Structural correlates of facial emotion recognition deficits in Parkinson's disease patients

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1. ABSTRACT

The ability to recognize facial emotion expressions, especially negative ones, is described to be impaired in Parkinson's disease (PD) patients. Previous neuroimaging work evaluating the neural substrate of facial emotion recognition (FER) in healthy and pathological subjects has mostly focused on functional changes. This study was designed to evaluate gray matter (GM) and white matter (WM) correlates of FER in a large sample of PD. Thirty-nine PD patients and 23 healthy controls (HC) were tested with the Ekman 60 test for FER and with magnetic resonance imaging. Effects of associated depressive symptoms were taken into account. In accordance with previous studies, PD patients performed significantly worse in recognizing sadness, anger and disgust. In PD patients, voxel-based morphometry analysis revealed areas of positive correlation between individual emotion recognition and GM volume: in the right orbitofrontal cortex, amygdala and postcentral gyrus and sadness identification; in the right occipital fusiform gyrus, ventral striatum and subgenual cortex and anger identification, and in the anterior cingulate cortex (ACC) and disgust identification. WM analysis through diffusion tensor imaging revealed significant positive correlations between fractional anisotropy levels in the frontal portion of the right inferior fronto-occipital fasciculus and the performance in the identification of sadness. These findings shed light on the structural neural bases of the deficits presented by PD patients in this skill.

2. INTRODUCTION

Parkinson's disease (PD) is more typically characterized by its motor features. In recent years, however, the interest in its non-motor manifestations has increased significantly. Among these manifestations, cognitive deficits are commonly found even in recently diagnosed PD patients. Memory and executive function are the most prominently, but not the only, affected domains (Muslimovic, Post, Speelman & Schmand, 2005). The capacity to accurately identify emotions in others' facial expressions, a skill of great importance for normal social interaction, has been described in several studies to be impaired in PD (Yip, Lee, Ho, Tsang & Li, 2003; Dujardin *et al.*, 2004; Kan, Kawamura, Hasegawa, Mochizuki & Nakamura, 2002; Ariatti, Benuzzi & Nichelli, 2008; Sprengelmeyer *et al.*, 2003; Lawrence, Goerendt & Brooks, 2007; Suzuki, Hoshino, Shigemasu & Kawamura, 2006), though somewhat inconsistently. While most of these studies suggest a selective deficit in identifying negative emotions, results vary as to which specific emotions have their identification selectively or predominantly affected. Still other studies failed to identify any facial emotion recognition impairments in PD patients (Pell and Leonard, 2005; Dujardin *et al.*, 2004; Biseul *et al.*, 2005). These different results might be due to different evaluation methods, as well as to different patient samples with respect to relevant variables such as age, education, medication status, cognitive impairment and disease severity or duration. Furthermore, not all studies have taken into account the presence of associated depressive disorders, present in up to 50% of PD patients (Reijnders, Ehrt, Weber, Aarsland & Leentjens, 2008; Slaughter, Nichols, Holmes & Martens, 2001), which also lead to facial emotion recognition (FER) deficits (Leppanen, 2006).

The finding that pathological processes such as PD, depression or Huntington's disease (Calder *et al.*, 2010) may cause deficits in the identification of specific emotions, as well as data obtained from functional neuroimaging and electrophysiological studies and studies with patients with focal lesions indicate that the recognition of different emotions relies on different (Adolphs, Tranel & Damasio, 2003; Fusar-Poli *et al*., 2009; Calder, Keane, Manes, Antoun &

Young, 2000; Krolak-Salmon *et al.*, 2003; Adolphs *et al.*, 2002; Adolphs, Tranel, Damasio & Damasio, 1994; Calder *et al.*, 1996; Phillips *et al.*, 1997) though overlapping neural substrates (Heberlein, Padon, Gillihan, Farah & Fellows, 2008; Hornak *et al*., 2003; Adolphs, Damasio, Tranel, Cooper & Damasio, 2000).

Most published neuroimaging studies concerning the neural substrate of emotional processing used functional techniques. Knowledge about the ability of MRI to identify structural correlates for individual emotion recognition is very limited, both in pathological and in healthy subjects samples. In the specific case of PD patients, only one published work addressed structural correlates of FER deficits. In this study, done by our group, gray matter (GM) volumes in the amygdalae and orbitofrontal cortex (OFC) were found to correlate positively with overall emotion recognition (Ibarretxe-Bilbao *et al.*, 2009). The neural substrate of the recognition of individual emotions, however, was not studied.

Besides the better-studied GM changes in PD, there is increasing evidence that white matter (WM) microstructural changes detectable by magnetic resonance diffusion tensor imaging techniques occur early in the course of the disease (Gattellaro *et al.*, 2009; Karagulle Kendi, Lehericy, Luciana, Ugurbil & Tuite, 2008) and that WM changes may contribute to cognitive deficits by means of impaired connectivity (Vernooij *et al*., 2009). There is little knowledge, however, about how such changes may relate to facial emotion recognition deficits.

Our aim in the present work was to study the relationship between the capacity to recognize specific emotions in facial expressions and gray and white matter structural parameters evaluated through state-of-the-art MRI techniques in a large sample of non-demented PD patients.

3. METHODS

3.1 Subjects

Thirty-nine PD patients and 23 age-matched healthy controls (HC) were included. Patients were recruited from the Movement Disorders Unit, Neurology Department, Hospital Clínic, in Barcelona. The inclusion criterion was the

fulfillment of the UK PD Society Brain Bank (PDSBB) diagnostic criteria for PD (Daniel & Lees, 1993). The exclusion criteria were: (i) presence of dementia according to the Movement Disorders Society criteria (Emre *et al*., 2007), (ii) presence of Beck Depression Inventory-II scores higher than 16, suggested as a specific cut-off point for diagnosing depression in PD patients by Leentjens, Verhey, Luijckx & Troost (2000), (iii) presence of other significant psychiatric or neurological comorbidity, (iv) pathological magnetic resonance imaging findings other than mild WM hyperintensities in long-TR sequences or those that could be related to PD.

All PD patients were taking antiparkinsonian drugs, consisting of different combinations of L-dopa (n=11), L-dopa with COMT inhibitors (n=12), MAO inhibitors (n=10), dopamine agonists (n=17) and amantadine (n=4). The medication was not changed for the study and all assessments were done while patients were in the *on* state. To evaluate possible medication effects, levodopa equivalent daily doses were calculated as suggested by Tomlinson *et al.* (2010).

The study was approved by the ethics committee of the University of Barcelona, and all subjects provided written informed consent to participate.

3.2 Neuropsychological assessment

All subjects underwent a thorough neuropsychological battery to assess the cognitive functions more frequently impaired in non-demented PD patients: memory, visuospatial, visuoperceptive and executive functions (Muslimovic, Post, Speelman & Schmand, 2005; Foltynie, Brayne, Robbins & Barker, 2004; Aarsland *et al.*, 2009). In addition to the Mini-Mental State Examination (MMSE), we administered the following tests: Rey Auditory Verbal Learning Test, Digits subset of the Wechsler Adults Intelligence Scale (WAIS-III), Stroop Color-Word Test, phonemic and semantic fluencies, Trail Making Tests A and B, Benton's Visual Form Discrimination Test and Judgment of Line Orientation Test, and Visual Object and Space Perception Battery (Lezak, Howieson, & Loring, 2004). We also administered the Cumming's Neuropsychiatric Inventory (Cummings et al., 1994) and the Beck Depression Inventory-II (Beck, Steer & Brown, 1996) to identify neuropsychiatric symptoms associated with PD.

3.3 Facial emotion recognition assessment

All subjects were tested with the Ekman 60 test for recognition of emotions in facial expressions. In this test, 60 pictures of faces from the Ekman and Friesen series of Pictures of Facial Affect (Ekman & Friesen, 1976) are presented consecutively. The subject is required to the label each picture as to the emotion predominantly expressed in it from a list of six possible choices (anger, fear, sadness, disgust, happiness and surprise, translated to Spanish as enfado, miedo, tristeza, asco, alegría y sorpresa, respectively). Each photograph is shown on a computer screen for 5 seconds, but there is no time limit to make the choice.

Each of the six individual emotions is represented in ten out of the total sixty pictures. Results are presented in number of correct answers out of 10 for each emotion and in total correct answers out of 60 for total Ekman scores.

3.4 Statistical analysis

Analyses were carried out using the PASW Version 17.0.2 (SPSS, Inc., Chicago, IL, USA). Group differences in demographic, clinical and neuropsychological characteristics were analyzed with independent two-tailed Student's t-tests for normally-distributed variables, the Mann-Whitney U test for non-normally distributed ones, and the chi-squared test for categorical variables. To control for possible effects of associated depressive symptoms and cognitive decline when measuring differences between Ekman test results between groups, BDI and MMSE scores were entered as covariates in two-level analyses of covariance (ANCOVAs). Associations between demographic, clinical and cognitive variables and FER scores were analyzed using Pearson's correlation for normally distributed variables and Spearman's rank correlations for those that did not present a normal distribution. Statistical significance threshold was set at $p<0.05$.

3.5 Image acquisition and analysis

Magnetic resonance images were acquired with a 3T scanner (TIM Trio, Siemens, Germany). High-resolution 3-dimensional T1-weighted images were acquired in the sagittal plane (TR 2300 ms, TE 2.98 ms, TI 900 ms; 256 x 256 matrix, 1 mm isotropic voxel). Sagittal diffusion tensor images were obtained

using a single-shot EPI sequence (TR 5533 ms, TE 88 ms), with diffusion encoding in 30 directions at b = 0 and 1000 s/mm^2.

Structural data was analyzed with FSL-VBM (Douaud *et al*., 2007), a voxel-based morphometry-style analysis carried out with FSL tools. First, nonbrain tissue from structural images was extracted. After segmentation, GM images were aligned to MNI152 standard space using affine registration. The resulting images were averaged to create a study-specific template, to which the native GM images were then non-linearly re-registered. The registered partial volume images were then modulated (to correct for local expansion or contraction) by dividing by the Jacobian of the warp field. The modulated segmented images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. Finally, voxelwise general linear model was applied using permutation-based non-parametric testing, correcting for multiple comparisons across space.

Voxelwise statistical analysis of the fractional anisotropy (FA) data was carried out using TBSS (Tract-Based Spatial Statistics, [Smith, 2006]), part of FSL (Smith *et al*., 2004). First, FA images were created by fitting a tensor model to the raw diffusion data using FDT, and then brain-extracted using BET (Smith *et al.*, 2002). All subjects' FA data were then aligned into a common space using the nonlinear registration tool FNIRT (Andersson *et al*., 2007a, 2007b), which uses a b-spline representation of the registration warp field (Rueckert *et al*., 1999). Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the centers of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics.

Structures used as regions of interest (ROIs) for GM analysis were chosen based on literature about the neural substrate of emotion processing, which includes data from lesion studies and functional MRI studies (Adolphs, 2002; Fusar-Poli et al., 2009; Adolphs et al., 2000; Calder, Keane, Lawrence & Manes, 2004). All GM structures were evaluated bilaterally. The masks for the GM ROI analyses were created based on the Harvard-Oxford probabilistic cortical and subcortical atlases (Smith *et al.*, 2004). For WM masks, some tracts used as ROIs were chosen based on previous studies indicating their relevance in emotional processing, such as the inferior fronto-occipital fasciculus and the

inferior longitudinal fasciculus (Philippi, Mehta, Grabowski, Adolphs & Rudrauf, 2009; Rudrauf *et al.*, 2008). We also included associative tracts that are anatomically connected to the cortical or subcortical structures we included as ROIs for the GM analysis, to investigate possible structural connectivity abnormalities between areas critical for emotion processing. The Johns Hopkins University white-matter tractography atlas was used to create the WM tract masks, which were evaluated bilaterally. Both atlases are available in FSL (http://www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html). For GM analyses, the ROIs used were:

OFC	Insula
Anterior cingulate cortex (ACC)	**Parahippocampal gyrus (PHG)**
Striatum	**Ventromedial prefrontal cortex**
Postcentral gyrus (PCG)	**Amygdala**
Hippocampus	**Inferior and middle frontal gyri**
Fusiform gyrus	

For WM analysis, the tracts used as ROIs were:

Inferior fronto-occipital fasciculus (IFOF)	**Uncinate fasciculus**
Superior longitudinal fasciculus (SLF)	**Cingulum**
Inferior longitudinal fasciculus (ILF)	**Forceps minor**

Statistical significance threshold was set at $p<0.05$, corrected for multiple comparisons through familywise error (FWE) correction (Worsley et al., 1996).

For all correlation analyses, BDI scores were entered as covariates of no interest. Analyses of correlation between FER scores and structural parameters were repeated adding age as another covariate of no interest. Correlation coefficients (r) were calculated using mean GM volume or FA levels from the whole clusters rather than from the maxima to avoid the non-independence error.

4. RESULTS

4.1 Subjects

There were no significant differences in age, gender or years of education between groups. Demographical and clinical results with group comparisons can be seen in Table 1. No subjects fulfilled the Movement Disorders Society criteria for dementia (Emre *et al*., 2007).

Table 2 shows neuropsychological assessment results with group comparisons. For the evaluation of visuospatial/visuoperceptive function, part of the sample (11 HC, 22 PD patients) was administered Benton's Visual Form Discrimination and Judgment of Line Orientation tests, whereas another part (12 HC, 17 PD patients) was administered Visual Object and Space Perception Battery Silhouettes test. No significant differences were observed between HC and PD patients' scores in these subsamples ($p>0.05$).

4.2 Facial emotion recognition

As can be seen in Table 3, PD patients' total Ekman test scores and subscores in the identification of fear, sadness, anger and disgust were significantly lower than controls'. *Happiness* scores were similar in the two groups, and a ceiling effect was observed for this emotion. Scores for the identification of surprise were lower in PD patients, approaching statistical significance. There were significant effects of group in the two-level ANCOVAs, using BDI and MMSE scores as covariates, for the identification of facial expressions of anger, sadness and disgust, as well as for total Ekman scores.

No significant correlations were found between individual emotion recognition subscores or total Ekman scores and clinical variables such as disease duration, motor severity scales (Hoehn and Yahr [HY] and UDPRS) or levodopa equivalent daily dose (LEDD) (see Table 4).

4.3 Gray matter analysis

Correlation analyses between GM volume and emotional Ekman 60 test subscores:

Whole-brain voxelwise analysis: this analysis showed no significant correlations between Ekman test scores and GM volume.

ROI analysis, *sadness* scores: significant positive correlations were found between patients' *sadness* scores and GM volume in the right OFC – a small cluster in its lateral portion, corresponding to Brodmann areas 11/47, and a medial cluster in the transition of Brodmann areas 11 and 14 –, in the medial part of the right amygdala, and in the dorsal part of the right postcentral gyrus (p<0.05, FWE-corrected) (Figure 1, A-C).

ROI analysis, *anger* scores: *anger* scores correlated positively with GM volume in the ventral striatum bilaterally (nuclei accumbens), in the right occipital fusiform gyrus and in the subgenual cortex (Brodmann areas 25 and 32) (Figure 1, D-F).

ROI analysis, disgust scores: a positive correlation was found between *disgust* scores and GM volume in the dorsal ACC (Brodmann area 24) (p<0.05, FWE-corrected) (Figure 1, G-I).

ROI analysis, total Ekman scores: total emotion recognition scores correlated positively with GM volume in the dorsal ACC, in an area that partially overlaps the cluster of significant correlation between GM volume and *disgust* scores (p<0.05, FWE-corrected) (Figure 1, H-I). Correlations between GM volume and Ekman scores in this area remained significant even after subtracting *disgust* scores from total Ekman scores (r=0.35, p=0.03).

Intergroup analyses revealed that PD patients had significantly reduced GM volumes compared with controls in all of the clusters described above, except in the right nucleus accumbens (Table 5, Supplementary Figure 1). The location of the maxima of the clusters of significant correlation as well as their volumes and correlation coefficients are presented in Table 5.

When adding age as a covariate of no interest, all correlations remained significant (p<0.05, FWE-corrected) with the exception of those between right amygdala GM volume and sadness scores (p=0.12, FWE-corrected), between right lateral OFC GM volume and sadness scores (p=0.09, FWE-corrected), and between total Ekman scores and ACC GM volume (p=0.06, FWE-corrected).

4.4 White matter analysis

Correlation analysis between FA and Ekman 60 test subscores in PD patients: Whole-FA skeleton voxelwise analysis revealed a strong positive correlation between *sadness* scores and FA levels in a cluster in the right frontal lobe WM, with its maximum located in the topography of the inferior fronto-occipital fasciculus but also involving the forceps minor and body of the corpus callosum (Figure 2 A-C). Intergroup analysis revealed that PD patients had significantly lower FA levels in this cluster than HC (Table 6, Supplementary Figure 1).

A smaller cluster was observed at the body of the corpus callosum extending to the left centrum semiovale ($p<0.05$, FWE-corrected). In this region, FA levels in PD patients were not significantly different from those of the control group (Table 6 and Figure 2B).

ROI analysis revealed additional areas of correlation between FA levels and *sadness* scores in the left temporal lobe white matter, comprising the topographies of the inferior fronto-occipital fasciculus and the inferior longitudinal fasciculus (Table 6 and Figure 2) ($p<0.05$, FWE-corrected). There were, however, no significant differences in FA levels between groups in these topographies.

All the correlations described above remained statistically significant after correcting for patient age ($p<0.05$, FWE-corrected). No correlations were found between FA and other Ekman subscores or total Ekman scores either in whole-FA skeleton or in ROI analyses.

5. DISCUSSION

In the present study, we found an overall impairment in FER in PD patients as this group's total Ekman test scores were significantly lower than those of the control group. Analyzing the performance for each emotion separately, PD patients presented an impaired recognition of all the negative emotions assessed, whereas no differences were observed for the recognition of surprise and happiness. Controlling for the potential confounding effects of associated mood changes and cognitive decline, however, performance in the recognition of all the negative emotions with the exception of fear (anger, sadness and disgust) remained significantly worse in PD patients than in HC.

As has also been observed in other studies (Suzuki *et al.*, 2006; Ibarretxe-Bilbao *et al.*, 2009; Kan *et al.*, 2002), a ceiling effect was observed for happiness, and fear was the least accurately identified emotion, both by HC and PD patients.

Given the multiple roles played by dopamine in distinct neural systems and the fact that the affectation of dopamine pathways in PD is heterogeneous and variable from one patient to another, dopaminergic medication can either have a corrective or an overdosing effect, depending on the structure or function evaluated (Gotham, Brown & Marsden, 1987; Delaveau *et al.*, 2009). Previous work has evidenced that dopamine manipulations can alter FER (Lawrence, Calder, McGowan, & Grasby, 2002; Lawrence *et al.*, 2007) or modulate the activity of structures involved in it (Delaveau, Salgado-Pineda, Wicker, Micallef-Roll & Blin, 2005; Cools, Lewis, Clark, Barker & Robbins, 2007). In our sample, however, there was no relationship between levodopa equivalent daily dose and performance in the recognition of any individual emotion or overall emotion recognition.

We found several brain regions where GM volume correlated positively with the ability to identify individual emotions – specifically, the same emotions PD patients did worse at recognizing than healthy controls –, and where patients presented GM loss compared with controls. Though depressive symptoms are known to be a cause of FER impairments (Leppanen, 1996), these were taken into account in our analyses. *A posteriori* analyses showed no correlation between severity of depressive symptoms and GM parameters in the regions where the latter correlated with FER.

The impaired recognition of sadness was associated with GM loss in two areas of the right OFC – a medial area and a smaller, more lateral one –, in the dorsal part of the right postcentral gyrus and in the medial right amygdala. All of these areas have been implicated in the recognition of emotions, especially negative ones (Adolphs, 2002; Fusar-Poli *et al.*, 2009). The orbitofrontal cortex plays a role in FER through different potential mechanisms, such as top-down perceptual processing modulation or through motor or somatosensory simulation of the observed state (Adolphs, 2002). Also, the critical role played by the right somatosensory cortex in facial emotion recognition, evaluated in lesion (Adolphs *et al.*, 2000) as well as transcranial magnetic stimulation studies

(Pitcher, Garrido, Walsh & Duchaine, 2008), supports the hypothesis that representation in this cortical area is critical for FER. These findings lend support to simulationist theories of emotion recognition, according to which the identification of a given emotion relies on the reactivation of sensorimotor networks involved in experiencing it (Niedenthal, 2007; Goldman & Sripada, 2005).

Performance in the recognition of anger correlated with GM volume in the right occipital fusiform gyrus, in the subgenual cortex and in the ventral striatum (nuclei accumbens). These findings are consistent with a study by Calder *et al.* (2004), in which patients with damage to the ventral striatal area were shown to have a disproportionate impairment in the recognition of this emotion.

The fusiform gyrus is classically implicated in the processing of static features of faces and in the recognition of identity (Kanwisher, McDermott & Chun, 1997; Adolphs, 2002). It also appears to play a role in the processing of emotional faces, although its activation has not usually been described to be associated specifically with the presentation of angry ones in functional studies (Fusar-Poli *et al*., 2009). The subgenual cortex is part of the so-called emotional subdivision of the ACC, and is involved in the evaluation of emotional salience of stimuli and in the regulation of emotional responses (Bush, Luu & Posner, 2000).

Previous work has evidenced that patients with lesions in ventromedial prefrontal cortical areas (including those we found to correlate with the identification of sadness and anger in PD patients) may have an impaired ability to process the affective attributes of emotional stimuli or to experience the emotion associated with these stimuli (Bechara, Damasio & Damasio, 2000), both of which might lead to the incorrect identification of emotions in others. Our results indicate that distinct parts of the ventromedial prefrontal cortex may play different roles in the processing of specific emotions.

GM volume in the dorsal ACC correlated positively with the identification of disgust. Though this area has classically been considered as part of the “cognitive” subdivision of the ACC, this dichotomic view restricting emotional processing to the ventral anterior cingulate has been called into question (Etkin, Egner & Kalisch, 2011). In fact, a similar part of the dorsal ACC was seen to be activated while healthy subjects watched facial expressions of disgust and also

when they experienced this emotion themselves in the study by Wicker *et al*. (2003).

Some of the pictures used in the Ekman 60 test are somewhat ambiguous, and the subject must weigh the conflicting information and determine which emotion predominates. The dorsal ACC is also involved in emotional conflict resolution (Etkin *et al.*, 2011; Egner, Etkin, Gale & Hirsch, 2007), and might therefore be engaged in this kind of task. Indeed, we found that the dorsal ACC GM volume correlates with overall Ekman performance.

When entering age as a covariate, statistical significance was lost for the correlations between sadness identification and both right amygdala and right lateral orbitofrontal cortex GM, and between total Ekman scores and ACC GM, though a trend remained for the last two. This could at first glance suggest that the observed effects are a result of aging rather than of PD; in our sample, however, patient's age did not correlate with the performance in identifying sadness. In fact, this is in line with the proposed biologic interaction between age and the pathological effects of PD on GM neuronal loss in non-dopaminergic structures (Levy, 2007). According to this model, brain structures more affected by PD (including the medial temporal lobe, the ACC and the OFC) would present age-related changes earlier than other structures, so that correcting for the effects of aging might also obscure PD-related effects. More studies are necessary to evaluate this effect in neuroimaging analyses.

It is noteworthy that group comparisons in the areas described above revealed GM loss in structures such as the occipital fusiform gyrus and the precentral gyrus in PD patients compared to HC. According to the progression model proposed by Braak, Ghebremedhin, Rüb, Bratzke and Del Tredici (2004), these structures should be affected by α-synucleinopathy late in the disease course – later than structures such as the right ventral striatum, where GM volume loss was not present – , and our sample was not composed of patients with advanced disease. It might however be misleading to expect GM loss patterns to correspond rigidly to the six-stage model proposed by Braak et al. (2004) of ascending Lewy body pathology. Not only because up to 43% of PD cases may fail to conform to this model (Jellinger, 2008), but also because PD-related factors other than synucleinopathy could lead to neuronal death. Long-term loss of cholinergic input secondary to nucleus basalis magnocellularis

lesion in rats is associated with frontoparietal cortical, hippocampal and amygdalar atrophy (Arendash, Millard, Dunn & Meyer, 1987). The equivalent nucleus in humans is affected relatively early in the course of PD (Braak et al., 2004). To our knowledge, however, the relationship between loss of cholinergic innervation and regional atrophy in PD has not been adequately studied, so this remains speculative. Another important contributor to cognitive dysfunction in PD is the coexistence of Alzheimer-type pathology (Jellinger, Seppi, Wenning & Poewe, 2002). The association of Lewy and Alzheimer-type pathologies has recently been found to be strongly associated with dementia in PD (Compta *et al.*, 2011), and could conceivably be associated with specific patterns of neuronal loss.

Recent neuroimaging studies point to the existence of early WM degeneration in PD (Gattellaro *et al.*, 2009; Karagulle Kendi *et al.*, 2008), and basic research studies support this. While it might be tempting to think that axonal changes would be a result of α-synucleinopathy-induced neuronal death and therefore a late finding in the disease course, recent evidence suggests that axonal degeneration may precede neuronal cell body death, and may contribute importantly to the manifestations of neurodegenerative diseases, including PD (Raff, Whitmore & Finn, 2002; Conforti, Adalbert & Coleman, 2007; Hilliard, 2008). Additionally, axons may present inflammatory changes even before degenerating, as suggested by an animal study with mutant α-synuclein transgenic mice which revealed early widespread axonal swelling (Martin *et al*., 2006). A similar process could feasibly take place in PD patients, in whom extensive axonal α-synuclein inclusions have been described (Braak, Sandmann-Keil, Gai, Braak, 1999). Taken together, these findings suggest that WM changes might occur independently from GM changes in PD, and at its early stages. FA decrements are a sensitive marker of WM degeneration, and may be related to axonal loss, demyelination or edema (Lu *et al*., 2004); as such, they could represent a useful marker for detecting these changes at an early stage.

We have found an area in the right frontal lobe where FA levels correlated with the performance in identifying facial expressions of sadness and were reduced compared to controls'. The fasciculus mostly affected was the IFOF, which runs from the frontal lobes to the parietal, temporal and occipital

lobes and is usually considered to be implicated in semantic processing (Martino, Brogna, Robles, Vergani & Duffau, 2010; Duffau *et al.*, 2005). Recently, however, Philippi *et al.* (2009), studying patients with focal brain lesions, described overall impairments in FER associated with damage to the right IFOF, more specifically in the recognition of fear, anger and sadness. These results indicate that the IFOF has an important role in emotional processing, as might be reasonably surmised since it connects areas such as the OFC, the medial temporal lobe and the insula to the visual cortex. Our findings provide neuroimaging evidence that the integrity of the IFOF is critical for the processing of facial emotions.

Besides the structures discussed above, we also found significant correlations between anger recognition and GM volume in the right ventral striatum, and between sadness recognition and FA levels in the temporal part of the left IFOF and ILF, but no group differences in these structural parameters could be found in these regions. Though we cannot exclude that disease-related degenerative processes in these structures might be contributing to FER impairments in some patients, these findings could also represent a physiological correlate of the recognition of these emotions.

Structural techniques may have limitations when studying anatomic correlates for functional deficits such as the ones addressed in this study. It has been demonstrated that cognitive deficits in PD do not correlate with Lewy body and Lewy neurite pathology (Jellinger, 2008), and that neurons affected by α-synucleinopathy probably cease to function long before dying (Braak *et al*., 2004). The same could be the case for Alzheimer-type pathology. Changes in cortical and subcortical innervation (not only dopaminergic) from brainstem or basal forebrain nuclei (Bohnen *et al*., 2006; Shimada *et al.*, 2009) are another factor that seems to contribute to functional deficits. Structural techniques may not have sufficient sensitivity to detect such changes until these factors amount to cell death. We have, nonetheless, been able to detect structural changes in a sample of patients that on average did not have advanced PD from either a motor or a cognitive perspective.

In conclusion, we have found evidence that strongly supports previously described impairments in the identification of negative facial emotions in PD patients. The results of our structural analyses are novel insofar as they reveal

that the deficits in the recognition of specific facial emotions in PD, rather than being solely accompanied by functional changes, have specific structural correlates, especially in GM structures but also related to WM microstructural integrity. And, to our knowledge, this is the first study to show that the neural substrate of the processing of individual emotions can be evaluated through structural gray and white matter MRI techniques.

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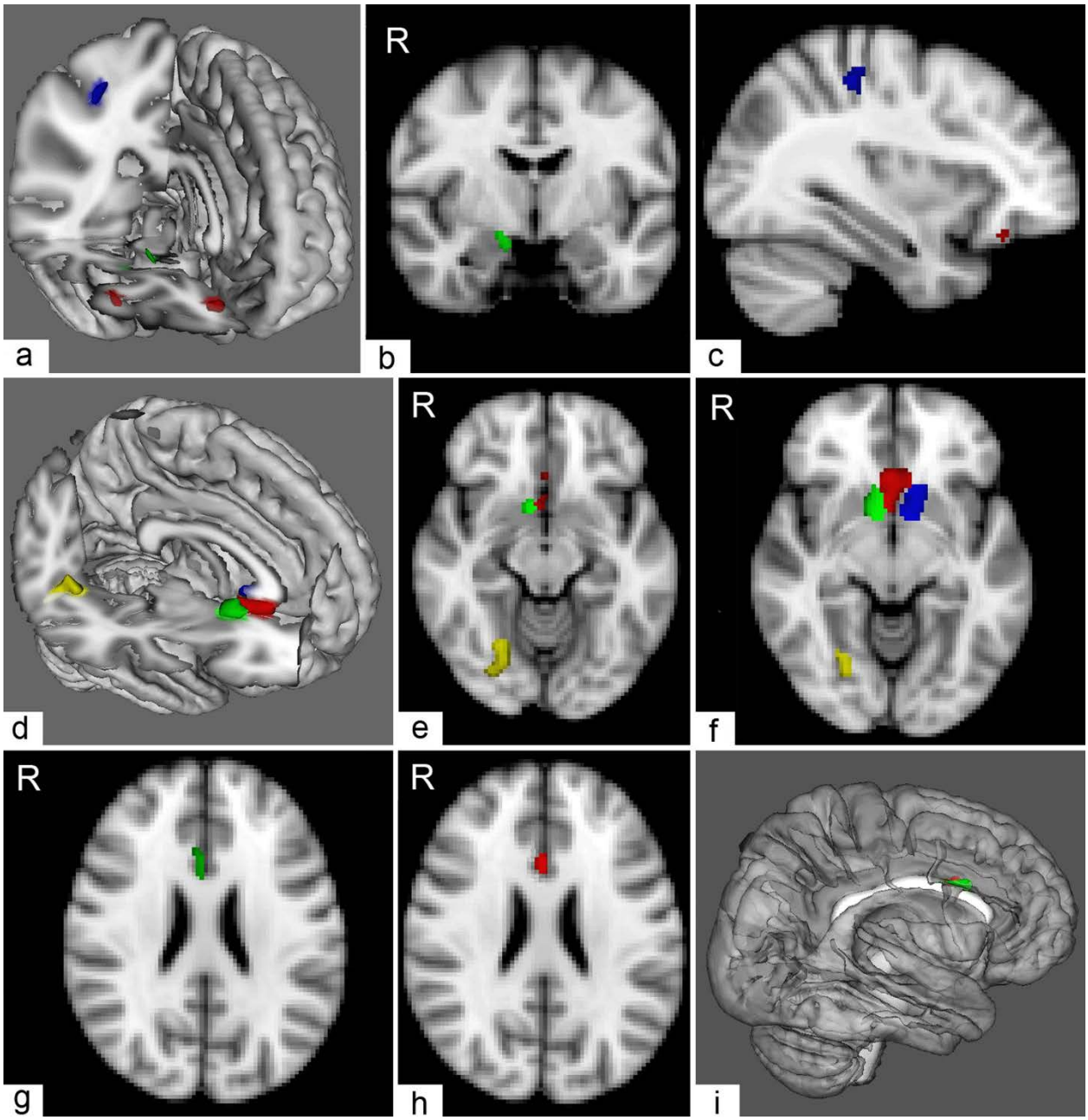

Figure 1

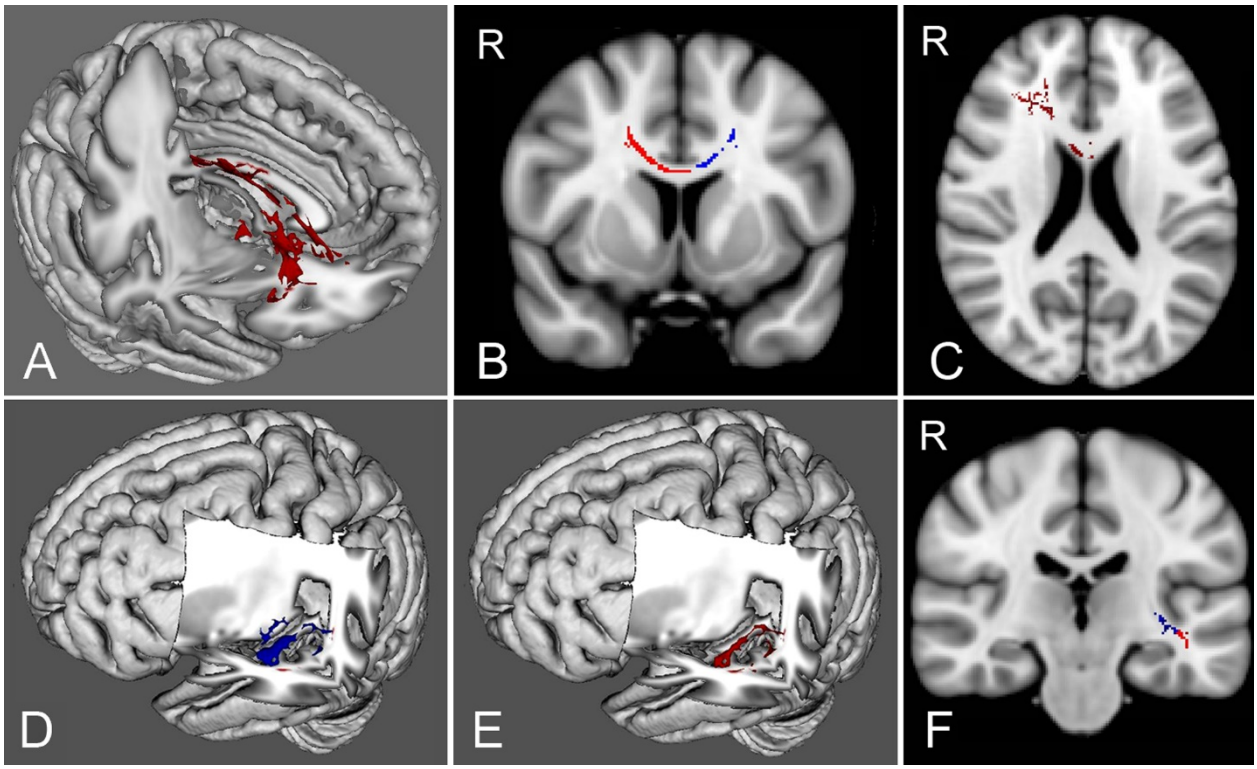

Figure 2