with a Hanning filter (cutoff frequency, 0.4 cycles per projection element), resulting in 31 slices with a 128 × 128-pixel matrix (pixel size, 2.0 mm) and interplane separation of 3.375 mm.

IMAGE TRANSFORMATION AND STATISTICAL ANALYSIS

Image processing was carried out with computers (Sun SPARC 2; Sun Computers Europe Inc, Surrey, England) with the use of PRO MATLAB (MathWorks Inc, Natick, Mass). Realignment, normalization into Talairach stereotaxic space, intersubject averaging, and statistical analysis was performed with established software (SPM96b; Welcome Department of Cognitive Neurology, London, England). Each image was smoothed with an isotropic gaussian kernel of 12 mm to increase signal-to-noise ratio. Global blood flow was normalized by scaling across the entire data set to a grand mean of 50 mL/100 mL per minute.

We tested for relative increases and decreases in rCBF by categorical comparisons of on vs off STN stimulation at rest. Relative differences in activation were assessed by comparing rCBF changes (ie, movement vs rest) during STN stimulation on with the movement-associated rCBF increases during STN stimulation off.

All comparisons were specified by appropriately weighted categorical contrasts and performed on a voxel-by-voxel basis by means of analysis of variance. This generated statistical parametric mapping (t) maps for the rCBF changes associated with each comparison. For the comparison of the activation effects, the statistical parametric mapping (t) maps were subsequently transformed into statistical parametric mapping (z) maps, and the level of significance of areas of activation was assessed by the peak height of their foci by means of estimations based on the theory of random gaussian fields.

Significance was accepted if voxels survived an uncorrected threshold of P<.001.

There were 2 main findings associated with STN stimulation in PD: first, as predicted, rostral premotor areas (lateral area 6 and rostral SMA) and, at a lower level of significance, dorsal prefrontal cortex, showed enhanced movement-associated activation coupled with improvement in akinesia during STN stimulation. Second, not predicted beforehand, we observed that STN stimulation induced ipsilateral resting rCBF decreases in primary motor cortex.

ENHANCED MOVEMENT-ASSOCIATED ACTIVATION WITH STN STIMULATION ON

The finding of STN-induced enhanced activation of motor association areas (rostral SMA, premotor cortex) during volitional movements, along with the improvement in akinesia, is consistent with our hypothesis that STN stimulation improves activity of motor association cortex, possibly by reducing inappropriate excitation of the
STN on inhibitory pallidothalamic projections. Positron emission tomographic studies have shown that SMA, in particular its rostral part (pre-SMA), subserves the central control of internally generated sequential movements.21 The SMA is functionally underactive in PD, but its function can be restored after administering dopaminergic agents,10,22,23 transplantation of embryonic tissue,24 and pallidotomy.25-27 The present study shows that restoration of SMA activity (mainly rostral) is also a feature of STN stimulation and adds further support to the pivotal role of the STN nucleus in the motor deficit of PD.

Our results are in reasonable agreement with the pattern of movement-associated rCBF changes caused by STN stimulation described by Limousin et al.28 In both studies, movement-associated increased activation was centered around the SMA, although the peak changes in medial frontal cortex were more rostral (pre-SMA) in our study. We also found, in contrast to Limousin et al, enhanced activation of the lateral premotor cortex ipsilateral to stimulation. It is likely that differences in patient selection, stimulation variables, and slight variation in targets within the STN may account for the differences in the frontal pattern of movement-associated rCBF changes.

A fludeoxyglucose F 18 PET study of covariance patterns of resting glucose metabolism in patients with PD demonstrated increased glucose metabolism after pallidotomy in ipsilateral dorsal prefrontal cortex, primary motor cortex, and lateral premotor cortex along with decreases in thalamic and lentiform metabolism.29 No relative increases in resting SMA metabolism were detected in that study. However, in an rCBF PET study on the effects of GPi stimulation, Davis et al4 showed increased rCBF in rostral SMA compared with baseline without stimulation. These authors required their patients with GPi stimulators to count silently during all scans, and therefore a direct comparison of these premotor rCBF increases with our rest condition may not be appropriate. However, our study design allowed us to examine task-specific changes in the activated motor system, and during STN stimulation we found movement-related enhanced activation in premotor cortex with no rCBF increases at baseline (rest). This could mean that STN, in contrast to GPi, stimulation is quite specific in movement-related disinhibition of thalamocortical circuits.

We also found decreased movement-associated activity in caudal SMA and primary motor cortex along with the increased activation in premotor and prefrontal cortex. Interestingly, this pattern of overactivity of frontal

| Table 1. Clinical Characteristics of 9 Patients With Parkinson Disease With STN Stimulators* |
|---|---|---|---|---|---|---|
| Patient No./ Age at Onset, y | Motor UPDRS Score† | Before Implantation of Electrodes and Impulse Generator | At Time of Evaluation Before PET Study |
| | Motor UPDRS Score† | L-Dopa/PDI, 1800; P, 1.5; S, 10 | L-Dopa/PDI, 800; P, 1.5; S, 10 |
| 1/M/50 | 33 | 26 | 49 | L-Dopa/PDI, 450; B, 10; S, 10 |
| 2/M/55 | 47 | 21 | 36 | L-Dopa/PDI, 340; P, 4.0; S, 10 |
| 3/M/42 | 33 | 17 | 23 | L-Dopa/PDI, 225; P, 10; A, 90 by pump, subcutaneous continuous infusion |
| 4/F/49 | 39 | 18 | 16 | L-Dopa/PDI, 400; B, 0.6; S, 10 |
| 5/M/58 | 54 | 31 | 48 | L-Dopa/PDI, 300; S, 10 |
| 6/M/51 | 44 | 7 | 34 | L-Dopa/PDI, 200; S, 5; A, 96 by pump, subcutaneous continuous infusion |
| 7/F/52 | 33 | 16 | 20 | L-Dopa/PDI, 400; S, 10 |
| 8/M/55 | 35 | 26 | 68 | L-Dopa/PDI, 300 |
| 9/M/72 | 65 | 6 | 12 | None |

*STN indicates subthalamic nucleus; UPDRS, Unified Parkinson’s Disease Rating Scale; PET, positron emission tomography; L-Dopa/PDI, levodopa plus peripheral decarboxylase inhibitor; P, pergolide mesylate; S, selegiline hydrochloride; B, bromocriptine mesylate; and A, apomorphine hydrochloride. The scans of patient 7 could not be completed because of dyskinesias and therefore are not included in the PET analysis.
†Tested after a drug withdrawal of more than 12 hours.

| Table 2. Stimulation Characteristics of 9 Patients With Parkinson Disease During PET Activation Study While STN Stimulator Is On* |
|---|---|---|---|---|---|---|
| Patient No. | Side of Stimulation | Electrode Polarity | | Case | Amplitude, V | Pulse Width, µs |
| | | 0 (Distal) | 1 | 2 | 3 | |
| 1 | Left | 0 | – | – | 0 | + | 2.0 | 60 |
| 2 | Right | 0 | 0 | – | – | + | 2.5 | 90 |
| 3 | Left | + | – | – | 0 | 0 | 4.7 | 90 |
| 4 | Left | + | – | – | 0 | 0 | 2.8 | 60 |
| 5 | Right | + | + | – | – | 0 | 3.2 | 90 |
| 6 | Right | 0 | – | – | 0 | + | 2.4 | 60 |
| 8 | Right | 0 | – | – | 0 | + | 2.3 | 60 |
| 9 | Right | 0 | 0 | – | 0 | + | 1.2 | 60 |

*The frequency of stimulation was 130 Hz in all patients. PET indicates positron emission tomography; STN, subthalamic nucleus; minus sign, negative; and plus sign, positive.
association areas and underactivity in motor executive cortex (mainly caudal SMA) has already been described in idiopathic dystonia. Parallels between idiopathic dystonia and STN stimulation in PD also occur clinically: STN stimulation may induce dystonia, and bradykinesia is common in idiopathic dystonia.

**STN STIMULATION–INDUCED rCBF CHANGES DURING REST**

We found rCBF decreases in primary motor cortex associated with STN stimulation during the resting condition, while akinesia improved. This pattern of resting rCBF changes caused by STN stimulation was similar to that described by Limousin et al. In contrast to their study, we observed statistically significant enhanced resting activity during stimulation in an area corresponding to the globus pallidus–ventral thalamus in the stereotaxic atlas. The predominance of unipolar stimulation in our study may represent the simple explanation of these subcortical increases in resting flow because of spread of current in adjacent pathways to the STN. However, other theories could be advanced here. Orthodromic activation, namely via the fasciculus thalamicus or the ansa lenticularis, or through a direct projection from STN to thalamus, could enhance synaptic activity in the thalamus. The increases in activity in the pallidal area may be caused by increased inhibitory activity on the internal pallidum through antidromic stimulation or backfiring toward the external pallidal segment from STN, a mechanism of action of STN stimulation that was already suggested by Limousin et al.

It has been argued that the strong direct excitatory projection from the cerebral cortex to STN could con-...
tribute to the increased neuronal activity in the STN after dopamine loss.\textsuperscript{32,33} This implies that rCBF decreases in primary motor cortex at rest could represent the cortical consequence of the functional inactivation of the STN on the system subserving the motor cortex efferents to STN. Alternatively, STN stimulation leads to less afferent noise from premotor areas because of improvement of signaling in thalamofrontal circuitry.

It could also be argued that the decrease in motor cortex activity at rest simply represents a decrease in proprioceptive input caused by stimulation-induced decrease in rigidity and off-dystonia. However, off-dystonia was minor in our patients and did not develop acutely after the stimulator was switched off. The same applies to rigidity. Moreover, the variability across individuals would argue against a relation between changes in these signs and the robust rCBF changes observed in the motor cortex ipsilateral to the stimulation.

Our study showed that improvement of akinesia with STN stimulation is coupled with movement-associated increased activation in lateral premotor cortex and rostral SMA. The decrease in motor cortex activity with STN stimulation at rest may represent relative normalization of defective cortical excitability in PD.

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\begin{table}
\centering
\footnotesize
\caption{Areas With Changes in rCBF Associated With STN Stimulation During Baseline*}
\begin{tabular}{|l|l|l|l|l|}
\hline
Areas & Talairach Coordinates of Peak in Decreased Activation & \(z\) Score of Maximal Decreased Activation & Voxels per Cluster & \(P\) \\
\hline
Increases at rest with stimulation & & & & \\
Globus pallidus/ventral anterior thalamus ipsilateral to stimulating electrode & –18, –10, 6 & 3.9 & 133 & <.001 \\
& –18, –20, 4 & 3.1 & 39 & <.001 \\
Mesial parieto-occipital & –14, –80, 38 & 3.9 & 108 & <.001 \\
Lateral parieto-occipital ipsilateral to stimulating electrode & –36, –70, 2 & 3.53 & 3.50 & 22 <.001 \\
& –28, –72, 8 & & & \\
& –46, –68, –4 & 3.47 & & \\
A10/A9 & 28, 60, 20 & 3.6 & & \\
Decreases at rest with stimulation & & & & \\
Primary motor cortex ipsilateral to stimulating electrode & –18, –28, 68 & 4.0 & 620 & <.001 \\
& –36, –28, 64 & 3.9 & 108 & <.001 \\
& –28, –20, 64 & 3.6 & & \\
& –6, 28, 26 & 3.4 & 23 & <.001 \\
Anterior cingulate (A32) & & & & \\
\hline
\end{tabular}
\footnotesize
\textsuperscript{*}rCBF indicates regional cerebral blood flow; STN, subthalamic nucleus. Height threshold, \(P<.001\).
\end{table}
for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the primates. Mov Disord. 1991;6:288-292.


