Preoperative factors of apathy in subthalamic stimulated Parkinson disease: A PET study
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Preoperative factors of apathy in subthalamic stimulated Parkinson disease
A PET study

ABSTRACT

Objective: The current literature provides discrepant results regarding preoperative sociodemographic and clinical factors, and no information about preoperative cerebral metabolic patterns associated with apathy after subthalamic nucleus deep brain stimulation (STN-DBS) in Parkinson disease.

Methods: To resolve this issue, we set out to identify preoperative metabolic patterns and sociodemographic and clinical factors associated with increased apathy after STN-DBS. Forty-four patients with Parkinson disease were enrolled in this study. They all underwent STN-DBS. Metabolic activity was assessed with F-18 fluorodeoxyglucose PET 3 months before surgery. Apathy was assessed on the Apathy Evaluation Scale 3 months before and after STN-DBS. We controlled for preoperative age, levodopa therapy, and overall cognitive functions.

Results: Increased apathy after STN-DBS was significantly associated with reduced preoperative metabolism within the right ventral striatum. None of the sociodemographic and clinical variables tested were associated with apathy after STN-DBS.

Conclusions: Preoperative PET, but not sociodemographic or clinical factors, is associated with apathy after STN-DBS.

GLOSSARY

AES = Apathy Evaluation Scale; AMDP-TA = Association for Methodology and Documentation in Psychiatry—Trait Anxiety; A-STN-DBS = subthalamic nucleus deep brain stimulation postoperative apathy; DRT = dopamine replacement therapy; 18-FDG-PET = F-18 fluorodeoxyglucose PET; GLM = general linear model; LEDD = levodopa equivalent daily dose; MCST = Modified Card Sorting Test; MDRS = Mattis Dementia Rating Scale; PD = Parkinson disease; ROI = region of interest; STN-DBS = subthalamic nucleus deep brain stimulation; TMT = Trail Making Test; UPDRS-III = Unified Parkinson's Disease Rating Scale–III; VS = ventral striatum; WFU = Wake Forest University.

Several nonmotor side effects, including apathy,1–4 are described following uni- and bilateral subthalamic nucleus deep brain stimulation (STN-DBS), compromising the overall surgical outcome5 and impairing quality of life.6

Some results suggest that age at surgery,3,7 wide preoperative variations in anxiety during a dopamine challenge, and the presence of preoperative nonmotor fluctuations4 are associated with greater postoperative apathy (A-STN-DBS). Identifying the clinical predictors of A-STN-DBS will help clinicians to select those patients who will benefit most from STN-DBS. However, attempts have so far lacked consistency.

The STN is a motor, cognitive, but also limbic structure,8 and it is suggested that A-STN-DBS occurs as a result of stimulating the limbic cortico-subcortical loops,9 independently of the reduction in dopamine replacement therapy (DRT) after STN-DBS.1,10 Another hypothesis is that A-STN-DBS stems from dopamine mesolimbic pathway degeneration that is unmasked by the DRT reduction.4 Thus, A-STN-DBS appears to be a complex and multifactorial behavioral disorder, arising from the massive disruption by STN limbic stimulation and DRT reduction of a gradual degenerative process.

*These authors contributed equally to this work.

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.
We sought to pinpoint preoperative metabolic activity associated with greater A-STN-DBS in Parkinson disease (PD) using F-18 fluorodeoxyglucose PET (18-FDG-PET) and a region-of-interest (ROI) approach with the Wake Forest University (WFU) PickAtlas toolbox.\(^1\) We hypothesized that preoperative metabolic activity within brain regions involved in goal-oriented behaviors is associated with greater A-STN-DBS, whereas potential clinical predictors will lack sensitivity.

**METHODS** Participants, study design, standard protocol approvals, and patient consents. All patients were consecutively recruited at Rennes University Hospital, France, between 2005 and 2012. All 44 patients with PD (24 males) met the clinical criteria of the Parkinson’s UK Brain Bank for idiopathic PD, and exclusion criteria for STN-DBS\(^1\) were applied, including severe cognitive impairments ( Mattis Dementia Rating Scale [MDRS] \(^1\) score <130) and major depression (according to the Mini-International Neuropsychiatric Interview 500\(^1\)). All patients underwent sociodemographic and clinical assessment 3 months before and after STN-DBS. All patients benefited from 18-FDG-PET 3 months before STN-DBS, under medication as prescribed by their neurologist. Patients with missing data were excluded from the study. Written informed consent was obtained from each participant and the study was approved by the local ethical standard committee on human experimentation.

**Psychiatric assessment.** Apathy was assessed on the Apathy Evaluation Scale (AES), Clinician Version.\(^1\) This is an 18-item scale with scores ranging from 18 to 72, the highest scores reflecting severe apathy. It is recognized as the most psychometrically robust apathy scale across all populations.\(^1\)

The main variable is the differential score (\(\Delta\)) between postoperative and preoperative AES (\(\Delta\)AES = postoperative AES – preoperative AES). The \(\Delta\)AES distribution is displayed in figure 1. Preoperative trait anxiety was assessed by the Montgomery and Åsberg Depression Rating Scale.\(^1\)

**Neuropsychological assessment.** Executive functions were assessed by means of a neuropsychological battery that included the Modified Card Sorting Test (MCST),\(^2\) the Trail Making Test (TMT),\(^3\) semantic and phonemic fluency, and the Stroop test.\(^4\)

**Motor assessment.** The motor part of the Unified Parkinson’s Disease Rating Scale–III (UPDRS-III) was administered both when patients were in the off-drug condition (i.e., after a 12-hour period without their DRT) and during a dopamine challenge (usual morning dose + 50 mg levodopa) in order to assess their motor dopamine response. A levodopa equivalent daily dose (LED) was calculated for each patient according to the DRT prescribed by their neurologist.\(^5\) The quantitative effect of STN-DBS was calculated as follows: pre-STN-DBS\(_{off\text{ levodopa}} – \) post-STN-DBS\(_{on\text{ min } & \text{ off levodopa}}/\)pre-STN-DBS\(_{off\text{ levodopa}} \times 100.\(^6\)

Sociodemographic and preoperative motor, psychiatric, and cognitive data are provided in the table.

**PET imaging procedure.** PET measurements were performed using a Discovery ST PET scanner (axial resolution): Y coordinates from the field of view center: 1 cm (full width at half maximum = 5.1 mm and full width with the tenth of maximum = 9.4 mm); Y coordinates from the field of view center: 10 cm (full width at half maximum = 6.2 mm and full width with the tenth of maximum = 12.6 mm; General Electric Medical Systems, Milwaukee, WI) in 2-dimensional (2D) mode, with an axial field of view of 15.2 cm. A 222- to 296-MBq injection of F-18 FDG was administered IV under standardized conditions. Stable positioning was attained using a crosshair laser system. Thirty minutes after the injection, patients were positioned at the center of the field of view and a 20-minute 2D scan was acquired. After x-ray CT-based attenuation, scatter, deadtime, and random corrections, the PET images were reconstructed with 2D filtered back-projection, yielding 47 contiguous transaxial 3.75-mm-thick slices.

The data were analyzed with Statistical Parametric Mapping software\(^7\) (SPM8; Wellcome Department of Cognitive Neurology, London) written in MATLAB version 7.9.0 (MathWorks, Natick, MA). Statistical parametric maps combine the general linear model (GLM) with the random field theory to make statistical inferences about regional effects.\(^8\)

All images were realigned and spatially normalized to a standard stereotactic space according to the Talairach-Tournoux atlas.\(^9\) Rigid and nonlinear transformations enable coregistering the images together. Then, images are spatially normalized onto the template space. Finally, the coregistered and normalized images are smoothed, using an isotropic 12-mm full width at half maximum isotropic gaussian kernel to ensure normal distribution and respect parametric statistics assumptions. The effects of whole-brain metabolism (i.e., global normalization) are removed by scaling proportionally the count of each voxel to the total brain count.

**Neurosurgery.** Methodology. Quadripolar DBS electrodes (3389; Medtronic, Minneapolis, MN) were implanted bilaterally in the subthalamic nucleus.\(^10\) The exact locations of the 2 selected

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**Figure 1** \(\Delta\)AES distribution within the sample (n = 44)

![Graph showing \(\Delta\)AES distribution](image-url)

AES = Apathy Evaluation Scale.

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One patient with tremor-dominant Parkinson disease had UPDRS-III Off scores of 10.

Electrode locations and parameters. The selected contacts were located 14.2 ± 1.6 mm (17.1–10.8) lateral to, 2.7 ± 1.7 mm (−5.3 to −1.5) posterior to, and 1.3 ± 1.9 mm (3.5–3.2) below the midcommissural point on the left side, and 13.5 ± 2.3 mm (10.8–18.1) lateral to, 2.5 ± 1.4 mm (4.3 to −1.9) posterior to and 1.2 ± 3.1 mm (6.9 to −6.4) below the midcomissural point on the right side. In all patients, chronic stimulation was monopolar. The stimulation characteristics are the ones that better improve motor scores: mean pulse width 60.7 μs for the right side (SD = 4.6) and 60.7 μs (SD = 4.6) for the left side, mean frequency 132.1 Hz (SD = 6.2) for the right side and 131.5 Hz (SD = 4.4) for the left side, and mean voltage 2.1 V (SD = 0.6) for the right side and 2.1 V (SD = 0.6) for the left side.

Statistics. Clinical factors. Because all the variables were normally distributed, we calculated correlations between the ΔAES and the sociodemographic and preoperative motor, cognitive, and psychiatric measures. We conducted independent *t* tests between male and female participants to determine whether there was a sex effect. The significance threshold was set at *p* = 0.05. To check for regression to the mean between preoperative apathy and ΔAES, we determined the so-called *a*(a − *b*) effect by examining the covariance between preoperative AES and ΔAES.23 If the preoperative AES score was found to be significantly related to ΔAES without any regression to the mean effect, we would also include preoperative AES as a covariate in the imaging analysis.

PET data: Statistical parametric mapping. ROI definition. The ROI mask includes the cerebral bases of apathy in PD24–27 and A-STN-DBS2,4 based on previous literature.2,4,24,27 We built our ROI mask using the automated anatomical labeling atlas41 from the WFU PickAtlas toolbox28 implemented in SPM8. The following regions were chosen as ROIs, all bilaterally: the superior frontal gyrus and its orbital part, the middle frontal gyrus and its orbital part, the inferior frontal gyrus and its orbital part, the anterior and posterior cingulate cortices, the caudate nucleus, and the putamen.

<table>
<thead>
<tr>
<th>Features</th>
<th>Range</th>
<th>Mean</th>
<th>SD</th>
<th>Pearson <em>r</em> with ΔAES</th>
<th><em>p</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>36–68</td>
<td>56.3</td>
<td>7.5</td>
<td>0.2</td>
<td>0.9</td>
</tr>
<tr>
<td>ΔAES</td>
<td>−11 to 16</td>
<td>0.18</td>
<td>5.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative AES (18–72)</td>
<td>18–44</td>
<td>31.4</td>
<td>6.4</td>
<td>−0.27</td>
<td>0.07</td>
</tr>
<tr>
<td>Postoperative AES (18–72)</td>
<td>18–51</td>
<td>31.6</td>
<td>7.1</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>5–21</td>
<td>11.4</td>
<td>4.1</td>
<td>−0.09</td>
<td>0.55</td>
</tr>
<tr>
<td>Preoperative MADRS (0–60)</td>
<td>0–17</td>
<td>4.45</td>
<td>4</td>
<td>−0.28</td>
<td>0.07</td>
</tr>
<tr>
<td>Preoperative AMDP-TA (0–85)</td>
<td>0–40</td>
<td>9.45</td>
<td>8.7</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Preoperative UPDRS-III off dopamine (0–108)</td>
<td>10–67</td>
<td>32.6</td>
<td>12.8</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Preoperative UPDRS-III on dopamine (0–108)</td>
<td>0–23</td>
<td>7.5</td>
<td>5.2</td>
<td>0.06</td>
<td>0.7</td>
</tr>
<tr>
<td>Postoperative UPDRS-III off dopamine-off stimulation (0–108)</td>
<td>8–61</td>
<td>29.2</td>
<td>12.7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Postoperative UPDRS-III off dopamine-on stimulation (0–108)</td>
<td>1–37</td>
<td>15.9</td>
<td>9.6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Postoperative UPDRS-III on dopamine-off stimulation (0–108)</td>
<td>0–27</td>
<td>8.8</td>
<td>7.1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Postoperative UPDRS-III on dopamine-on stimulation (0–108)</td>
<td>0–11</td>
<td>5.2</td>
<td>2.5</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Preoperative motor dopamine response</td>
<td>5–64</td>
<td>25.2</td>
<td>11.7</td>
<td>−0.03</td>
<td>0.8</td>
</tr>
<tr>
<td>Preoperative LEDD, mg/d</td>
<td>240–2,990</td>
<td>1,280.8</td>
<td>632.4</td>
<td>0.25</td>
<td>0.09</td>
</tr>
<tr>
<td>LEDD reduction after STN-DBS, mg/d</td>
<td>−1,470 to 455</td>
<td>−390.9</td>
<td>−413.1</td>
<td>0.23</td>
<td>0.1</td>
</tr>
<tr>
<td>Preoperative MDRS (144)</td>
<td>132–144</td>
<td>140.6</td>
<td>2.5</td>
<td>0.17</td>
<td>0.3</td>
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<tr>
<td>Preoperative stroop interference score</td>
<td>−22.6 to 15.1</td>
<td>1.2</td>
<td>7.6</td>
<td>−0.25</td>
<td>0.1</td>
</tr>
<tr>
<td>Preoperative TMT B-A</td>
<td>12–309</td>
<td>64.4</td>
<td>54</td>
<td>0.16</td>
<td>0.3</td>
</tr>
<tr>
<td>Preoperative semantic fluency</td>
<td>13–53</td>
<td>28.1</td>
<td>9.8</td>
<td>0.05</td>
<td>0.7</td>
</tr>
<tr>
<td>Preoperative phonemic fluency</td>
<td>12–36</td>
<td>22.6</td>
<td>6.8</td>
<td>0.06</td>
<td>0.7</td>
</tr>
<tr>
<td>Preoperative MCST-Criteria</td>
<td>3–6</td>
<td>5.7</td>
<td>0.7</td>
<td>−0.18</td>
<td>0.26</td>
</tr>
<tr>
<td>Preoperative MCST-Errors</td>
<td>0–18</td>
<td>4.5</td>
<td>4.7</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Preoperative MCST-Perserverations</td>
<td>0–10</td>
<td>1.4</td>
<td>2.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Table: Sociodemographic and preoperative motor, psychiatric, and cognitive variables (n = 44)

Abbreviations: ΔAES = postoperative AES – preoperative AES; AES = Apathy Evaluation Scale; AMDP-TA = Association for Methodology and Documentation in Psychiatry–Trait Anxiety; LEDD = levodopa equivalent daily dose; MADRS = Montgomery and Åsberg Depression Rating Scale; MCST = Modified Card Sorting Test; STN-DBS = subthalamic nucleus deep brain stimulation; TMT = Trail Making Test; UPDRS-III = Unified Parkinson’s Disease Rating Scale–III.

One patient with tremor-dominant Parkinson disease had UPDRS-III Off scores of 10.
**RESULTS**

**Sociodemographic and clinical factors.** Pearson correlation coefficients and \( p \) values are displayed in the table. Because we found that preoperative AES and \( \Delta AES \) were inversely associated with a trend toward significance, we sought for a regression to the mean effect between those 2 variables. The method\(^2^\) applied shows that the correlation between the preoperative AES score and \( \Delta AES \) is not accounted for by a regression to the mean effect.

We did not find any relationship between \( \Delta AES \) and any of the demographic (age), motor (disease duration, LEDD, UPDRS-III off and on dopamine, dopamine motor response, LEDD reduction), cognitive (MDRS, Stroop interference score, TMT B-A, MCST criteria, MCST errors and MCST perseverative answers, semantic and phonemic fluency scores), or psychiatric (AMDP-TA scores) variables. We did not find any \( \Delta AES \) differences between male and female participants (\( p = 0.7 \)). Mean LEDD reduction was 28.6% after STN-DBS within the whole sample. The quantitative effect of STN-DBS was equal to 51%.

**PET results.** We found that decreased metabolism within the right ventral striatum (VS) (Talairach coordinates: \( x = 18, y = 20, z = -8; z = 3.12, \) cluster threshold \( k = 100 \)) was associated with greater \( \Delta AES \) (figure 2). We did not find any brain region where increased metabolism was associated with greater \( \Delta AES \). We found that preoperative metabolism within the identified cluster was inversely associated with \( \Delta AES \) (\( r = -0.48; p = 0.002 \)). Figure 3 displays the correlation between the \( \beta \) values within the right VS and \( \Delta AES \).

**DISCUSSION**

Our results can be interpreted in light of previous results supporting the theory of degeneration of the mesolimbic dopamine pathway (which includes the VS) in patients who develop apathy after STN-DBS.\(^4\) Mesolimbic dopamine manipulations in animals suggest that dopamine has a key role in regulating motivated behaviors, especially their reward-seeking (wanting, or anticipating).\(^3^0\) Wanting is associated with the anticipation phase of a reward and VS activity;\(^3^1\) the latter has also been related to apathy in schizophrenia.\(^3^2\) Alternatively, our results may be attributable to broad lesions of the limbic cortico-subcortical loop. Indeed, apathy in PD is likely to be associated with decreased gray matter volumes within the anterior cingulate and the orbitofrontal cortex,\(^2^5\) both part of the limbic loop.\(^3^5\) The right-sided lateralization is consistent with a previous study that found that the right side of the brain is particularly involved in apathy’s metabolic network in PD.\(^2^4\) The predominance of the right side in apathy’s cerebral bases is also described in Alzheimer disease.\(^3^5\) Moreover, some researchers suggest that the reward-related dopamine system is predominantly associated with the right VS, especially in men.\(^3^6\) The age-related decline in dopamine transmission is suggested to be lower within the right (vs left) anterior caudate and putamen.\(^3^7\) These results are consistent with the decreased metabolism within the right VS and greater A-STN-DBS in our sample of patients with a mean age of 56.3 (±7.5) years and a slight predominance of men (24 of 44 patients). When the present result is set against the available literature, it suggests that A-STN-DBS could be either related to...
abnormal preoperative limbic dopamine secretion or dysfunctional cortico-subcortical limbic loop in combination with the stimulation of the limbic and associative parts of the STN. In the context of the gradual degeneration of motor and limbic dopamine neurons in PD, it suggests that STN-DBS brutally disrupts a precarious preoperative balance among brain plasticity, residual dopamine resources, and dopaminergic medication.

The clinical and sociodemographic factors associated with increased apathy after STN-DBS are inconsistent across studies. Middle-aged (vs older) patients are found to experience a steeper increase in apathy in unilateral stimulation, whereas age is found to magnify apathy after bilateral STN-DBS. Our results do not highlight age as an associated factor for increased apathy after bilateral STN-DBS. However, our sample included patients who were younger (mean age 56.3 ± 7.5 years) than those of the latter study (mean = 60.1 ± 8.7 years), and our follow-up time point was 3 months after surgery, as opposed to 12 months in their study. These differences may account for the discrepant results. The presence of nonmotor fluctuations and a greater variation in Beck Anxiety Inventory scores during a dopamine challenge in the off-drug state may be associated with apathy after STN-DBS. There was, however, no significant association between trait anxiety and apathy after STN-DBS in our study, possibly because we used a different anxiety scale. We also failed to find an association between motor score variations during a dopamine challenge and higher apathy scores after STN-DBS. This is in line with the absence of reports of significant links between motor structure metabolism and A-STN-DBS both here and in previous research. We failed to find association between preoperative AES and ΔAES scores. Instead, we found an inverse relationship between the 2, with a trend toward significance that was not accounted for by a regression to the mean effect. However, had the correlation between preoperative AES and ΔAES been clearly significant, there might have been a regression to the mean effect. Further studies with larger samples are needed to test this hypothesis. The LEDD reduction observed here was smaller than that in other reports, but we found a similar effect of the stimulation on the UPDRS-III scores and we attribute this to the neurologists’ sensitization toward the nonmotor effect of LEDD reduction after STN-DBS, such as apathy. Our negative results regarding the sociodemographic and clinical factors are in line with the discrepant results in the literature. We suggest that these inconsistencies can be ascribed to a lack of homogeneity in the studies conducted thus far, combined with the absence of specific tools for spotting altered limbic functions.

Several limitations must be borne in mind when interpreting these results. First, our research focus on apathy scores 3 months after STN-DBS, and some results, suggest that apathy scores may continue to increase beyond the 3-month mark. Even so, the literature suggests that 3 months is a reasonable point at which to study the chronic effects of bilateral STN-DBS, because any motor, cognitive, or psychiatric complications arising from the surgery itself are unlikely to occur after 3 months. Second, the mean ΔAES score is 0.18, suggesting minimal variation in apathy across the group as a whole, whereas our sample displays a relatively wide range of ΔAES scores (−11 to +16) that yields stronger results at the metabolic level. Further studies are warranted to replicate this result with larger samples and 2 measurement points after surgery. They should also specifically address the predictive value of individual preoperative imaging patterns in patients candidate to STN-DBS combining a 1-vs-many 2-sample t-test univariate and multivariate pattern analysis.

This study suggests that only metabolic activity within the right VS is associated with apathy after STN-DBS in patients with PD without depression and dementia. By contrast, none of the sociodemographic and clinical factors tested were found to be related to apathy. This suggests that, if replicated,
preoperative activity within the right VS will be a candidate biomarker for predicting apathy after STN-DBS at an individual level and result in a major improvement in the care of patients with PD.

AUTHOR CONTRIBUTIONS
G.H. Robert: psychiatric assessment, statistical analyses, SPM analyses, writing of the first draft. F. Le Jeune: PET acquisition, SPM analyses, conception of the study, writing of the first draft. C. Lozachmeur: psychiatric assessment, revision of the manuscript. S. Drapier: neurologic assessment, revision of the manuscript. T. Dondaine: neuropsychological assessment, revision of the manuscript. J. Péron: neuropsychological assessment, revision of the manuscript. J.-F. Houvenaghel: neuropsychological assessment, revision of the manuscript. D. Travers: conception of the study, revision of the manuscript. P. Sauleau: conception of the study, revision of the manuscript. B. Miller: conception of the study, revision of the manuscript. M. Vérin: conception of the study, revision of the manuscript. T. Dondaine: neuropsychological assessment, revision of the manuscript. S. Drapier: neurologic assessment, revision of the manuscript. C. Lozachmeur: psychiatric assessment, writing of the first draft. F. Le Jeune: PET acquisition, SPM analyses, conception of the study, writing of the first draft. M. Vérin: conception of the study, revision of the manuscript. F. Le Jeune: PET acquisition, SPM analyses, conception of the study, writing of the first draft. C. Lozachmeur: psychiatric assessment, writing of the first draft. F. Le Jeune: PET acquisition, SPM analyses, conception of the study, writing of the first draft. M. Vérin: conception of the study, revision of the manuscript.


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