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Regional volumetric change in Parkinson's disease with cognitive decline

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ABSTRACT

Background: Parkinson's disease (PD), characterized by motor dysfunction and cognitive decline, may demonstrate specific patterns of brain atrophy. Although cross-sectional magnetic resonance imaging (MRI) studies show correlation between regional brain volume loss and cognitive impairment, there is only scarce evidence from longitudinal studies validating the link between cognition and brain anatomy in PD.
Objective: To test the relationship between magnitude and spatial extent of atrophy in PD patients with progressive, significant cognitive decline and dementia (PDD).
Methods: We followed thirty-three initially non-demented patients with prevalent PD for three years while monitoring cognitive function and brain atrophy. Longitudinally acquired T1-weighted magnetic resonance images were analyzed in the voxel-based morphometry framework of SPM.
Results: Groups did not differ significantly with respect to age or gender. More males developed PDD (7 males, 3 females) compared to those remaining intact (12 males, 11 females). Clusters of lower grey matter volume were found in PDD compared to PD in left uncus at baseline and an expanded region that included the left hippocampus and parahippocampal gyrus at 36 months. The cognitive status by scan interaction showed differential changes between groups in the right insula. At a more liberal statistical threshold we observed changes in the right insula and bilateral hippocampi as well as the right cuneus additional to the lower brain stem.
Conclusions: Region specific atrophy, consistent with the pattern of cortical Lewy body deposition seen in autopsy studies, can be detected with MRI in PD patients with significant cognitive decline. MRI may be useful for tracking cognitive decline in PD.

1. Introduction

Parkinson's disease (PD) is the most common neurodegenerative movement disorder, and is characterized by loss of dopaminergic nigrostriatal projections; however, over time more generalized pathology leads to widespread neurodegeneration [1], which leads to significant loss of motor response to dopamine replacement, cognitive decline and dementia [2,3,4]. The latter are the major determinants on nursing home placement and increased mortality [5,6]. The neurologic bases for these changes are not fully understood. Imaging biomarkers might assist in tracking pathological changes, in predication of dementia and in development of treatments. Magnetic resonance imaging may be one such approach that is readily available [7,8].

Patients with PD with dementia (PDD) have progressive atrophy on MRI [9,10] that likely begins with mild cognitive impairment, which occurs in at least 24% of patients [11] prior to significant cognitive decline. Recent studies show that longitudinal cortical grey matter changes occur in incident/early Parkinson's disease cases [12,13,14,15,16]. These findings are consistent with prior studies that suggest that subtle changes occur prior to overt cognitive decline [17,18] and can be detected in prevalent cases [19]. Grey matter atrophy rates may depend on duration of disease [20] and can complement other biomarkers of change [21].

We have shown that whole brain atrophy and ventricular enlargement occur in older patients with PD developing incident dementia or significant cognitive decline [22] and might be accelerated in patients with hyper-homocysteinemia [23]. In the current study we analyze this same cohort for regional changes in brain atrophy using state-of-the-art optimized voxel-based morphometry to test for more focal changes driving the previously observed whole-brain atrophy and ventricular dilations. We hypothesized that atrophy is localized in a pattern

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consistent with reported pathological Lewy body changes in the anterior cingulate, insula and medial temporal lobes [24].

2. Methods

Subject selection and follow up has been described in detail previously [22]. In brief, 33 subjects with PD, meeting criteria consistent with UK brain bank criteria according to a movement disorders specialist [25] achieving 36-month follow up are included here. All subjects were assessed at 0, 18 and 36 months.

Baseline age, sex, education and other demographic features were measured. As previously described, at baseline and every 18 months Mini-Mental Status Examination (MMSE), Frontal Assessment Battery (FAB), Dementia Rating Scale (DRS-II), the 15-item Geriatric Depression scale (GDS) were scored [22]. The short Blessed-Orientation-Concentration Test, FAB and a general and neurological examination (including rating the Unified Parkinson's Disease Rating Scale (UPDRS), Part III) were performed by a neurologist (RC) who recorded co-morbid medical conditions (Cumulative Illness Rating Scale (CIRS)) [22]. Levodopa equivalent doses were calculated as previously described. Assessments of PD patients were performed in the ON state.

2.1. Dementia classification

Patients were classified as previously described [22]. Subject and caregiver-derived Clinical Dementia Ratings scores (CDR, and CCDR) were obtained as previously described [26]. Dementia was defined as cognitive impairment in two domains with functional impairment due to cognitive decline based on all available information, independent of neuro-imaging. Memory impairment was not necessary (i.e., modified from DSM-IV which was available at the time of study inception) [27]. Participants with significant cognitive or functional decline (on the MMSE, DRS or CDR or CCDR) were considered impaired (PDD). Subjects with questionable changes in cognitive function, or without functional impairment, were grouped with non-impaired subjects (PDND).

2.2. MR imaging

Images were acquired on a Siemens Sonata 1.5T system between December 2004 and August 2009. T1-weighted images were obtained using a 3-D magnetization prepared rapid acquisition gradient echo sequence (MPRAGE) (TR = 1800 ms, TE = 3.2 ms, TI = 1100 ms, 1 average, flip angle = 15°, field of view (FOV) = 256 mm, image matrix = 256 × 256, 128 slices, 1.5 mm slices) with image slices oriented perpendicular to the AC-PC line. Native spatial resolution was 1 × 1 × 1.5 mm which was zero-filled to 0.5 × 0.5 × 1.5 mm. Standard axial FLAIR images (TR = 8000 ms, TE = 99 ms, 2 averages, FOV = 220 mm, 25 slices, 5 mm slice thickness) oriented to the inferior margin of the corpus callosum were used to examine white matter changes and exclude pathological lesions as previously described [22].

2.3. Intracranial volumes

Intracranial volumes (ICV) were measured from the T1-weighted images using the program DISPLAY (Montreal Neurological Institute, Quebec, Canada (http://www.bic.mni.mcgill.ca/ServicesSoftwareVisualization/HomePage) as previously described [22]. The intracranial volumes were used to correct the grey and white matter volumes for individual differences.

2.4. Statistical analysis of baseline characteristics

Groups were compared using Chi-square or ANOVA as appropriate using SPSS 20 (Armonk, NY). Statistical thresholds were set at $p < 0.05$.

2.5. Voxel-based morphometry

Image processing was done using the VBM8 (r435) toolbox (http://dbm.neuro.uni-jena.de/vbm/) for longitudinal data in SPM8 running in Matlab 7.8.0. In VBM8 toolbox, the 18 month and 36 month volumes were initially realigned to the baseline volume, then a mean image was created and the three volumes realigned again to the mean image. All three volumes were then bias corrected and segmented into GM, WM and CSF. Spatial normalization parameters were obtained from the baseline image using the DARTEL (Diffeomorphic Anatomical Registration using Exponentiated Lie algebra) [28] toolbox and applied to all three volumes. The standard template images provided by the VBM8 toolbox, based on the MNI152 average brain, were used for spatial normalization. The VBM8 toolbox for longitudinal image processing produces unmodulated tissue segment volumes, hence changes observed represent tissue concentration and not tissue volumes [29,30]. An 8 mm Gaussian smoothing kernel was applied prior to statistical analysis. SPM8 was used for both cross-sectional and longitudinal comparisons. The comparisons between PDND and PDD groups at baseline and 36 months, were modeled using two between group factors, dementia status and gender. To examine changes with respect to time, a flexible factorial model was used, with dementia status and gender as between subject factors and scan time (baseline, 18 month, and 36 month) as a within subject factor. The interaction between dementia classification and scan time was examined, to see if and where the two groups changed differently over time. Baseline age and intracranial volume (ICV) were also included in all models. For cluster-level inference [31,32], a cluster-defining threshold of uncorrected $p < 0.001$ was used, with the non-stationarity adjustment [33], which accounts for differences in smoothness in the images. The threshold cluster size that corresponded to FWE cluster level corrected p-value <0.05 was then used to filter the results. Only significant clusters are displayed in the figures. Additionally, to test for more focal but stronger effects a voxel-wise family wise error [34] (FWE) corrected p-value <0.05 was applied.

3. Results

There were no significant baseline demographic or clinical differences at baseline between those who became cognitively impaired and those who remained intact as shown in Table 1. The 36-month data have been reported previously [22].

3.1. Voxel-based morphometry

Contrasting dementia groups at baseline yielded no between-group voxel-based differences at a peak FWE-corrected significance of $p < 0.05$. Examining clusters, we found a significant cluster of decreased grey matter density in the left uncus (Brodmann area 38) (Fig. 1 and Table 2). At 36 months, a much larger cluster that also included the left hippocampus and parahippocampal gyrus was evident (Fig. 2 and Table 2).

Examining the dementia by time interaction, a significant cluster of accelerated atrophy in PDD compared to PDND was found on the right insula with a peak FWE p-corrected threshold of $p < 0.05$ (Fig. 3). The maximum t-statistic is located at (33, −21, 19) mm in Talairach space with a cluster extent of 133 voxels. Using a cluster level threshold at FWE p-corrected <0.05, significant clusters were identified in the right insula, and right and left hippocampus as well as low in the brain stem, indicating accelerated atrophy in these areas for PDD patients (Table 3 and Fig. 4).

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4. Discussion

Here we show that there are clear differences in brain volume and the rate of atrophy progression between PD patients showing

Table 1
Baseline characteristics of patients overall and divided by final dementia status in subjects with complete follow up (±SD).[a]

	PD	PDND	PDD	*p*-Value (PDND vs. PDD)
Number of subjects	33	23	10	Not sig.
Males/females	19/14	12/11	7/3	
Age (years)	70.1 ± 3.3	69.4 ± 3.3	71.6 ± 2.7	0.09
Education (years)	14.3 ± 3.1	14.7 ± 3.6	13.2 ± 1.5	0.09[b]
Disease duration (years)	8.4 ± 4.3	7.7 ± 4.3	9.8 ± 4.2	0.2
UPDRS III	15.0 ± 7.0	15.3 ± 6.3	14.4 ± 8.7	0.8
MMSE	28.4 ± 1.7	28.9 ± 1.2	27.3 ± 2.2	0.05[b]
CIRS	18.6 ± 2.7	18.8 ± 2.9	18.2 ± 2.4	0.6
NART	106 ± 8	106 ± 8	105 ± 5	0.6
GDS	1.33 ± 1.63	1.35 ± 1.64	1.30 ± 1.70	0.9
L-Dopa total Equivalents (mg)	632 ± 335	587 ± 341	736 ± 315	0.2

[a] PD = subjects with Parkinson's disease, PDND = subjects with Parkinson's disease without dementia, PDD = subjects with Parkinson's disease and dementia.
[b] Fail Levene's test for equality of variances, *p*-values are for *t*-test with equal variances not assumed.

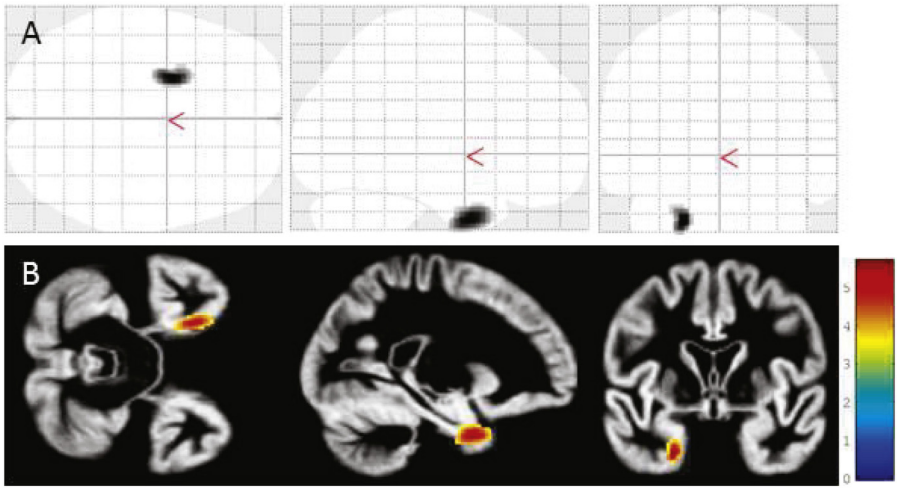

Fig. 1. Significant cluster (cluster threshold at FWE p-corrected < 0.05) of atrophy at baseline in PDD compared to PDND. The glass brain depiction from SPM is shown in (a). The cluster is overlaid on the mean GM volume in (b). Transverse, sagittal and coronal slices at x = −21, y = 0, and z = 34 mm are shown.

significant cognitive decline compared to those remaining cognitively stable. Our previous study showed that simple to obtain global measures can be used to reliably track decline [22]. Here we demonstrate that the focal nature of these changes is consistent with regions that have been shown to be affected at autopsy and correlate with cognitive status [24]. The summation of these changes likely leads to global change as reflected in ventricular dilatation.

Among the earlier longitudinal studies one showed an increased rate of atrophy in PDD with no difference in the rate of atrophy between cognitively intact PD patients and controls [9] contrasting with another study that found atrophy in both PD and PDD using VBM [10]. PD patients with hallucinations, who are at risk for dementia, have been shown to have focal atrophy [35]. Longitudinal volumetric scans with patients grouped according to smell abnormalities (another potential risk factor for dementia) rather than cognitive decline [36] showed that group with normal olfaction, showed progressive changes in the right amygdala and bilateral temporal lobes. Recent studies suggest that progressive cortical thinning is likely accelerated in patients with mild cognitive impairment, [37] and may be associated with incident MCI [13]. In addition to areas we show to be involved, progressive changes can be seen in more widespread cortical areas including the temporal, parietal and frontal lobes and deep structures such as the thalamus and basal ganglia [38]. Differences between studies are likely based on imaging methods and characteristic of the subjects. Our study highlights the utility of brain MRI to track cognitive decline in a typical treated patient population in agreement with Melzer et al. [19].

A weakness of our study includes its relatively small sample size with only 10 incident significant cognitive decline/dementia subjects. On the other hand a strength is the systematic longitudinal follow up. We did not use currently proposed PD dementia criteria, which are still being validated [39] since they were not available at the time of study inception, rather we used modified DSM-IV criteria (not requiring memory impairment). Our grouping is likely clinically meaningful, however, given the fact that cognitive decline correlated strongly with atrophy in our previous study [22] and that functional decline related to cognitive impairment was evident in our subjects. It should be acknowledged that the pathological contributions to cognitive decline in Parkinson's disease may be

Table 2
Significant clusters of GM atrophy in PDD compared to PDND at baseline and 36 months.

Cluster size (num. voxels)	FWE-corrected cluster *p*-value	Talairach coordinates (mm)			Location
Baseline		x	y	z	
557	0.01	−23	0	−32	Left uncus, BA 38
36 months					
2915	0.001	−33	−18	−13	Left hippocampus
		−20	4	−25	Left uncus, BA 28
		−30	−50	0	Left parahippocampal gyrus, BA 19

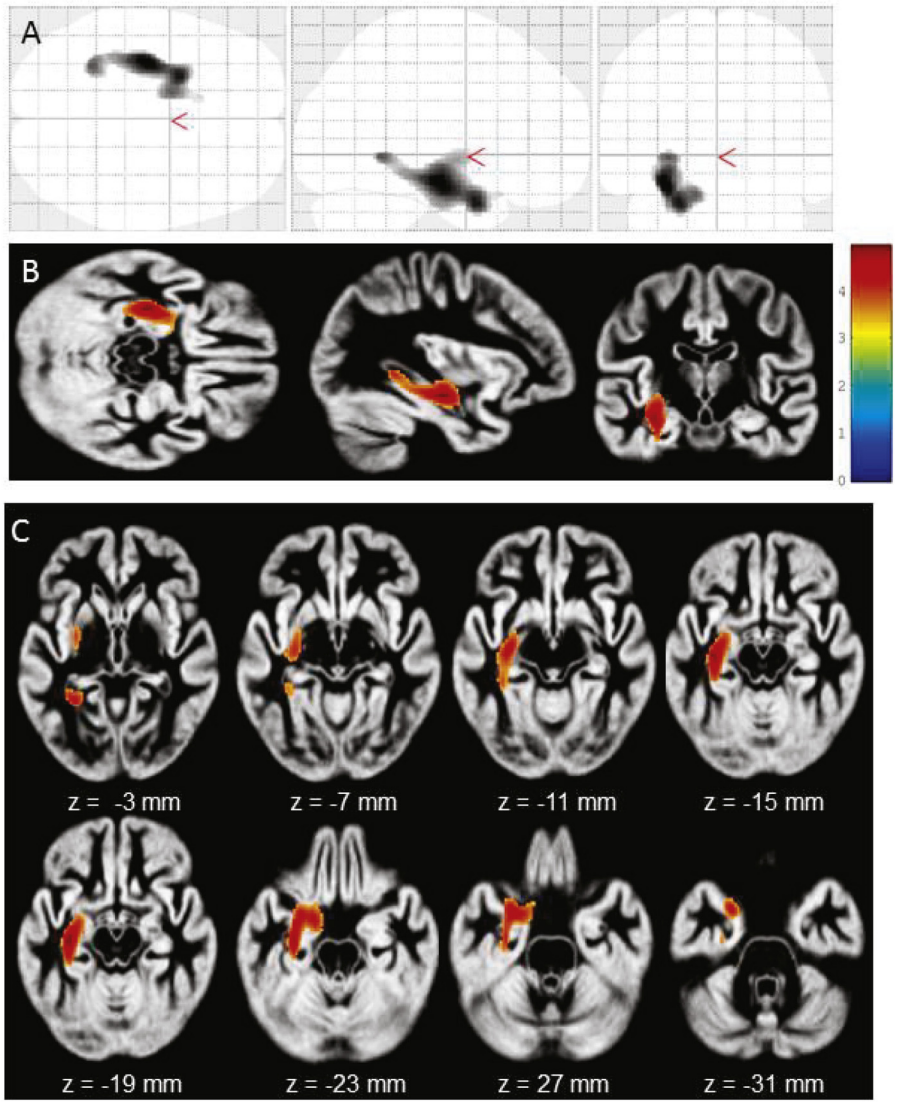

Fig. 2. Significant cluster of atrophy (cluster threshold at FWE p-corrected < 0.05) of atrophy at 36 months in PDD compared to PDND. The glass brain representation is shown in (a). The cluster is overlaid on the mean GM volume in (b), with orthogonal views at x = −33, y = −15, and z = −18 mm. The same cluster is shown on a series of axial slices in (c).

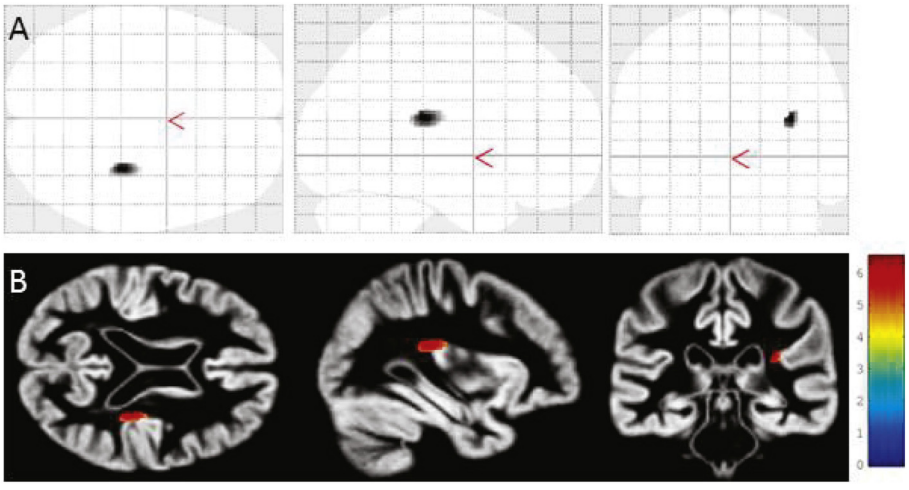

Fig. 3. Significant cluster of accelerated atrophy (peak-level FWE p-corrected < 0.05) in PDD compared to PDND. The glass brain representation is shown in (a). The cluster is overlaid on the mean GM volume in (b), with orthogonal views obtained at x = 33, y = −31, and z = 18 mm.

Table 3
Significant clusters of accelerated GM atrophy in PDD compared to PDND.

cluster size (num. Voxels)	FWE-corrected cluster *p*-value	Talairach Coordinates (mm)			Location
		x	y	z	
1852	<0.001	32	−29	19	Right insula, BA13 (cluster also includes the right hippocampus)
2807	0.001	5	−35	−43	Brain stem
1379	0.005	14	−89	24	Right cuneus BA19
1113	0.03	−33	−27	−5	Left caudate tail (cluster also included the left hippocampus)

mixed; while we eliminated patients with obvious cerebrovascular disease, Alzheimer pathology (plaques, tangles) likely contribute to cognitive decline and brain atrophy [40]. In addition, give imbalances (statistically insignificant) in duration of disease and sex distribution, ideally we would include more subjects to allow better matching and include more patients with dementia. It should also be acknowledged that at baseline we excluded patients with dementia and hence our study, which is clinic based, is likely a selected group.

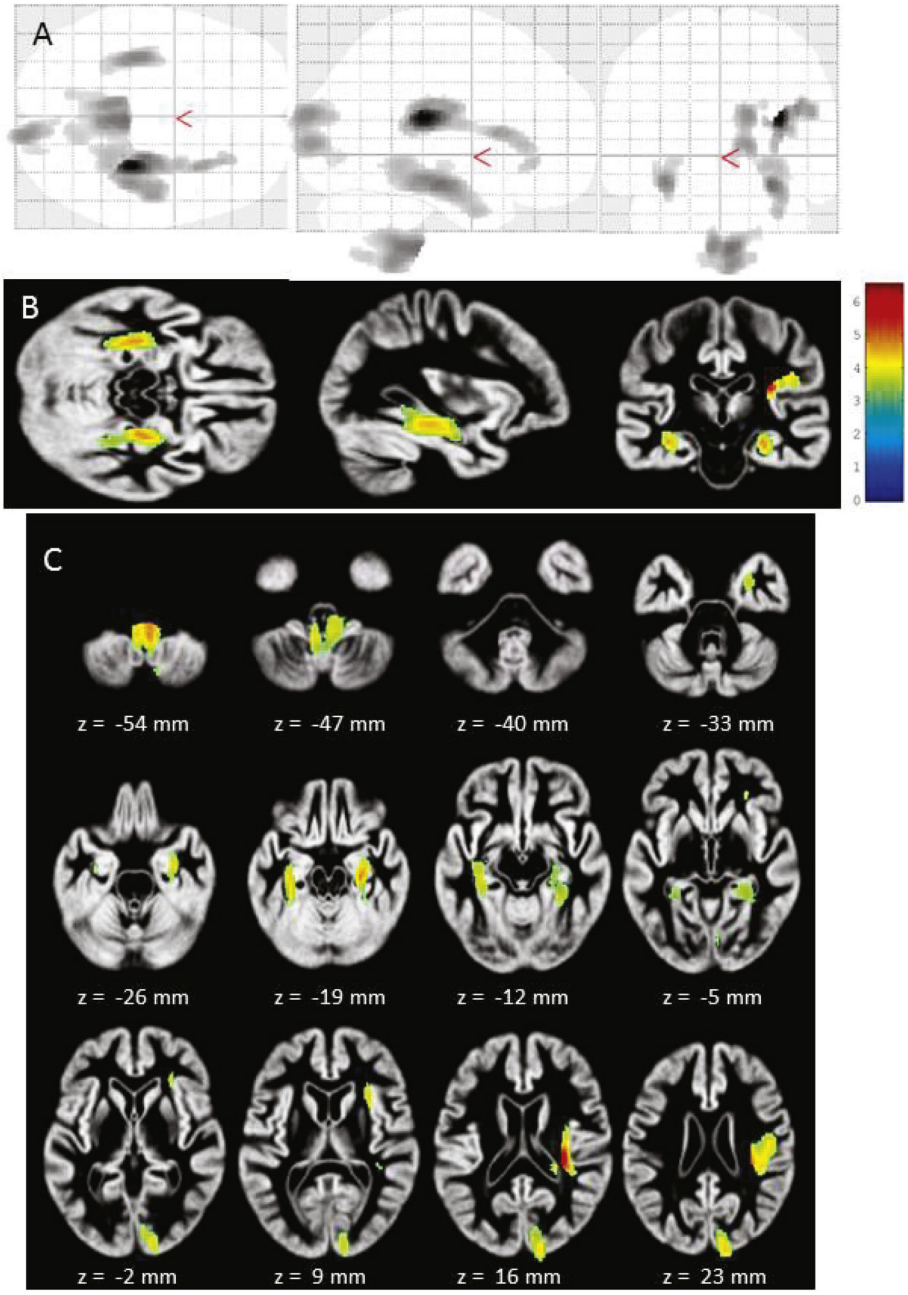

Fig. 4. Significant clusters of accelerated atrophy (cluster threshold at FWE p-corrected < 0.05) in PDD compared to PDND. The glass brain depiction is shown in (a). The clusters are overlaid on the mean GM volume in (b), with orthogonal views obtained at x = −31, y = −22, and z = −17 mm. The clusters are also depicted on a series of axial slices in (c).

The use of cluster level inference limits the ability to be precise about the affected regions in the brain [32]. In our case, for example, we were able to specify a particular region in the right insula where GM atrophy is accelerated in PDD compared to PDND using peak level inference. When we used cluster level inference, a larger cluster in the right insula as well as clusters in the hippocampi and brain stem are revealed; however we cannot specify where within these structures these changes are occurring. We identified a cluster [41] in the brainstem that showed atrophy consistent with a previous study, potentially consistent with pathological progression as hypothesized by Braak et al. [1].

Our study examined subjects who are at high risk for dementia, by virtue of age and examined incident significant cognitive decline and dementia. This suggests that MRI imaging can be used to track the onset of meaningful decline. There is some evidence that atrophy may be reversible with interventions such as mindfulness therapy [42], suggesting that MRI may be useful as a biomarker in intervention studies. The correspondence of the areas of change with pathologic data gives support to the notion that the findings are biologically meaningful. Clearly future studies should follow patients to autopsy to see if there is a correspondence between imaging findings and autopsy findings. Our data add further support to the notion that MRI detects meaningful changes, which can complement other biomarkers in predicting and tracking cognitive decline in Lewy body diseases.

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