Neuroanatomical Correlates of Apathy in Parkinson’s Disease: A Magnetic Resonance Imaging Study Using Voxel-Based Morphometry

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Abstract: Apathy is generally defined as a disorder of motivation and is considered one of the most common neuropsychiatric disturbances in Parkinson’s disease (PD). Only few studies addressed the neuroanatomical correlates of apathy in PD. The aim of this article was to determine the structural correlates of apathy in PD patients. Fifty-five PD patients underwent a neuropsychiatric and neuropsychological examination, and a 3 T magnetic resonance imaging scan was acquired. A voxel-based multiple regression analysis was used to calculate correlation between gray matter density and severity measures of apathy. Apathy correlates with decreased cognitive functioning and more depressive symptoms but not with more severe motor symptoms. High apathy scores were correlated with low gray matter density values in a number of cortical brain areas: the bilateral precentral gyrus (BA 4, 6), the bilateral inferior parietal gyrus (BA 40), the bilateral inferior frontal gyrus (BA 44, 47), the bilateral insula (BA 13), the right (posterior) cingulate gyrus (BA 24, 30, 31), and the right precuneus (BA 31). Apathy in PD correlates with reduced gray matter density in a number of brain regions. The involvement of the cingulate gyrus and inferior frontal gyrus is in line with the results of earlier studies addressing apathy in patients with Alzheimer’s disease or depressive disorder. Further studies addressing the pathogenesis of apathy are needed.

Key words: apathy; Parkinson’s disease; magnetic resonance imaging; voxel-based morphometry

Apathy is defined as a disorder of motivation and is considered one of the most common neuropsychiatric disturbances in Parkinson’s disease (PD), occurring in up to 70% of patients.1 Apathy is characterized by diminished motivation and effort to perform everyday activities, lack of intellectual interest and initiative regarding personal and social issues, and indifference or flattening of affect.2–4 Although apathy overlaps with depression, several studies have shown that apathy and depression are different constructs.5,6 Apathy has been associated with decreased quality of life,7 decreased performance on activities of daily living,7 and more severe cognitive dysfunction, more specifically executive dysfunction.8–10 A recent study of Pedersen et al. reported that dementia and a more rapid decline in speech and axial impairment—features predominantly associated with dysfunction of nondopaminergic subcortical structures—were independent risk factors for apathy in PD.11

The involvement of the prefrontal-basal ganglia system in apathy has often been hypothesized.8,12 There are only few studies addressing the neuroanatomical correlate of apathy in PD. Isella et al. studied the morphometric correlates of apathy in 26 PD patients but did not find any specific measure of frontotemporal atrophy correlating with severity of apathy.5 A PET study of Remy et al. showed that apathy was inversely correlated with 11C-RTI-32 binding (dopamine and noradrenaline) in the ventral striatum bilaterally.13

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Another PET study by Le Jeune et al. investigated apathy in PD patients after deep brain stimulation (DBS) of the subthalamic nucleus. They showed that postoperative apathy scores were correlated with decreased glucose metabolism in the bilateral posterior cingulate gyrus and left middle frontal gyrus.14

The objective of our study is to investigate the structural correlates of apathy, correlating the level of apathy with anatomical changes in gray matter density derived from magnetic resonance imaging (MRI) scans, as detected with voxel-based morphometry (VBM).

**METHODS**

**Patients**
Sixty consecutive outpatients with idiopathic PD, visiting the Neurology Clinic or the Memory Clinic of Maastricht University Medical Centre, were included. The diagnosis of idiopathic PD was established by use of the Queens Square Brain Bank criteria.15 Exclusion criteria were neurological or psychiatric diseases other than PD, the use of psychopharmacological medication, abuse of alcohol and/or drugs, and cognitive deterioration, which was operationalized by a score of <24 on the Mini Mental State Examination (MMSE).16 Additionally, patients treated with DBS, or those meeting MRI contraindications, such as having a cardiac pacemaker, were excluded. All patients gave written informed consent before the study. The local Medical Ethics Committee of the Maastricht University Medical Centre approved the study.

**Assessment**
All patients underwent a neuropsychiatric examination, a neuropsychological test battery, and a 3 T MRI scan on the same day. The neuropsychiatric examination included part 3 of the Unified Parkinson’s Disease Rating Scale (UPDRS)17 to measure the severity of motor symptoms, the Hoehn and Yahr staging scale (H&Y)18 to assess disease stage, the 17-item Hamilton Depression Rating Scale (HAMD)19 to measure depressive symptoms, and the Neuropsychiatric Inventory (NPI)20,21 to assess the presence and severity of 12 neuropsychiatric disturbances (delusions, hallucinations, agitation, depressed mood, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, night-time behavior disturbances, and eating abnormalities).

In addition, the Apathy Evaluation Scale (AES-I)22,23 and the Lille Apathy Rating Scale (LARS)24 were used to assess apathy. The LARS provides an overall apathy score and four composite subscores that presumably reflect four distinct dimensions of apathy: intellectual curiosity, action initiation, emotion, and self-awareness.25 Apathy was measured with three different scales to compare the results of these scales.

The neuropsychological test battery included the cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly part B (CAMCOG),26 which incorporates the MMSE.16 Subdomains in the CAMCOG are as follows: attention, orientation, language comprehension, expression, memory, praxis, abstract reasoning, and perception.

**MR Imaging Data Acquisition**
MRI scans were acquired with a 3.0 T Gyroscan NT MRI scanner (Philips Medical Systems, Best, The Netherlands). A coiled gradient was used, which provided high anatomical resolution and good gray/white matter contrast for subsequent segmentation. In addition to other MRI scan sequences, a T1-weighted three-dimensional isosurface scan (3D-ISO) was obtained for VBM analysis. The following parameters were used: voxel size: = 1 mm × 1 mm × 1 mm; TR = 8.1 ms; TE = 3.7 ms; TFE = 230 ms; flip angle = 8°; matrix = 224 × 224 pixels; FOV = 224 cm × 224 cm.

**Voxel-Based Morphometry**
Image preprocessing was performed using Statistical Parametric Mapping 8 (SPM 8) (Wellcome Trust Centre for Neuroimaging, London). The first step was a 12-parameter affine registration with the Montreal Neurologic Institute27 template as a target. The registered images were segmented into gray matter, white matter, and cerebrospinal fluid probability maps, using the SPM 8 segmentation priors. Registration accuracy of the gray matter probability maps was further enhanced by a registration method that uses alignment and scaling to spread the registration bias among the whole group. The transformation matrix is averaged by projection to a manifold, a method described in more detail in Karas et al.28 and Woods.29 The registered gray matter volumes were smoothed using a Gaussian kernel filter set at 10 mm (full with half maximum) to reduce possible error from between-subject variability in local anatomy and render the data more normally distributed.

**Statistical Analysis**
The smoothed gray matter images were entered into a voxel-based multiple regression analysis to calculate linear correlations between gray matter density and severity of apathy assessed with different scales. More specifically, the LARS total score and four composite...
subscores for different domains of apathy (intellectual curiosity, action initiation, emotion, and self-awareness), the AES total score, and the NPI apathy subscale were used in the analysis. Age, MMSE, and global gray matter volume were entered in this model as covariates for all variables. Global gray matter voxel intensity was included as a covariate to determine the regionally specific pattern of loss within the gray matter compartment, over and above global or generalized gray matter change. The threshold for statistical significance was set at \( P < 0.05 \) corrected for multiple comparisons by false discovery rate correction; subsequently suprathreshold clusters were further filtered to \( P < 0.1 \), corrected for multiple comparisons.

The \( x \), \( y \), and \( z \) coordinates of areas with a significant correlation between gray matter density and scores on the apathy assessments were identified using the Talairach Deamon Client tool (www.talairach.org). An image of the average gray matter volume of the current population was used to map the significant results.

Statistical analysis of the behavioral data was performed using the Statistical Package for Social Sciences version 16.0 (SPSS, Chicago). Descriptive statistics were used to describe the demographical and clinical characteristics of the PD patients. Fisher Exact tests were used to compare proportions. Normality and linearity check was performed before Pearson’s correlation coefficients were calculated to determine the relationships between the several apathy assessments and the demographical and clinical correlates. Correlation coefficients of \( <0.3 \) (percent explained variance \( = R^2 \) of \( <9\% \) were considered weak; between 0.3 and 0.5 (percent explained variance between 9 and 25\%) moderate; between 0.5 and 0.7 (percent explained variance between 25 and 49\%) fair; and correlation coefficients of \( >0.7 \) (percent explained variance \( >49\% \) were considered strong. \( P \) values of \( <0.05 \) were considered significant.

## RESULTS

### Demographical and Clinical Characteristics

A total of 60 PD patients were included in this study; 43 men (72\%) and 17 women (28\%). Because of movement artifacts, the MR images of 5 PD patients had to be excluded from the analysis, so the remaining sample size was 55 PD patients. None of the patients had a clinical diagnosis of PD dementia. Baseline characteristics are shown in Table 1 and indicate that PD patients included had mild to moderate PD motor symptoms and no clinically significant mood disorders. A fair percentage of patients scored above the cutoff for clinically relevant apathetic symptoms: 16.4\% on the LARS (cutoff score \(-16/-17\)), 12.7\% on the AES (cutoff score 37/38), and 32.7\% on the NPI (frequency*severity score 4 or higher). There were no associations between the proportion of patients on levodopa (L-dopa) or dopamine agonist and clinically relevant apathetic symptoms as measured with the LARS, AES, and NPI (\( P = 0.473, 0.360, 0.584, 0.211, 0.640, \) and 0.168, respectively).

Correlation analyses were carried out with demographical and clinical variables, and with apathy scores (see Table 2). The LARS correlated moderately with age (\( r = 0.30, P = 0.026, \)) HAMD (\( r = 0.36, P = 0.007, \)) H&Y (\( r = -0.42, P = 0.001, \)) and CAMCOG total scores (\( r = -0.49, P < 0.000, \)). There were no significant correlations between the LARS score and disease duration or the UPDRS part 3 total score. Scores on the AES correlated moderately with MMSE (\( r = -0.32, P = 0.016, \)) and CAMCOG total scores (\( r = -0.31, P = 0.022, \)) but fair with HAMD total scores (\( r = 0.55, P < 0.000, \)). There were no significant correlations with age, disease duration, and the UPDRS part 3 total score. The score on the apathy subscale of the NPI had a moderate correlation with the HAMD total score (\( r = 0.49, P < 0.000, \)). No significant correlations were found between score on the apathy subscale of the NPI and age, disease duration, UPDRS part 3, and MMSE and CAMCOG total scores.

### Table 1. Demographical and clinical characteristic of the included patients (\( N = 55 \))

<table>
<thead>
<tr>
<th></th>
<th>Mean (standard deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>62.0 (10.1); range: 42–80</td>
</tr>
<tr>
<td>Education level(^a)</td>
<td>4.0 (1.9)</td>
</tr>
<tr>
<td>UPDRS part 3</td>
<td>17.3 (4.9)</td>
</tr>
<tr>
<td>H&amp;Y</td>
<td>median: 2; range: 1.5–3.0</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>6.6 (4.3)</td>
</tr>
<tr>
<td>HAMD</td>
<td>6.2 (3.4)</td>
</tr>
<tr>
<td>MMSE</td>
<td>27.8 (1.9)</td>
</tr>
<tr>
<td>CAMCOG</td>
<td>92.0 (7.0)</td>
</tr>
<tr>
<td>% on levodopa</td>
<td>62(^b)</td>
</tr>
<tr>
<td>% on DA agonist</td>
<td>62(^b)</td>
</tr>
<tr>
<td>LARS</td>
<td>-22.2 (6.8)</td>
</tr>
<tr>
<td>Intellectual curiosity</td>
<td>-2.0 (1.1)</td>
</tr>
<tr>
<td>Action initiation</td>
<td>-2.6 (1.1)</td>
</tr>
<tr>
<td>Emotion</td>
<td>-3.0 (1.1)</td>
</tr>
<tr>
<td>Self-awareness</td>
<td>-2.9 (1.3)</td>
</tr>
<tr>
<td>AES</td>
<td>28.7 (6.0)</td>
</tr>
<tr>
<td>NPI</td>
<td>2.1 (2.3)</td>
</tr>
</tbody>
</table>

\(^a\)Education level ranging from primary education (1) to university degree (8).

\(^b\)Thirty-five percent of patients were using both levodopa and DA agonist.

UPDRS, Unified Parkinson’s Disease Rating Scale; H&Y, Hoehn and Yahr scale; HAMD, Hamilton Depression Rating Scale; MMSE, Mini Mental State Examination; CAMCOG, Cambridge Cognitive Examination; DA, dopamine; LARS, Lille Apathy Rating Scale; AES, Apathy Evaluation Scale; NPI, Neuropsychiatric Inventory.
Voxel-Based Multiple Regression Analysis

As shown in Table 3, the voxel-based multiple regression analysis showed significant correlations between gray matter density values and apathy scores on the LARS, AES, and NPI. High apathy scores on the LARS correlated with low gray matter density values in the bilateral precentral gyrus, the bilateral inferior parietal gyrus, the right precuneus, the bilateral insula, the bilateral inferior frontal gyrus, and the right (posterior) cingulate gyrus (see Fig. 1). Looking at the four different subscales of the LARS (intellectual curiosity, action initiation, emotion, and self-awareness) by four separate multiple regression models, no correla-

<table>
<thead>
<tr>
<th>TABLE 2. Correlations between demographical variables, clinical variables, and apathy scores (assessed with the LARS, AES, and NPI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Disease duration</td>
</tr>
<tr>
<td>UPDRS part 3</td>
</tr>
<tr>
<td>HAMD</td>
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<td>MMSE</td>
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<tr>
<td>CAMCOG</td>
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<tr>
<td>LARS</td>
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<tr>
<td>AES</td>
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<tr>
<td>NPI</td>
</tr>
</tbody>
</table>

*Value is significant at $P < 0.05$ (two-tailed).
UPDRS, Unified Parkinson’s Disease Rating Scale; HAMD, Hamilton Depression Rating Scale; MMSE, Mini Mental State Examination; CAMCOG, Cambridge Cognitive Examination; LARS, Lille Apathy Rating Scale; AES, Apathy Evaluation Scale; NPI, Neuropsychiatric Inventory.

Table 3. Brain regions showing a significant (negative) correlation between gray matter density values and apathy scores

<table>
<thead>
<tr>
<th>Brain area</th>
<th>Cluster size</th>
<th>Right/Left</th>
<th>Brodmann area</th>
<th>MNI coordinate</th>
<th>Z value at maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>LARS</td>
<td>Precentral gyrus</td>
<td>12,598</td>
<td>L</td>
<td>6</td>
<td>−52 − 8 37</td>
</tr>
<tr>
<td></td>
<td>Inferior parietal gyrus</td>
<td>5,618</td>
<td>R</td>
<td>4</td>
<td>44 − 11 47</td>
</tr>
<tr>
<td></td>
<td>Precuneus/Posterior cingulate gyrus</td>
<td>5,225</td>
<td>R</td>
<td>51</td>
<td>−63 27</td>
</tr>
<tr>
<td></td>
<td>Insula</td>
<td>4,596</td>
<td>R</td>
<td>13</td>
<td>44 10</td>
</tr>
<tr>
<td></td>
<td>Inferior frontal gyrus</td>
<td>4,471</td>
<td>L</td>
<td>13</td>
<td>−60 10</td>
</tr>
<tr>
<td></td>
<td>Cingulate gyrus</td>
<td>2,649</td>
<td>R</td>
<td>24</td>
<td>23 12</td>
</tr>
<tr>
<td>AES</td>
<td>Precentral gyrus</td>
<td>6,639</td>
<td>L</td>
<td>6</td>
<td>−52 − 8 37</td>
</tr>
<tr>
<td></td>
<td>Inferior frontal gyrus</td>
<td>4,080</td>
<td>R</td>
<td>13</td>
<td>44 2</td>
</tr>
<tr>
<td></td>
<td>Insula</td>
<td>4,086</td>
<td>L</td>
<td>13</td>
<td>−60 10</td>
</tr>
<tr>
<td></td>
<td>Inferior parietal gyrus</td>
<td>2,807</td>
<td>R</td>
<td>31</td>
<td>−63 40</td>
</tr>
<tr>
<td>NPI</td>
<td>Precentral gyrus</td>
<td>6,165</td>
<td>L</td>
<td>6</td>
<td>−52 − 8 36</td>
</tr>
<tr>
<td></td>
<td>Inferior frontal gyrus</td>
<td>3,464</td>
<td>R</td>
<td>13</td>
<td>44 3</td>
</tr>
<tr>
<td></td>
<td>Insula</td>
<td>3,464</td>
<td>L</td>
<td>13</td>
<td>−44 15</td>
</tr>
<tr>
<td></td>
<td>Inferior parietal gyrus</td>
<td>2,674</td>
<td>L</td>
<td>13</td>
<td>−44 15</td>
</tr>
<tr>
<td></td>
<td>Posterior cingulate gyrus</td>
<td>2,674</td>
<td>R</td>
<td>13</td>
<td>−44 15</td>
</tr>
</tbody>
</table>

LARS, Lille Apathy Rating Scale; AES, Apathy Evaluation Scale; NPI, Neuropsychiatric Inventory.
tions between these subscales and low gray matter density values in distinct anatomical regions other than those mentioned above were observed. High apathy scores on the AES correlated significantly with gray matter density values in the left precentral gyrus, the bilateral insula, the bilateral inferior frontal gyrus, the left inferior parietal gyrus, and the right (posterior) cingulate gyrus. High apathy scores on the NPI correlated significantly with low gray matter density values in the left precentral gyrus, the bilateral insula, the bilateral inferior frontal gyrus, the left inferior parietal gyrus, and the right (posterior) cingulate gyrus.

DISCUSSION

Our study shows that apathy occurs frequently in PD, but also that the exact frequency is dependent on the rating scale used to measure apathy. The prevalence of apathy was 16.4% on the LARS, 12.7% on the AES, and 32.7% on the NPI. In line with previous studies, we found an association between apathy and cognitive dysfunction: higher apathy scores were correlated with lower MMSE and CAMCOG scores. Higher apathy scores also correlated with higher depression scores, as measured with the HAMD. Our study confirms previous findings showing no association between apathy and severity of motor symptoms or disease duration, although one recent community-based study of Pedersen et al. did show a relationship between apathy and more severe motor symptoms in PD patients. In this study that could be due to the large number of patients included with depression and dementia.

The MRI data showed significant correlations between high apathy scores and low gray matter density values in a number of cortical brain areas: the bilateral precentral gyrus (BA 4, 6), the bilateral inferior parietal gyrus (BA 40), the bilateral inferior frontal gyrus (BA 44, 47), the bilateral insula (BA 13), the right (posterior) cingulate gyrus (BA 24, 30, 31), and the right precuneus (BA 31). Apathy was measured with three different apathy scales (LARS, AES, and NPI) in separate regression models, which showed consistent results. The four different subscales of the LARS (intellectual curiosity, action initiation, emotion, and self-awareness) were also analyzed in separate regression models. The results showed no correlations between these subscales and low gray matter density values in distinct anatomical regions other than those resulting from the LARS total score (see Table 3).

These results are in line with the PET study of Le Jeune et al. showing that higher scores on apathy rating scales were correlated with decreased glucose metabolism in the bilateral posterior cingulate gyrus. Isella et al. did not find any specific measure of fronto-temporal atrophy that correlated with severity of apathy. In this particular study that could be due to small sample size or lack of sensitivity or accuracy of the morphometric linear technique used.

Functional and structural neuroimaging studies addressing apathy in Alzheimer’s disease (AD) showed that apathy is associated with gray matter density loss in the (anterior) cingulate and the inferior frontal gyrus. A pathological study of apathy in AD also showed a fair correlation between more severe apathy and an increased pathological burden in the anterior cingulate gyrus. Lavretsky et al. examined the neuro-anatomical correlates of apathy in older adults with and without major depression. Higher apathy scores were associated with decreased gray matter volume in the right anterior cingulate gyrus.

To summarize, in line with previous studies in AD patients and depressive patients, we found evidence for involvement of the cingulate gyrus and the inferior frontal gyrus in apathy in PD as well. This stresses the stability of neural substrates of apathy across different pathologies.

Our results also showed associations between more severe apathy and low gray matter density in other areas: the premotor cortex, the bilateral insula, the right precuneus, and the bilateral inferior parietal
gyrus. As the premotor cortex is involved in the initiation of voluntary movements, one could speculate that the gray matter density loss in this area may result in less initiative and motivation to initiate movements in PD patients with apathetic symptoms. As the insula plays a role in subjective emotional experience, gray matter density loss in this area may be related to loss of spontaneous emotion or emotional responsiveness, which is one of the characteristics of apathy. The parietal lobe plays an important role in integrating information from different senses and processes. Kjaer et al. hypothesized that the precuneus, the inferior parietal gyrus, and the anterior cingulate gyrus constitute a functional network of reflective self-awareness. This network has previously been described to be impaired in apathy, although nowadays there is still a debate whether this is a dimension of apathy. In addition, the inferior parietal gyrus has been linked to executive dysfunction in PD when assessed with the Frontal Assessment Battery. As apathy is associated with executive dysfunction, one could hypothesize that executive dysfunction in apathetic PD patients is not only linked to frontal lobe dysfunction but also to parietal lobe dysfunction.

Levy and Dubois hypothesized that apathy can be described as the clinical consequence of disruption of the prefrontal-basal ganglia system. They differentiate three subtypes of disrupted processing: emotional–affective, cognitive, and autoactivation. Involvement of the cingulate gyrus and premotor cortex, as was shown in our study, indicates that autoactivation processing deficits could be associated with apathy in PD.

Little is known about the neurochemical mechanisms of apathy in PD. A PET study of Remy et al. showed that the severity of apathy in PD patients was inversely correlated with $^{11}$C-RTI-32 binding (dopamine and noradrenaline) bilaterally in the ventral striatum. Czernecki et al. showed that L-dopa treatment might improve motivation in some patients with PD, indicating that apathy in PD is at least partly a dopamine-dependent syndrome. Dujardin et al. suggested that nondopaminergic circuits participate in the pathophysiology of apathy in PD because the apathy level is mainly determined by cognitive impairment and not by association with the severity of motor symptoms. PD-specific pathology with multiple transmitter deficiencies in mesocortical monoaminergic systems may play a major role in the pathogenesis of apathy, including the mesocorticolimbic dopamine projection and the mesocortical noradrenergic and serotonergic projections.

Our study has several limitations. First, sample size may not be large enough to detect small cerebral areas that are associated with apathy in addition to those detected in this study. Second, patients included in this study are characterized by only mild apathy scores and mild motor symptoms. Possibly, by including patients with more severe apathy, the contrast between groups may increase, resulting in significant correlations with other areas such as the basal ganglia or other limbic regions. Next, a correlational design instead of a between-groups design was used to study the structural correlates of apathy in PD. This was done because of the small sample size, the mild apathy scores, and the lack of consensus diagnostic criteria for apathy at the time of study inclusion. Finally, the VBM method used to analyze our MRI data has been criticized because of the risk of misregistration, caused by the spatial normalization procedure. In our study, registration accuracy was enhanced by alignment and scaling with an advanced registration method, spreading the registration bias among the whole group. VBM has the major advantage of analyzing the whole brain and not being restricted by a priori assumptions about regions of interest.

CONCLUSION

More severe apathy was correlated with decreased cognitive functioning and more severe depressive symptoms but not with more severe motor symptoms. This suggests that, in addition to dopaminergic systems, nondopaminergic systems may be involved as well. In line with previous studies in AD patients and depressive patients, we found evidence for involvement of the cingulate gyrus and the inferior frontal gyrus in the pathophysiology of apathy in PD. Our results will have to be confirmed by future structural and functional imaging studies investigating apathy in larger samples of PD patients. Moreover, further studies are needed that specifically address the role of the dopaminergic and nondopaminergic systems in the pathogenesis of apathy, in the hope of revealing new treatment options.

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