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Progression of Brain Atrophy in the Early Stages of Parkinson's Disease: A Longitudinal Tensor-Based Morphometry Study in De Novo Patients Without Cognitive Impairment

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Abstract: The presence of brain atrophy and its progression in early Parkinson's disease (PD) are still a matter of debate, particularly in patients without cognitive impairment. The aim of this longitudinal te nucleus, and thalamus when compared to control subjects. study was to assess whether PD patients who remain cognitively intact develop progressive atrophic changes in the early stages of the disease. For this purpose, we employed high-resolution T1-weighted MR imaging to compare 22 drug-naïve de novo PD patients without cognitive impairment to 17 age-matched control subjects, both at baseline and at three-year follow-up. We used tensor-based morphometry to explore the presence of atrophic changes at baseline and to compute yearly atrophy rates, after which we performed voxel-wise group comparisons using threshold-free cluster enhancement. At baseline, we did not observe significant differences in regional atrophy in PD patients with respect to control subjects. In contrast, PD patients showed significantly higher yearly atrophy rates in the prefrontal cortex, anterior cingulum, caudaOur results indicate that even cognitively preserved PD patients show progressive cortical and subcortical atrophic changes in

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regions related to cognitive functions and that these changes are already detectable in the early stages of the disease. *Hum Brain Mapp 35:3932–3944, 2014.*

Key words: de novo PD; TBM; brain atrophy; longitudinal study; cognitive status

INTRODUCTION

Several structural magnetic resonance imaging (MRI) studies have consistently highlighted widespread cortical and subcortical atrophic changes in Parkinson's disease (PD) patients in advanced disease stages, and in particular in PD patients with dementia (PDD) (Beyer et al., 2007; Burton et al., 2004; Melzer et al., 2012; Nagano-Saito et al., 2005; Summerfield et al., 2005; Weintraub et al., 2011). These results have been confirmed by pathological studies showing how the degenerative process (and signally the inclusion bodies pathology that is the hallmark of the disease) is first detectable in the brain stem, subsequently extends into the limbic system and finally progresses to increasingly involve the cerebral cortex (Braak et al., 2004).

There is increasing evidence that a substantial portion of PD patients (including those in the early, drug-naïve stages of the disease) suffer from quantifiable cognitive deficits that do not meet the criteria for dementia (Aarsland et al., 2010; Poletti et al., 2012). These patients have been categorized as suffering from PD-related mild cognitive impairment (PD-MCI) (Litvan et al., 2012) and are considered at increased risk of developing dementia (Pedersen et al., 2013). MR studies in PD-MCI patients have consistently revealed atrophic changes in a number of cortical regions. Such alterations were less extensive than those found in PDD patients, and the findings related to their precise regional distribution remain contradictory (Lee et al., 2012; Meltzer et al., 2012; Song et al., 2011; Weintraub et al., 2011).

In contrast, the presence and extent of atrophic changes in PD patients without cognitive impairment is still a matter of debate. While some cross-sectional MR studies reported no significant atrophy in cognitively intact PD patients (Feldmann et al., 2008; Hattori et al., 2012; Meltzer et al., 2012; Weintraub et al., 2011), other authors described diverse patterns of cortical and subcortical atrophy in non-demented PD patients (Beyer et al., 2007; Bouchard et al., 2008; Brenneis et al., 2003; Brück et al., 2004; Burton et al., 2004; Jubault et al., 2011; Lyoo et al., 2010; Nishio et al., 2010; Pereira et al., 2012; Song et al., 2011; Summerfield et al., 2005; Tam et al., 2005; Tinaz et al., 2011). The longitudinal/time-dependent progression of regional brain atrophy in PD patients has been investigated in relatively few MR studies, with conflicting results. For instance, previous papers have described gray matter (GM) loss in limbic-paralimbic structures in non-demented PD patients and neocortical changes in PD patients (Ramírez-Ruiz et al., 2005), widespread limbic, paralimbic, and neocortical grey-matter loss in PD patients with visual hallucinations (Ibarretxe-Bilbao et al., 2010), volume reduction in amygdala and temporal cortex in PD patients without severe hyposmia and (conversely) only sparse longitudinal volume changes in patients with hyposmia (Baba et al., 2012), progressive amigdalar atrophy and cortical thinning in frontotemporal regions in the early stages of the disease (Ibarretxe-Bilbao et al., 2012), and greater progression of cortical thinning in frontal, limbic, and posterior cortical regions in advanced PD patients that converted to dementia with respect to non-converters (Compta et al., 2013), whereas others reported no differences in regional brain atrophy rates between PD patients and healthy controls (Brenneis et al., 2003).

Also, some longitudinal MR studies employed measures of global atrophy in order to monitor the progression of the degenerative process in PD. Hu et al. (2001) found that annual brain volume loss was greater in patients with PD than in controls, whereas others studies reported no differences in global atrophy rates between controls and non-demented patients with PDD (Burton et al., 2005; Paviour et al., 2006) but found significantly increased atrophy in patients with PD (Burton et al., 2005) with respect to non-demented PD and controls or reported a higher rate of ventricular dilatation in PD patients that developed significant cognitive decline compared to PD patients who remained cognitively intact (Camicioli et al., 2011).

One possible explanation for the high variability in the findings described above could be the heterogeneous characteristics of PD patients under consideration. In particular, especially in less recent studies, non-demented PD patients were often grouped into a single cohort which (a) also included advanced PD patients and (b) did not differentiate between cognitively intact and PD-MCI patients. Therefore, in spite of the growing interest in evaluating patients in the initial stages of PD (warranted by a potentially greater responsiveness to putative neuroprotective and disease-modifying treatment effects), the progression of structural brain changes in early, cognitively preserved PD patients remains uncertain.

Several methodological approaches have been applied to MR-based investigation of brain atrophy in PD patients, including ROI-based methods (Bouchard et al., 2008; Camicioli et al., 2003; Junque et al., 2005; Laakso et al., 1995), measurement of global atrophy (Burton et al., 2005; Camicioli et al., 2011; Hu et al., 2001), whole-brain voxel-wise techniques such as voxel-based morphometry (VBM) (Beyer et al., 2007; Burton et al., 2004; Melzer et al., 2012; Nagano-Saito et al., 2005; Nishio et al., 2010; Ramírez-Ruiz et al., 2005; Song et al., 2011; Summerfield et al., 2005; Weintraub et al., 2011), and surface-based methods that produce measures of cortical thickness and folding (Compta et al., 2013;

Ibarretxe-Bilbao et al., 2012; Jubault et al., 2011; Pereira et al., 2012; Tinaz et al., 2011; Zarei et al., 2013).

Tensor-based morphometry (TBM) is a promising image processing technique that allows automated voxel-wise analysis of brain tissue changes. In particular, local differences in brain tissue volume are evaluated by computing high-dimensional nonlinear deformations to adjust the anatomy of each individual to match a custom-built group-average template and successively comparing maps of the Jacobian determinant ($|\mathbf{J}|$) of the deformation fields in order to estimate the degree of tissue contraction/expansion at each location/voxel (Ashburner and Friston, 2003; Chung et al., 2001; Fox et al., 2001; Freeborough and Fox, 1998; Hua et al., 2009, 2011, 2013; Riddle et al., 2004; Studholme et al., 2001; Thompson et al., 2000). TBM has been proven to be an unbiased, robust, high-throughput imaging marker in Alzheimer's disease (AD) and MCI and is particularly suited for longitudinal studies (Hua et al., 2013).

To the best of our knowledge, only few cross-sectional studies employed TBM for the evaluation of PD. In a pilot report (Lu et al., 2009), PDD subjects showed cortical atrophic changes in more areas of the brain than PD-MCI subjects (relative to healthy controls), while patients with normal cognition had only few areas of significant tissue loss. Borghammer et al. (2010) employed a TBM method based on a non-linear deformation algorithm with a limited number of degrees of freedom (Klein et al., 2009). In this study, early PD patients showed an isolated cluster of GM loss in the right cerebellum with respect to controls. More recently, TBM has also been employed to detect tissue damage in an animal model of the disease (Westphal et al., 2013).

The aim of the present longitudinal study was to track the progression of regional brain atrophy in the early stages of the disease in cognitively intact PD patients. To this purpose, we employed an optimized TBM strategy based on high resolution T1-weighted images in a cohort of newly diagnosed drug-naïve (de novo) PD patients with preserved cognitive functioning at baseline and at three-year follow-up.

MATERIALS AND METHODS

Subjects

Thirty-four (8 women and 26 men, mean age 63.1 ± 7.9 years) patients with de novo parkinsonian syndrome consecutively referred to a neurology unit for the diagnostic evaluation of PD over a 24-month interval (from March 2004 to March 2006) were recruited in this prospective study. At baseline, clinical evaluation included history of disease-related symptoms and signs, neurological examination and levodopa challenge test as a supportive criterion for the diagnosis of idiopathic PD. All patients were screened for cardiovascular autonomic dysfunction, which was considered as exclusion criterion. Severity of parkinsonism was evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al., 1987) and the Hoehn–Yahr (HY) staging system (Hoehn and Yahr, 1967). All patients were required to satisfy the UK Brain Bank criteria for the diagnosis of PD (Gibb and Lees, 1988). We administered the Geriatric Depression Scale Short Form (GDS-15: Sheik and Yesavage, 1986) to screen for depressive features in all PD patients, and diagnosis of depression was made according to DSM IV-TR (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text-Revision) criteria (American Psychiatric Association, 2000). Patients also underwent a comprehensive neuropsychological assessment. Global cognitive status was assessed through the Mini Mental State Examination (Folstein et al., 1975). The battery of standardized neuropsychological tests included at least two tests within each of the five cognitive domains: attention and working memory, executive functions, language, memory, and visuospatial ability. We employed the Visual Search Test (Spinnler and Tognoni, 1987), the Digit Span (Orsini et al., 1987), and the Corsi Span (Spinnler and Tognoni, 1987) to assess attention and working memory, the Stroop Test (Caffarra et al., 2002a) and the Frontal Assessment Battery (Dubois et al., 2000) to evaluate executive functions, the Boston Naming Test short form (Kaplan et al., 1983), and the Phonemic and Semantic Fluency Test (Carlesimo et al., 1996) to assess language, the Rey Auditory Verbal Learning Task (Carlesimo et al., 1996) and Rey–Osterrieth Complex Figure Recall Test (Caffarra et al., 2002b) to evaluate memory and the Rey–Osterrieth Complex Figure Copy Test (Caffarra et al., 2002b), Benton Judgment of Line Orientation Test (Benton et al., 1978) and Raven Colored Progressive Matrices (Raven et al., 2003) to assess visuospatial ability. Due to the lack of specific criteria for evaluating MCI in PD at the time of inception of the current investigation, the presence of MCI was initially declared when a neuropsychological impairment was demonstrated within one or more cognitive domains; otherwise, patients were classified as cognitively preserved. In retrospective evaluation, the classification of our cohort members according to this criterion was seen to coincide with the assessment later performed using the recently proposed Movement Disorder Society Task Force diagnostic criteria for PD-MCI (Litvan et al., 2012), which state that PD-MCI may be diagnosed when a neuropsychological impairment is demonstrated by performances 1 to 2 standard deviations below appropriate norms in at least two tests of the same cognitive domain (PD-MCI single domain) or in at least one test in two different cognitive domains (PD-MCI multiple domains). The presence of depression or MCI at baseline or at follow-up was considered as exclusion criterion.

Twenty healthy volunteers (8 women and 12 men, mean age 62.5 ± 9.1 years) with no history of familial or personal neurological diseases and normal neurological examination were recruited as controls. All subjects gave their written informed consent to participate in the study, which was approved by the Local Ethics Committee.

Study Design

One of the 34 de novo patients enrolled in the study was excluded after baseline clinical assessment because

the cardiovascular autonomic test indicated autonomic dysfunction, and eight additional patients were excluded after cognitive assessment because of a MCI-PD single domain diagnosis. The remaining 25 patients underwent baseline MRI scanning and began chronic dopaminergic treatment shortly thereafter.

Subsequently, patients were clinically evaluated every six months during the follow-up. Two further patients were excluded from the study because of the lack of dopaminergic response and the appearance of atypical signs and/or symptoms during clinical follow-up (for those two patients, respective diagnoses of possible Progressive Supranuclear Palsy and Multiple System Atrophy were made). At the end of the follow-up, all subjects underwent a second comprehensive neuropsychological evaluation to ascertain possible development of cognitive impairment. One patient was excluded from the study because of the appearance of cognitive deficit classified as MCI-PD single domain. Our cohort did not comprise any patients with a diagnosis of MCI multiple domain, neither at baseline, nor at follow-up. Three control subjects did not consent to the follow-up MR study. Overall, 22 patients (4 women and 18 men, mean age 61.5 ± 8.8) and 17 control subjects (8 women and 9 men, mean age 59.1 ± 8.5 years) completed the study and underwent a second MRI examination. The mean ($\pm$ standard deviation) follow-up time for patients and controls was 2.8 ± 0.6 (range 2–4) years and 3.9 ± 2.2 (range 2–7) years, respectively. Differences for age between PD patients and control subjects were not significant ($P = 0.48$, Mann-Whitney U-test). Clinical and neuropsychological data of the patients that completed the study are summarized in Table I.

TABLE I. Clinical and neuropsychological data of PD patients at baseline and follow-up

	Baseline assessment	Follow-up assessment
Disease duration (years)	1.32 (0.80)	–
HY*	1.25 (0.40)	1.41 (0.43)
UPDRS II*	6.3 (4.1)	7.0 (3.5)
UPDRS III*	10.5 (5.7)	12.2 (5.0)
MMSE	29.45 (0.73)	28.77 (0.65)
Visual search	48.28 (3.49)	47.33 (2.55)
Digit span	4.8 (1.1)	4.6 (1.3)
Corsi span	4.6 (0.9)	4.2 (1.1)
Stroop interference: time	17.00 (8.25)	19.31 (9.50)
Stroop interference: errors	0.39 (0.83)	0.62 (1.14)
Frontal assessment battery	16.37 (1.12)	15.38 (1.40)
RAVLT immediate recall	37.89 (6.80)	37.70 (7.03)
RAVLT delayed recall	7.30 (1.86)	6.58 (1.98)
Rey figure immediate recall	16.79 (4.25)	13.98 (0.97)
Boston naming test short form	26.93 (3.10)	26.12 (3.37)
Semantic verbal fluency	11.68 (2.37)	11.67 (1.66)
Phonemic verbal fluency	31.35 (6.22)	31.30 (4.93)
CPM 47	31.35 (3.58)	28.75 (4.06)
Rey–Osterrieth Complex Figure Copy Test	32.71 (1.99)	31.91 (2.34)
Benton JOL	26.15 (2.66)	25.05 (2.71)

Mean (standard deviation) data are reported.
CPM 47 = Raven's Colored Progressive Matrices; HY = Hoehn and Yahr; JOL = Judgment of Line Orientation; MMSE = Mini Mental State Examination; PD = Parkinson's disease; RAVLT = Rey Auditory Verbal Learning Task; UPDRS = Unified Parkinson's Disease Rating Scale.
*$P < 0.05$, General Linear Model, independent variables: HY, UPDRS II e UPDRS III, continuous between-factors: age and follow-up time, categorical between-factors: gender, within-factor: time.

MRI Data Acquisition

MRI was performed on a 1.5 T MR scanner system (Magnetom Symphony, Siemens, Erlangen-Germany) with 30 mT/m maximum gradient strength and a standard quadrature birdcage head coil.

T1-weighted MR images were acquired with an axial high resolution 3D sequence (Magnetization Prepared Rapid Gradient Echo, MPRAGE) with repetition time (TR) = 2500 ms, echo time (TE) = 3.7 ms, inversion time (TI) = 730 ms, flip angle = 15°, slice thickness = 1 mm, field of view (FOV) = 256 mm × 256 mm, matrix size = 256 × 256, number of excitations (NEX) = 1. The acquisition protocol also included axial T2 weighted images [fluid attenuated inversion recovery (FLAIR) sequence with TR = 9,000 ms, TE = 114 ms, TI = 2,500 ms, slice thickness = 4 mm, FOV = 230 mm × 230 mm, matrix size = 256 × 256, turbo factor = 21, NEX = 1, and turbo spin echo TSE sequence (TR = 4,730 ms, TE = 104 ms, slice thickness = 4 mm, FOV = 230 mm × 230 mm, matrix size = 256 × 256, turbo factor = 13, NEX = 2)].

Tensor-Based Morphometry

In order to optimize TBM analysis, all registration procedures were based on variations of the SyN algorithm which, along with another registration strategy, has been shown to provide the most consistent high accuracy (Klein et al., 2009). We employed the Greedy SyN implementation of the SyN algorithm included in the ANTs package (Avants et al., 2011). All image registrations were initialized through a 12-degree of freedom (DOF) affine transform, which was followed by a nonlinear diffeomorphic step, and employed neighborhood cross-correlation as similarity metric. For improved accuracy with respect to the default package settings, in the second (nonlinear) registration step, we used four multiresolution levels with a maximum number of 200 iterations per level and smoothing resolutions of 3, 2, 1, and 0 mm per level (from coarsest to finest).

Custom T1 Template Construction

In order to generate an unbiased, population-specific T1 template, we used baseline T1 images from all (number of subjects = 17) controls and an equal number of randomly selected patients. The template was generated using a procedure similar to that described in Avants et al. (2010).

Briefly, after N4 bias field correction (Tustison et al., 2010), coregistrations of individual brain images were iteratively refined to create a group average, which is often referred to as an optimal average template. In particular, the algorithm works within the diffeomorphic space toward building an average shape and appearance brain by reducing dependence on the topological idiosyncracy of any individual brain. Within the ANTs package, the SyN tool is called to nonlinearly coregister all brain images to one another in an iterative manner for subsequent intensity averaging. The procedure is repeated recursively, thereby iteratively refining the co-registration of the constituent images. Five global iterations were used to build the final template in this study. Creation of the custom template required approximately 420 hours of CPU time.

Image Registration

All N4-corrected baseline images were registered to the unbiased template as described above. The voxel-wise jacobian determinant of the nonlinear component of the warpfield ($|\mathbf{J}|_{\text{baseline}}$) was then computed for each subject. In particular, when the local volume in N4-corrected image is greater/less than local volume in the unbiased template image the $|\mathbf{J}|_{\text{baseline}}$ values are less/greater than 1, respectively.

Also, every N4-corrected follow-up image was registered (intra-subject) to the N4-corrected baseline image as described above, and the voxel-wise jacobian determinant $|\mathbf{J}|_{\text{longitudinal}}$ of the nonlinear component of the inverse warpfield (i.e., relative to the transformation which takes the baseline image into the space of the follow-up image) was computed (resulting in $|\mathbf{J}|_{\text{longitudinal}}$ being in baseline image space). The voxel-wise yearly warp rate (WR) was then computed as $\text{WR} = (|\mathbf{J}|_{\text{longitudinal}} - 1)/t$, where t is time (in years) between baseline and follow-up imaging. In particular, WR values less/greater than 0 indicate contraction/expansion of local tissue volume, respectively. WR is largely insensitive to differences both in follow-up time and in spread around mean follow-up time. Specifically, normalizing absolute volume changes by time and hence working with per-year volume change yields a quantitative index (i.e., WR), which is statistically comparable across different follow-up times both intra- and inter-subject groups. Finally, maps of voxel-wise WR were transformed into custom template space by applying the transformations computed in the previous step (which take baseline images into custom template space).

Statistical Analysis

All voxel-wise statistical analyses were performed within the framework of the general linear model (GLM) while controlling for age and gender as nuisance covariates. We employed a non-parametric, permutation-based inference approach which included full correction for multiple comparisons over space. In particular, *P*-values were calculated and corrected for multiple comparisons using the "3D" parameter setting with threshold-free cluster enhancement (TFCE), thereby avoiding the use of an arbitrary amount of spatial smoothing as well as threshold for the initial cluster-formation, which can affect the sensitivity of statistical analysis and bias results (Smith and Nichols, 2009). For each comparison, we employed 50,000 permutation for increased accuracy, and corrected *P*-values smaller than 0.05 were considered statistically significant. The comparisons we performed were (a) patients vs. controls at baseline (quantity of interest: $|\mathbf{J}|_{\text{baseline}}$), (b) follow-up vs. baseline (quantity of interest: WR), and (c) within-patient group correlation of WR with clinical/cognitive variables and their yearly changes. In (a) we tested the effect of group, in (b) we tested the effect of time (in each group) and of group x time interaction, and in (c) we tested the hypothesis of a regression slope being larger or smaller than zero. Resulting *P*-value maps were transformed into MNI-152 space by applying an affine, 12-DOF transformation computed by registering the custom template to the MNI-152 template. In order to avoid creating false *P*-values, nearest neighbor interpolation was employed in this step.

RESULTS

Baseline Evaluation

No difference in local volume between patients and control subjects was revealed (i.e., the $|\mathbf{J}|_{\text{baseline}}$ analysis showed no significant differences between PD patients and control subjects).

Longitudinal Evaluation

Control subjects: Baseline versus follow-up

During the follow-up period, control subjects developed atrophic changes (i.e., WR values were significantly smaller than 0) involving several white matter (WM) and GM regions (Fig. 1a) and showed cerebrospinal fluid (CSF) enlargement (i.e., WR values were significantly greater than 0; not shown). Atrophy clusters involved mainly WM and were more widespread in the frontal lobe. GM changes included paracentral lobule, precuneus, parietal superior gyrus, and anterior cingulum bilaterally, right frontal superior medial gyrus and left temporal middle gyrus, precentral gyrus, postcentral gyrus, middle cingulum, cuneus, and superior and middle occipital gyrus.

PD patients: Baseline versus follow-up

With respect to baseline examinations, PD patients at follow-up displayed a number of clusters of reduced WM and GM volume (i.e., WR values were significantly less than 0), which were more widespread in WM and signally in the frontal lobe (Fig. 1b), and showed CSF enlargement (i.e. WR values were significantly greater than 0; not shown). GM involvement in PD patients was more

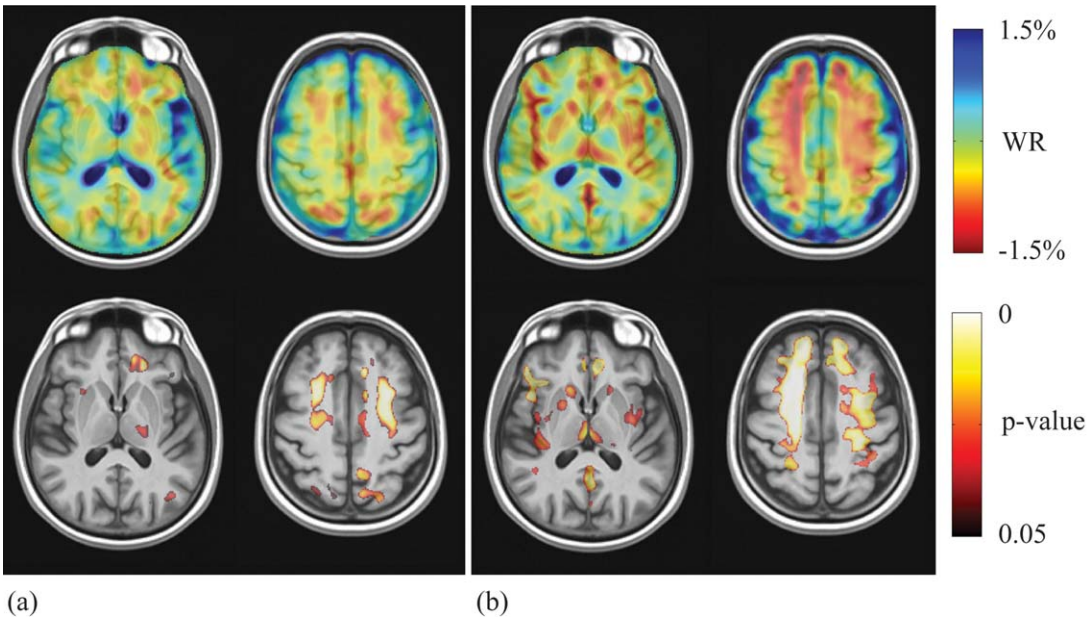

Figure 1.

Top pane: Sample axial views of average WR maps in control subjects (**a**) and PD patients (**b**), where red indicates local atrophy and blue indicates local enlargement. Bottom pane: voxel-wise corrected p-value maps (threshold-free cluster enhancement, TFCE) testing the null hypothesis of zero WR in control subjects (**a**) and PD patients (**b**) separately. Highlighted clusters indicate significant ($p < 0.05$) atrophic changes (i.e., WR significantly lower than zero) within the respective groups. All maps are overlayed on population-specific template. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

widespread than in control subjects and included bilaterally the thalamus, caudate, putamen, superior and middle frontal gyrus, postcentral gyrus, anterior cingulum, insula, Rolandic operculum, Heschl gyrus, temporal middle and inferior gyrus, frontal inferior triangular gyrus, frontal inferior operculum, precuneus, frontal middle orbital gyrus, rectus gyrus and amygdala, right parahippocampal gyrus, olfactory gyrus and fusiform gyrus, and left precentral gyrus and posterior cingulum.

PD patients versus control subjects

With respect to control subjects, during the follow-up period PD patients developed bilateral clusters of increased atrophy (i.e., WR values in PD patients were significantly lower than WR values in control subjects) in frontal superior and middle gyrus, anterior cingulum, caudate nucleus, and thalamus (Fig. 2). No other significant time (baseline vs. follow-up) × group (PD patients vs. control subjects) interaction was revealed.

Correlation analyses

In PD patients, no significant correlation between warp-rates and motor or neuropsychological test scores or their average changes per year between baseline and follow-up were identified.

DISCUSSION

TBM has been previously employed in few pilot, cross-sectional PD studies both in patients (Borghammer et al., 2010; Lu et al., 2009) and in an animal model of the disease (Westphal et al., 2013). In this study, we employed TBM for the longitudinal evaluation of PD and focused on the progression of regional atrophy in a cohort of cognitively preserved de novo patients. Our main finding is that early PD patients who remain cognitively intact develop clusters of increased atrophy rates (when compared to control subjects) in cortical and subcortical regions related to cognitive functions.

Baseline Evaluation: De Novo PD Patients Versus Control Subjects

Our PD patients without cognitive impairment showed no detectable differences in atrophic changes with respect to controls subjects at baseline examination. Several studies have described inconsistent patterns of regional atrophy in the frontal (Burton et al., 2004; Jubault, et al., 2011;

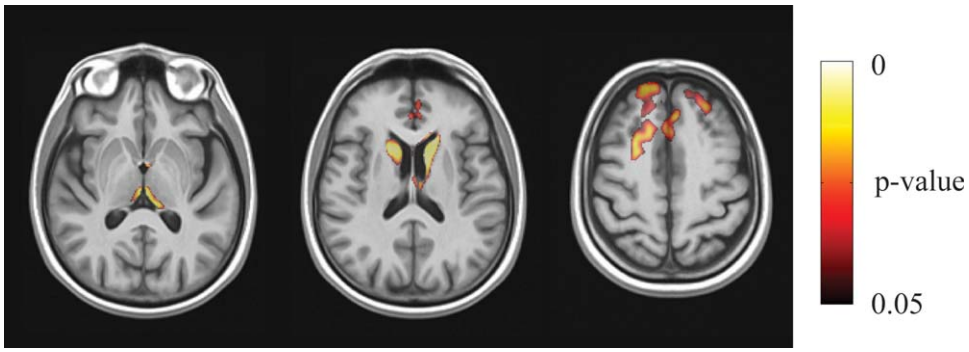

Figure 2.

Voxel-wise corrected *p*-value maps (threshold-free cluster enhancement, TFCE), testing the null hypothesis of zero differences in WR between in PD patients and control subjects. Highlighted clusters indicate significantly ($p < 0.05$) more pronounced mean atrophy in PD patients when compared to control subjects (i.e., WR in PD patients significantly lower than WR in control subjects). All maps are overlayed on population-specific template. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Lyoo et al., 2010; Nishio et al., 2010; Pereira et al., 2012; Tinaz et al., 2011), temporal (Beyer et al., 2007; Bouchard et al., 2008; Brück et al., 2004; Jubault et al., 2011; Lyoo et al., 2010; Nishio et al., 2010; Pereira et al., 2012; Summerfield et al., 2005; Tam et al., 2005), parietal (Jubault et al., 2011; Lyoo et al., 2010; Pereira et al., 2012; Tinaz et al., 2011), and occipital cortex (Pereira et al., 2012; Song et al., 2011; Tinaz et al., 2011), the cerebellum (Borghammer et al., 2010; Camicioli et al., 2009), and the striatum (Brenneis et al., 2003; Tinaz et al., 2011) of non-demented PD patients. The majority of these reports did not distinguish between cognitively intact and PD-MCI patients that do not fulfill the criteria for dementia, or included patients in moderate stages of the disease. In our opinion, the results of the present study reflect the early stage of PD in our patients, and they are in agreement with the findings of previous papers, which include an accurate distinction between patients with normal cognition and PD-MCI patients (Hattori et al., 2012; Meltzer et al., 2012; Weintraub et al., 2011).

Longitudinal Evaluation: Baseline Versus Follow-Up

We found that, during the follow-up period, both PD patients and controls subjects developed atrophic changes that encompassed several WM and GM regions, although those changes were more widespread in WM and in particular in the frontal lobe. There is consensus that GM volume decreases linearly with age (Allen et al., 2005; Courchesne et al., 2000; Ge et al., 2002; Smith et al., 2007). In contrast, WM volume has been demonstrated to peak in the 40–50 year age range and subsequently to decline quickly in particular after 60 years of age (Allen et al., 2005; Barzokis et al., 2001; Courchesne et al., 2000; Ge et al., 2002; Guttman et al., 1998; Salat et al., 2009).

Further, MRI-based studies have indicated that aging selectively affects different cortical regions, and frontal lobes have been described to show the largest volume reduction and WM changes (Allen et al., 2005; Grieve et al., 2005; Michielse et al., 2010; Raz et al., 2004). Our results essentially confirm an accelerated decrease in WM volume in the elderly population which is particularly pronounced in the frontal lobes.

Longitudinal Evaluation: PD Patients Versus Control Subjects

We found that, with respect to control subjects, cognitively intact PD patients displayed a higher atrophy rate bilaterally in the prefrontal cortex, anterior cingulum, head of caudate nucleus, and thalamus.

To the best of our knowledge, only one recent longitudinal MR study evaluated the progression of structural brain changes in early PD patients (Ibarretxe-Bilbao et al., 2012) employing cortical thickness analysis, VBM, and volumetric measures of cortical and subcortical structures. The study found no significant VBM differences between PD patients and control subjects; however, when compared to controls, PD patients presented a faster rate of cortical thinning in bilateral frontotemporal regions, higher total GM and total cortical volume loss, and higher amygdalar atrophy after an average interval of 35 months. In the study by Ibarretxe-Bilbao et al. (2012), the patient group had both a more severe clinical deficit (mean baseline UPDRS III 15.44 on treatment vs. 10.5 off treatment) and a longer disease duration (2.97 vs. 1.32 years at baseline) than our patient group. This could contribute to explaining why the cortical thickness changes described by Ibarretxe-Bilbao et al. were more widespread than the ones presented in our whole brain TBM study.

In the following sections, areas of increased atrophy rates in PD patients with respect to control subjects are discussed in relation to their functions.

Prefrontal cortex

Atrophic changes in the prefrontal cortex of PD patients have been described in several cross-sectional imaging studies (Beyer et al., 2007; Burton et al., 2004; Brück et al., 2004; Meltzer et al., 2012; Meppelink et al., 2011; Nagano-Saito et al., 2005; Nishio et al., 2010; Pereira et al., 2012; Song et al., 2011; Tinaz et al., 2011), and prefrontal WM damage was reported in diffusion tensor imaging (DTI) studies (Karagulle-Kendi et al., 2008; Rae et al., 2012). Further, decreased frontal lobe perfusion has been observed in Parkinson's disease without dementia (Antonini et al., 2001) and selective prefrontal hypometabolism has been detected in cognitively preserved PD (Hosokai et al., 2009). Neurodegeneration is expected to involve prefrontal cortex in Braak's stage 4/5. Although an exact clinical-pathological correlation can only be established through pathological verification, considering the disease duration and the clinical scores it is likely that our patients were crossing this stage of the disease.

Structural changes in the frontal lobe have been hypothesized to contribute to the dysexecutive syndrome (Brück et al., 2004; Nagano-Saito et al., 2005; Rae et al., 2012), the hallmark of cognitive impairment of early PD patients that has been attributed to functional derangement of specific prefrontal cortex-striatal circuits (Williams-Gray et al., 2007). Furthermore, pathological studies found a positive correlation between Lewy bodies load in the frontal cortex and cognitive impairment in PD (Mattila et al., 2000; Van den Berge et al., 2012).

Anterior cingulum

According to Braak's staging system, the anterior cingulate cortex is one of the cortical areas more precociously and severely affected by Lewy bodies pathology (Braak et al., 2004; Braak and Del Tredici, 2008), and atrophic changes in this region in cognitively impaired PD patients have been detected by previous cross-sectional VBM studies (Nagano-Saito et al., 2005; Summerfield et al., 2005), while in another study (Jubault et al., 2011) local surface area analysis (corticometry) showed anterior cingulate atrophy in a series of cognitively preserved PD patients. Furthermore, WM microstructural changes in the anterior cingulum of PD patients were reported in DTI studies (Gattellaro et al., 2009; Hattori et al., 2012; Kamagata et al., 2012).

Several studies have demonstrated the role of the cingulate cortex in attention and executive functioning, especially in inhibitory control and in the sensitivity to interference (Duncan and Owen, 2000; Fichtenholtz et al., 2004; Meindl et al., 2010; Silton et al., 2010), and a correlation between structural changes in the anterior cingulum and cognitive impairment in PD was suggested by pathological (Kövari et al., 2003) and imaging (Kamagata et al., 2012) studies.

Caudate nucleus

Both ROI-based (Apostolova et al., 2010; Lisanby et al., 1993; Pitcher et al., 2012) and VBM (Brenneis et al., 2003; Burton et al., 2004; Melzer et al., 2012; Nagano-Saito et al., 2005) cross sectional studies have revealed atrophic changes in the caudate nucleus of PD patients. The majority of this previous data concerned patients in advanced stages of the disease, and mostly dealt with demented subjects. However, Pitcher et al. (2012) found decreased caudate volumes, in particular of the head of the caudate nuclei, in both cognitively intact and impaired patients, although the changes were less conspicuous in the former than in the latter. In PD, the striatum is an elective site of Lewy body pathology in both neurons and astrocytes (Braak and Del Tredici, 2008); furthermore, pathological studies have described a decrease in dendritic spine density and dendrite atrophy in the caudate nuclei of PD patients, and these changes may contribute to a volume reduction (Stephens et al., 2005; Zaja-Milatovic et al., 2005).

It is well known that the caudate nucleus is involved in a variety of cognitive processes and that it plays a regulatory role in different behavioral contexts, such as mood and motivation; lesions of this nucleus can cause a dysexecutive syndrome, learning difficulties, and affective disturbance (Cummings and Benson, 1984; Mendez et al., 1989; Richfield et al., 1987).

Moreover, reduced caudate dopaminergic function (Holthoff-Detto et al., 1997; Jokinen et al., 2009) as well as caudate atrophy (Camicioli et al., 2009) have been associated with cognitive impairment in PD.

Thalamus

Atrophic changes in the thalamus have been described in a few previous VBM studies in PD patients (Burton et al., 2004; Hattori et al., 2012; Nagano-Saito et al., 2005; Summerfield et al., 2005). Furthermore, in a ROI-based study, PD patients in mild to moderate stages of the disease showed differences in shape, but not volume of the thalami, with respect to healthy subjects (McKeown et al., 2008).

Functional changes of thalamic neurons are traditionally related to motor symptoms of PD. According to the basal ganglia-thalamocortical circuit model, activity changes in basal ganglia (which are due to the loss of dopaminergic regulation) are thought to cause a cortical hypo-activity via a reduced excitatory outflow from the motor thalamus (Albin et al., 1989). This classic view assumes that there is no structural damage to the thalamus itself. However, more recently, several studies revealed that the thalamus is one of select targets of extranigral inclusion body pathology and that it undergoes significant neuronal loss in PD (Brooks and Halliday 2009; Halliday, 2009; Henderson et al., 2000; Rüb et al., 2002; Truong et al., 2009).

Furthermore, recent views posit that the thalamus is more than just a relay for information coming from the basal ganglia and instead that it actively modulates the function of both the basal ganglia and cortical neurons (Halliday, 2009; Sherman, 2007). Therefore, since

pathological changes in PD also involve the non-motor thalamus, it has been suggested that thalamic damage, while underlying motor symptoms, might also have an impact on cognitive functions and in particular on arousal, awareness, attention, memory, and dementia (Brooks and Halliday, 2009; Halliday, 2009; Kimura et al., 2004; Van der Werf et al., 2002).

Correlation Analyses

In our sample of PD patients, we found no significant correlation between TBM measures and clinical/cognitive variables or their yearly changes. This may reflect the relatively narrow range of scores in tests evaluating motor impairment and cognitive functions in our homogeneous sample of early de novo PD patients. In particular, we only selected patients who were cognitively intact at baseline and did not develop cognitive deficits during the follow-up period, and this may contribute to explaining why we failed to find correlations between the rate of atrophic changes and cognitive measures. On the other hand, the lack of association between TBM data and motor scores or their yearly changes is not surprising, given the distribution of regional atrophy that predominantly involved cortical and subcortical structures belonging to cognitive circuits.

Inverse Consistency and Practical Implementation of TBM

Since our optimized TBM studies the Jacobian determinant of the deformation fields, accurate computation of intra-subject transformations between baseline and follow-up is crucial. In this context, one key property of TBM should be that the deformation field be *inverse consistent*. This means the computed deformations will be identical if the chronological order of the images is inverted (i.e., TBM results, in terms of regions with significant volume change, should be identical regardless if the deformation target is the baseline or the follow-up image) (Hua et al., 2011). While analytically the SyN algorithm employed in our study is fully inverse consistent, a computer program which calculates deformations fields will only be able to work with finite precision, possibly creating small discrepancies in inverse consistency. We minimized this effect by employing double-precision arithmetics for all our computations.

Also, our optimized TBM requires large computing times/resources, and in this study we circumvented this problem by running all registrations as well as permutation-based inference on a parallel computing cluster with 512 Intel Xeon compute cores and 4GB RAM/core.

Possible Interactions Between Dopaminergic Treatment and Brain Morphometry

At follow-up examination, all patients were receiving L-dopa, dopamine-agonists, or both. We are not aware of any proven effect of dopaminergic treatment on brain morphometry; however, a pilot VBM study reported midbrain volume increases in healthy controls after acute levodopa administration (Salgado-Pineda et al., 2006). Furthermore, two recent MR studies by one group (Cerasa et al., 2011; 2013) found increased gray matter volume of the inferior frontal cortex in PD patients with levodopa-induced dyskinesias when compared to non-dyskinetic patients and raised an interesting debate regarding possible plastic effects of long term L-dopa administration (Aron and Obeso, 2012; Vernon and Modo, 2012). For ethical reasons, a completely drug-free longitudinal evaluation of PD patients is difficult if not impossible. Actually, since long-duration symptomatic effects of dopaminergic drugs can persist for weeks or months (Hauser et al., 2000; Hauser and Holford, 2002; Olanow et al., 2009), the washout of 12–24 h commonly prescribed before imaging studies probably is not fully adequate even in fMRI. In this context, it seems even more unlikely that hypothetical therapy-induced plasticity effect could reverse so rapidly. We therefore decided not to suspend treatment before follow-up MR examination.

CONCLUSIONS

Cognitively intact de novo PD patients show no significant GM or WM loss with respect to control subjects. However, already in these initial stages of the disease, these patients exhibit increased yearly atrophy rates in regions mainly related to cognitive functions, including prefrontal cortex, anterior cingulum, head of caudate nucleus, and thalamus. These structural changes could increase the susceptibility to developing cognitive impairment. In view of our findings, a longer term clinical follow-up study is warranted in order to elucidate if the above changes can predict the onset of cognitive deficits.

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