RESEARCH PAPER

Apathy and impaired emotional facial recognition networks overlap in Parkinson’s disease: a PET study with conjunction analyses

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ABSTRACT

Apathy is a disabling non-motor symptom that is frequently observed in Parkinson’s disease (PD). Its description and pathophysiology suggest that it is partially mediated by emotional impairment, but this research issue has never been addressed at a clinical and metabolic level. We therefore conducted a metabolic study using 18fluorodeoxyglucose positron emission tomography (18FDG PET) in 36 PD patients without depression and dementia. Apathy was assessed on the Apathy Evaluation Scale (AES), and emotional facial recognition (EFR) performances (ie, percentage of correct responses) were calculated for each patient. Confounding factors such as age, antiparkinsonian and antidepressant medication, global cognitive functions and depressive symptoms were controlled for. We found a significant negative correlation between AES scores and performances on the EFR task. The apathy network was characterised by increased metabolism within the left posterior cingulate (PC) cortex (Brodmann area (BA) 31). The impaired EFR network was characterised by decreased metabolism within the bilateral PC gyrus (BA 31), right superior frontal gyrus (BA 10 and 9) and left superior frontal gyrus (BA 10 and 11). By applying conjunction analyses to both networks, we identified the right premotor cortex (BA 6), right orbitofrontal cortex (BA 10), left middle frontal gyrus (BA 8) and left posterior cingulate gyrus (BA 31) as the structures supporting the association between apathy and impaired EFR. These results confirm that apathy in PD is partially mediated by impaired EFR, opening up new prospects for alleviating apathy in PD, such as emotional rehabilitation.

INTRODUCTION

Parkinson’s disease (PD) is a severe and disabling degenerative disease characterised by both motor and non-motor symptoms, such as apathy.1 Apathy is defined as a lack of motivation that has a behavioural, cognitive and emotional impact on daily life activities,2 leading to a lack of spontaneous and sustained goal-oriented activities. It also presupposes a reduction in the emotional component of goal-oriented behaviour and emotional reactivity to the environment. However, there is a dearth of clear data on the emotional deficit in apathy,’ although impaired emotional facial recognition (EFR) has been repeatedly described in PD.3–8 Both dopamine enhancers and dopamine receptor blockers have improved and impaired EFR in healthy volunteers.5–6 Moreover, dopaminergic medications improve EFR in PD.7–8 On the other hand, numerous studies have shown a dopamine modulation of motivated behaviours.7 This suggests that both EFR and apathy are mediated by dopamine at transmitter level.

Apathy and impaired EFR networks in PD suggest that some brain structures may be involved in both networks. Apathy cerebral networks characterised using structural MRI have shown that it is related to reduced grey matter within the inferior frontal (Brodmann area (BA) 44 and 47), premotor cortex (BA 6), insula and posterior cingulate cortices (BA 31).10 As apathy worsens, resting state perfusion MRI activity increases within the inferior frontal cortex (including the orbitofrontal cortex (OF), BA 10 and 9) and decreases within the bilateral cerebellum and premotor cortex (BA 6).11 Using 18F-fluoro-deoxyglucose positron emission tomography (18FDG-PET), Robert et al (2012) recently showed that severe apathy is associated with increased metabolism within the inferior frontal cortex (BA10 and 47) and insula while metabolism decreased within cerebellum.12 Finally, apathy induced by bilateral subthalamic nucleus deep brain stimulation (STN-DBS) has been related to increased metabolic activity within the inferior frontal cortex (BA 10, 45 and 46) and decreased metabolic activity within posterior cingulate and dorsolateral prefrontal cortex (DLPFC, BA 9).13

As for impaired EFR scores, studies using voxel-based morphometry (VBM) have related them to bilateral OFC (BA 10) grey matter loss in PD.14 Using functional MRI (fMRI) during an EFR task, some authors have observed the activation of an extended network in PD patients who are not on medication that includes the frontal cortex (OFC (BA 10), DLPFC (BA 8 and 9) and premotor cortex (BA 6)), and limbic structures such as amygdala, anterior cingulate and insula.15 During the same EFR task (vs a non-emotional task) administered to PD patients, the authors observed deactivation of the posterior cingulate (BA 31), premotor cortex (BA 6) and insula.16 Finally, the increased perfusion within premotor cortex during a facial
gesture task in unaffected heterozygous Parkin mutation carriers (ie, individuals with a high risk of early-onset PD) compared with controls correlates with performances on an EFR task. This suggests the premotor cortex compensates for the effects on EFR in the very early stages of the disease. Taken together, these results suggest that both apathy and impaired EFR in PD are sustained by limbic structures involving the frontal cortex (with a marked contribution of the OFC) and the posterior cingulate as well as the premotor cortex at cerebral networks level.

At the clinical/behavioural level, a previous study found that overall performances on an EFR task, and more especially the recognition of fear, anger and sadness, was impaired in apathetic PD patients compared with non-aphathetic patients. However, only age, education and overall cognitive performances were controlled for, and we know that apathy and impaired EFR in PD are confounded by depressive symptoms and by antiparadigm medication.

Since previous results suggest that apathy and impaired EFR share some commonalities at transmitter, networks and clinical levels, we tested PD as a suitable model for verifying that apathy is mediated by impaired EFR at a clinical and metabolic level in a homogeneous sample of PD patients. We formed the following hypotheses:

1. Apathy scores are correlated with EFR performances in non-depressed and non-demented PD patients, after controlling for confounding factors.
2. A brain network encompassing the frontal cortex (OFC, DLPFC and premotor cortex) and the posterior cingulate cortex is implicated in impaired EFR.
3. In the light of the literature on the brain networks implicated in apathy and impaired EFR in PD, the OFC, posterior cingulate cortex and premotor cortex appear to be involved in both networks.

METHODS
Participants
All 36 PD patients met the clinical criteria of the Parkinson’s UK Brain Bank for idiopathic PD and were consecutively recruited at Rennes University Hospital, France. They were selected from a larger sample of PD patients who were eligible for STN-DBS. Exclusion criteria were abnormal structural MRI, history of stroke, dementia, significant cognitive impairment, depression and apperceptive prosopagnosia. All assessments and metabolic imaging were performed when patients were receiving their usual antiparkinsonian treatment.

Standard protocol approvals, registrations and patient consents
Written informed consent was obtained from each participant, and the study was approved by an ethical standards committee on human experimentation.

Psychiatric assessment
Apathy was assessed on the Apathy Evaluation Scale, Clinician Version (AES). This is an 18-item scale with scores ranging from 18 to 72, the highest scores reflecting severe apathy. It is recognised as the most psychometrically robust apathy scale. The French version of the Mini-International Neuropsychiatric Interview (MINI 500) was used to exclude dementia and depression. We adopted a cut-off score of 130 on the Mattis Dementia Rating Scale (MDRS) to exclude significant cognitive impairment. Depressive symptoms severity was measured on the Montgomery–Asberg Depression Rating Scale.

Emotional facial recognition
After the patients had been familiarised with the EFR task and the list of emotions, they were individually shown a randomised sequence of 55 photographs of seven different facial expressions (happiness, sadness, fear, surprise, disgust, anger and no emotion). After observing a photo for 3 s, the patients were prompted to give an answer by choosing the most suitable response from the list of seven emotions. We calculated the percentage of correct emotion identification for each patient and this for each discrete emotion and across all emotions (ie, overall score).

Motor assessment
The motor part of the Unified Parkinson’s Disease Rating Scale (UPDRS-III) was used to assess motor symptom severity. A levodopa equivalent daily dose (LEDD) was calculated for each patient.

PET imaging procedure
PET measurements were performed using a dedicated Discovery ST PET/CT scanner (General Electric Medical System, Milwaukee, WI) in 2D mode. A 222–296 MBq injection of 18F-FDG was administered intravenously. A 20 min 2D scan was performed 30 min postinjection, with participants positioned at the centre of the field of view. X-ray CT-based attenuation correction was performed prior to the emission scan. Following scatter, dead time and random corrections, the PET images were reconstructed by means of 2D filtered backprojection, yielding 47 contiguous transaxial 3.75 mm thick slices.

PET image transformation
Data were first preprocessed, manually realigned, normalised to the Talairach and Tournoux atlas space, registered to a template with affine and non-linear transformation and smoothed using an isotropic 12 mm full-width at half-maximum Gaussian kernel. The data were then analysed using statistical parametric mapping software (SPM2; Wellcome Department of Cognitive Neurology, London); written in Matlab V7 (MathWorks, Sherborn, MA). Statistical parametric maps combine the general linear model with the theory of Gaussian fields to make statistical inferences about regional effects.

Statistical analyses
Clinical data
As the variables were not normally distributed, we calculated Spearman’s rank correlation coefficient between the AES scores and overall performances on the EFR task. We applied a multiple linear regression to better estimate the shared covariance between AES score and overall EFR score, controlling for the confounding factors on apathy, with the AES scores as the dependent variable and overall EFR, MADRS and MDRS scores, LEDD and antidepressant medication (yes/no) as the independent variables.

PET data analysis
Steps 1 and 2: Apathy and impaired EFR metabolic networks
To identify the metabolic bases of apathy and impaired EFR, we created two contrasts with the ‘single subject: covariates only’ general linear model (GLM), which were tested at each voxel. The first contrast used the apathy score as a covariate, the second EFR performance. Each GLM was applied independently. Clusters of a minimum of 20 contiguous voxels, with a threshold of p<0.005, were deemed to be significant.
We first looked for correlations between the AES scores and glucose metabolism within the whole sample. LEDD, age and the MDRS scores were introduced into the SPM analysis as covariates (step 1).\textsuperscript{12} We then looked for correlations between impaired EFR (ie, low overall performance on the EFR) and glucose metabolism within the whole sample (step 2). Negative correlations showed increased metabolism when EFR scores were low (inverse relation) and positive correlations showed decreased metabolism when EFR scores were low (same relation). LEDD, the MADRS score and antidepressant medication were introduced into the SPM analysis as covariates, as previous research had underlined their potentially confounding effect on EFR.

Step 3: Metabolic bases common to both apathy and impaired EFR: conjunction analysis
Conjunction analysis allows to identify the common areas involved in two (or more) activation t-maps.\textsuperscript{11} We calculated two t-maps in step 1: one for positive correlations with apathy and one for negative correlations with EFR. We then performed a conjunction analysis between these two t maps at p=0.05 and k=20. In other words, conjunction analysis runs the GLM estimated at step 2 at the voxels that have been found to be significant at step 1. Thus, all the confounding factors for apathy and EFR were considered in the SPM2 conjunction analysis, namely, age, LEDD, MDRS, MADRS and antidepressant medication.

RESULTS
Clinical results
Descriptive results are provided in table 1. Mean and SD EFR composite scores of each discrete emotions and overall score are displayed in table 2. Eight patients (22\%) were on antidepressant medication. Clinical results revealed a significant univariate negative correlation between the AES and overall EFR scores (estimate=−0.4, p=0.01), reflecting that patients with greater apathy were less able to correctly identify facial emotions. This relationship survived the multiple regression analyses (estimate=−0.18, p=0.04). Multiple regression analyses failed to reveal significant correlations between the AES score and composite subscores, as mentioned in table 2.

Imaging results
Step 1: Apathy metabolic network
We found a correlation between increased metabolism within the left posterior cingulate gyrus (BA 31; z score=3.02, cluster size=83 voxels) and higher AES scores (ie, more severe apathy). We did not find any brain structure with significantly decreased metabolism that was correlated with higher AES scores. Step 2: Impaired EFR metabolic network

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic, motor and neuropsychological data of the sample</th>
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<tbody>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45–74</td>
</tr>
<tr>
<td>AES (18–72)</td>
<td>18–53</td>
</tr>
<tr>
<td>MADRS (0–60)</td>
<td>0–17</td>
</tr>
<tr>
<td>UPDRS III (0–108)</td>
<td>0–23</td>
</tr>
<tr>
<td>LEDD</td>
<td>240–2720</td>
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<tr>
<td>MDRS (1/44)</td>
<td>132–144</td>
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<th>Table 2</th>
<th>EFR task</th>
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<tr>
<td>Composite EFR score (0–100%)</td>
<td>Mean</td>
</tr>
<tr>
<td>Happiness</td>
<td>99</td>
</tr>
<tr>
<td>Sadness</td>
<td>67.2</td>
</tr>
<tr>
<td>Fear</td>
<td>47.9</td>
</tr>
<tr>
<td>Surprise</td>
<td>93.2</td>
</tr>
<tr>
<td>Disgust</td>
<td>90.9</td>
</tr>
<tr>
<td>Anger</td>
<td>84.1</td>
</tr>
<tr>
<td>No emotion</td>
<td>81.8</td>
</tr>
<tr>
<td>Overall</td>
<td>79.4</td>
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We found impaired EFR scores (ie, low scores on the EFR task) were positively correlated with metabolism (ie, decreased metabolism) within the precuneus and the inferior occipital gyrus. We found negative correlations (ie, increased metabolism) within an extended limbic network with bilateral posterior cingulate and bilateral superior frontal gyri. Talairach coordinates, BAs, cluster sizes and z scores are provided in table 3. Decreased metabolism network correlated with poor performances on the EFR task (ie, low overall EFR score) is displayed in figure 1. Step 3: Overlap between the two networks highlighted by the conjunction analyses
We found bilateral frontal gyri, right premotor cortex and left posterior cingulate are the structures both involved in the apathy and the impaired EFR networks. Talairach coordinates, BAs, cluster sizes and z scores are provided in table 4. Clusters are displayed in figure 2.

DISCUSSION
Our results allowed us to identify the metabolic network implicated in impaired EFR in PD and partially replicated previous results concerning the metabolic network implicated in apathy in PD.\textsuperscript{12} \textsuperscript{13} We found a clinical correlation between apathy severity and impaired EFR in our sample. The conjunction

<table>
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<tr>
<th>Table 3</th>
<th>Impaired emotional facial recognition (EFR) metabolic networks: positive and negative correlations with low EFR scores (ie, poor recognition abilities)</th>
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<tbody>
<tr>
<td>Metabolism</td>
<td>Anatomical structure</td>
</tr>
<tr>
<td>Positive correlations (decreased metabolism)</td>
<td>Right precuneus</td>
</tr>
<tr>
<td></td>
<td>Left inferior occipital gyrus</td>
</tr>
<tr>
<td>Negative correlations (increased metabolism)</td>
<td>Bilateral posterior cingulate cortex</td>
</tr>
<tr>
<td></td>
<td>Right superior frontal gyrus</td>
</tr>
<tr>
<td></td>
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| BA, Brodmann area. |
analyses we used to identify the overlap between the apathy and impaired EFR networks highlighted the right premotor cortex (BA 6), right OFC (BA 10), left middle frontal gyrus (BA 8) and left posterior cingulate gyrus (BA 31) as the structures supporting this correlation.

Our results of correlation between apathy and EFR are partially consistent with previous study18 because we failed to find a discrete emotional deficit associated with apathy. Rather, our results suggest a general deficit whereas the previous study found specific impairment in ‘fear’, ‘anger’ and ‘sadness’. This may come from the differences in methods since we controlled for depressive symptom severity and antidepressant medication21 and using a dedicated and validated 18-item scale.

Our imaging results only partially replicated previous results on the metabolic network implicated in apathy in PD.12 This may have been due to the smaller size of our sample (N=36) compared with that of the earlier study (N=45), possibly resulting in a lack of statistical power. Nonetheless, when we checked our results using a less conservative statistical cut-off (p<0.01 uncorrected; data not shown), our findings remained similar to those of the previous study (ie, increased metabolism within the bilateral OFC and decreased metabolism within the bilateral cerebellar posterior lobes).12 Another explanation would be that apathy in the present sample might be more related to emotional apathy than in our previous work since some results suggest that emotional apathy is supported by increased metabolism in posterior cingulate (Robert et al, in preparation), which is not the case in cognitive and behavioural apathy metabolic networks in PD.

Using disjunction analysis in order to define specific apathy (assessed with the neuropsychological inventory) metabolic pattern in degenerative dementia, some results suggest specific decreased metabolism within ventral tegmental area, inferior and middle temporal gyrus.32 These different results may arise from the difference regarding the population studied and the apathy scale used. Indeed, it has been shown that different apathy scales might yield different structural imaging results.10

Our results regarding the metabolic network implicated in impaired EFR were consistent with our expectations based on previous studies, where poor performances had been associated with metabolism within an extended limbic network encompassing a major part of the right frontal lobe, including the OFC (BA 10), DLPFC (BA 9) and premotor cortex (BA 6), a smaller
but also limbic part of the left frontal lobe (BAs 10 and 11), and the bilateral posterior cingulate (BA 31). Using exactly the same task in a PD group, a previous study had found that poor performances were correlated with grey matter loss within the bilateral OFC in early PD patients. However, we found increased metabolism within a larger proportion of the right frontal lobe, encompassing the DLPFC and premotor cortex. These differences may have arisen from the nature of the population being studied as our patients had disease durations ranging from 6 to 21 years (mean 11.6±4.03 years), whereas the sample studied in Ibarrexe-Bilbao et al were early PD (3.06±1.6) years of evolution. Increased metabolism could be interpreted as compensatory mechanisms. It is worth noting that researchers have long argued for the predominance of the right hemisphere in processing emotions. The premotor cortex has been found to be part of the apathy network in PD in both structural and resting state perfusion imaging studies with similar methods assessment. In another setting, functional imaging evidence of premotor cortex overactivity in unaffected carriers of the Parkin mutation during a passive gesture task that correlates with performances on an EFR task support the idea that it is implicated in impaired EFR in PD. Moreover, healthy volunteers whose premotor activity has been disrupted by transcranial magnetic stimulation display an EFR deficit. This structure’s involvement in EFR is thought to be linked to the embodiment of emotion, in that it plays a role in motor simulation (i.e., mimicry). Recent results from imaging meta-analysis in healthy volunteers suggest the posterior cingulate is part of an extended limbic network, along with the OFC and the premotor cortex, to process positive rewards. Moreover, it can be regarded as a nexus, relaying emotions to emotion facilitation or inhibition processes via its connections with the medial OFC and DLPFC. The OFC has been repeatedly found to belong to the neural networks that subserve apathy in PD, whether it be in metabolic, functional or structural imaging studies. It is now widely acknowledged as a critical brain structure for processing reward value and therefore plays a key role in goal-directed behaviour in humans. Moreover, some results suggest the OFC holds a key role in recognising emotions. Although these studies are from different settings, assessed with different methods and various populations, there is a growing body of literature that suggests premotor cortex, posterior cingulate and OFC are higher-order and interconnected brain structures involved in complex behaviour.

Our results suggest that motivation and emotion recognition are dopamine-related and inter-dependent psychological process. Each process have been related to dopamine in healthy, pathological human states and animal models separately. However, our results do not allow to determine the contribution of dopamine to emotion recognition with regard to motivation since we controlled for the dopaminergic medications throughout the study.

Several limitations should be borne in mind, however. First, the PD patients in our sample were all eligible for STN-DBS and therefore represented just a subpopulation of PD patients. Second, they exhibited only moderate apathy. Furthermore, the interpretation of the role played by the network encompassing the right inferior frontal cortex, posterior cingulate and left premotor cortex in supporting the overlap between impaired EFR

Figure 2  PET Results. Conjunction analyses of areas commonly associated with apathy and low recognition performances on the emotional facial recognition task (p<0.05, uncorrected).
and apathy cannot be completely confirmed, as the PET scans were performed at rest and results are drawn from GLM. To remedy this shortcoming, a specific paradigm is needed that takes better account of both emotion processing and apathy. Our assessment of apathy only concerned daily-life activities and various types of goal-directed behaviour. Moreover, the AES only assesses behaviour over the previous few months. The challenge is thus to use a dynamic paradigm in order to assess chronic apathy, as well as apathy in daily-life activities.

In conclusion, these results support the existence of an anatomical and functional relationship between apathy and impaired EFR in PD patients, mediated by the high-order and integrative brain structures involved in both motivation and emotion processes. Further research is needed to confirm these results using a paradigm that simultaneously measures apathy and emotion. In doing so, the specific contribution of dopamine on emotion recognition and motivation may be clarified either in healthy humans or PD. It should be noted that additional studies should be conducted to confirm these results to other subcomponents of emotion, such as emotional experience and expression.

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Contributors GR and FLeJ were responsible for acquisition, analysis, interpretation of the data, drafting, and final approval of the manuscript. TD and SD were responsible for acquisition and interpretation of the data, revising and final approval of the manuscript. PS and DT were responsible for conception and design, revising and final approval of the manuscript. BM was responsible for conception and design, interpretation of the data, drafting, revising, and final approval of the manuscript.

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Ethics approval Comité de Protection des Personnes de la Faculté de Médecine de Rennes.

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