



This is a repository copy of *Apathy in Mild Parkinson's Disease: Neuropsychological and Neuroimaging Evidence.*

White Rose Research Online URL for this paper:
<http://eprints.whiterose.ac.uk/106079/>

Version: Accepted Version

Article:

Alzahrani, H., Antonini, A. and Venneri, A. (2016) Apathy in Mild Parkinson's Disease: Neuropsychological and Neuroimaging Evidence. *Journal of Parkinson's Disease*, 6 (4). pp. 821-832. ISSN 1877-7171

<https://doi.org/10.3233/JPD-160809>

The final publication is available at IOS Press through
<http://dx.doi.org/10.3233/JPD-160809>.

Reuse

Unless indicated otherwise, fulltext items are protected by copyright with all rights reserved. The copyright exception in section 29 of the Copyright, Designs and Patents Act 1988 allows the making of a single copy solely for the purpose of non-commercial research or private study within the limits of fair dealing. The publisher or other rights-holder may allow further reproduction and re-use of this version - refer to the White Rose Research Online record for this item. Where records identify the publisher as the copyright holder, users can verify any specific terms of use on the publisher's website.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

Apathy in mild Parkinson's disease: Neuropsychological and neuroimaging evidence

Hamad Alzahrani^{1,2}, Angelo Antonini³, Annalena Venneri^{1,3}

1 Department of Neuroscience, University of Sheffield, UK

2 National Neuroscience Institute, King Fahad Medical City, Riyadh, Saudi Arabia

3 IRCCS Fondazione Ospedale San Camillo, Venice, Italy

Running title: Correlates of apathy in early Parkinson's disease

Keywords: magnetic resonance imaging, executive function, neuropsychiatry, cognitive impairments

Corresponding Author

Prof. Annalena Venneri
Department of Neuroscience - Medical School
University of Sheffield
Beech Hill Road
Royal Hallamshire Hospital, N floor, room N130
Sheffield - S10 2RX - United Kingdom
a.venneri@sheffield.ac.uk

Background

Apathy is one of the most common neuropsychiatric symptoms in Parkinson's disease (PD). Few studies have investigated the cognitive and neuroanatomical correlates of apathy in PD, and those which have done so have not controlled for the presence of other neuropsychiatric comorbidities.

Objective

To explore the cognitive and neuroanatomical correlates of apathy in PD at a mild disease stage.

Methods

Sixty-five PD patients and 24 healthy controls participated in this study. Patients underwent extensive neuropsychological screening, neuropsychiatric assessment using the Neuropsychiatric Inventory, structural MRI scanning, and neurological examination. A voxel-based multiple regression analysis was used to assess the relationship between grey matter volumes and apathy scores.

Results

Higher apathy scores correlated with lower grey matter volume in several brain areas including the left insula, left inferior/middle/medial frontal gyrus, right anterior cingulate, and the left superior temporal gyrus. Significant impairments were found in tests assessing executive functions, and a trend-level significant difference was observed in long term memory tests in patients with apathy, when compared with patients without apathy.

Conclusions

Apathy was associated with greater levels of atrophy in the frontal and temporal cortex, and anterior cingulate, as well as overall lower level of cognitive performance, particularly in executive function and memory skills. Apathy appears to be associated with cognitive impairments in PD, therefore, treatment of this symptom might mitigate its effects on cognitive performance in this clinical population.

1. INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder characterised by both motor symptoms (resting tremor, rigidity and bradykinesia) and non motor symptoms such as cognitive and neuropsychiatric symptoms [1]. One of the most frequent neuropsychiatric symptoms in PD is apathy [2-4]. Apathy refers to a combination of behavioural, emotional and cognitive features that leads to a reduced interest, and participation in daily life activities, together with lack of initiative, and lack of concern or indifference [5]. The prevalence of apathy in PD varies from 17- 70%, depending on the assessment procedures and the characteristics of the population [2, 5-8]. A recently published systematic review, and meta-analysis found that apathy affects about 40% of patients with PD [9]

Several studies have indicated that apathy is correlated with cognitive impairments in patients with PD [4, 7, 10-18]. For instance, a study investigated cognitive abilities in a patient group (23 with apathy and 25 without apathy) using the Apathy Evaluation Scale (AES) [19] and digit span [20], the Delis-Kaplan Executive Function Test [21], the California Verbal Learning Test [22] and the Wisconsin Card Sorting Test (WCST) [23]. There was a significant difference between patients with and without apathy on immediate free recall, short delay free recall, long delay free recall, long delayed cued recall, delayed recognition, digit span backward, and WCST (total correct, non-perseverative errors and categories completed) [24]. A further study reported that in patients with PD with left-side onset, apathy scores significantly correlated with scores on non-verbal tasks e.g. Trail Making Test (part B), Wechsler Memory Test and Visual Symbol Search Test [25]. Another recent study indicated that apathetic patients with PD with akinetic-rigid type performed significantly worse on tasks assessing functions associated with the frontal lobe e.g. the Frontal Assessment Battery (FAB) [26], phonemic fluency [27] and the interference error score on the Stroop test [28] when compared with patients with PD with tremor-dominant type [15].

Only a limited number of neuroimaging studies have investigated apathy in PD [29]. Apathy has been associated with deficits of the prefrontal-basal ganglia system [30]. A VBM study found that apathy was not correlated with the severity of motor symptoms, disease duration or proportion of

patients taking levodopa or a dopamine agonist. In addition, high apathy scores were negatively correlated with less grey matter density in the left precentral gyrus, the bilateral inferior parietal gyrus, the bilateral inferior frontal gyrus, the bilateral insula and the right posterior cingulate gyrus [17]. Another PET study reported positive correlations between AES scores and cerebral metabolism in the right inferior frontal gyrus, right middle frontal gyrus, right cuneus and right insula. Negative correlations were identified between AES scores, and cerebral metabolism in the bilateral cerebellum particularly the inferior semilunar lobule [31]. A recent PET study reported that, after deep brain stimulation of the subthalamic nucleus, apathy was associated with reduced preoperative metabolism within the right ventral striatum [32].

From the above literature, it appears that executive dysfunction and memory impairment are the most frequent cognitive difficulties in patients with PD with apathy, with imaging studies reporting associations between the presence of apathy in PD, and volumetric loss in frontal lobe and cingulate cortex. None of the previous studies investigated patients with apathy at a mild stage of PD, however, and previous findings might have not necessarily depicted the apathetic phenotype in PD, but rather a more severe disease level. In addition, these studies included a limited number of participants, and some only used screening instruments that assessed general cognitive abilities, but did not evaluate in detail a broader range of cognitive functions. Furthermore, there is no study which has assessed the possible presence of other neuropsychiatric comorbidities, and no study has investigated white matter volume in patients with PD with apathy. In fact, in other neurological disorders, for instance AD, a structural MRI study has found that patients with AD with apathy showed a significantly greater amount of frontal white matter hyperintensities than patients without apathy [8]. In addition, the cingulate area was also identified, when comparing patients with AD with apathy with patients with AD without apathy [33].

Therefore, taking into account the limitations of previous work, the present study was designed to explore both the cognitive and neuroanatomical correlates of apathy in a large sample of

patients with mild PD, exploring associations between the presence of this symptom, and volumetric changes in both grey and white matter. This study assessed the cognitive profile of non-demented PD patients at early stages of disease using an extensive battery of neuropsychological tests that explored multiple cognitive domains.

2. METHOD

2.1. SAMPLE

Sixty-five patients with idiopathic PD (31 male and 34 female) participated in this study. The patients were recruited among those who had had extensive assessment in a PD specialised clinic. The patients were diagnosed based on the UK PD Brain Bank Criteria [34]. All patients had extensive neuropsychological screening, neuropsychiatric assessment using the NPI, structural MRI scanning and neurological examination. All patients were in the mild disease stage, according to the Hoehn and Yahr (1967) staging [35] (specifically, patients were between stages 1 and 3). None of the patients had a history of psychiatric disorders and the neuropsychiatric symptoms started after the onset of PD. A larger cohort of 88 PD patients was originally recruited, but for 23 patients the MRI scans were of poor quality because of excessive movement artifacts and therefore not suitable for segmentation. The imaging study also included twenty-four healthy controls (6 males and 18 females) for comparison. None in the control group had a history of neurological or psychiatric diseases. For further detail, see table 1.

- Insert Table 1 about here

2.2. ASSESSMENTS OF APATHY

Apathy was defined and assessed according to both the NPI [36], and DSM-IV- TR [37]. Each patient and their caregiver had had an interview with an experienced psychologist who also completed the NPI. The NPI assesses the presence or absence, severity and frequency of 14 symptom

fields (patients who scored 1 or more were classified as having apathy). Apathy scores from the NPI were then entered in the statistical analyses. The NPI was chosen because it allows the exclusion of other neuropsychiatric symptoms, avoiding, therefore, possible contamination of findings through the presence of comorbidities, a major limitation of earlier studies. The use of a single symptom based assessment such as for example The Lille Apathy Rating Scale [38] or The Apathy Evaluation Scale [19], although providing a more in depth characterisation of the symptom, would not have allowed the selection of a sample free from potential other neuropsychiatric comorbidities.

2.3. NEUROPSYCHOLOGICAL ASSESSMENTS

An extensive battery of cognitive tests was administered to each participant in order to assess various cognitive domains. A trained neuropsychologist administered the assessments. The cognitive domains included global cognitive abilities assessed by the MMSE [39], executive ability measured by the FAB [26, 40-42], Letter Fluency Test [41], Trail Making Test (TMT) [43], Stroop Test [28, 41, 42, 44] and Digit Span (Backward) [45], abstract reasoning ability assessed by the Raven's Progressive Matrices, version 1938 (PM38) (Black and white) [44] and Similarities Test [45], non-verbal memory examined by the Rey Complex Figure Test (Delay) [41, 42, 46] and the Corsi Block-tapping Test (Visual-spatial span) [41, 42, 47], verbal memory assessed by the Category Fluency Test (Verbal retrieval of semantic materials) [41], the Digit Span (Forward) [45] and the Rey 15-word Memory Test (Delay) [48] and visual-construction abilities measured by the Rey Complex Figure Test (Copy) [41, 42, 46].

2.4. STATISTICAL ANALYSES

Univariate analyses of variance were carried out to compare demographical data and global cognitive screening as assessed by the MMSE of the three groups (patients with apathy, patients without any neuropsychiatric symptoms and healthy controls). This study also used an independent T-test and a series of independent T-tests to compare the neuropsychological test scores of the two subgroups (patients with apathy and without neuropsychiatric symptoms). Further statistical analyses were also

carried out to examine the relationship between apathy scores and neuropsychological test scores using the Pearson correlation test. To account for multiple comparisons, this study used a significance level of 0.004 for both overall comparisons among groups and for paired correlations. Post hoc (Bonferroni) comparisons were also used in order to determine possible significant differences between the patient subgroups (with and without apathy) and healthy control group in the demographical data and the MMSE and in this case significance level was 0.01.

2.5. STRUCTURAL MRI SCANNING: ACQUISITION AND ANALYSIS

Three dimensional T1- weighted MRI images were acquired on a 1.5 T Philips Achieva Scanner. Voxel dimensions were 1.04 x 1.04 x 0.6 mm. Field of view was 230 mm with a matrix size of 240 x 240 x 280. A number of pre-processing steps were followed to isolate the grey and white matter from the 3D T1-weighted structural scans before performing the statistical analysis using SPM8 imaging analysis software (Wellcome Centre for Neuroimaging, London, UK).

To correct for global differences in brain shape, structural images were warped to standard stereotactic space and segmented to extract grey matter, white matter, and cerebrospinal fluid using the default segmentation procedure available in SPM8. The grey and white matter segments were then modulated to correct for changes in volume induced by non-linear normalization and smoothed using a Gaussian filter set at 8 mm to reduce possible error from between subject variability in local anatomy and render the data more normally distributed. These smoothed grey and white matter segments were entered into a voxel-based independent T test analysis for group comparisons to investigate the differences in grey and white matter volumes between the sample groups (PD with apathy versus PD without any neuropsychiatric symptoms, PD patients with apathy versus healthy control, PD without any neuropsychiatric symptoms versus healthy control). Age, number of years of education, gender, and Total Intracranial Volume were also included in the model as covariates. The x, y, z coordinates of significant areas obtained from the analyses were first converted into Talairach coordinates using the mni2tal Matlab routine and then identified using the Talairach Daemon Client (<http://www.talairach.org/>). Unless otherwise stated, a cluster corrected height threshold of $p < 0.001$ was used in all analyses. An extent threshold was also applied to the different analyses. A T2–

weighted axial scan and a coronal Fluid Attenuated Inversion Recovery (FLAIR) scan were acquired after the 3-dimensional scan acquisition to better highlight any vascular load and ensure that all participants included in the 3-dimensional structural imaging study had no significant vascular burden.

3. RESULTS

3.1 DEMOGRAPHICAL AND MENTAL STATE SCREENING DATA ANALYSES

Univariate analyses of variance were carried out to compare the three groups (PD with apathy, PD without neuropsychiatric symptoms and controls) in age, education, disease duration and MMSE. The control and patient subgroups showed no significant difference in age [$F(2, 63) = 2.31, P > .01$] or education [$F(2, 63) = .39, P > .01$], but there was a significant difference in MMSE [$F(2, 63) = 25.965, p = .000$]. Post hoc (Bonferroni) comparisons showed that there was no significant difference between the patient subgroup with apathy and those without neuropsychiatric symptoms in MMSE, but there was a significant difference between controls and each of the two subgroups of patients. Also, patients with apathy and patients without neuropsychiatric symptoms did not differ for duration of disease [$F(1, 39) = 2.1, P > .01$] (Table 1).

- Insert Table 1 about here -

3.2 COGNITIVE PROFILE OF PATIENTS WITH PD WITH AND WITHOUT APATHY

A series of independent T-tests was also carried out to compare the performance of patients with PD with and without neuropsychiatric symptoms on the neuropsychological tests in the battery. The subgroup with apathy had lower scores than the subgroup without apathy on the Stroop Test (error) $t(63) = -3.16, p < .004$ and the Letter Fluency Test $t(63) = 3.17, p < .004$. There were no significant differences between the two subgroups in any of the other neuropsychological tests, i.e. Raven's Progressive Matrices $t(63) = 2.91, p > .004$, Stroop Test (time) $t(63) = 0.43, p > .004$, TMT $t(63) = 1.54, p > .004$, Category Fluency Test $t(63) = 2.64, p > .004$, Similarities Test $t(63) = 1.26, p > .004$, Rey Complex Figure (copy) $t(63) = 2.92, p > .004$, Rey Complex Figure (delayed) $t(63) = 1.75,$

$p > .004$, Digit Span (forward) $t(63) = 0.80$, $p > .004$, Digit Span (backward) $t(63) = 1.01$, $p > .004$, Frontal Assessment Battery $t(63) = 2.63$, $p > .004$, Visual-spatial span $t(63) = 1.02$, $p > .004$ and Rey 15-word Memory Test $t(63) = 2.47$, $p > .004$ (see Table 2).

- Insert Table 2 about here -

Additional correlation analyses were carried out with apathy scores as the dependant variable and neuropsychological test scores as the independent variable in turn. There was a significant relationship between apathy scores and Letter Fluency scores ($r = -.38$, $P = 0.002$). Higher apathy scores were associated with lower performance on the Letter Fluency Test. Apathy scores were not significantly correlated with scores on Raven's Progressive Matrices ($r = -.22$, $P = .08$), TMT ($r = -.13$, $P = .29$), Category Fluency ($r = -.32$, $P = 0.009$), Similarities Test ($r = -.12$, $P = .34$), Rey Complex Figure (copy) ($r = -.26$, $P = 0.04$), Rey Complex Figure (delayed) ($r = -.23$, $P = .08$), Stroop Test (time) ($r = .036$, $P = .79$), Stroop Test (error) ($r = .27$, $P = .03$), Frontal Assessment Battery ($r = -.34$, $P = .04$), Digit Span (forward) ($r = -.23$, $P = .15$), Digit Span (backward) ($r = -.199$, $P = .22$), Visual-spatial span ($r = -.18$, $P = .26$), Rey 15-word Memory Test ($r = -.304$, $P = .04$) and MMSE ($r = -.28$, $P = .02$).

3.3 VOXEL-BASED MORPHOMETRY GROUP COMPARISONS OF GREY MATTER

Patients with PD with apathy versus patients with PD without neuropsychiatric symptoms: At the corrected cluster level ($p < 0.01$), significant grey matter volume differences between the subgroups were detected in several brain areas including the left inferior frontal gyrus, left middle frontal gyrus, left precentral gyrus, left cingulate gyrus, right anterior cingulate, left superior temporal gyrus and the left insula in which patients with apathy had significantly less grey matter volume when compared with patients without apathy (Table 3 Figure 1).

- Insert Table 3 and Figure 1 about here -

Patients with PD with apathy versus controls: At the corrected cluster level, patients with apathy had significantly less grey matter volume in the bilateral inferior frontal gyrus, bilateral middle frontal gyrus, right inferior parietal lobule, left parahippocampal gyrus, left cerebellum (anterior lobe, culmen), left cerebellum (posterior lobe, tuber), left fusiform gyrus and the left cingulate gyrus when compared with healthy controls (Table 3 Figure 1).

Patients with PD without neuropsychiatric symptoms versus controls: At the corrected cluster level, patients without neuropsychiatric symptoms had less grey matter volume in the left inferior frontal gyrus and the left middle frontal gyrus when compared with healthy controls (Table 3 Figure 1).

3.4 VOXEL-BASED MORPHOMETRY GROUP COMPARISONS OF WHITE MATTER

Patients with PD with apathy versus patients with PD without neuropsychiatric symptoms: There was no significant difference between patients with apathy and patients without neuropsychiatric symptoms in white matter volume values.

Patients with PD with apathy versus controls: At the corrected cluster level, patients with apathy had less white matter volume in the bilateral middle frontal gyrus, right insula, bilateral anterior cingulate gyrus, and left precentral gyrus when compared with healthy controls (Table 4 Figure 2).

- Insert Table 4 and Figure 2 about here -

Patients with PD without neuropsychiatric symptoms versus controls: At the corrected cluster level, patients without neuropsychiatric symptoms had significantly less white matter volume values in the right medial frontal gyrus, left precentral gyrus and left middle frontal gyrus when compared with healthy controls (Table 4 and Figure 2).

4. DISCUSSION

This study is the first to have explored both the behavioural and the neuroanatomical correlates of apathy in the same cohort of patients with mild PD. The behavioural results showed that although patients with apathy performed lower than those without neuropsychiatric symptoms on all neuropsychological tests, significant differences were detected in those tasks assessing executive functions. Correlation analyses confirmed that high apathy scores correlated significantly with poorer performance on tests of executive function. Executive dysfunction might reflect the difficulty in response inhibition, in thinking flexibly, and switching response sets in the present sample, suggesting that executive function tasks should be made a priority when evaluating patients with apathy at the mild stages of PD.

The impairment of executive functions in patients with PD with apathy detected with the Stroop test has been found in previous studies [10, 12, 15]. Functional imaging studies have indicated the important role of the anterior cingulate cortex, which is activated during the Stroop test [49]. The evidence from this activation study might provide an explanation for the differences between the two subgroups on the Stroop task in the current study. Additionally, the current study found a significant association between apathy and letter fluency scores, which is also in line with previous findings in more severe patients [4, 13, 15]. Moreover, a similar pattern of executive dysfunction has been reported in apathetic patients with PD with dementia and apathetic patients with AD [50]. Taken together, the findings of the present study highlight the presence of a strong association between apathy and the presence of executive deficits. Impairments of executive functions most likely reflect

frontal lobe dysfunction. Although previous anatomical studies have reported an association between apathy and deficits in structures or in the functioning of the frontal lobe [17, 51, 52], the link between cognitive and neuroimaging features has always been speculative. There is, therefore, no previous study, which has investigated the cognitive and neuroimaging features associated with apathy in the same sample of patients with PD.

Apathy in PD, mainly in more advanced severity stages, has been the object of investigation of other studies. These, however, have failed to control for other concomitant neuropsychiatric symptoms which, potentially, could have contaminated their results. In this study the NPI was used as a tool to explore the neuropsychiatric profile of patients with PD since it would help the exclusion of other concurrent symptoms when exploring apathy. The underlying mechanism of apathy is still unclear. Although there are some published studies which have investigated the neural correlates of apathy using different approaches, little is known about the structural brain areas that may associate with this symptom. For this purpose a VBM approach was chosen given that it offers a suitable way to explore grey and white matter volume changes as it has been championed for its powerful approach for unbiased hypothesis testing across the whole brain [53].

The present study identified some brain regions that may play an important role in the presence of apathy in mild PD. In patients with apathy, a large cluster of grey and white matter loss was found in frontal lobe areas, anterior cingulate cortex and the insula. These findings are partly in line with a previous study that found grey matter reduction in the frontal lobe regions, insula and the cingulate gyrus [17]. Consistent with the present findings, parallel earlier studies in AD patients with apathy also reported a white matter reduction in the frontal lobe [8] and in the anterior cingulate cortex [54]. Functionally, the insular regions are connected with the anterior cingulate cortex and the frontal lobe, particularly, the inferior frontal gyrus [55], and all these areas are functionally connected in healthy participants. Dysfunction in this brain network may contribute to the presence of apathy in PD as there seems to be both functional and structural grounds for this explanation. It has been suggested that the insula plays a role in subjective emotional experience; atrophy in this area may reflect loss of emotional responsiveness or spontaneous emotion, which is considered as one of the

most prominent features of apathy [56]. In older people with only apathy (without PD), higher apathy scores were associated with grey matter reduction in the right anterior cingulate gyrus [57]. This brain area has a major functional impact in terms of the initiation and motivational drivers for goal directed behaviours and activities, and atrophy in this region, therefore, may lead to behavioural and cognitive changes with a consequent loss of goal directed actions [58]. A recent resting-state fMRI study [59] reported that apathetic PD patients showed functional connectivity reductions in the frontal, limbic and striatum areas when compared with non-apathetic PD patients or healthy controls [59]. These findings are in line with the present results, particularly the involvement of the frontal cortex and the limbic system, and together would provide an explanation for the presence of apathy in PD from a structural and functional perspective.

Levy and Dubois [30] suggested that apathy may occur as a consequence of disturbance in the prefrontal-basal ganglia system, and distinguished three subtypes of processing disturbance which are emotional-affective, cognitive, and auto-activation. Specifically, the auto-activation deficit has been associated with frontal white matter lesions [30]. In addition, the involvement of the cingulate gyrus and premotor cortex, as found in the present study, lends support to the hypothesis that deficits of auto-activation processing could be responsible for apathy in PD. The behavioural results lend support to the present imaging findings of greater structural atrophy particularly in the frontal lobe, temporal lobe and the anterior cingulate cortex in patients with apathy.

In this study, we identified some structural brain regions that might underlie the occurrence of apathy symptom in patients who have PD. In patients with apathy, significant grey and white matter loss was found mainly in the frontal lobe areas and the insula region. An fMRI study reported that the orbital frontoinsula regions are connected with other brain areas including subcortical structures [60]. The basal ganglia, part of a subcortical network of structures, when dysfunctional may be crucially involved in the genesis of apathy in patients with PD [61]. In particular, dysfunction of the dopaminergic system may be crucial because it plays an integrative and regulatory role in the development and interpretation of emotions, motor control and reward processes [61, 62]. These data

suggest that perturbation of homeostasis of the brain network which includes the frontal lobe, insula and the basal ganglia might be an important factor contributing to the appearance of apathy in PD.

Grey matter loss in the inferior parietal gyrus was also observed in apathetic patients with PD [17]. This structural loss has also been linked to executive dysfunction in PD [63]. It has been suggested that the parietal lobe plays a crucial role in incorporating information from different senses and processes [17]. Kjaer et al [64] hypothesised that the inferior parietal gyrus, the precuneus and the anterior cingulate gyrus constitute a functional network of reflective self-awareness. These findings therefore imply that executive dysfunction in patients with PD with apathy may reflect damage not only in the frontal lobe, but also in the parietal lobe with the consequent disruption of associated functions and cognitive processing.

Interestingly, the present study also identified grey matter loss in the left cerebellum. This result supports the findings of a recent PET study, which demonstrated negative correlations between apathy and metabolism in the cerebellum bilaterally in patients with PD [31]. There is some evidence indicating the role of the cerebellum in cognition and emotion with some clinical case reports having demonstrated that cerebellar lesions are responsible for a range of behavioural abnormalities (such as apathy), emotional dysregulation and executive dysfunction [65], all relevant for apathy. These observations are supported by the existence of structural connections between the cerebellum and the prefrontal cortex via the thalamus [66]. The current findings seem to support this view, suggesting that an overall disruption of a cerebellum/frontal network of structures may be a relevant prerequisite for the presence of apathy and executive dysfunction in PD. Apathy in this sample was measured not with a symptom specific scale, but with a multi-symptom neuropsychiatric inventory such as the NPI. Although this might be seen as a limitation of this study, it also represents a strength since the use of the NPI allowed the selection of a sample free from contamination of other possible neuropsychiatric comorbidities, which would have lowered the reliability of the findings.

In conclusion, the present finding on apathy provides evidence of a specific association between aspects of cognitive decline, and regional brain atrophy in patients with PD and apathy. The

neuropsychological findings emphasise that patients with apathy have cognitive impairment, particularly, executive dysfunction and memory deficits. In addition, the imaging results identified loss of volume in brain regions, which are normally associated with cognitive abilities on which patients with apathy performed more poorly.

The current findings have several implications for patients with PD, their families and clinicians. For example, increasing awareness of the potential presence of apathy while the symptom is still mild may help treatment of this symptom, before it begins to have an even greater negative impact on the cognitive abilities of patients. Apathy appears to be associated with cognitive impairments in PD, therefore, treatment of this symptom might mitigate its effects on cognitive performance in this clinical population.

Acknowledgement: King Fahad Medical City, Riyadh, Saudi Arabia for funding this project.

Ethical standards

This study was carried out according to the Declaration of Helsinki and was approved by the Institutional Review Board of the IRCCS Fondazione Ospedale San Camillo (Venice, Italy). Written informed consent was obtained from each study participant.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCE

1. Jankovic, J., Parkinson's disease: clinical features and diagnosis. *Journal of Neurology Neurosurgery and Psychiatry*, 2008. **79**(4): p. 368-376.
2. Cubo, E., et al., Clinical correlates of apathy in patients recently diagnosed with Parkinson's disease: the ANIMO study. *Neuroepidemiology*, 2012. **38**(1): p. 48-55.
3. Pedersen, K.F., et al., Prevalence and clinical correlates of apathy in Parkinson's disease: a community-based study. *Parkinsonism & Related Disorders*, 2009. **15**(4): p. 295-9.
4. Zgaljardic, D.J., et al., Relationship between self-reported apathy and executive dysfunction in nondemented patients with Parkinson disease. *Cognitive and Behavioral Neurology*, 2007. **20**(3): p. 184-192.
5. Dujardin, K., et al., Characteristics of apathy in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society*, 2007. **22**(6): p. 778-84.
6. Ahearn, D.J., et al., An exploration of apathy and impulsivity in Parkinson disease. *Current gerontology and geriatrics research*, 2012. **2012**: p. 390701.
7. Pluck, G.C. and R.G. Brown, Apathy in Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry*, 2002. **73**(6): p. 636-42.
8. Starkstein, S.E., et al., Neuroimaging Correlates of Apathy and Depression in Alzheimer's Disease. *Journal of Neuropsychiatry and Clinical Neurosciences*, 2009. **21**(3): p. 259-265.
9. den Brok, M.G., et al., Apathy in Parkinson's disease: A systematic review and meta-analysis. *Mov Disord*, 2015. **30**(6): p. 759-69.

10. Aarsland, D., et al., Range of neuropsychiatric disturbances in patients with Parkinson's disease. *Journal of Neurology Neurosurgery and Psychiatry*, 1999. **67**(4): p. 492-496.
11. Drijgers, R.L., et al., Validation of diagnostic criteria for apathy in Parkinson's disease. *Parkinsonism & Related Disorders*, 2010. **16**(10): p. 656-60.
12. Dujardin, K., et al., Apathy may herald cognitive decline and dementia in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society*, 2009. **24**(16): p. 2391-7.
13. Isella, V., et al., Clinical, neuropsychological, and morphometric correlates of apathy in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society*, 2002. **17**(2): p. 366-71.
14. Levy L., C.L., Fairbanks A., Masterman., Miller L., Craig H., Paulsen S., Litvan., Apathy Is Not Depression. *The Journal of neuropsychiatry and clinical neurosciences*, 1998. **10**: p. 314-319.
15. Moretti, R., et al., Apathy: a complex symptom specific to the clinical pattern of presentation of Parkinson's disease? *American journal of Alzheimer's disease and other dementias*, 2012. **27**(3): p. 196-201.
16. Pedersen, K.F., et al., Occurrence and risk factors for apathy in Parkinson disease: a 4-year prospective longitudinal study. *Journal of neurology, neurosurgery, and psychiatry*, 2009. **80**(11): p. 1279-82.
17. Reijnders, J.S., et al., Neuroanatomical correlates of apathy in Parkinson's disease: A magnetic resonance imaging study using voxel-based morphometry. *Movement disorders : official journal of the Movement Disorder Society*, 2010. **25**(14): p. 2318-25.

18. Starkstein, S.E., et al., Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *The Journal of neuropsychiatry and clinical neurosciences*, 1992. **4**(2): p. 134-9.
19. Marin, R.S., R.C. Biedrzycki, and S. Firinciogullari, Reliability and validity of the Apathy Evaluation Scale. *Psychiatry research*, 1991. **38**(2): p. 143-62.
20. Wechsler, D., WAIS-R manual. New York: Psychological Corporation. 1981.
21. Delis, C.E. and E. Kaplan, The Delis Kaplan Executive Function System – trial making test. The psychological Corporation. 2001.
22. Delis, C.E., J.H. Kramer, and E.e.a. Kaplan, California verbal learning test-second edition. The Psychological Corporation. 2002.
23. Heaton, R.K., G.J. Chelune, and J.L. Talley, et al., Wisconsin Card Sorting Test. Manual revised and expanded. Odessa, FL: Psychological Assessment Resources. 1993.
24. Varanese, S., et al., Apathy, but not depression, reflects inefficient cognitive strategies in Parkinson's disease. *PloS one*, 2011. **6**(3): p. e17846.
25. Bogdanova, Y. and A. Cronin-Golomb, Neurocognitive correlates of apathy and anxiety in Parkinson's disease. *Parkinson's disease*, 2012. **2012**: p. 793076.
26. Dubois, B., et al., The FAB - A frontal assessment battery at bedside. *Neurology*, 2000. **55**(11): p. 1621-1626.
27. Thurstone, L.L. and T.G. Thurstone, Primary Mental Abilities. Chicago: Science Research Associates. 1962.
28. Stroop, J.R., Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, 1935. **18**: p. 643-662.
29. Pagonabarraga, J., et al., Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. *Lancet Neurol*, 2015. **14**(5): p. 518-31.

30. Levy, R. and B. Dubois, Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cerebral cortex*, 2006. **16**(7): p. 916-28.
31. Robert, G., et al., Apathy in patients with Parkinson disease without dementia or depression A PET study. *Neurology*, 2012. **79**(11): p. 1155-1160.
32. Robert, G.H., et al., Preoperative factors of apathy in subthalamic stimulated Parkinson disease: a PET study. *Neurology*, 2014. **83**(18): p. 1620-6.
33. Benoit, M., et al., Brain perfusion in Alzheimer's disease with and without apathy: a SPECT study with statistical parametric mapping analysis. *Psychiatry research*, 2002. **114**(2): p. 103-11.
34. Hughes, A.J., et al., Accuracy of Clinical-Diagnosis of Idiopathic Parkinsons-Disease - a Clinicopathological Study of 100 Cases. *Journal of Neurology Neurosurgery and Psychiatry*, 1992. **55**(3): p. 181-184.
35. Hoehn, M.M. and M.D. Yahr, Parkinsonism: onset, progression and mortality. *Neurology*, 1967. **17**(5): p. 427-42.
36. Cummings, J.L., et al., The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*, 1994. **44**(12): p. 2308-14.
37. American Psychiatric Association, Diagnostic and statistical manual of mental disorders 4th., text rev. ed. 2000, Washington, DC: Author.
38. Sockeel, P., et al., The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry*, 2006. **77**(5): p. 579-84.
39. Folstein, M.F., S.E. Folstein, and P.R. McHugh, "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research*, 1975. **12**(3): p. 189-98.

40. Appollonio, I., et al., The Frontal Assessment Battery (FAB): normative values in an Italian population sample. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, 2005. **26**(2): p. 108-16.
41. Lezak, M., et al., *Neuropsychological Assessment*. 5th ed. 2012: New York: Oxford University Press.
42. Lezak, M., D. Howieson, and D. Lorind, *Neuropsychological assessment*. 4th ed. 2004: New York: Oxford University Press.
43. Reitan, R.M., Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills*, 8, 271-276. 1958.
44. Caffarra, P., et al., Una versione abbreviata del test di Stroop. Dati normativi nella popolazione italiana. *Nuova Riv Neurol*, 2002. **12**: p. 111-115.
45. Wechsler, D., *Wechsler Adult Intelligence Scale-III*. San Antonio: The Psychological Corporation, 1997a.
46. Caffarra, P., et al., Rey-Osterrieth complex figure: normative values in an Italian population sample. *Neurol Sci*, 2002a. **22**: p. 443-447.
47. Spinnler, H., & Tognoni, G. , Standardizzazione e taratura italiana di test neuropsicologici. *Ital J Neurol Sci*, 1987. **6**: p. 1-120.
48. Rey, A., *L'examen Clinique en psychologie*. Paris: Presses Universitaires de France, 1964.
49. Ravnkilde, B., et al., Putative tests of frontal lobe function: a PET-study of brain activation during Stroop's Test and verbal fluency. *Journal of Clinical and Experimental Neuropsychology*, 2002. **24**(4): p. 534-47.
50. Grossi, D., et al., Apathy and related executive syndromes in dementia associated with Parkinson's disease and in Alzheimer's disease. *Behavioural neurology*, 2012.

51. Le Jeune, F., et al., Subthalamic nucleus stimulation in Parkinson disease induces apathy: a PET study. *Neurology*, 2009. **73**(21): p. 1746-51.
52. Skidmore, F.M., et al., Apathy, depression, and motor symptoms have distinct and separable resting activity patterns in idiopathic Parkinson disease. *Neuroimage*, 2011. **81**: p. 484-495.
53. Luo, W.L. and T.E. Nichols, Diagnosis and exploration of massively univariate neuroimaging models. *Neuroimage*, 2003. **19**(3): p. 1014-32.
54. Migneco, O., et al., Perfusion brain SPECT and statistical parametric mapping analysis indicate that apathy is a cingulate syndrome: a study in Alzheimer's disease and nondemented patients. *Neuroimage*, 2001. **13**(5): p. 896-902.
55. van den Heuvel, M.P., et al., Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. *Human brain mapping*, 2009. **30**(10): p. 3127-41.
56. Davidson, R.J. and W. Irwin, The functional neuroanatomy of emotion and affective style. *Trends in cognitive sciences*, 1999. **3**(1): p. 11-21.
57. Lavretsky, H., et al., Neuroanatomical characteristics of geriatric apathy and depression: A magnetic resonance imaging study. *American Journal of Geriatric Psychiatry*, 2007. **15**(5): p. 386-394.
58. Allman, J.M., et al., The anterior cingulate cortex. The evolution of an interface between emotion and cognition. *Annals of the New York Academy of Sciences*, 2001. **935**: p. 107-17.
59. Baggio, H.C., et al., Resting-state frontostriatal functional connectivity in Parkinson's disease-related apathy. *Mov Disord*, 2015. **30**(5): p. 671-9.

60. Seeley, W.W., et al., Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 2007. **27**(9): p. 2349-56.
61. Ring, H.A. and J. Serra-Mestres, Neuropsychiatry of the basal ganglia. *Journal of neurology, neurosurgery, and psychiatry*, 2002. **72**(1): p. 12-21.
62. Aarsland, D., L. Marsh, and A. Schrag, Neuropsychiatric symptoms in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society*, 2009. **24**(15): p. 2175-86.
63. Matsui, H., et al., Frontal assessment battery and brain perfusion image in Parkinson's disease. *Journal of Geriatric Psychiatry and Neurology*, 2006. **19**(1): p. 41-5.
64. Kjaer, T.W., M. Nowak, and H.C. Lou, Reflective self-awareness and conscious states: PET evidence for a common midline parietofrontal core. *Neuroimage*, 2002. **17**(2): p. 1080-6.
65. Schmahmann, J.D., J.B. Weilburg, and J.C. Sherman, The neuropsychiatry of the cerebellum - insights from the clinic. *Cerebellum*, 2007. **6**(3): p. 254-67.
66. Middleton, F.A. and P.L. Strick, Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. *Science*, 1994. **266**(5184): p. 458-61.

Table 1 Mean (SD, range) Age, Education, Duration of disease and MMSE of all patients with PD, patients with PD with apathy, patients with PD without neuropsychiatric symptoms (NPSS), and controls

	All PD (N =65)	PD with apathy (N = 25)	PD without NPSS (N =40)	Controls (N = 24)	P
Age	67.73 (8.06, 48-80)	68.7 (8.4, 49-80)	66.1 (8.5, 48-80)	62.79 (9.77, 50-81)	.108
Education	11.1 (4.56, 5-18)	10.9 (4.5, 5-18)	11.2 (4.7, 5-18)	12.21 (5.49, 5-24)	.678
Duration of disease	8.98 (5.27)	10.3 (5.98)	7.9 (4.5)	---	.162
MMSE	27.9 (1.7, 24-30)	27.22 (1.8, 24-30)	28.2 (1.4, 26-30)	30.00 (.000)	.000*

*Significant difference between controls and the two groups of patients (with and without apathy) using Bonferroni Post-hoc test

Table 2 Mean (SD), and P value of scores on neuropsychological tests achieved by PD with apathy and PD without neuropsychiatric symptoms (NPSS).

	PD with apathy (N = 25)	PD without NPSS (N = 40)	p
Raven's Progressive Matrices	20.44 (13.57)	28.7 (9.35)	.005
Stroop test			
Time interference effect	33.43 (18.82)	37.16 (35.49)	.671
Error interference effect	3.88 (5.68)	.93 (1.37)	.002*
Trail Making Test	31.28 (46.67)	51.08 (52.68)	.129
Letter Fluency Test	26.32 (8.88)	36.15 (13.78)	.002*
Category Fluency Test	29.36 (11.03)	36.73 (10.87)	.010
Similarities Test	13.84 (6.27)	15.80 (5.99)	.212
Rey Complex Figure			
Direct copy	23.50 (9.79)	29.56 (6.92)	.005
Delayed copy	10.78 (5.40)	13.49 (6.06)	.086
Digit Span			
Forward	5.86 (1.29)	6.15 (1.01)	.426
Backward	3.79 (.69)	4.12 (1.11)	.320
Frontal Assessment Battery	13.77 (2.56)	15.69 (1.93)	.012
Visual-spatial span	4.36 (1.08)	4.72 (1.06)	.316
Rey 15-word Memory Test	6.33 (2.98)	9.02 (2.03)	.029

*Significant difference between PD with apathy and PD without neuropsychiatric symptoms $P < 0.004$ (corrected for multiple comparison)

Table 3 Areas of significant grey matter volume value differences between the two PD patients and controls

Brain areas	R/L	BA	Cluster Size	Cluster-level P-value (corrected)	Z value at Local Maximum	Talairach coordinates		
						X	Y	Z
PD with apathy vs PD without NPSS								
Inferior frontal gyrus	L	46	164	0.022	3.67	-44	39	9
Middle frontal gyrus	L	10			3.44	-48	34	15
Precentral gyrus	L	6			3.42	-44	21	34
Cingulate gyrus	L	32	177	0.019	3.64	0	34	26
Anterior cingulate	R	32			3.37	4	41	13
	R	32			2.79	2	44	-6
Superior temporal gyrus	L	41	161	0.023	3.42	-48	-32	13
Sub-lobar (Insula)	L				3.26	-40	-12	-1
	L				2.86	-42	-19	3
PD with apathy vs controls								
Inferior frontal gyrus	R	45	834	0.000	5.35	50	37	7
Middle frontal gyrus	R	10			4.77	40	51	7
	R	9			4.74	44	34	26
Inferior parietal lobule	R	40	100	0.001	5.09	44	-39	44
Middle frontal gyrus	L	9	719	0.000	4.81	-44	31	28
	L	10			4.68	-42	43	14
Inferior frontal gyrus	L	9			4.66	-51	7	25
Parahippocampal gyrus	L	34	67	0.021	4.59	-16	1	-12
Cerebellum (Anterior lobe)	L		295	0.001	4.37	-34	-40	-23
(Posterior lobe)	L				4.14	-44	-52	-23
Fusiform gyrus	L	19			4.08	-24	-61	-7
Cingulate gyrus	L	24	69	0.032	4.03	-2	-2	42
PD without NPSS vs controls								
Inferior frontal gyrus	L	9	56	0.001	5.28	-51	5	26
Middle frontal gyrus	L	10	71	0.002	4.63	-36	45	5

R = Right L = Left BA = Brodmann Area

Table 4 Areas of significant white matter volume value differences between patients and controls

Brain areas	R/L	Cluster Size	Cluster-level P-value (corrected)	Z value at Local Maximum	Talairach coordinates		
					X	Y	Z
PD with apathy vs controls							
Middle frontal gyrus	R	2655	0.000	5.28	28	4	37
Sub-lobar (Insula)	R			4.55	28	26	12
Anterior cingulate gyrus	R			4.44	20	41	5
	L	2669	0.000	4.95	-14	17	30
Precentral gyrus	L			4.51	-32	1	22
Middle frontal gyrus	L			4.48	-26	23	23
PD without NPSS vs controls							
Medial frontal gyrus	R	396	0.002	4.34	20	47	9
Frontal lobe (sub-gyral)	R			3.37	26	28	12
	R			3.32	18	33	-7
Precentral gyrus	L	143	0.010	4.19	-32	-15	43
Middle frontal gyrus	L			3.54	-28	21	28

R = Right L = Left

Figure captions

Figure 1 Areas of significantly less grey matter volume values in patients groups and healthy controls

Figure 2 Areas of significantly less white matter volume values in patients with PD when compared with healthy controls

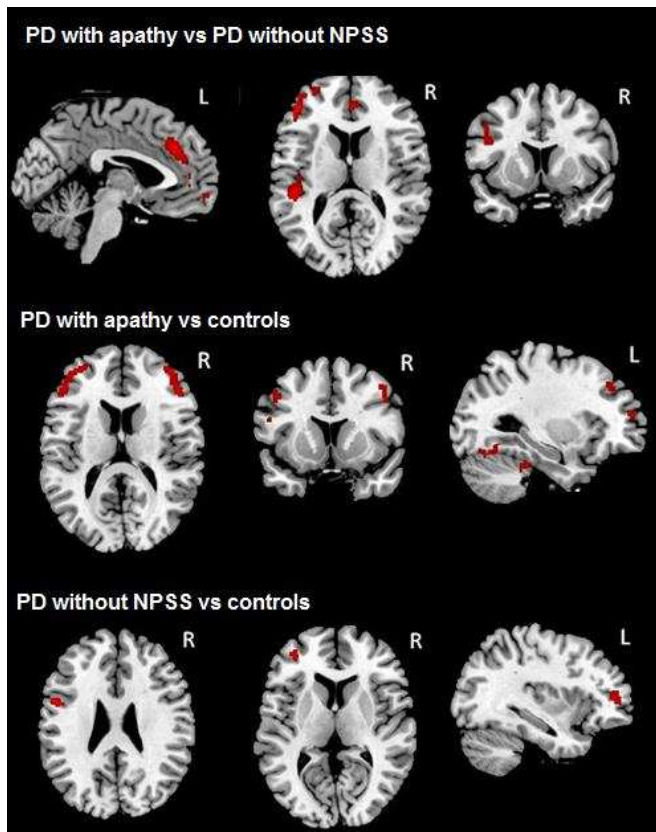


Figure 1

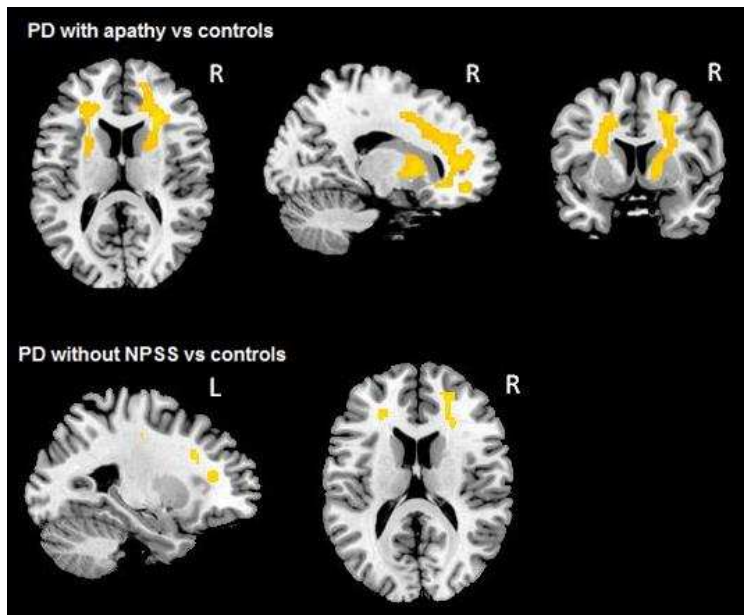


Figure 2