Subthalamic nucleus stimulation in Parkinson disease induces apathy: A PET study
Neurology 2009;73:1746-1751
DOI: 10.1212/WNL.0b013e3181c34b34

This information is current as of January 18, 2010

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://www.neurology.org/cgi/content/full/73/21/1746
Subthalamic nucleus stimulation in Parkinson disease induces apathy
A PET study

ABSTRACT

Objective: Apathy may be induced by subthalamic nucleus deep brain stimulation (STN-DBS) in Parkinson disease (PD). We therefore wished to test the hypothesis that apathy induced by STN-DBS correlates with changes in glucose metabolism, using 18FDG-PET.

Methods: Twelve patients with PD were assessed 3 months before (M−3) and 3 months after (M+3) STN-DBS with 18FDG-PET and the Apathy Evaluation Scale.

Results: Apathy had significantly worsened at M+3 after STN-DBS. Positive correlations were observed between this variation in apathy scores and changes in glucose metabolism, especially in the right frontal middle gyrus (Brodmann area [BA] 10) and right inferior frontal gyrus (BA 46 and BA 47). Negative correlations between the two were observed in the right posterior cingulate gyrus (BA 31) and left medial frontal lobe (BA 9).

Conclusion: These preliminary results confirm the role of the subthalamic nucleus in associative and limbic circuitry in humans and suggest that it is a key basal ganglia structure in motivation circuitry.

Neurology® 2009;73:1746–1751

Glossary

Apathy Evaluation Scale (clinician version); Association for Methodology and Documentation in Psychiatry anxiety scale; Brodmann area; levodopa equivalent dose; Montgomery-Åsberg Depression Rating Scale; Mattis Dementia Rating Scale; Mini-International Neuropsychiatric Interview; Parkinson disease; subthalamic nucleus deep brain stimulation; Trail Making Test; Unified Parkinson’s Disease Rating Scale; Wisconsin Card Sorting Test.
METHODS

Participants. The sample consisted of a series of 12 patients with medically intractable PD who underwent bilateral STN-DBS at the University Hospital in Rennes, France. All patients met the clinical criteria of the United Kingdom PD Society Brain Bank for idiopathic PD and were found to display a change in their motivational behavior in postoperative conditions, with increased apathy scores. Among a larger group of patients with PD (n = 18), assessed with [18F]FDG-PET and apathy evaluation scale in pre and post STN-DBS, we selected 12 patients who showed an impairment of apathy evaluation scale in postoperative conditions.

Standard selection and exclusion criteria for surgery were applied to all patients.5 In particular, brain atrophy was excluded on the basis of a preoperative MRI scan. There were 8 men and 4 women. Mean (±SD) age at surgery was 57.4 (±8.00) years. All 12 patients with PD were right-handed, according to the criteria of the Edinburgh Handedness Inventory. Mean (±SD) disease duration at surgery was 11.2 (±2.4) years. The total (LED) was calculated on the basis of correspondences adapted from Lozano et al.10

PET imaging procedure. All subjects underwent 2 [18F]FDG-PET scans in a resting state. The first one was performed 3 months before surgery and the second one 3 months after surgery (“on” stimulation), with their antiparkinsonian medication on both occasions.

PET measurements were performed using a dedicated Discovery ST PET scanner (GEMS, Milwaukee, WI) in 2D mode, with an axial field of view of 15.2 cm. A 222–296 MBq injection of [18F]-FDG was administered IV under standardized conditions (in a quiet, dimly lit room with patient’s eyes and ears open). During the acquisition, the patient’s head was immobilized using a head holder. A crosshair laser system was used to ensure stable and reproducible positioning. A 20-minute 2D emission scan was performed 30 minutes postinjection. Attenuation correction was provided by X-ray CT prior to the emission scan. These studies were performed with the subjects positioned at the center of the field of view. Following scatter, dead time, and random corrections, PET images were reconstructed by means of 2D filtered backprojection, yielding 47 contiguous transaxial 3.75-mm-thick slices.

PET image transformation. We used the same method for the present study as that described in our previous one.2 The data were analyzed using Statistical Parametric Mapping software (SPM2: Wellcome Department of Cognitive Neurology, London, UK) written in Matlab version 7 (The MathWorks, Inc., Sherborn, MA). Statistical parametric maps are spatially extended statistical processes used to characterize specific regional effects in imaging data. They combine the general linear model (to create the statistical map) with the theory of Gaussian fields to make statistical inferences about regional effects.22

All patient images were first realigned and spatially normalized to a standard stereotactic space according to the Talairach-Tournoux atlas.22 An affine transformation was performed to determine the 12 optimal parameters for registering the brain onto the template. The subtle differences between the transformed image and the template were then removed by applying a nonlinear registration method. Finally, spatially normalized images were smoothed, using an isotropic 12-mm full-width at half-maximum isotropic Gaussian kernel to compensate for interindividual anatomic variability and render the imaging data more normally distributed.

Statistical analysis. Psychiatric and neuropsychological data. Given the small number of patients included in the study,
Clinical and motor results. A significant motor improvement was observed 3 months after surgery, as evidenced by changes in the UPDRS motor score when "off" levodopa \((p = 0.007)\). A significant decrease in LED was also observed after surgery \((p = 0.02)\) (mean ± SD 1,200 mg ± 426.5 before STN-DBS and 796.66 mg ± 620 after STN-DBS). Table 1 shows the effects of surgery on motor symptoms.

**Psychiatric results.** The results are presented in table 2. Apathy scores increased significantly post-STN-DBS \((p = 0.002)\). No correlation was found between increase of apathy and reduction in medication dose.

The MINI had failed to reveal any notable psychiatric condition prior to surgery.

There was no difference between the mean MADRS scores before surgery \((M – 3)\) and at \(M + 3\) under STN-DBS \((p = 0.5)\).

There was no significant difference between the mean preoperative \((M – 3)\) and postoperative \((M + 3)\) AMDP-AT scores \((p = 0.2)\).

**Neuropsychological results.** None of the patients included in this study had dementia (Mattis: mean ± SD = 140 ± 3.2). No significant difference was found between the preoperative and postoperative conditions for the neuropsychological background tests, except for the interference score of the Stroop test \((p = 0.05)\) and the number of perseverative WCST errors \((p = 0.02\) and \(p = 0.01)\).

Cerebral metabolic results. **First step:** Differences between preoperative and postoperative "on" stimulation conditions. Areas of significant difference found by comparing the patients in preoperative and postoperative "on"-stimulation conditions are shown in figure 1.

In our analysis of postoperative decreases in metabolism, 3 clusters were significant. Hypometabolism was observed in the bilateral anterior cingulate gyrus (right and left Brodmann area [BA] 24) and left superior frontal gyrus (BA 8 and 9).

When we studied postoperative increases in metabolism, 2 clusters were found to be significant. Hypermetabolism was observed in the bilateral cerebellum and right inferior parietal lobe (BA 40).

**Second step:** Correlation studies. Correlation between apathy and changes in glucose metabolism. All significant findings obtained by correlating changes in glucose metabolism with modified apathy scores (poor performances) are summarized in table 3.

Increase of metabolism was correlated with modified apathy scores in the right frontal lobe, middle gyrus (BA 10) and inferior gyrus (BA 45 and 46),

---

**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>&quot;Off&quot; -dopa score</th>
<th></th>
<th>&quot;On&quot;-dopa score</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preoperative</td>
<td>Postoperative</td>
<td>Preoperative</td>
<td>Postoperative</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>(baseline)</td>
<td>(stim M-3)</td>
<td>(baseline)</td>
<td>(stim M-3)</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr</td>
<td>31.1 ± 12.7</td>
<td>14.3 ± 9.0</td>
<td>6.7 ± 4.9</td>
<td>5.5 ± 3.4 (NS)</td>
</tr>
<tr>
<td>Schwab &amp; England (%)</td>
<td>70.0 ± 23.5</td>
<td>74.5 ± 22.9  (NS)</td>
<td>93.0 ± 6.7</td>
<td>90.9 ± 9.4 (NS)</td>
</tr>
<tr>
<td></td>
<td>2.2 ± 11.1</td>
<td>1.6 ± 12 (NS)</td>
<td>1.1 ± 0.8</td>
<td>0.9 ± 1.0 (NS)</td>
</tr>
</tbody>
</table>

*p = 0.007.

UPDRS – Unified Parkinson’s Disease Rating Scale; NS – nonsignificant.

---

**Table 2**

<table>
<thead>
<tr>
<th></th>
<th>Preoperative condition (baseline M-3)</th>
<th>Postoperative condition (M+3)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AES</td>
<td>30.91 ± 4.07</td>
<td>39.16 ± 6.05</td>
<td>0.002</td>
</tr>
<tr>
<td>MADRS</td>
<td>4.8 ± 6.0</td>
<td>6.2 ± 8.2</td>
<td>0.5</td>
</tr>
<tr>
<td>AMDP-AT</td>
<td>6.5 ± 6.1</td>
<td>11.1 ± 9.6</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

AES – Apathy Evaluation Scale; MADRS – Montgomery–Åsberg Depression Rating Scale; AMDP-AT – Association for Methodology and Documentation in Psychiatry-Anxiety.
temporal lobe (fusiform gyrus, BA 20), and postcentral gyrus (BA 43) (figure 2).

Decrease of metabolism was correlated with modified apathy scores in the bilateral cingulate gyrus (BA 31) and left middle frontal gyrus (BA 9).

DISCUSSION

This study correlates motivational changes with modifications in cerebral glucose metabolism in patients with PD following STN-DBS. Our group had already demonstrated that apathy can be induced by STN-DBS in patients with PD.25 In the present study, we confirmed that motivational impairment is not correlated with decrease of levodopa. We provided here, in 12 patients with PD, a preliminary demonstration of correlations between changes of glucose metabolism, mainly in the right prefrontal cortex (BA 10, 45, and 46), in the right posterior cingulate gyrus (BA 31), and left middle frontal gyrus (BA 9), and increased apathy scores after STN-DBS. The postoperative PET scans were performed 3 months after surgery, so that we could exclude the microlesional effects of STN implantation which failed to find any significant clusters when preoperative FDG scans were compared with scans performed 3.8 ± 1.8 months after STN-DBS in the “off”-levodopa condition.26

Furthermore, in this series of patients, we were able to confirm our previous findings of metabolic modifications pre- and poststimulation.6 Postoperative hypometabolism was observed in the bilateral anterior cingulate gyrus (BA 24 and 32) and prefrontal lobe (BA 8 and BA 9), and postoperative hypermetabolism was observed in the bilateral cerebellum and right inferior parietal lobe (BA 40).

From a methodologic point of view, the severe motor deficit in the “off-drug” state prohibited reliable neuropsychological testing in patients with PD with advanced disease. In order to perform both metabolic and behavioral assessments in the same medication condition, our study design therefore compared “on-drug” states in both PET and neuropsychological testing. It is worth noting that, in a recent study, an analysis of covariance using daily consumption of dopaminergic medication as the covariate of interest failed to reveal any significant relationship between the postoperative reduction in medication and functional changes at rest.27

Clinically, apathy is defined as a decrease in or lack of motivation, interest, or emotions, which cannot be ascribed to any impairment of consciousness or any emotional or cognitive disorder,11 leading to a complex emotional withdrawal with emotional, behavioral, and cognitive dimensions, as reflected by the different subscores of Marin’s apathy scale.28 The processes responsible for apathy were divided into 3 subtypes: emotional-affective, cognitive, and autovolition.29 The latter refers to a fundamental deficit in the activation of behavior that is not primarily due to an emotional or cognitive deficit. Apathy is therefore a clinical consequence of the disruption of the PFC-basal ganglia axis, one of the functional systems involved in the control of voluntary behavior.30

<table>
<thead>
<tr>
<th>Region</th>
<th>Talairach coordinates</th>
<th>Z value</th>
<th>Voxel number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive correlations with apathy scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right parietal lobe, postcentral gyrus, BA 43</td>
<td>71 -19 16</td>
<td>3.62</td>
<td>141</td>
</tr>
<tr>
<td>Right frontal lobe, inferior gyrus, BA 46</td>
<td>55 41 13</td>
<td>3.36</td>
<td>119</td>
</tr>
<tr>
<td>Right frontal lobe, inferior frontal gyrus, BA 45</td>
<td>50 16 14</td>
<td>3.34</td>
<td>249</td>
</tr>
<tr>
<td>Right frontal lobe, middle frontal gyrus, BA 10</td>
<td>30 47 9</td>
<td>3.29</td>
<td>249</td>
</tr>
<tr>
<td>Left temporal lobe, fusiform gyrus, BA 20</td>
<td>-60 -16 -34</td>
<td>3.20</td>
<td>42</td>
</tr>
<tr>
<td>Negative correlations with apathy scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left limbic lobe, cingulate gyrus, BA 31</td>
<td>-10 -41 30</td>
<td>3.51</td>
<td>167</td>
</tr>
<tr>
<td>Right limbic lobe, cingulate gyrus, BA 31</td>
<td>6 -45 41</td>
<td>3.45</td>
<td>167</td>
</tr>
<tr>
<td>Left frontal lobe, middle frontal gyrus, BA 9</td>
<td>-55 15 61</td>
<td>3.28</td>
<td>280</td>
</tr>
</tbody>
</table>

BA – Brodmann area.
involved in the generation and control of self-generated purposeful behavior. From this perspective, a prefrontal-like syndrome (including apathy) may be encountered in diseases mainly involving the basal ganglia or following basal ganglia lesions. However, more subtle clinical analyses may reveal functional differences between lesions affecting the PFC or the basal ganglia in different anatomic or functional territories (e.g., cognitive and limbic territories) within these structures. Thus, according to this model, impaired emotional-affective processing in apathy would be caused by lesions or dysfunctions in the orbital and medial PFC (BA 13, 14, ventral part of BA 10), cognitive dysfunction would be explained by lesions or dysfunctions in the dorsolateral PFC (BA 9, 46, lateral part of BA 10), and behavioral disturbances (autoactivation deficit) would be associated with lesions or dysfunctions in the medial PFC (medial part of BA 9/10) and dorsal and ventral cingulate gyrus.

The neuroanatomy of apathy has already been explored in patients with AD in functional brain imaging studies, mainly with SPECT. Results have revealed the involvement of the anterior cingulate gyrus and inferior frontal regions in apathetic patients with AD. These results are in line with our neuroimaging findings, showing that apathy scores are correlated with modifications in glucose metabolism in the medial part of BA 10, in the cingulate gyrus, mainly the posterior part close to dorsal BA 24, and in BA 46 and BA 9. In another FDG-PET study, a significant reduced activity in the bilateral anterior cingulate region extending inferiorly to the medial orbitofrontal region was observed in subjects with AD and apathy. Morphometric studies have also been conducted in AD, focusing on its neuropsychiatric symptoms. Using voxel-based morphometry, apathy was associated with gray matter density loss in the anterior cingulate and bilateral frontal cortex, which again is in line with our own results and those of other authors. All these results underline the stability of apathy’s neural substrate across different pathologies.

The metabolic cortical modifications following STN-DBS suggest that the STN region influences widespread cortical projection areas. The STN is described as occupying a central position in each of the 5 corticobasal ganglia-thalamocortical circuits, which each have specific motor, oculomotor, associative, or limbic functions. Animal neuroanatomic studies have demonstrated that the STN can be functionally divided into sensorimotor (dorsolateral), limbic (medial), and cognitive-associative (ventromedial) areas. Although the motor neurons (dorsolateral territory) are the target of functional surgery, our data suggest that other territories may also be affected. The very small size of the STN (10 mm in the mediolateral axis, 8 mm in the anteroposterior axis, and 6 mm in the ventrodorsal axis) could account for current diffusion and for the active effects of stimulation on territories other than the motor one. Several clinical studies (for a review, see Temel et al.) have shown that modulating neuronal activity in the STN results in substantial improvements in motor symptoms, but may be accompanied by behavioral changes. All the data presented in these studies underline the potent regulatory function of the STN in processing associative and limbic information sent to the cortical and subcortical regions. Even if the prevalence of apathy in PD remains under debate, the fact that we studied parkinsonian patients means that we can make only limited speculations about the role of the STN and cingulate cortex in motivation in normal brains, although it is worth noting that our patients with PD had a satisfactory neuropsychological status and their preoperative MRI scans were normal.

As in previous imaging studies, the present work confirms this hypothesis and suggests that the STN participates in the apathy’s neural substrate.

Received May 5, 2009. Accepted in final form August 17, 2009.

REFERENCES

Subthalamic nucleus stimulation in Parkinson disease induces apathy: A PET study


Neurology 2009;73:1746-1751
DOI: 10.1212/WNL.0b013e3181c34b34

This information is current as of January 18, 2010

Updated Information & Services
including high-resolution figures, can be found at:

http://www.neurology.org/cgi/content/full/73/21/1746

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):

PET
http://www.neurology.org/cgi/collection/pet

Parkinson's disease/Parkinsonism
http://www.neurology.org/cgi/collection/parkinsons_disease_parkinsonism

All Neuropsychology/Behavior
http://www.neurology.org/cgi/collection/all_neuropsychology_behavior

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:

http://www.neurology.org/misc/Permissions.shtml

Reprints
Information about ordering reprints can be found online:

http://www.neurology.org/misc/reprints.shtml