Emotional and Cognitive Processing Deficits in People with Parkinson’s Disease and Apathy

Martha F Hanby¹, Michelle Barraclough², Shane McKie³, Neal Hinvest⁴, Kathryn McDonald³, Rebecca Elliott¹ and Iracema Leroi¹,³,*

¹Department of Cardiovascular sciences, University of Leicester, UK
²Institute of Inflammation and Repair, University of Manchester, UK
³Institute of Brain, Behaviour and Mental Health, Manchester Academic Health Sciences Centre, University of Manchester, UK
⁴University of Bath, UK
⁵Manchester Mental Health and Social Care Trust, UK

Abstract

Background: Apathy is a common non-motor syndrome of Parkinson’s disease (PD), understood as a quantitative reduction in goal-directed behaviour consisting of cognitive and emotional dimensions.

Methods: Participants with PD (n=61) were assessed in different medication states on tasks of executive function and emotional processing. Performance was compared to that of a healthy control group (HC, n=19). The PD group was further divided into those with and without clinically significant apathy and compared using the same measures in an exploratory manner.

Results: Compared to the HC group, the PD participants performed significantly worse on tests of executive function, the Iowa Gambling Task, and recognition of happiness on the Facial Emotional Recognition Task. Compared to PD participants without apathy, those with PD and apathy were found to have selective impairments on tasks of attention and the recognition of disgust, fear and happiness. No effects of dopamine were seen.

Conclusion: The presence of apathy in PD is associated with selective cognitive and emotional processing deficits, which do not appear to be dopamine dependent.

Keywords: Apathy; Emotional processing; Parkinson’s disease


Introduction

In people with Parkinson’s disease (PD), deficits in cognition and emotional processing may be associated with behavioural and psychiatric disturbances such as depression, anxiety, impulse control disorders and apathy [1-3]. Apathy is understood as a quantitative reduction in goal-directed behaviour consisting of cognitive and emotional dimensions [4-6]. Many people with PD will develop apathy at some point during the course of the disease [7]. The presence of apathy has a significant negative impact on quality of life, disability and caregiver burden [8,9] and may be a predictor of conversion to dementia in PD [10]. In spite of this, little is known about the neurocognitive mechanisms that mediate apathy and its dimensions of cognitive impairment and emotional blunting.

Cognitive impairment in PD may be present from the point of diagnosis and may initially manifest as a dysexecutive syndrome. Over time, a syndrome of ‘mild cognitive impairment’ in PD (PD MCI) may emerge which may eventually develop into full dementia with impairment in multiple cognitive domains severe enough to impact on functional ability. Apathy in particular has been shown to be associated with executive dysfunction, in particular slowness in performance tasks such as the Stroop tests, but also on executive tasks less dependent on speed of visual processing. Such differences have been demonstrated when comparing those with PD and apathy to those with PD and no apathy as well as healthy control (HC) groups [10-15].

A greater understanding of the characteristics of apathy is crucial for the planning and development of appropriate, specifically targeted interventions that will reduce the negative impact apathy has on patients and their families. This argues for investigations into discrete aspects of PD-related emotional processing in apathy using targeted behavioural tasks. In PD, there is a growing literature on deficits in decoding of emotional faces in early disease, later disease and in the un-medicated and medicated state. Previous studies in PD have found in the un-medicated state, people with PD have been found to be impaired in the recognition of disgust, anger, sadness and fear [1,2,16,17] and medicated PD patients to be impaired in the recognition of fear and anger in comparison to age-matched HC [2].

Emotional decision-making in PD, using other behavioural tasks such as the Iowa Gambling Task (IGT) [18], has also been investigated in various disease stages and medication states [19-21].

*Corresponding author: Iracema Leroi, Senior Lecturer in Psychiatry/Honorary Consultant, Older Adult Psychiatry, Manchester Academic Health Sciences Centre, University of Manchester, Institute of Brain, Behaviour and Mental Health, Jean McFarlane Building, 3rd Floor, Oxford Road, Manchester, M13 9PL, United Kingdom; Tel: +44 (0) 161 306 7942; E-mail: Iracema.Leroi@manchester.ac.uk

Received May 27, 2014; Accepted July 25, 2014; Published August 15, 2014


Copyright: © 2014 Hanby MF, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
The results from these studies have also been inconsistent with some demonstrating impaired performance on the IGT [19,21] and others finding no such difference [20]. A possible explanation for the variable results could be due to differences in disease stages in the respective patient populations, with some studies including de novo PD patients [1,2,16,20] and others including participants in more advanced stages of the disease [17,19,21].

To date, findings from studies remain inconsistent and decoding of emotional faces and decision-making have not been thoroughly evaluated in specific behavioural syndromes, such as apathy.

In order to investigate this further, we sought to determine firstly whether PD participants, who were free of dementia, would display altered cognitive and emotional processing in comparison to HC participants. Secondly, we investigated whether apathy in PD was associated with specific deficits in cognitive and emotional processing, compared to PD without apathy. Lastly we undertook an exploratory analysis to assess the effects of dopaminergic medication on emotional processing. We hypothesised that participants with PD and apathy would have more impaired executive function, more impulsive decision-making, and more impaired decoding of emotional faces compared to those with PD but no apathy. We further hypothesised that being in the ‘on’ medication state would result in even greater impulsivity in decision-making compared to being in the ‘off’ medication state.

**Methods**

All participants had the capacity to provide informed consent for the study and signed an approved consent form. All study procedures were approved by our regional ethics committee in the UK.

Participants

A total of 61 PD participants meeting UK Brain Bank criteria [22] were consecutively recruited from neurology clinics in the North West of England. The study sample was divided into two groups: (1) those with clinically significant apathy (PD+A; n=22) according to a cut-off score >37 on the Marin Apathy Evaluation Scale-Clinician version (AES-C) [23]; and (2) those without apathy (PD-A; n=39) as determined on this same scale. All participants were clinically stable and responding well to their dopamine replacement therapy at the time of the study assessment and had not had any medication changes four weeks prior to this. Participants were excluded if they had a Mini-mental State Exam [24] score of <26 and/or met the clinical consensus criteria for dementia in PD (PDD) [25,26]. Those with clinically significant depression, diagnosed using the Structured Clinical Interview for DSM-IV-TR axis I [27] at the time of, or in the three months leading up to, the first study assessment were also excluded. A further group of participants (n=19) who were age-, sex-, and education-matched healthy volunteers were included as a HC group.

**Assessment of clinical characteristics and psychiatric assessment**

Disease characteristics were assessed as per the Unified Parkinson’s Disease Rating Scale (UPDRS) [28], parts III and IV (rated during the “on” medication state, defined as 30-90 minutes after the medication dose) and the Hoehn-Yahr (HY) scale [29]. Levodopa equivalent daily dose (LEDD) was calculated using a previously reported formula [30]. As we have described previously, apathy was assessed using the 18 item AES-C [23], which is one of the recommended scales in PD [31].

### Table 1: Demographic and clinical variables in three groups: Parkinson’s disease participants with and without apathy; healthy controls.

<table>
<thead>
<tr>
<th></th>
<th>PD+A (n=22)</th>
<th>PD-A (n=39)</th>
<th>HC (n=19)</th>
<th>Statistic (ANOVA or t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic variables</strong></td>
<td></td>
<td></td>
<td></td>
<td>F; p</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.32 (6.32)</td>
<td>66.16 (4.92)</td>
<td>65.79 (5.55)</td>
<td>F=2.87; p=0.06</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>17 (77.3)</td>
<td>29 (74.4)</td>
<td>9 (47.4)</td>
<td>x²=5.36; p=0.07</td>
</tr>
<tr>
<td>Level of formal education (years)</td>
<td>12.45 (2.30)</td>
<td>13.00 (2.26)</td>
<td>13.31 (2.33)</td>
<td>F=0.76; p=0.47</td>
</tr>
<tr>
<td><strong>Disease variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levodopa equivalent daily dose</td>
<td>812.92 (522.16)</td>
<td>854.84 (621.21)</td>
<td>t=-0.27; p=0.79</td>
<td></td>
</tr>
<tr>
<td>Duration of PD motor symptoms (months)</td>
<td>123.27 (82.49)</td>
<td>89.24 (64.90)</td>
<td>t=1.65; p=0.11</td>
<td></td>
</tr>
<tr>
<td>Age of onset of motor symptoms (years)</td>
<td>59.73 (10.41)</td>
<td>58.43 (8.34)</td>
<td>t=0.53; p=0.59</td>
<td></td>
</tr>
<tr>
<td>UPDRS* motor (Part III)</td>
<td>37.68 (12.39)</td>
<td>25.73 (10.00)</td>
<td>t=4.07; p=0.000</td>
<td></td>
</tr>
<tr>
<td>UPDRS* complications (Part IV)</td>
<td>3.95 (1.58)</td>
<td>3.27 (1.39)</td>
<td>t=0.74; p=0.47</td>
<td></td>
</tr>
<tr>
<td>Hoehn-Yahr stage</td>
<td>2.68 (0.73)</td>
<td>2.29 (0.79)</td>
<td>t=2.32; p=0.02</td>
<td></td>
</tr>
<tr>
<td><strong>Behavioural variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apathy Evaluation Scale-Clinician version</td>
<td>47.27 (12.13)</td>
<td>23.86 (7.69)</td>
<td>22.95 (5.06)</td>
<td>F=58.74; p&lt;.001 (post hoc: p&lt;.001 for both PD+A vs PD-A and PD-A vs HC)</td>
</tr>
<tr>
<td>Depression of any kind**, (%DSM IV criteria)</td>
<td>8 (37.3)</td>
<td>28 (62.7)</td>
<td>x²=0.32; p=0.58</td>
<td></td>
</tr>
</tbody>
</table>

*Unified Parkinson’s Disease Rating Scale

- Including major and minor depression, dysthymia; excludes adjustment disorder or pathological grief reaction, and mood disorder due to substance abuse
Cognitive assessment

The cognitive test battery (Table 2) conducted during the “on” medication state only, consisted of standardised cognitive measures with emphasis on executive function (Table 3) [32-35]. The cognitive battery was performed once by each participant [36,37].

Emotional behavioural tasks

Decision-making task: A computerized version of the IGT was administered [38]. For the purposes of this study, outcome variables chosen were: (1) “total IGT” score (difference between the advantageous decks (C+D) and the disadvantageous decks (A+B)); (2) net amount won (amount won-lost); and (3) IGT scores across the 5 “blocks” of card choices, which allowed for an analysis of reward-related reinforcement learning. Each participant with PD undertook the task twice: once while taking regular dopaminergic medication (“on”, defined as 30-60 minutes after the participants’ regular dopaminergic replacement medication); and once following a 12 hour medication wash-out period (“off”), in a randomized counterbalanced design in order to obviate a medication); and once following a 12 hour medication wash-out period ("off"), in a randomized counterbalanced design in order to obviate a

Facial Emotional Recognition Task (FERT): The FERT task used in our study was a modified version previously used by our group [39]. Images of four actors depicting the 6 basic emotions (happy, sad, fear, anger, disgust and surprise) at three levels of intensity, (30%, 50%, and 70%) were presented to each participant four times in random order on a computer screen and participants were asked to indicate which emotion they believed was being displayed. The FERT assessments were done “on” medication in 26 participants and “off” medication (defined as at least 12 hours since the last dose) for the remaining 33 participants.

Table 2: Description of cognitive tests administered.

<table>
<thead>
<tr>
<th>Cognitive Test</th>
<th>Description of test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal fluency, F.A.S [32]</td>
<td>The participant had to list as many words beginning F in 60 seconds; A in 60 seconds and S in 60 seconds.</td>
</tr>
<tr>
<td>Attention (serial 7’s) [33]</td>
<td>A test where a participant counts down from one hundred by sevens.</td>
</tr>
<tr>
<td>Modified Wisconsin Card Sorting Test [34]</td>
<td>There are 4 stimulus cards. The participant is instructed to match each of the cards to one of the key cards. The participant is informed as to whether the answer is right or wrong but is not told of the sorting principle. The sorting category is changed without warning and the administration includes six sets of three possible scoring categories.</td>
</tr>
<tr>
<td>5 minute recall [35]</td>
<td>A memory screening test of the participant being asked to recall 3 words after 5 minutes.</td>
</tr>
<tr>
<td>n-back [36]</td>
<td>The participant is presented with a sequence of stimuli, and the task consists of indicating when the current stimulus matches the one from n steps earlier in the sequence.</td>
</tr>
<tr>
<td>Trial-making test [37]</td>
<td>The participant is instructed to connect alternating letters and numbers (1, A, 2, B) as fast as possible.</td>
</tr>
</tbody>
</table>

Table 3: Comparison of cognitive measures in three groups: Parkinson’s disease patients with and without apathy; healthy controls (HC).

<table>
<thead>
<tr>
<th>Cognitive Test</th>
<th>Parkinson’s disease patients with apathy (n=22)</th>
<th>Parkinson’s disease patients without apathy (n=39)</th>
<th>Healthy Controls (n=19)</th>
<th>Statistic (ANOVA or t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal fluency, (FAS; adjusted for age, sex and education)</td>
<td>35.27 (10.46)</td>
<td>41.62 (15.13)</td>
<td>53.31 (12.42)</td>
<td>F=7.41; p&lt;0.001</td>
</tr>
<tr>
<td>Attention (Serial 7’s)</td>
<td>3.36 (1.79)</td>
<td>4.34 (0.76)</td>
<td>5.16 (0.69)</td>
<td>F=19.21; p&lt;0.001</td>
</tr>
<tr>
<td>mWCST: Total</td>
<td>34.05 (6.10)</td>
<td>34.15 (10.52)</td>
<td>38.63 (8.41)</td>
<td>3.15; p=0.21</td>
</tr>
<tr>
<td>mWCST: perseverative errors</td>
<td>4.86 (5.65)</td>
<td>4.15 (6.02)</td>
<td>1.53 (2.76)</td>
<td>3.44; p=0.18</td>
</tr>
<tr>
<td>mWCST: non-perseverative errors</td>
<td>19.19 (8.57)</td>
<td>16.15 (10.94)</td>
<td>16.42 (10.70)</td>
<td>0.54; p=0.73</td>
</tr>
<tr>
<td>5 minute recall</td>
<td>2.18 (1.01)</td>
<td>2.51 (0.85)</td>
<td>2.74 (0.99)</td>
<td>4.43; p=0.11</td>
</tr>
<tr>
<td>n-back (correct responses)</td>
<td>13.27 (3.21)</td>
<td>16.09 (3.32)</td>
<td>18.89 (3.31)</td>
<td>F=13.38; p&lt;0.001</td>
</tr>
<tr>
<td>TMT-B-TMT-A, (seconds)</td>
<td>132.36 (85.86)</td>
<td>83.0 (57.27)</td>
<td>62.16 (31.50)</td>
<td>21.16; p&lt;0.001</td>
</tr>
</tbody>
</table>

Post-hoc Scheffe or Mann Whitney U for two-group comparison:
PD+A vs. HC: † at p<0.05; ‡ at p<0.01; ‡‡ at p<0.001;
PD-A vs. HC: † at p<0.05; ‡‡ at p<0.01; ‡‡‡ at p<0.001;
PD+A vs PD-A: † at p<0.05; †† at p<0.01; ††† at p<0.001

performed to compare PD participants “on” and “off” medication who undertook the FERT task.

Differences in performance on the IGT between the entire PD group and HC group were analysed by initially comparing the “total IGT score” and the net amount won. Repeated measures ANOVA (2x5) was performed to examine IGT performance across blocks of advantageous card choices (within-subjects factor) between the two groups (between-subjects factor). The same method of analysis was used to assess the effects of apathy on IGT performance. The scores for the PD patients on the IGT task was taken as the mean score of their ‘on’ and ‘off’ conditions. IGT scores ‘on’ and ‘off’ medication were analysed as above and used to assess the effects of dopamine on performance on the IGT.

Mean total FERT scores were compared between the PD and the HC groups. A repeated measures ANOVA (2x6) was performed to examine the effect of the different emotions (within-subjects factor) across the two groups (between-subjects factor).

Finally, a series of repeated measures ANOVA (2x3) were used to examine the three different intensities (within-subjects factor) within each emotion separately. Subsequently, this same method of analysis was used to assess the effects of both apathy and dopaminergic status separately. A final analysis was conducted to determine whether any interaction between apathetic status and dopaminergic status affected the performance in FERT. ANCOVA was utilised in all calculations to take into consideration co-variates between the groups identified from earlier analyses. The \( p \) value of significance was set at <0.05.

Results

Demographic and clinical factors

As outlined in Table 1, the PD+A and the PD-A groups were well matched with the HC group on age, sex, and level of education. The two PD groups were also well matched on LEDD, duration of motor symptoms, age at onset of motor symptoms, and UPDRS complications of therapy score. Motor severity (UPDRS motor) and disease stage (HY) was significantly greater in the PD+A compared to the PD-A group (\( p<0.001 \) and \( p=0.02 \) respectively). On behavioural ratings, the PD+A group did not differ significantly in level of depression (\( p=0.38 \)) from the PD-A group. UPDRS motor and HY scores were used as co-variates in all subsequent analyses between PD+A and PD-A. Furthermore, PD participants undertaking the FERT task “on” medication were found to be significantly older than those “off” medication (68.7 vs. 65.7, \( p=0.04 \)) therefore age was used as a co-variate in assessment of dopaminergic status on FERT performance. No other significant differences between medicated and un-medicated PD participants were seen.

Cognitive tasks compared among PD+A, PD-A, and HC

The comparison of cognitive functioning among the groups is outlined in Table 3. In tasks of verbal fluency (FAS), attention, attentional set shift (serial 7s, TMT B-A), and working memory (digit n-back), both PD groups were significantly more impaired compared to the HC group. In addition, the PD+A group was significantly more impaired than the PD-A group on the attention task (TMT B-A, \( p=0.05 \)). The groups did not differ on short-term memory recall (5 minute word recall), nor the set shifting task (mWCST). The differences between groups on cognitive testing were taken into consideration in subsequent analyses.

Emotional decision making task (Iowa Gambling Task)

Comparison of IGT performance between the PD and the HC groups: The HC participants were found to have significantly higher total IGT scores in comparison to the PD group (-0.5088, SD 19.48) vs. 16.46, SD38.09; \( F (1, 64)=7.433, p=0.01 \). The PD group lost significantly more compared to the HC group (-1202.24, SD901.48) vs. -212.69, SD1678.10); \( F (1, 64)=8.16, p=0.01 \). Neither group displayed reward reinforced learning across blocks (\( F(3.04, 197.76)=0.392, p=0.76 \)). A significant effect of group was seen (\( F (1, 65)=5.96, p=0.02 \)) but no significant group x blocks interaction (\( F(3.04, 197.76)=0.32, p=0.81 \)) was evident.

Comparison of IGT performance between the PD groups only: The presence of apathy in participants with PD was not found to have a significant effect on total IGT scores nor net amount won (F(1, 51)=0.06, \( p=0.81 \) and F(1, 51)=0.08, \( p=0.78 \) respectively). Both groups displayed reward reinforced learning across blocks (\( F(2.69, 137.10)=2.78, p=0.05 \)). However no significant effect of group (F(1, 51)=0.06, \( p=0.81 \)) nor group x blocks interaction (\( F(2.69, 137.10)=0.89, p=0.44 \)) was seen.

Effects of dopaminergic medication on IGT: No significant effect on either total IGT scores (1.22 (23.70) vs. -1.90 (24.90), \( T=0.80, p=0.43 \)) nor net amount won (-1192.50 (1041.50) vs. -1194.40 (1276.00), \( T=0.01, p=0.43 \)) was found with medication status. PD participants “off” medication were found to demonstrate reward reinforcement learning (\( F(3.22, 186.70)=3.72, p=0.01 \)), whereas those ‘on’ medication did not (\( F(3.07, 184.40)=1.94, p=0.12 \)).

In summary, PD participants with and without apathy and in the un-medicated state demonstrated reward-reinforced learning whilst PD participants overall and those in the HC group did not.

Receptive emotional processing task (Facial Emotional Recognition Task; FERT)

Comparison of FERT between the PD and HC groups: The mean FERT scores for the different emotions across the PD group overall and the HC group are shown in Table 4. The initial repeated

## Table 4: Mean Facial Emotional Recognition Task scores of Parkinson’s disease participants in comparison to Healthy Controls.

<table>
<thead>
<tr>
<th>Facial Emotion</th>
<th>Parkinson’s disease (n=59)</th>
<th>Healthy Controls, (n=19)</th>
<th>Statistic (ANOVA) (Mean, (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fert (1, 66)=0.033, p=0.86</td>
</tr>
<tr>
<td>Anger</td>
<td>3.05 (2.19)</td>
<td>2.38 (1.89)</td>
<td>(Fert (1, 66)=0.033, p=0.86</td>
</tr>
<tr>
<td>Disgust</td>
<td>3.59 (2.39)</td>
<td>4.77 (2.05)</td>
<td>(Fert (1, 66)=1.80, p=0.18</td>
</tr>
<tr>
<td>Fear</td>
<td>3.66 (2.32)</td>
<td>5.15 (2.08)</td>
<td>(Fert (1, 66)=0.50, p=0.83</td>
</tr>
<tr>
<td>Happy</td>
<td>7.07 (1.42)</td>
<td>7.31 (1.18)</td>
<td>(Fert (1, 66)=0.70, p=0.41</td>
</tr>
<tr>
<td>Sad</td>
<td>3.66 (2.54)</td>
<td>4.23 (2.31)</td>
<td>(Fert (1, 66)=0.00, p=0.99</td>
</tr>
<tr>
<td>Surprise</td>
<td>6.25 (2.62)</td>
<td>7.08 (2.84)</td>
<td>(Fert (1, 66)=0.07, p=0.79</td>
</tr>
<tr>
<td>Total FERT</td>
<td>27.3 (7.54)</td>
<td>30.9 (7.34)</td>
<td>(Fert (1, 66)=0.03, p=0.86</td>
</tr>
</tbody>
</table>
measures ANOVA of all emotions across these two groups did not show a significant effect of group (F (1, 66)=0.03; p=0.71), emotion (F (4.53, 298.83)=1.65; p=0.15) nor a significant group x emotion interaction (F (4.53, 298.83)=0.57, p=0.71).

When we investigated participants’ ability to decode facial emotions expressed with different intensities, we found that in the decoding of happy there was a significant main effect of intensity (F (1, 98, 130.67)=5.11, p=0.01) but not of group with HC being able to recognise intensities of happiness significantly more easily than PD participants. No interaction between group and intensity was seen. Likewise, in the decoding of all other emotions, no significant effects of group, intensity or interactions were revealed.

**Comparison of FERT between PD participants with and without apathy:** For the PD participants alone, when analysing the effect of the presence of apathy (between-subjects factor 1) on total FERT scores, a significant effect was seen (F (1,53)=4.73, p=0.03) with the PD-A group having a lower total mean FERT score compared to the PD-A group (23.14, SD 7.56) vs. 29.29, SD 5.90). However, no significant differences between the two groups were found for any individual emotion. A repeated measures ANCOVA of all emotions between PD + A and PD – A again found a significant effect of group (F (1, 53)=4.73, p=0.03) but not of emotion (F (4.50, 238.70)=1.69, p=0.16). A significant emotion x group interaction (F (4.50, 238.70)=0.15, p=0.97) was not seen. The ability of the PD + A group to decode different intensities of emotion in comparison to the PD – A group revealed a significant effect of intensity for the recognition of disgust (F (2.00, 106.00)=4.15, p=0.02); fear (F (2.00, 106.00)=4.15, p=0.02); happiness (F (1.94, 102.70)=6.71, p<0.01) with non-apathetic PD participants being significantly more able to recognise these emotions in comparison to apathetic PD participants. No significant main effect of group or group x intensity interaction was found.

**Comparison of FERT between PD participants “on” and “off” medication:** Differences in total FERT scores (30.48 (7.26) vs. 30.67 (9.13); F (1, 57)=0.048, p=0.83) or on the recognition of individual emotions were found not to be significant between PD participants ‘on’ medication to those ‘off’ medication. Repeated measures ANCOVA incorporating the six different emotions confirmed no effect of emotion, group or any emotion x group interaction. Dopaminergic status also failed to reveal any significant difference in the recognition of different intensities of each emotion with repeated measures ANCOVA.

No significant interactions were found between medication status and apathy status for the recognition of any emotion or any intensity of emotion.

**Discussion**

Here we have demonstrated the presence of significant and specific deficits in cognitive and emotional processing associated firstly with PD, secondly with PD-associated apathy, and thirdly, in an exploratory manner, with dopaminergic status.

Evidence of executive impairments, specifically verbal fluency, attention and working memory, between PD participants and HC supports previous findings [41-43]. Similarly, attention and working memory deficits in PD participants with and without apathy correspond with those reported in previous literature [44-48]. These results are consistent with our initial hypothesis. We have previously shown that apathy is one of the most frequently reported behavioural disturbances in those with mild cognitive impairment in PD (PD-MCI), which is commonly characterised by executive dysfunction [49].

It is notable that no differences were found among the three groups in the performance on the mWCST, a task involving strategic planning, organised searching and directed behaviour towards achieving a goal. This is a task which one might expect to be impaired in association with apathy and the absence of impairment in our findings suggests that apathy in PD may be selectively associated with certain aspects of executive function but not others.

Executive dysfunction in PD was initially thought to be solely a consequence of dopamine depletion in the striatum disrupting thalamo-cortical circuits and resulting in frontal lobe dysfunction [50]. However MRI studies in recent years have found that multiple brain regions may be involved, including brainstem nuclei, limbic structures and the cerebral cortex [51-53]. Altered functioning in these regions likely underpins executive dysfunction in PD and likely reflects involvement of non-dopaminergic neurotransmitter systems which play a role in behavioural syndromes. Our findings of selective executive functions being affected in PD-related apathy likely represents the complexity of clinical presentations of cognitive impairment within PD [54].

We also found that those with PD performed less well on the IGT compared to the HC group. Both groups did not, however, demonstrate reward reinforcement learning. These results are consistent with previous findings in early [18,55] and advanced-stage PD [19,56,57].

The performance in the IGT of PD participants with apathy in comparison to those without apathy did not significantly differ. Both groups demonstrated reward reinforcement learning.

Deficits in decision-making on the IGT have been attributed to lesions in the orbito-frontal cortex [58] and with its dense reciprocal connections to the anterior cingulate cortex [59,60] impairments in this task would be expected in those with apathy. Previous findings however have shown PD participants with apathy perform significantly better on decision making tasks than HC participants [61]. In contrast, our findings here demonstrate that apathetic status in PD has no effect on performance in the IGT, which does not support our initial hypothesis. In the context of our subsequent finding of apathy-related deficits in the emotional decoding task, it is possible that emotional processes underlying apathy in PD are quite specific to some aspects of motivated behaviour, but not others. This notion is supported by evidence of the presence of dissociable dimensions of apathy, for example loss of initiative, loss of interest and emotional blunting, which may not be uniformly present in all apathy sufferers and may have separable pathophysiological underpinnings [62-64].

Our exploratory investigation of the effect of dopaminergic status on reward reinforcement learning revealed that PD participants ‘off’ medication did indeed demonstrate such learning, as seen by their ability to modify their choices based on reward across blocks on the IGT. When ‘on’ medication, this type of learning was not seen. These findings are consistent with previous studies in which medicated PD participants demonstrate impaired performance on reversal learning tasks in comparison to un-medicated PD participants [65-67]. Such behavioural processing relies on ventral striato-frontal circuitry including the ventral striatum and the orbito-frontal cortex [68-70]. In our study, dopamine replacement status was associated with impaired performance in tasks underpinned by the ventral striatum. This is consistent with previous findings of impaired performance in a simple selection task being associated with patients on dopamine replacement in comparison to an un-medicated PD group [71].

The ability to recognise an emotional facial expression did not differ between the HC and PD participants, other than the emotion of
happiness. Furthermore, those with PD and apathy had more difficulty with emotional recognition compared to those without apathy, which may be attributed to certain specific emotions (disgust, fear and happiness). An earlier study found that individuals with PD and apathy were more impaired in recognition of fear, anger and sadness than those with PD and no apathy. Differences in the specific emotions of interest between these two studies may be attributed to the ascertainment of apathy. We used a well-validated apathy scale that has previously been used in PD [72] in contrast to the more subjective assessment of apathy used by Martínez-Corral et al., 2010 [3]. Moreover, we avoided a possible ceiling effect of emotional recognition by administering variable intensities of each emotion. The impaired decoding of disgust in people with PD and apathy is more specific than previous reports in PD literature, where authors omitted the diagnostic status of apathy [1,2,16,73]. This suggests that future studies of emotional processing in PD should take account of the presence of apathy. Importantly, our findings support the involvement of the “emotional–affective” dimension in PD-related apathy and are also consistent with our initial hypothesis. The decoding of both fear and disgust are dependent on key neural pathways which may be disrupted in PD related apathy [39,74-80]. Fear recognition has been linked to the anterior cingulate cortex, orbito-frontal cortex and the amygdala [81-83] whereas disgust to the insula [1].

Finally, dopaminergic status did not appear to affect the ability of PD participants to recognise particular emotions, which is in contrast to existing evidence of dopamine replacement therapy enhancing the recognition of disgust and anger [2,17]. Other studies have attempted to control for the effects of dopaminergic medication on facial emotion decoding by only assessing un-medicated PD participants in the early stages of the disease [1]. In this case, those with PD were less accurate in decoding angry, sad and disgusted emotional faces compared to healthy control participants. This suggests that the emotional-processing deficits in PD may be independent of a medication effect and that perhaps other dimensions of apathy such as deficits in interest and initiative, which may not be emotionally-based, may be more sensitive to the effects of dopaminergic medication.

Certain limitations in our study have to be acknowledged. Our sample size became relatively small when comparing the different medication subgroups within PD sub-groups in the emotional decision-making task. Furthermore, although a strength of the study was the examination of the response to different behavioural tasks in both the ‘on’ and the ‘off’ medication states, a possible ‘cross-over’ effect on the IGT task may have occurred resulting in DRT having an effect on performance. A counter-balanced administration was used to minimise any carry-over effects and this was avoided in the FERT task through the use of separate ‘on’ and ‘off’ medication groups. The two groups in the FERT were well-matched on all baseline demographics except age which has not been the case in previous studies [2]. Our group has previously used this task in conjunction with a more subtle, covert functional magnetic imaging-based facial recognition task and findings between tasks were found to be consistent [39].

In conclusion, highly specific aspects of executive function and emotional processing were found to be associated with apathy in PD but were not found in association with dopaminergic status. Further studies investigating executive function and emotional processing in greater depth are needed and should involve participants with apathy or depression and MCI. A better understanding of emotional processing underlying behavioural disturbances in PD will improve the clinical management of behavioural problems associated with PD with the ultimate aim of enhancing quality of life for those living with the condition.

Acknowledgements
1. The people with PD in the North West UK who so kindly participated in this study.
2. Drs Mark Kellett, Jeremy Dick and Philip Tidswell and the Clinical Research Network, DeNDRoN for their significant support with recruitment of participants.
3. DeNDRoN North West for study coordination.
4. Parkinson’s UK (Fellowship grant F-0060) for providing grant funding to IL.

References


