Grey matter hypometabolism and atrophy in Parkinson’s disease with cognitive impairment: a two-step process

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The pathophysiological process underlying cognitive decline in Parkinson’s disease is not well understood. Cerebral atrophy and hypometabolism have been described in patients with Parkinson’s disease and dementia or mild cognitive impairment with respect to control subjects. However, the exact relationships between atrophy and hypometabolism are still unclear. To determine the extension and topographical distribution of hypometabolism and atrophy in the different cognitive states of Parkinson’s disease, we examined 46 patients with Parkinson’s disease (19 female, 27 male; 71.7 ± 5.9 years old; 14.6 ± 4.2 years of disease evolution; modified Hoehn and Yahr mean stage 3.1 ± 0.7). Cognitive status was diagnosed as normal in 14 patients, as mild cognitive impairment in 17 and as dementia in 15 patients. Nineteen normal subjects (eight female, 11 male; 68.1 ± 3.2 years old) were included as controls. 18F-fluorodeoxyglucose positron emission tomography and magnetic resonance imaging scans were obtained, co-registered, corrected for partial volume effect and spatially normalized to the Montreal Neurological Institute space in each subject. Smoothing was applied to the positron emission tomography and magnetic resonance imaging scans to equalize their effective smoothness and resolution (10 mm and 12 mm full-width at half-maximum and Gaussian kernel, respectively). Z-score maps for atrophy and for hypometabolism were obtained by comparing individual images to the data set of control subjects. For each group of patients, a paired Student’s t-test was performed to statistically compare the two Z-map modalities (P < 0.05 false discovery rate corrected) using the direct voxel-based comparison technique. In patients with mild cognitive impairment, hypometabolism exceeded atrophy in the angular gyrus, occipital, orbital and anterior frontal lobes. In patients with dementia, the hypometabolic...
Introduction

Cognitive impairment is common in Parkinson’s disease, which is associated with a long-term prevalence of dementia of up to 80% (Aarsland et al., 2005b; Hely et al., 2008). Mild cognitive impairment (MCI) is a cognitive decline that is not normal for age, but where normal functional activities can be maintained (Folstein et al., 2004; Caviness et al., 2007; Williams-Gray et al., 2007; Litvan et al., 2011). MCI and age represent the two major risk factors for the development of dementia in Parkinson’s disease (Janvin et al., 2006; Broeders et al., 2013; Federsani et al., 2013). Studies using MRI analysed with voxel-based morphometry and PET with 18F-FDG (fluorodeoxyglucose) have shown that patients with dementia in Parkinson’s disease have extensive areas of cerebral atrophy (i.e. reduction of grey matter volume) (Burton et al., 2004; Nagano-Saito et al., 2005; Summerfield et al., 2005; Beyer et al., 2007a, b; Ibarretxe-Bilbao et al., 2008; Song et al., 2011; Melzer et al., 2012) and hypometabolism (i.e. reduced uptake of FDG) in comparison with control subjects (Peppard et al., 1992; Huang et al., 2007a, 2008; Yong et al., 2007; Hosokai et al., 2009; Liepelt et al., 2009; Garcia-García et al., 2012). In patients with Parkinson’s disease with MCI, more localized atrophy in the temporal, parietal and frontal cortices and hypometabolism in the occipito-temporo-parietal junction and the frontal cortex are observed (Huang et al., 2008; Hosokai et al., 2009; Lyoo et al., 2010; Pappata et al., 2011; Garcia-García et al., 2012). Simple comparisons of the results obtained in these studies point to consider that hypometabolism is more extended than atrophy both in patients with Parkinson’s disease with MCI and those with dementia in Parkinson’s disease. Interestingly, while there are no significant differences in the extent of cerebral atrophy between patients with Parkinson’s disease with MCI and cognitively normal patients with Parkinson’s disease (Apostolova et al., 2010; Dalaker et al., 2010; Hattori et al., 2012), patients with Parkinson’s disease with MCI exhibit a reduced FDG uptake in the frontal and parietal regions (Huang et al., 2008; Hosokai et al., 2009; Lyoo et al., 2010; Garcia-García et al., 2012). Based on these data, we hypothesized that in the neurodegenerative process leading to dementia, the reduction of FDG uptake precedes and exceeds the loss of grey matter volume. To test this hypothesis, we directly compared the cerebral regions where atrophy and hypometabolism are located in patients with Parkinson’s disease with MCI and Parkinson’s disease with dementia. For this purpose, we generated MRI PET Z-score maps for each patient relative to normative data obtained from a sample of control subjects; this was done by following the method developed by Chételat et al. (2008) to study patients with Alzheimer’s disease. This approach permits one to integrate MRI grey matter volume and 18F-FDG-PET metabolism data from the same subject for direct comparison (Chételat et al., 2008). We show here that there is a gradient of severity in the cortical changes associated with the development of cognitive impairment in Parkinson’s disease whereby hypometabolism and atrophy could be consecutive stages of the same neurodegenerative process.

Materials and methods

Subjects

A cross-sectional study was conducted in patients with Parkinson’s disease, diagnosed according to the UK Brain Bank criteria (Hughes et al., 1992) aged over 60 years and with a disease duration of at least 10 years, as this profile represents the Parkinson’s disease population at highest risk of developing cognitive impairment (Hobson and Meara, 2004). Exclusion criteria were other neurological or major psychiatric illness (including major depression), abnormal findings in the cerebral MRI (i.e. tumour, hydrocephalus or severe vascular lesions), previous cerebral surgery or metabolic co-morbidities that could contribute to cognitive impairment. Age and sex-matched healthy control subjects were recruited from members of the Association of Blood Donors of Navarra (Spain). Cases with any history of neurological, psychiatric or major medical illness, memory complaints, scores below normal for age and education-appropriate test norms in the neuropsychological assessment, having MRI abnormalities or taking drugs with CNS effects were ruled out. The Ethics Committee for Medical Research of the University of Navarra approved the study, and all patients or legal representatives and controls provided informed consent to participate in accordance to the Declaration of Helsinki. All evaluations were performed for each subject within a 1-week period.

Neuropsychological evaluation

Global cognitive function, five cognitive domains (memory, attention, language, executive and visuospatial function), and functional state were evaluated by using an extensive battery of neuropsychological tests (Garcia-García et al., 2012; González-Redondo et al., 2012) (Supplementary Table 1). All tests were administered by an experienced neuropsychologist to control subjects and patients in the ON medication state. The Movement Disorder Society criteria were used to diagnose patients with Parkinson’s disease as having dementia (Emre et al., 2007) or MCI (Litvan et al., 2012). With respect to MCI, the
level II category guidelines of the Movement Disorder Society were applied (Litvan et al., 2012). This features that there was a cognitive decline reported by either the patient or informant, or observed by the neurologist, but this decline did not interfere significantly with the functional independence of the patient as evaluated with the Interview for Daily Living Activities (Teunisse and Derix, 1991) and that the patient scored >1.5 standard deviations (SD) below control values in at least two tests in the neuropsychological battery, either within a single cognitive domain or across different cognitive domains. An insidious onset of the cognitive decline from premorbid level, slow progression, impairment in at least two cognitive domains with deficits severe enough to impair activities of daily living were required for the diagnosis of dementia (Emre et al., 2007). Patients not fulfilling criteria for MCI or dementia were considered as cognitively normal Parkinson’s disease.

### Image data acquisition

**Magnetic resonance imaging**

For each subject, a 3D T1-weighted gradient-echo sequence was acquired with a 1.5 T Siemens Symphony scan using the following parameters: 144 coronal slices, repetition time/echo time/inversion time 1900/3.36/1100, flip angle 15°, field of view 187 × 250, matrix 192 × 256 and voxel size 0.98 × 1.5 × 0.98 mm.

**Positron emission tomography**

Patients were studied under the effect of their usual dopaminergic regime. Other CNS drugs such as benzodiazepines, antipsychotic, anti-depressant or anti-acetyl-cholinesterase treatments were withdrawn according to their pharmacological kinetics. Quetiapine was used in four patients with Parkinson’s disease with MCI and in eight patients with Parkinson’s disease with dementia because of mild visual hallucinations. Five patients with dementia were on treatment with rivastigmine. Selective serotonin reuptake inhibitors were used in three patients with normal cognition, in five patients with Parkinson’s disease with MCI and in seven patients with Parkinson’s disease with dementia because of sleep disorders, anxiety or mild depression. Benzodiazepines were given to two patients with normal cognition, three patients with Parkinson’s disease with MCI and four patients with Parkinson’s disease with dementia because of anxiety or sleep disorders. Additionally, subjects fasted overnight before PET scanning. Before injection of the radiopharmaceutical agent, blood glucose was checked and confirmed to be <120 mg/dl in all cases. After a few minutes of rest in silence and with dimmed lighting, 18F-FDG 3 (370 MBq) was injected intravenously and subjects were required to rest for 40 min in the supine position in the PET scanner bed with their eyes closed. Then 74 planes (128 × 128 matrix) were acquired with a voxel size of 2.06 × 2.06 × 2.06 mm during a 20-min scan using a Siemens ECAT EXAT HR+ scanner. A transmission scan in 3D mode for attenuation correction was performed at the end of the acquisition period. Images were reconstructed by means of a filtered back-projection method using ECAT software (version 7.4; Siemens).

### Magnetic resonance imaging

Images were segmented using the SPM8 new segmentation tool (Wellcome Department of Neurology, London, UK) (Ashburner and Friston, 2005) in Matlab 7.4 (Mathworks Inc.). Grey and white matter templates were generated from the entire image data set using the DARTEL technique (Ashburner, 2007). After an initial affine registration of the grey matter DARTEL templates to the tissue probability maps in Montreal Neurological Institute (MNI) space (Collins et al., 1994), non-linear warping was performed to the grey matter images to normalize them onto the MNI space. Finally, the normalized grey matter partitions were masked and smoothed as described in Fig. 1.

### Positron emission tomography

Images were processed using SPM8 software implemented in Matlab 7.4. FDG-PET images for each patient were co-registered with their corresponding MRI images. All images were corrected for partial volume effect using the voxel-by-voxel method proposed by Müller-Gärtner et al. (1992) combined with the modification proposed by Rousset et al. (1998) as previously used by others (Chetelat et al., 2003, 2008; Villain et al., 2010). Correction was undertaken using ‘PVE-lab’ software (Quarantelli et al., 2004) including as inputs the co-registered FDG-PET and the segmented MRI images obtained from the segmentation process (Fig. 1). The spatial normalization parameters of each MRI were then applied to each partial volume corrected FDG-PET image. For every spatially normalized PET image, voxel values were normalized to pons activity (Bq/cm³) using the pons volume of interest (Nifti format) from WFU PickAtlas v3.0.

**Figure 1** Schematic representation of the procedures for MRI and PET data handling and transformation steps. GM = grey matter.
Differential smoothing
A smoothing procedure was used to blur individual variations in the anatomy of gyri and to increase the signal-to-noise ratio. Different smoothing was applied to the masked spatially-normalized grey matter and PET-FDG images to equalize their effective smoothness and resolution (12 mm and 10 mm full-width at half-maximum Gaussian kernel, respectively) (Richardson et al., 1997; Van Laere and Dierckx, 2001).

Masking
All images were masked to include only grey matter voxels of interest and to prevent contamination by misclassified voxels. The mask was obtained by thresholding the grey matter DARTEL template above a value of 0.2 and then spatially normalizing this to the MNI space (Chetelat et al., 2008). This binary mask was applied to both MRI and PET data sets twice (before and after smoothing), to avoid contamination of misclassified voxels by smoothing.

Z-score maps
Z-score maps for each patient and each image (MRI and PET) were respectively obtained by comparing individual images to the data set of control subjects [(patient individual value – control mean) / control SD], for each patient and each modality (Kawachi et al., 2006; Chetelat et al., 2008). Individual Z-score maps were then averaged across patients to provide the whole-brain profile of grey matter atrophy and hypometabolism, both expressed as mean Z-scores, for each particular group (cognitively normal patients with Parkinson’s disease; patients with Parkinson’s disease with MCI; patients with Parkinson’s disease with dementia).

Comparison between atrophy and hypometabolism
Z-scores
For each group of patients (above) a paired Student’s t-test was performed to statistically compare the two Z-map modalities using SPM8 software (P < 0.05, false discovery rate corrected) to contrast the extent of grey matter reduction and FDG hypometabolism. A mean PET-hypometabolism map and a mean MRI-atrophy Z-score map were obtained separately for the cognitively normal patients with Parkinson’s disease, patients with Parkinson’s disease with MCI and patients with Parkinson’s disease with dementia groups. For each group, a mask image was created from the mean Z-map to consider exclusively those voxels with a mean MRI Z-map and/or a mean FDG-PET Z-map > 1.5. The obtained mask was then applied to the individual Z-maps (Fig. 1). The regional mean Z-scores for PET and MRI were calculated from masked images (mask including mean MRI and/or mean FDG-PET Z-map > 1.5), using an Automated Anatomical Labelling tool (Tzourio-Mazoyer et al., 2002) to provide quantitative insight into the regional hypometabolism and atrophy. This analysis was implemented for each group of patients with a custom-designed software running under Matlab 7.4. Gender is implicitly modelled as a confounding factor in this type of statistical design.

Statistics
Differences in the demographic and clinical characteristics between the distinct Parkinson’s disease groups and controls were analysed using Fisher’s exact test in cases of categorical variables, ANOVA with post hoc Bonferroni multiple comparison test in cases of continuous normally distributed variables, and the Kruskal-Wallis and Mann-Whitney U-tests for continuous non-parametric variables. The normal distribution of the variables was assessed using the Kolmogorov-Smirnov test. A value of P < 0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS 15.0 software.

Results

Demographic and clinical features
Forty-six patients with Parkinson’s disease, classified as cognitively normal patients with Parkinson’s disease (n = 14), patients with Parkinson’s disease with MCI (n = 17) and patients with Parkinson’s disease with dementia (n = 15), and 19 healthy control subjects were studied. The general demographic and clinical features of the groups are summarized in Table 1. Patients with Parkinson’s disease with dementia were older on average than cognitively normal patients and controls. They also had more severe parkinsonism (significant higher Unified Parkinson’s Disease Rating Scale-III score and Hoehn and Yahr scale) than the cognitively normal patients with Parkinson’s disease and patients with Parkinson’s disease with MCI. The educational level was higher in control subjects and cognitively normal patients with Parkinson’s disease than in the patients with Parkinson’s disease with dementia. The neuropsychological data of each group are summarized in Supplementary Table 1.

Atrophy
Patients with Parkinson’s disease with MCI had bilateral (predominantly on the left) areas of atrophy in angular and middle occipital gyri, left middle frontal and precentral gyri, the left supplementary motor area and right inferior frontal gyrus (Fig. 2 and Supplementary Table 2). Patients with dementia exhibited bilateral grey matter loss in the angular, middle occipital, medial-superior frontal and middle temporal gyri, and in the right inferior frontal gyrus and left hippocampus. The olfactory cortices and the left precentral and supplementary motor areas were also reduced in those with Parkinson’s disease with dementia (Fig. 3 and Supplementary Table 3). In cognitively normal patients with Parkinson’s disease, small areas of reduced grey matter volume were observed bilaterally in the angular gyri, right occipital and left frontal lobes (Supplementary Fig. 1).

Hypometabolism
Patients with Parkinson’s disease with MCI exhibited bilateral reduction of FDG uptake in the parietal (angular > inferior > supramarginal > superior gyri), occipital (calcarine > middle > lingual > superior gyri) and frontal (middle-orbital > superior-medial > superior-orbital > superior > middle > inferior-orbital > inferior-opercular gyri) lobes. Small hypometabolic regions were also observed in the temporal lobe (middle and inferior gyri) (Fig. 2 and Supplementary Table 2). Patients with Parkinson’s disease with dementia exhibited hypometabolism in those areas...
affected in patients with Parkinson’s disease with MCI, but with a greater extension in the parietal, occipital, frontal, and temporal lobes (Fig. 3 and Supplementary Table 3) and also in the caudate and right thalamus. In cognitively normal patients with Parkinson’s disease, hypometabolism was restricted to very small areas of the angular gyrus and occipital and frontal lobes (Supplementary Fig. 1).
disease with dementia group (Figs 2–4 and Supplementary Tables 2 and 3). In the Parkinson’s disease with dementia group, atrophy and hypometabolism in the caudate nucleus were overall of similar degree. Patients with normal cognition did not exhibit areas of hypometabolism or atrophy.

PET and MRI images of each group of patients were superimposed to further assess whether atrophic regions were contained in hypometabolic zones. In patients with Parkinson’s disease with dementia, regions where atrophy coincided with hypometabolism were displayed at the core of the hypometabolic areas of the occipito-parietal junction and frontal regions. In patients with Parkinson’s disease with MCI, a similar small region was found in the left occipito-parieto-temporal junction (Fig. 5).

Discussion

We have performed a direct voxel-by-voxel comparison of MRI and PET in a cohort of patients with Parkinson’s disease from normal to dementia. This allowed us to compare the extension of grey matter volume loss and FDG uptake reduction at different cognitive stages compared with controls. Patients with Parkinson’s disease with cognitive decline have (i) regions showing only hypometabolism; (ii) regions showing an overlap of atrophy and hypometabolism; and (iii) small regions showing atrophy only. Patients with Parkinson’s disease with dementia showed large areas (occipito-parietal > frontal) of coincidental hypometabolism and atrophy which were surrounded by areas of reduced FDG uptake. In patients with Parkinson’s disease with MCI, hypometabolism was the main feature. Nevertheless, small atrophic areas were also identified in regions with hypometabolism in the left occipito-parieto-temporal junction. In addition, small areas of atrophy exceeding that of hypometabolism were observed in the precentral and supplementary motor areas of the frontal lobe in patients with Parkinson’s disease with MCI and patients with Parkinson’s disease with dementia, and in the temporal lobe, hippocampus, putamen, pallidum and thalamus exclusively in the Parkinson’s disease with dementia group. These results suggest that hypometabolism in Parkinson’s disease predates and is replaced by atrophy in a progressive and expanding manner as the cognitive state worsens. However, the relationship between changes in metabolism and atrophy is neither uniform nor complete, given that there are some regions in which atrophy seems to be independent of metabolic changes.

Strengths and limitations

We have directly compared, for the first time in patients with Parkinson’s disease with different cognitive states, the relative amounts of atrophy and hypometabolism by applying step-by-step the methodology previously used in patients with Alzheimer’s disease by Chełtala et al. (2008). Patients were evaluated with a comprehensive neuropsychological battery and the cognitive diagnosis was performed using the Movement Disorder Society consensus criteria for MCI (Litvan et al., 2012) and dementia in Parkinson’s disease (Emre et al., 2007). Although the methodology here applied (Z-map scores) has not been generally applied to ascertain cerebral defects in Parkinson’s disease, our results are supported by the fact that the patterns of atrophy and hypometabolism here identified are consistent with those previously reported using standard methodology (Burton et al., 2004; Summerfield et al., 2005; Huang et al., 2008; Hosokai et al., 2009; Song et al., 2011; Weintraub et al., 2011; Garcia-Garcia et al., 2012; Melzer et al., 2012).

On the other hand, there are obvious limitations for MRI and PET techniques mostly regarding brain shape transformations in the normalization processes, which could cause to some degree a mismatch between the images obtained with MRI and PET. This...
Figure 4 Representation of the extracted mean regional MRI and PET Z-scores in cerebral regions where atrophy exceeded hypometabolism in patients with Parkinson’s disease with mild cognitive impairment (PD-MCI) and patients with Parkinson’s disease with dementia (PDD). On the y-axis, negative values correspond to higher FDG uptake (white) in patients than in controls and positive values denote reduced FDG uptake. For grey matter volume (grey), positive values indicate reduced grey matter volume and negative values indicate increased grey matter volume. Error bars represent 95% confidence intervals.
is especially relevant for the regions where atrophy exceeded hypometabolism, as it cannot be excluded that the use of the ‘double-masking’ procedure causes some slight increases in atrophy Z-scores, especially in deep grey structures, such as the caudate nucleus, putamen, pallidum, thalamus or the hippocampus, even though atrophy in these structures has been reported in patients with Parkinson’s disease (Laakso et al., 1996; Camicioli et al., 2003; Burton et al., 2004; Junque et al., 2005; Nagano-Saito et al., 2005; Summerfield et al., 2005; Beyer et al., 2007a, b; Ibarretxe-Bilbao et al., 2008, Melzer et al., 2012).

Atrophy as a core of hypometabolic areas and hypometabolism

A critical question to be addressed is whether hypometabolism and atrophy are independent processes in the same regions, or conversely if they are two stages of a single process evolving in a step-wise pattern. Thus, extensive regions of hypometabolism surrounding a central area of atrophy were located bilaterally in the occipito-temporo-parietal junction and some regions of the frontal lobe in patients with Parkinson’s disease with dementia. In contrast, in patients with Parkinson’s disease with MCI, a small region of atrophy encircled by a broad hypometabolic area was only present in the left occipito-temporo-parietal junction. Moreover, MCI patients exhibited only hypometabolism in the right occipito-temporo-parietal junction and frontal pole, regions that showed atrophy surrounded by hypometabolism in patients with Parkinson’s disease with dementia. Accordingly, our data suggest that hypometabolism and atrophy are two steps of the same process initiated with a reduction of cortical glucose uptake evolving towards a decrease in grey matter volume, which seems to expand in an exocentric pattern. This is compatible with an evolving neurodegenerative process within the cortex probably paralleling cognitive decline. Thus, it is tantalizing to equate this evolution pattern with the concept of ischaemic penumbra for stroke. Here, the ‘neurodegenerative penumbra’ would imply areas where cell loss is putatively reversible. This concept requires definitive evidence in a prospective and longitudinal assessment and studies to unravel its histopathological and biochemical basis. This in turn could lead to newer and relevant therapeutic approaches.

We can only speculate the possible basis for the sequential pattern of hypometabolism exceeding atrophy in some brain regions. Synapses are the physiologically most active compartments of neurons and a dysfunction at this level can account for reduced glucose uptake. Limbic and cortical Lewy bodies are associated with dementia in Parkinson’s disease (Hurtig et al., 2000; Apaydin et al., 2002; Aarsland et al., 2005a) although this association is not always present (Halliday et al., 2008; Kalaitzakis et al., 2008a). In dementia with Lewy bodies, the majority of alpha-synuclein aggregates are located at presynaptic terminals, thus causing a pathological impact on synaptic function (Kramer

**Figure 5** Overlapping areas of hypometabolism and atrophy in patients with Parkinson’s disease with MCI (left, PD-MCI) and dementia (right, PDD).
and Schulz-Schaeffer, 2007) and probably on metabolism. On the other hand, a lack of function of alpha-synuclein in genetically modified mice impairs the release of glutamate from the synaptic pool (Gureviciene et al., 2007), which is necessary for the maintenance of dendrites in the postsynaptic component and synaptic connectivity (Verhage et al., 2000). In this sense, significant synaptic pathology with almost complete loss of dendritic spines at the postsynaptic level is observed in the cortex of patients with dementia with Lewy bodies (Kramer and Schulz-Schaeffer, 2007) and in patients with Parkinson’s disease with dementia (Zhan et al., 1999). Thus, a putative neuronal damage would follow the maintenance of prolonged periods of synaptic dysfunction. In addition, astrocytes have a key role in regulating synaptic glucose use (Magistretti, 2006) and failure of metabolic coupling between neurons and glia might be another potential explanation for the reduction of FDG signal.

On the other hand, cortical atrophy is associated with cell death but it may also be related to the reduced size of cell bodies and dendritic arborization or the loss of synapsy terminals (Freeman et al., 2008). Thus, it can be hypothesized that an early step in the neurodegenerative process underlying cognitive dysfunction in Parkinson’s disease might be a synaptic dysfunction due to primary neuronal changes and/or neuron-glia decoupling detected by a reduced uptake of FDG in PET, which is the major finding in patients with Parkinson’s disease with MCI. This defect might in turn lead to a loss of dendritic arborization and presynaptic terminals, thus accounting for a reduction in grey matter volume, which is more evident in Parkinson’s disease with dementia. Moreover, other anomalies such as abnormal lipid metabolism that take place in the cortex and correlate with cognitive decline in Parkinson’s disease could also play a part in the metabolic and structural changes encountered in in vivo studies (Fabelo et al., 2011).

Atrophy exceeding hypometabolism

We identified a few regions in which atrophy does not coincide with nor is encircled by hypometabolic areas. This was the case for the precentral and supplementary motor areas of the frontal lobe, in patients with Parkinson’s disease with MCI and patients with Parkinson’s disease with dementia, and for the right temporal lobe, left hippocampus, bilateral putamen, pallidum and left thalamus in the Parkinson’s disease with dementia group. As discussed above, these findings could be related to methodological issues, especially in regions with small volume such as the pallidum, left putamen and left thalamus. Nevertheless, some alternative explanations need to be considered.

A previous pathological study described early neuronal loss in regions involved in motor control such as the presupplementary motor cortex in patients with Parkinson’s disease (MacDonald and Halliday, 2002). Accordingly, the extension of the atrophy in the precentral and supplementary motor area is similar in patients with Parkinson’s disease with MCI and those with Parkinson’s disease with dementia, suggesting that this finding is not related to cognition and therefore the causative process might be different. In contrast, only patients with Parkinson’s disease with dementia showed greater atrophy in the temporal lobe and hippocampus, putamen, pallidum and thalamus suggesting some relationship between these cortico-subcortical changes and progression of cognitive impairment. However, we do not have any direct evidence for the underlying putative mechanisms. Amyloid-β deposition in the allocortex/hippocampus and in the striatum strongly correlates with dementia in Parkinson’s disease (Jellinger and Attems, 2006; Kalaitzakis et al., 2008b) and it could be that the molecular interaction between different pathological proteins could lead to higher neuronal or synaptic loss (Kalaitzakis and Pearce, 2009). Theoretically, as shown in Alzheimer’s disease, disruption in hippocampus or temporal lobe circuitry could also lead to remote metabolic reduction in functionally connected areas but not in the hippocampus or temporal lobe themselves (Minoshima et al., 1999). However, this interpretation could be hardly applied to our subcortical findings as increased metabolism in the putamen, globus pallidus and thalamus is a feature of the parkinsonian state (Eidelberg et al., 1994; Ma et al., 2007; Teune et al., 2010) which increases linearly with progression of motor disability (Huang et al., 2007b), and atrophy of these nuclei have been reported in Parkinson’s disease with dementia (Burton et al., 2004; Nagano-Saito et al., 2005; Duncan et al., 2013). Nevertheless, it is noteworthy that the volume where atrophy exceeded hypometabolism was very small in these nuclei (<10%) and therefore its pathophysiological relevance is uncertain.

Conclusions and perspectives

Our findings suggest the existence of a severity gradient in the cortical changes associated with the development of cognitive impairment in Parkinson’s disease in which hypometabolism and atrophy are consecutive stages of the same process. In this hypothesis, hypometabolism would represent a synaptic or cellular dysfunction which, if maintained, evolves towards histological changes and neuronal death which manifests as a reduced grey matter volume. Thus, in Parkinson’s disease with dementia the greatest metabolic injury is focused on a central core of hypometabolism and atrophy surrounded by a broader area of non-atrophic hypometabolism. In MCI this pattern is less extensive, with predominance of hypometabolism, which is replaced by atrophy in the dementia stage. Thus, cognitive decline in Parkinson’s disease is heralded by an overlapping pattern of hypometabolism and atrophy, where non-atrophic hypometabolism might be considered the “metabolic penumbra” that precedes the definitive cortical changes associated with atrophy and progression to dementia. We like to postulate that such ‘penumbral’ areas are putative pharmacological targets to halt cognitive decline in Parkinson’s disease. This supports the notion that recognition of the earliest cognitive changes in Parkinson’s disease may be critically important for recovering dysfunctional brain regions before the process evolves towards a definitive loss of grey matter volume and dementia. The data shown here could provide an approach to ascertain potential therapeutic interventions. Finally, regions of atrophy exceeding hypometabolism, such as the hippocampus and specially putamen, pallidum and thalamus observed only in patients with Parkinson’s disease with dementia should be interpreted cautiously.
Acknowledgements

We acknowledge Isabel Lamet for her assistance with the neuro-psychological assessments and Dr Pablo Martinez-Lage for his contribution in the study of control subjects.

Funding

This study was funded in part by a grant from the Health department of Government of Navarra Government of Navarra (32/2007), by the University of Navarra-UTE agreement, Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED); Spain CIBERNED and by a grant from Spanish Health Institute Carlos III (FIS- PI08/1539) FIS (PI08/1539) in Spain.

Conflict of interest

Dr Rodriguez Oroz reports grants from Government of Navarra (32/2007) and FIS (ISCIII) PI08/1539, Spain, and from CIBERNED, Spain, during the conduct of the study; personal fees from UCB, Lundbeck and Medtronic and grants from Government of Navarra, Spain, Government of Basque Country, Spain, Spanish Health Institute and Eran-net. Europe, outside the submitted work. Dr Obeso reports personal fees from GSK, Lundbeck, UCB, TEVA (USA) and Boehringer Ingelheim (Mexico), grants from Spanish Science and Education Ministry and from European Union outside the submitted work; Dr Clavero reports personal fees and non-financial support from UCB, Lundbeck, and Novartis outside the submitted work. The rest of authors have no conflicts of interest concerning the research dealt with in this manuscript or outside the submitted work.

Supplementary material

Supplementary material is available at Brain online.

References


