Apathy in patients with Parkinson disease without dementia or depression: A PET study
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Apathy in patients with Parkinson disease without dementia or depression
A PET study

ABSTRACT
Objective: We sought to identify apathy metabolic bases in Parkinson disease (PD).
Methods: A total of 45 patients with PD who were not clinically depressed [Montgomery-Åsberg Depression Rating Scale (MDRS) <21] and had no dementia [Mattis Dementia Rating Scale (MDRS) >130] were assessed with the Apathy Evaluation Scale (AES) and underwent a resting-state F-18 fluorodeoxyglucose PET (FDG-PET) scan. A motor assessment comprising the Unified Parkinson’s Disease Rating Scale Part III (UPDRS-III) was conducted and total levodopa equivalent daily dose (LEDD) was calculated. Imaging data were analyzed with statistical parametric mapping. Age, LEDD, and MDRS scores were introduced as covariates.
Results: Positive correlations were observed between the AES score and cerebral metabolism in the right inferior frontal gyrus (Brodmann area [BA] 47), right middle frontal gyrus (BA 10), right cuneus (BA 18), and right anterior insula (BA 13). Negative correlations were observed between the AES score and cerebellar metabolism in the semilunar lobules bilaterally, within the posterior lobe. Using an AES score equal to or above 42 to define clinical apathy, prevalence in our patient group was 17.8%. The AES score was negatively correlated with the MDRS score and positively correlated with the “retardation” subscore of the MADRS. It was not correlated with either UPDRS III or LEDD.
Conclusions: Results indicate that the frontal, temporal, and cerebellar areas known to be involved in reward, emotion, and cognition are also implicated in apathy in patients with PD without dementia or depression. Their roles in the etiopathology of apathy are discussed.

GLOSSARY
ACA = anterior cerebral artery; ACC = anterior cingulate cortex; AES = Apathy Evaluation Scale; AES-C = clinician version of the Apathy Evaluation Scale; BA = Brodmann area; BOLD = blood oxygen level-dependent; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; FDG-PET = F-18 fluorodeoxyglucose PET; LARS = Lille Apathy Rating Scale; LEDD = levodopa equivalent daily dose; MADRS = Montgomery-Åsberg Depression Rating Scale; MDRS = Mattis Dementia Rating Scale; MINI = Mini-International Neuropsychiatric Interview; OFC = orbitofrontal cortex; PD = Parkinson disease; PFC = prefrontal cortex; STN-DBS = subthalamic nucleus deep brain stimulation; TMT = Trail Making Test; UPDRS-III = Unified Parkinson’s Disease Rating Scale Part III; VBM = voxel-based morphometry; WCST = Wisconsin Card Sorting Test.

Apathy is defined as a lack of feeling, emotion, interest, concern, or motivation. Cognitive impairments and depressive symptoms are reported to be associated with apathy in Parkinson disease (PD), but they are neither necessary nor sufficient to induce it.1–3 Apathy’s neural bases in PD have yet to be fully identified, although studies using voxel-based morphometry (VBM)4 and fMRIs5 studies report the involvement of the inferior frontal, cingulate, insular, and cerebellar cortices.

In order to further characterize apathy’s metabolic bases in PD and control for possible confounding factors (i.e., depression and dementia), we examine 45 patients with PD without dementia or depression clinically using F-18 fluorodeoxyglucose PET (FDG-PET). Based on previous literature, we hypothesize that apathy’s metabolic bases in patients with PD without dementia or depression are correlated with the metabolism of the inferior prefrontal cortex and limbic structures, as apathy involves reduced goal-oriented and emotional behaviors.6 We predict that apathy severity

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scores will be correlated with depression symptom severity in this sample of nondepressed patients. Some dimensions or symptoms of apathy may be part of the depressive symptomatology, or may be confused with negative depressive symptoms, such as reduced spontaneous or effortful activity, lack of motivation, reduced interest, and ability to feel, which are also observed in depression. Moreover, since apathy is reported to be associated with cognitive impairments in patients with PD without dementia, we predict that apathy scores will be negatively correlated with cognitive performances in our sample.

**METHODS**

Participants. All 45 patients with PD meet the clinical criteria of the Parkinson’s UK Brain Bank for idiopathic PD and are consecutively recruited at Rennes University Hospital, France. All patients are selected from a larger sample of patients with PD who have been identified as candidates for subthalamic nucleus deep brain stimulation (STN-DBS) according to the standard criteria. In order to control for possible confounding factors (i.e., depression and dementia), trained psychiatrists administer the French version of the Mini-International Neuropsychiatric Interview (MINI 500), which distinguishes between different neuropsychiatric disorders according to the DSM-IV depression severity symptoms are assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS). As clinical dementia is regarded as an exclusion criterion, only participants with Mattis Dementia Rating Scale (MDRS) scores above 130 are included.

Standard protocol approvals, registration, and patient consent. Written informed consent is obtained from each participant and the study meets the ethical standards of the responsible committee on human experimentation.

Psychiatric assessment. Apathy is assessed with the clinician version of the Apathy Evaluation Scale (AES-C). This is an 18-item scale with scores ranging from 18 to 72, the highest score reflecting severe apathy. It is recognized as the most psychometrically robust apathy scale across any population and was given “suggested scale” status for PD in a recent review. Depression symptom severity is based on the MADRS score. We use a 3-factor model to disentangle depressive symptoms. The “dysphoria” factor includes “pessimistic thoughts,” “suicidal thoughts,” and “reported sadness” items. The “retardation” factor includes “lassitude,” “inability to feel,” “apparent sadness,” and “concentration difficulties” items. The “vegetative” factor includes “reduced sleep,” “reduced appetite,” and “inner tension” items. Patients are assessed by trained psychiatrists sensitized to psychiatric disorders in PD (C.L. and G.R.).

Neuropsychological assessment. Executive functions are assessed with a neuropsychological battery (J.P. and T.D.) that includes the Wisconsin Card Sorting Test (WCST), the Trail Making Test (TMT), categorical and literal fluency, and the Stroop Test.

Motor assessment. The motor part of the Unified Parkinson’s Disease Rating Scale (UPDRS-III) is administered when patients are in their best “on” condition (i.e., with their antiparkinsonian medication) and “off” condition (i.e., 12 hours after their last antiparkinsonian medication) (S.D. and M.V.). A levodopa equivalent daily dose (LEDD) is calculated for each patient.

PET imaging procedure. A detailed description of a very similar procedure has been published elsewhere by our group. All participants undergo an FDG-PET scan in a resting state in the “on” state (F.L.J.). PET measurements are performed using a dedicated Discovery ST PET/CT scanner (General Electric Medical Systems, Milwaukee) in 2D mode, with an axial field of view of 15.2 cm and axial resolution of 4.8 mm. A 222–296 MBq injection of F-18 FDG is administered IV in a quiet, dimly lit room. During the acquisition, the patient’s head is immobilized using a head holder. A crosstalk laser system ensures stable positioning. A 20-minute 2D scan is performed 30 minutes postinjection, with participants positioned at the center of the field of view. X-ray CT-based attenuation correction is performed prior to the emission scan. Following scatter, dead time, and random corrections, the PET images are reconstructed by means of 2D filtered backprojection, yielding 47 contiguous transaxial 3.75-mm-thick slices.

**PET image transformation.** The data are analyzed using statistical parametric mapping software (SPM2; Welcombe Department of Cognitive Neurology, London) written in Matlab version 7 (MathWorks, Sherborn, MA). Statistical parametric maps are spatially extended statistical processes used to characterize specific regional effects in imaging data. They combine the

### Table 1 Demographic, motor, psychiatric, and cognitive data for the sample (n = 45)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean ± SD</th>
<th>Range</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>60.5 ± 7.8</td>
<td>47–77</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>11.3 ± 4.1</td>
<td>2–24</td>
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<tr>
<td>UPDRS-III “on” state</td>
<td>8.4 ± 5.9</td>
<td>0–26</td>
</tr>
<tr>
<td>UPDRS-III “off” state</td>
<td>29.9 ± 12.2</td>
<td>10–58</td>
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<tr>
<td>Levodopa equivalent daily dose, mg</td>
<td>1,215 ± 492.7</td>
<td>230–2,575</td>
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<td>AES</td>
<td>35.1 ± 6.6</td>
<td>18–53</td>
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<tr>
<td>MADRS</td>
<td>5.76 ± 0.7</td>
<td>0–20</td>
</tr>
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<td>MDRS</td>
<td>139.36 ± 0.5</td>
<td>131–144</td>
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<tr>
<td>Stroop interference</td>
<td>0.93 ± 8.3</td>
<td>22–15</td>
</tr>
<tr>
<td>TMT B–A, s</td>
<td>87.1 ± 89.7</td>
<td>16–528</td>
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</table>

**Abbreviations:** AES – Apathy Evaluation Scale; MADRS – Montgomery-Åsberg Depression Rating Scale; MDRS – Mattis Dementia Rating Scale; TMT – Trail Making Test; UPDRS – Unified Parkinson’s Disease Rating Scale; WCST – Wisconsin Card Sorting Test.
general linear model (to create the statistical map) with the theory of Gaussian fields to make statistical inferences about regional effects.25 All patient images are first realigned and spatially normalized to a standard stereotactic space according to the Talairach-Tournoux atlas.23 An affine transformation is performed to determine the 12 optimum parameters for registering the brain onto the template. The subtle differences between the transformed image and the template are then removed by applying a nonlinear registration method. Finally, the spatially normalized images are smoothed, using an isotropic 12-mm full-width at half-maximum Gaussian kernel to compensate for interindividual anatomic variability and render the imaging data more normally distributed.

**Statistical analyses.** We look for correlations between the AES scores and the clinical and PET data within the whole sample. LEDD and age are introduced into the SPM analysis as covariates, based on previous literature underlining their potential confounding roles in regional cerebral metabolism14 and apathy.25 As MDRS scores are negatively correlated with the AES scores, we also introduce the MDRS into the SPM analysis. However, we do not introduce the “retardation” subscore of the MADRS, as it reflects the apathy dimension of depression.

**Clinical data.** As the variables are not normally distributed, we use the Spearman rank correlation coefficient.

**PET data: statistical parametric mapping.** To identify the brain regions whose metabolism is significantly correlated with apathy, a “single subject: Covariates only” general linear model is tested at each voxel, with the apathy score as the covariate. Two contrasts are performed: we study the correlations between increased apathy scores and increased voxel values (i.e., positive correlations), and between increased apathy scores and decreased voxel values (i.e., negative correlations). Clusters of a minimum of 20 contiguous voxels with a threshold of \( p < 0.005 \) are deemed to be significant.

**RESULTS Clinical data.** We find a prevalence of clinical apathy of just 17.8%. Apathy is not correlated with age (\( p = 0.25, p = 0.09 \)), UPDRS-III (\( p = 0.2, p = 0.2 \)), disease duration (\( p = 0.06, p = 0.7 \)), LEDD (\( p = 0.18, p = 0.2 \)), or the executive functions assessed with specific tests (Stroop interference \( [\rho = -0.1, p = 0.5] \); TMT B-A \( [\rho = 0.2, p = 0.2] \); WCST-time \( [\rho = 0.3, p = 0.1] \); WCST-categories \( [\rho = -0.1, p = 0.3] \); WCST-errors \( [\rho = 0.2, p = 0.3] \); WCST-perseverative errors \( [\rho = 0.2, p = 0.3] \); categorical fluency \( [\rho = -0.2, p = 0.1] \); lexical fluency \( [\rho = -0.2, p = 0.1] \)). As we find a negative correlation between the MDRS scores and the AES scores (\( p = -0.4, p = 0.006 \)), we introduce them into the SPM analyses as a covariate for their possible confounding effects on apathy’s neural substrates. As expected, we find a positive correlation between the MADRS and AES scores (\( p = 0.36, p = 0.01 \)). Using the 3-factor model of the MADRS,19 we find that the “retardation” factor is strongly correlated with the AES scores (\( p = 0.46, p = 0.003 \)). Conversely, neither the “dysphoria” (\( [\rho = 0.17, p = 0.3] \)) nor the “vegetative” (\( [\rho = 0.19, p = 0.2] \)) subscores are correlated with the AES scores. We do not introduce the “retardation” subscore into the analyses, due to its theoretical overlap with apathy.7,8

**PET data.** With age, LEDD, and MDRS as covariates, FDG-metabolic brain activity positively (i.e., greater metabolic activity with greater apathy severity) and negatively correlates (i.e., lower metabolic activity with greater apathy severity) with the AES score. Correlations are displayed in tables 2 and 3, and in figures 1 and 2.

**DISCUSSION** A previous VBM study using the AES to investigate the structural correlates of apathy in 55 patients with PD found decreased gray matter density in the left precentral gyrus (Brodmann area [BA] 4), left inferior frontal gyrus (BA 44), bilateral

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<th>Y</th>
<th>Z</th>
<th>Z score</th>
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<td></td>
<td>54</td>
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<td>2.98</td>
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<td>-30</td>
<td>6</td>
<td>8</td>
<td>2.92</td>
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<th>Z score</th>
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<td>Left cerebellum, posterior lobe, inferior semilunar lobule</td>
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<td>-34</td>
<td>-70</td>
<td>-44</td>
<td>4.04</td>
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<tr>
<td>Right cerebellum, posterior lobe, inferior semilunar lobule</td>
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<td>32</td>
<td>-70</td>
<td>-42</td>
<td>3.81</td>
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Abbreviations: AES – Apathy Evaluation Scale; MNI – Montreal National Institute.
inferior frontal gyrus (BA 47), bilateral insula (BA 13), left inferior parietal gyrus (BA 40), and posterior cingulate gyrus (BA 31). Our results appear to confirm the involvement of the inferior frontal gyrus (BA 47), medial frontal gyrus (BA 10), and insula (BA 13). This study did not find any correlation between decreased gray matter volume within the cerebellum and the AES score. However, it is not clear whether the cerebellum was included in the analyses. We find that metabolism within the bilateral cerebellum posterior lobe correlates negatively with apathy severity. This result is consistent with very recent data showing the involvement of the cerebellum in apathy in PD. In a resting-state fMRI exploration using the blood oxygen level-dependent (BOLD) technique in 15 patients with PD without dementia (Mini-Mental State Examination >24), the authors showed significant correlations between the BOLD signal and apathy severity, as assessed by the caregiver version of the Lille Apathy Rating Scale (LARS), with depression severity (assessed with the Hamilton DRS) and UPDRS scores as covariates of no interest. The authors showed positive correlations between the caregiver LARS score and the BOLD signal within the right orbitofrontal cortex (OFC) (BA 10) and bilateral subgenual cingulate (BA 25). They also established a negative correlation between the LARS score and the BOLD signal within the left supplementary motor area (BA 6), left inferior parietal lobule (BA 40), left fusiform gyrus (BA 37), and the posterior part of the cerebellum bilaterally (Crus I). However, we cannot exclude the possibility that a cognitive deficit contributed to these findings. Unfortunately, the data did not provide any clues as to the relationship between cognitive abilities and apathy severity in this sample. Since apathy and cognitive impairments may be related in PD, as supported by our results, these findings must be viewed with caution.

The present results are also partially consistent with the metabolic correlates of STN-DBS–induced apathy in patients with PD without dementia or depression that were recently identified by our group. In this study, we found that metabolism correlated with apathy severity within the right frontal inferior gyrus (BA 46 and 45), middle frontal gyrus (BA 10), middle frontal gyrus (BA 9), and bilateral posterior cingulum cortex (BA 31).

The metabolic correlates of apathy have also been characterized in AD using FDG-PET. Results in this study showed a significant relationship between apathy and cerebral metabolism in the medial OFC (BA 11) and anterior cingulate cortex (ACC) (BA 24). Our results in PD, showing the involvement of the lateral OFC (BA 10) and lateral prefrontal cortex (PFC) (BA 47), are in line with the involvement of the inferior frontal cortex in apathy. The ACC, however, has not been identified as one of the metabolic bases of apathy in PD. These discrepant results may arise from the different scales used to evaluate apathy. In the AD study, apathy was assessed with the
“avolition/apathy” and “emotional blunting” subscales of a larger scale developed to assess negative symptoms in AD, whereas we use a comprehensive and dedicated tool to assess apathy as a behavioral, cognitive, and emotional deficit of motivation. In the same way, structural correlates of apathy are not strictly identical, depending on the scale that is used.4

Our results are in line with data showing the involvement of the lateral OFC (BA 10) and lateral inferior PFC (BA 47) in emotional experience: a stereotactic meta-analysis of imaging studies using emotion induction paradigms in healthy participants identified the lateral PFC (BA 47) and rostral and subgenual ACC as the areas most frequently involved in emotion experience.27 Metabolic activity within the left anterior insula correlates with the AES score, which is consistent with the involvement of the anterior insula in emotion28 and motivation.29 If apathy is regarded as a disturbance of volition that may be expressed through altered emotions, the involvement of emotion-related brain regions such as the lateral OFC and the insula is entirely logical. The right frontal and inferior cortex have been found to be involved in the neural bases of apathy in other neuro-psychiatric populations.5,20,30,31 Furthermore, some results support the view of greater motivational impairment associated with right anterior cerebral artery (ACA) stroke than with left ACA.32

Surprisingly, we find that metabolism within bilateral posterior lobe of the cerebellum inversely correlates with the AES score. However, there is a growing body of evidence that the cerebellum is involved not only in the coordination of movement but also in cognition and emotion. Clinical case reports show that cerebellar lesions are responsible for a variety of behavioral disturbances, ranging from autistic behavior to pathologic laughing and crying.33 These observations have led some authors to talk about a “cerebellar cognitive affective syndrome,” characterized by executive dysfunction, behavioral disturbances, and emotional dysregulation.34 These clinical observations are supported by anatomic connections between the cerebellum and the prefrontal cortices via the thalamus,35 with motor and nonmotor cortical areas related to topographically distinct cerebellar areas.36 These topographically distinct loops subserve separate functions such as motor, cognitive, and emotional processes.37 The cerebellum’s sensory-motor functions seem to be supported by the anterior lobe, whereas the posterior lobe supports higher-order functions such as memory, executive functions, and emotional processing.38 consistent with the present results. Animal models of cerebellar lesions show that the cerebellum is a critical region for reinforcing behaviors (for a review, see reference 37), underlying its involvement in reward. More specifically, isolated lesions of the dentate nucleus, a structure connected to the posterolateral cerebellum that includes the semilunar lobule, have recently been shown to result in hedonic and purposive motivational reduction.38 Together, these results support the view of a topographic segmentation of the cerebellum, with some structures dedicated to motivation and behavioral regulation, and, more generally, of a limbic partition of the cerebellum supported by the posterior lobe. Our findings are in line with this view, in that apathy is regarded as a lack of motivation that reduces goal-directed behaviors.

This study has several limitations. First, the patient with PD sample is composed of patients with PD thought likely to benefit from STN-DBS. Furthermore, it is made up of patients without dementia or depression, who do not reflect the entire population of patients with PD. The advantage of this method is that it avoids any confounding factors with depression and dementia, and thus yields stronger results. Second, 10 patients (22%) are on antidepressant medications and this bias cannot be taken into account due to sample size. However, antidepressants are reported to have mixed effects on apathy results.39,40 To date, the literature on this point is too scarce to consider that antidepressant medication represents a confounding factor for apathy in PD. However, this point should be specifically addressed in future studies.

Our results contribute to a growing body of literature suggesting that the metabolic bases of apathy include key limbic structures known to be involved in motivation and emotion. Our results are in line with previous findings for the correlates of apathy, not just in PD but also in AD. When seen in the light of the available literature, they suggest that apathy has common neural bases across pathologies, encompassing both the PFC limbic regions and the basal ganglia.

AUTHOR CONTRIBUTIONS
G. Robert: psychiatric assessment, statistical and SPM analyses, writing of the first draft. F. Le Jeune: PET procedure, SPM preprocessing and analyses, conception of the study, revision of the manuscript. C. Lo Zachmeur: psychiatric assessment, revision of the manuscript. S. Drapier: neurological assessment, revision of the manuscript. T. Dondaine: neuropsychological assessment, revision of the manuscript. J. Peron: neuropsychological assessment, revision of the manuscript. D. Travers: scientific advice, revision of the manuscript. P. Sauleau: scientific advice, revision of the manuscript. B. Miller: conception of the study, revision of the manuscript. M. Verin: conception of the study, revision of the manuscript. D. Drapier: conception of the study, revision of the manuscript. All the authors belong to the “Behavior and Basal Ganglia” host team 4712 (Equipe Accueil), University of Rennes 1, France.

DISCLOSURE
The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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