Brain Topography (2019) 32:142–160
https://doi.org/10.1007/s10548-018-0675-2

ORIGINAL PAPER

Patterns of Grey Matter Atrophy at Different Stages of Parkinson's and Alzheimer's Diseases and Relation to Cognition

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Received: 26 April 2018 / Accepted: 4 September 2018 / Published online: 11 September 2018
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Abstract

Using MRI, a characteristic pattern of grey matter (GM) atrophy has been described in the early stages of Alzheimer's disease (AD); GM patterns at different stages of Parkinson's disease (PD) have been inconclusive. Few studies have directly compared structural changes in groups with mild cognitive impairment (MCI) caused by different pathologies (AD, PD). We used several analytical methods to determine GM changes at different stages of both PD and AD. We also evaluated associations between GM changes and cognitive measurements. Altogether 144 subjects were evaluated: PD with normal cognition (PD-NC; n = 23), PD with MCI (PD-MCI; n = 24), amnestic MCI (aMCI; n = 27), AD (n = 12), and age-matched healthy controls (HC; n = 58). All subjects underwent structural MRI and cognitive examination. GM volumes were analysed using two different techniques: voxel-based morphometry (VBM) and source-based morphometry (SBM), which is a multivariate method. In addition, cortical thickness (CT) was evaluated to assess between-group differences in GM. The cognitive domain z-scores were correlated with GM changes in individual patient groups. GM atrophy in the anterior and posterior cingulate, as measured by VBM, in the temporo-fronto-parietal component, as measured by SBM, and in the posterior cortical regions as well as in the anterior cingulate and frontal region, as measured by CT, differentiated aMCI from HC. Major hippocampal and temporal lobe atrophy (VBM, SBM) and to some extent occipital atrophy (SBM) differentiated AD from aMCI and from HC. Correlations with cognitive deficits were present only in the AD group. PD-MCI showed greater GM atrophy than PD-NC in the orbitofrontal regions (VBM), which was related to memory z-scores, and in the left superior parietal lobule (CT); more widespread limbic and fronto-parieto-occipital neocortical atrophy (all methods) differentiated this group from HC. Only CT revealed subtle GM atrophy in the anterior cingulate, precuneus, and temporal neocortex in PD-NC as compared to HC. None of the methods differentiated PD-MCI from aMCI. Both MCI groups showed distinct limbic and fronto-temporo-parietal neocortical atrophy compared to HC with no specific between-group differences. AD subjects displayed a typical pattern of major temporal lobe atrophy which was associated with deficits in all cognitive domains. VBM and CT were more sensitive than SBM in identifying frontal and posterior cortical atrophy in PD-MCI as compared to PD-NC. Our data support the notion that the results of studies using different analytical methods cannot be compared directly. Only CT measures revealed some subtle differences between HC and PD-NC.

Keywords Parkinson's disease · Alzheimer's disease · Mild cognitive impairment · Voxel-based morphometry · Source-based morphometry · Cortical thickness

Handling Editor: Christoph M. Michel.

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Introduction

There is significant grey matter (GM) atrophy in both Alzheimer's disease (AD) and Parkinson's disease (PD), leading to gradual and irreversible cognitive decline. This GM loss is well described in both AD and amnestic mild cognitive impairment due to AD (aMCI) (Dickerson et al. 2009a, b; Ferreira et al. 2011; Chételat et al. 2005; Jack et al. 2013), in which temporal lobe atrophy, including a loss of GM in

both hippocampi, together with atrophy in the occipital and parietal lobes creates a typical pattern. Results are inconsistent in all stages of PD (Duncan et al. 2013). Some studies have shown clear atrophy already in the early stage of PD (e.g. Brück et al. 2004; Beyer et al. 2007; Madhyastha et al. 2015; Lee et al. 2013; Rektorova et al. 2014); others reported little or no change compared to HC (e.g. Dalaker et al. 2009; Weintraub et al. 2011; Agosta et al. 2013; Rektor et al. 2018). The same applies for PD-MCI: some authors did not demonstrate any changes in GM (Dalaker et al. 2010), while others report GM atrophy in various areas of the brain (e.g. Melzer et al. 2012; Weintraub et al. 2011; Gasca-Salas et al. 2017; Ye et al. 2017; Xu et al. 2016). Distinct atrophy patterns have been observed in demented PD patients by many authors, involving mainly hippocampal structures and the temporal, occipital, and frontal lobes as well as the basal ganglia and other subcortical structures (Weintraub et al. 2011; Rektorova et al. 2014; Apostolova et al. 2010; Ibarretxe-Bilbao et al. 2011; Pan et al. 2013; Burton et al. 2004). Some of these studies correlated the atrophy levels with cognitive outcomes; however, the inconsistency is even greater in these data (e.g. Almeida et al. 2003; Tinaz et al. 2011). A recently published study by Duncan et al. (2013) addressed this incongruence by evaluating different studies and suggesting issues that future studies should address, stating mainly that unified criteria for PD-MCI diagnosis should be applied. Study results are also difficult to compare due to the use of various methods such as voxel-based morphometry, source-based morphometry, cortical thickness, or graph theory-based analyses.

The aim of this paper was to use two different morphometric approaches in order to assess grey matter volumes (GMV) in the same groups of patients and healthy controls to describe GM changes at different stages of AD and PD and correlate these data with the results of cognitive domain z-scores. Like most authors, we used voxel-based morphometry (VBM); based on the results of our previous studies (Rektorova et al. 2014; Anderkova et al. 2015), we also included source-based morphometry (SBM), i.e. a multivariate technique for data analysis. This method finds independent components of changes in GMV common to a group of subjects and compares it to another group, thus displaying functionally connected areas in the brain where GMV changes occur. The method makes it possible to identify smaller changes that co-occur within larger brain networks (Xu et al. 2009).

Cortical thickness (CT) was also evaluated in order to assess between-group differences in GM when comparing early neurodegeneration cases (aMCI, PD-NC, and PD-MCI) with HC. We included this method as most researchers currently use it to measure distinct patterns of cortical atrophy in PD and AD, claiming that this method is more sensitive in depicting early GM changes, particularly where there are smaller changes occurring over a larger cortical area (Lehericy et al. 2017; Duncan et al. 2013). The presumably high sensitivity can be achieved partly through reduced registration errors across different brains; however, there is a potential for error in the segmentation process (Hutton et al. 2009).

In the current study, we specifically aimed to compare two groups with MCI as a result of different brain pathologies, i.e. PD-MCI and aMCI groups. Some authors have reported that memory-related patterns of cortical atrophy characteristic of AD may be also associated with dementia in PD (Weintraub et al. 2012; Rektorova et al. 2014; Tam et al. 2005). However, to our knowledge no study has yet directly compared the patterns of cortical atrophy between predementia stages of the two neurodegenerative brain diseases.

Methods

A total of 147 participants were recruited. Of these 147 participants, three were excluded because of motion artefacts on MRI images (2 PD, 1 PD-MCI). From the 144 remaining subjects, 27 had amnestic MCI (aMCI) (Petersen et al. 2001), 12 had probable AD with documented progression of cognitive deficits (McKhann et al. 2011), 23 were clinically established PD patients (Postuma et al. 2015) with normal cognition (PD-NC), 24 were diagnosed with mild cognitive impairment in PD (PD-MCI) (Litvan et al. 2012), and 58 were age-matched healthy controls (HC). All subjects underwent MR imaging in 3 T Siemens Prisma machine (at CEITEC, Masaryk University) and were cognitively tested by experienced neuropsychologists using a cognitive test battery (Anderkova et al. 2017, see in more detail below). PD-NC and PD-MCI subjects were examined and scanned in the ON medication state without dyskinesias. Patients with major tremor and with dyskinesias were not enrolled. Subjects with any diagnosed psychiatric disorder and subjects with alcohol/drug abuse were excluded. All patients were longitudinally followed at the First Department of Neurology, Masaryk University and St. Anne's Hospital, Brno, Czech Republic. Each participant signed an informed consent form and the study was approved by the local ethics committee.

Neuropsychological Assessment

We used the cognitive test battery described in our previous publications (Anderkova et al. 2017; Nemcova-Elfmarkova et al. 2017). The complex neuropsychological testing evaluated global cognitive functions (MMSE) and five domains: memory (Rey-Osterrieth Complex Figure Test: Immediate Recall, Delayed Recall, Recognition Task; Wechsler Memory Scale III: Word List I, Word List II, Recognition Task);

attention (Stroop Color and Word Test (SCWT): Word and Color parts and Trail Making Test part A); executive functions (SCWT: Color-Word part, Trail Making Test part A, Verbal Fluency Test: semantic; lexical, and Clock test); visuospatial functions (Rey-Osterrieth Complex Figure Test: Copy, Visual Object, and Space Perception Battery—Silhouettes); language (Mississippi Aphasia Screening Test—Receptive, Expressive, and Total index), activities of daily living (Functional Activities Questionnaire); and depression (Geriatric Depression Scale). Five cognitive domains (memory, attention, executive function, visuospatial function, and language) were inspected for cognitive decline. All of the subjects who scored below − 1.5 SD in two tests in one domain compared to normative data were categorized as MCI subjects. We applied the MCI criteria of Petersen et al. (2001) and Litvan et al. (2012), according to which all subjects who have concern regarding a change in cognition, impairment in one or more cognitive domains, preservation of independence in functional abilities, and are not demented have MCI. The cognitive domain z-scores were computed as the average z-scores of the tests included in the particular domain (Anderkova et al. 2017).

MRI Data Acquisition

All subjects were scanned using MPRAGE sequence with 240 sagittal slices, TR = 2300 ms, TE = 2.36 ms, FOV = 256 mm, FA = 8°, matrix size 256 × 256, slice thickness = 1 mm, in 3 T Siemens Prisma MR scanner.

Pre-processing

SPM12 software was used to pre-process all anatomical T1 and T2 weighted images. Spatial normalization was performed to create a study-specific template so that all images could be registered in the same stereotactic space. MRI images were segmented into grey and white matter segments and spatially registered to the MNI coordinate system using the DARTEL toolbox. Images were smoothed with a spatial filter with a Gaussian kernel (FWHM = 8 mm). The resolution of the resulting GMV images was 1.5 × 1.5 × 1.5 mm.

Voxel Based Morphometry (VBM)

This morphometric method compares GMV in specific voxels of two different groups. Specific contrasts were applied using a paired T-test in SPM12—HC versus each patient group and certain patient groups among themselves. The effects of age, gender, education, and depression (using Geriatric Depression Scale) was filtered out each time. Group differences were considered significant if $p < 0.05$ after family-wise error (FWE) correction was performed. Cluster threshold was set at $t > 2.5$. Loadings from significant contrasts were extracted for further statistical correlation.

Source-Based Morphometry (SBM)

This morphometric method uses spatial Independent Component Analysis (ICA) to find naturally grouping, spatially independent sources of local GMV variability with common co-variation among subjects—components. The GM images from all subjects were concatenated and reshaped to a 2D matrix with the number of voxels and the number of subjects as matrix dimensions. Principal Components Analysis (PCA) was performed to reduce the data dimensionality together with the Minimum Description Length algorithm in order to estimate the optimal number of components (Li et al. 2007). Spatial ICA was performed on the reduced data using the Infomax algorithm. The result was a number of components that each comprised two features—subjects' loadings and a spatial map. The subjects' loadings, after filtering out the effects of age, gender, education, and depression (using Geriatric Depression Scale), were subjected to inter-group comparisons using the Mann–Whitney U test to identify significant differences between pairs of groups. There were three SBM analyses: HC versus aMCI versus AD, HC versus PD-NC versus PD-MCI, and HC versus aMCI versus PD-MCI. False Discovery Rate (FDR) was used to address the issue of multiple testing, and the significance level was set to $p = 0.05$. Significant component images were spatially normalized to MNI space with a threshold set to $Z > 2.5$. The clusters with 500 and more adjacent voxels were superimposed on the study-specific GM images to visualize regions with strong inter-group differences.

Surface-Based Morphometry—Cortical Thickness (CT) Analysis

Images were analysed using FreeSurfer 6.0 (http://surfer.nmr.mgh.harvard.edu). Data was first processed with the *recon-all* pipeline, resulting in segmented images and cortical thickness maps. Upon completion, grey and white matter boundaries were visually inspected for each subject. Altogether nine subjects were excluded for surface-based analysis due to abberations that were not possible to correct manually (3 HC, 2 AD-MCI, 2 AD, 1 PD-MCI, 1 PD). Small imprecisions in temporal pole segmentation were handled by excluding the temporal lobe label (Desikan-Killiany atlas—Desikan et al. 2006) from all further analyses. CT maps were then resampled onto the *fsaverage* subject and smoothed with a FWHM of 10 mm. To identify differences between relevant groups, data were entered into the Freesurfer GLM model, and age, gender, education, and GDS scores were used as covariates of no interest. Based

on previously published studies (Uribe et al. 2016; Hanganu et al. 2014; Biundo et al. 2013; Liu et al. 2010), we hypothesized that we would find more cortical thinning in the patient groups with early degeneration (aMCI, PD-NC, PD-MCI) than in HC. In line with the literature, we accepted significance at the uncorrected p-value of 0.001 (Ashburner et al. 2003; Lyoo et al. 2006; Tae et al. 2008) with additional cluster extension thresholds of 40 mm^2 to describe distinct cortical atrophy in our cohorts of interest. However, we had no a priori hypothesis when comparing both MCI groups since no such studies exist except our own VBM studies (Anderkova et al. 2017; Nemcova-Elfmarkova et al. 2017). Therefore, we used a more conservative approach to exclude false positive results. To correct for multiple comparisons, we used a precached clusterwise Monte Carlo simulation with 10,000 iterations, with the absolute vertex-wise cluster-forming threshold of $p = 0.001$ and cluster-wise threshold of $p = 0.05$.

Table 1 Demographic and clinical data of HC and patient groups

	HC; n = 58	aMCI; n = 27	AD; n = 12	PD-NC; n = 23	PD-MCI; n = 24
Age	67.5 ± 7.3	69.8 ± 6.9	72.9 ± 8.6	61 ± 8.4	65.1 ± 10.0
Education duration	15.4 ± 2.5	14.3 ± 3.0	14.6 ± 5.6	16.2 ± 3.3	14 ± 3.1
Sex. % of male	31	37	8	74	67
MMSE	28.5 ± 1.2	27.1 ± 1.3	20.9 ± 2.3	28.2 ± 1.2	27 ± 2.2
GDS	2.3 ± 2.5	3.7 ± 3.4	2.1 ± 1.8	2.8 ± 2.8	2.9 ± 2.3
LED	–	–	–	815.5 ± 21.5	909 ± 482.5
UPDRS III	–	–	–	17.6 ± 8.8	17.7 ± 8.8

MMSE mini mental state examination, *GDS* geriatric depression scale, *LED* levodopa equivalent dose, *UPDRS III* unified Parkinson's disease rating scale subsection III

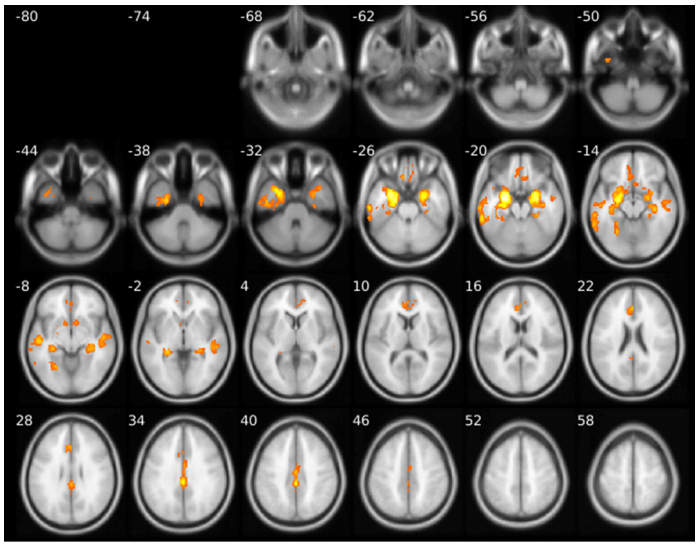
Table 2 Demographic and clinical data—differences between groups

	HC versus AD (p value)	HC versus aMCI (p value)	HC versus PD-NC (p value)	HC versus PD-MCI (p value)	aMCI versus PD-MCI (p value)	PD-NC versus PD-MCI (p value)
Age	0.15	0.57	0.02	0.87	0.23	0.43
Gender	0.53	0.98	< 0.01	0.01	0.15	0.98
Education duration	0.93	0.55	0.86	0.38	0.99	0.13
MMSE	< 0.01	< 0.01	0.96	< 0.01	0.99	0.04
GDS	0.99	0.18	0.95	0.91	0.82	0.99
LED	–	–	–	–	–	0.97
UPDRS III	–	–	–	–	–	0.54

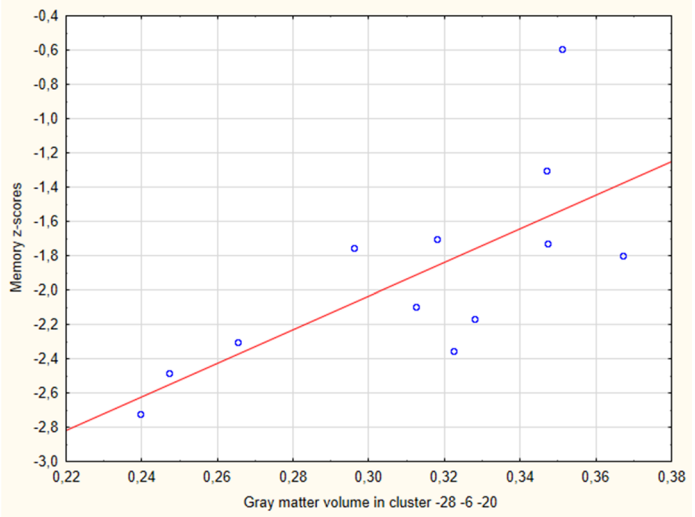
MMSE mini mental state examination, *GDS* geriatric depression scale, *LED* levodopa equivalent dose, *UPDRS III* unified Parkinson's disease rating scale subsection III

Table 3 Cognitive tests results

	Memory	Attention	Executive	Visuospatial	Language
HC	0.63 ± 0.5	−0.06 ± 0.7	0.59 ± 0.8	0.44 ± 0.6	0.44 ± 0.4
AD	−1.92 ± 0.6	−2.23 ± 1.1	1.52 ± 0.7	−0.92 ± 1.2	−1.01 ± 1.5
aMCI	−0.22 ± 0.8	−0.89 ± 0.9	−0.60 ± 0.7	0.10 ± 0.6	0.14 ± 0.6
PD-NC	0.24 ± 0.7	−0.27 ± 0.9	0.36 ± 0.7	0.44 ± 0.6	0.32 ± 0.6
PD-MCI	−0.67 ± 0.7	−1.21 ± 0.9	−0.56 ± 0.8	−0.14 ± 0.8	−0.04 ± 0.9
HC versus AD (p value)	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
HC versus aMCI (p value)	< 0.01	< 0.01	< 0.01	0.36	0.54
HC versus PD-NC (p value)	0.20	0.84	0.74	1.00	0.97
HC versus PD-MCI (p value)	< 0.01	< 0.01	< 0.01	0.02	0.12
AD versus aMCI (p value)	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
aMCI versus PD-MCI (p value)	0.20	0.57	0.99	0.78	0.93
PD-NC versus PD-MCI (p value)	< 0.01	< 0.01	< 0.01	0.08	0.59



(a)



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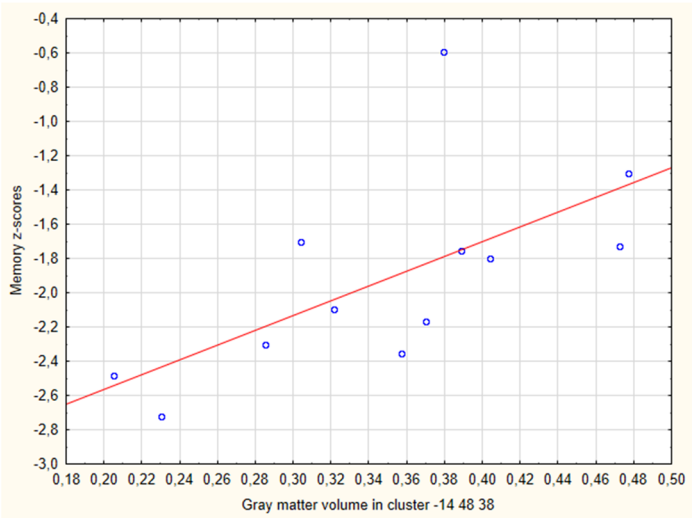


(c)

Fig. 1 **a** VBM analysis HC versus AD. **b** Correlation of cognitive z-scores in HC versus AD VBM analysis. **c** Correlation of cognitive z-scores in HC versus AD VBM

Statistics

Statistical analysis was performed in STATISTICA 12 (StatSoft, Inc.) software.

Correlation with Cognitive z-Scores

Spearman correlation was used to reveal any potential relationship between the GMV/CT regions of significant between-group differences and cognitive domain z-scores. The multiple testing problem was handled by FDR and the significance level was set to $p = 0.05$.

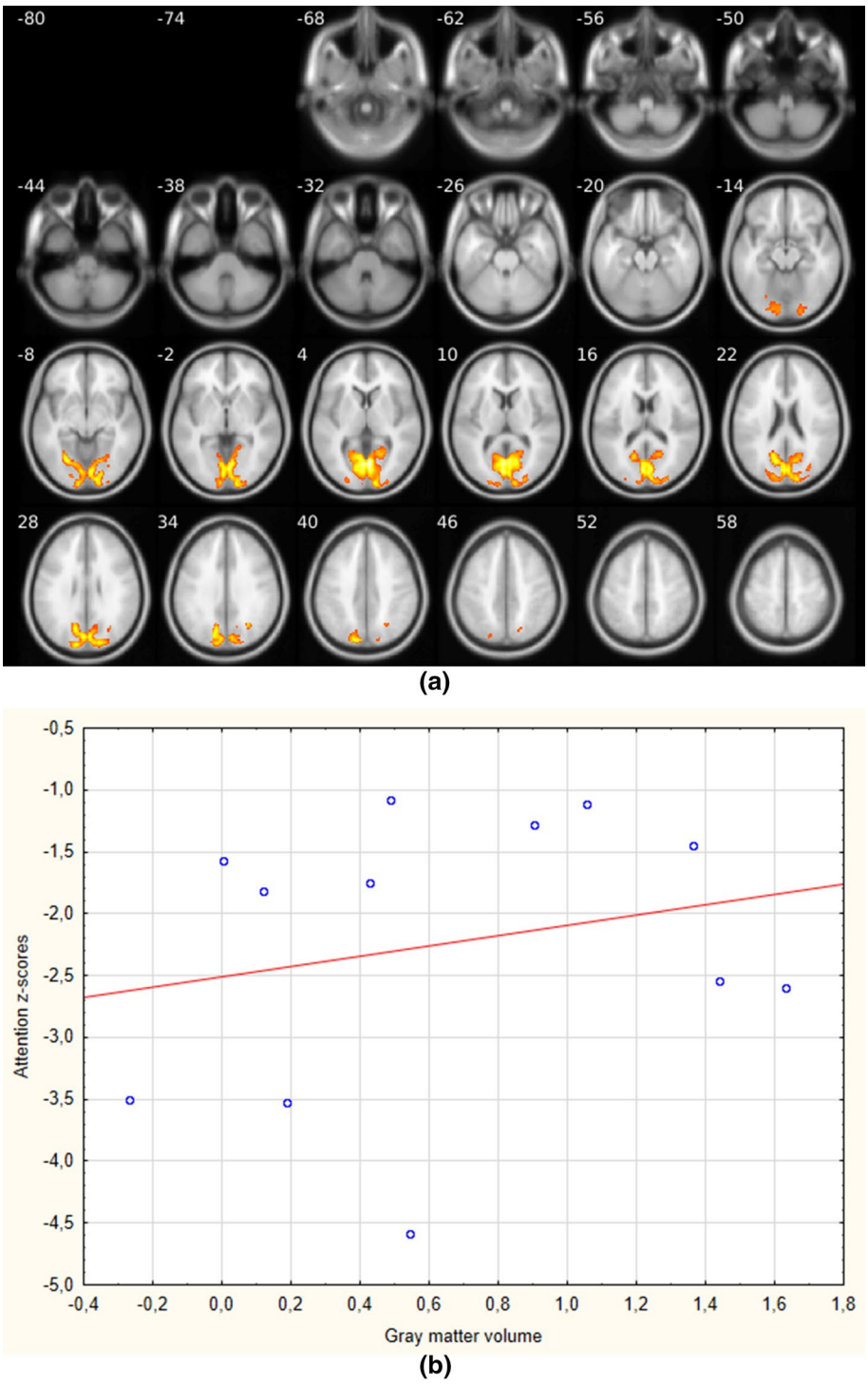


Fig. 2 **a** SBM analysis HC versus aMCI versus AD—component 2. **b** Correlation of cognitive z-scores in component 2

Results

For the demographic and clinical data of subjects, see Tables 1 and 2.

There was a significant difference in age between the groups of HC and PD-NC, due to the younger PD-NC patients enrolled. The two Parkinson disease groups (PD-NC and PD-MCI) had significantly different gender distribution compared to HC. Every cognitively impaired group (AD, aMCI, and PD-MCI) scored significantly lower in MMSE according to their diagnosis. PD-MCI also differed from PD-NC in MMSE.

For cognitive tests results, see Table 3.

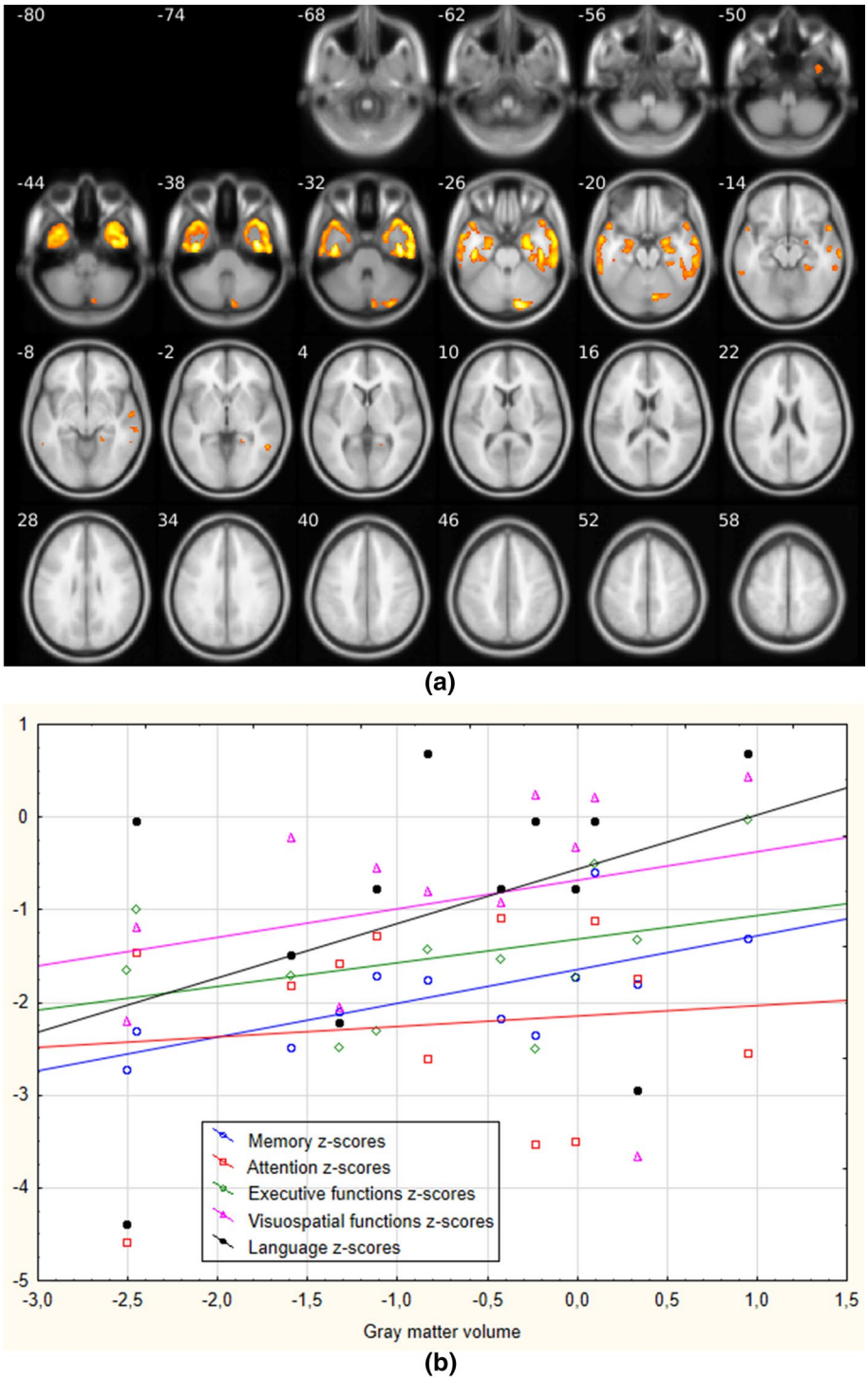


Fig. 3 **a** SBM analysis HC versus aMCI versus AD—component 8. **b** Correlation of cognitive z-scores in component 8

SBM Results

HC Versus aMCI Versus AD (Comparing Different Cognitive Stages of AD and HC)

Out of ten components, only three showed significant differences between groups not caused by artefacts as verified by visual inspection (C1, C2 and C8), see also Tables 4 and 5.

HC Versus PD-NC Versus PD-MCI (Comparing Different Cognitive Stages of PD-NC and HC)

Nine components were found in this analysis; however, none was significant.

HC Versus PD-MCI Versus aMCI: (Comparing Two Different MCI Groups and HC)

Ten components were found, of which one showed significant differences between groups (C9), see also Table 7.

Results According to Groups

HC Versus AD

The AD group presented a typical hippocampal and temporal lobe atrophy compared to HC using VBM (see Fig. 1a); GMV in these regions correlated with memory z-scores in the AD group (see Fig. 1b, c; $R_{1b} = 0.71$, $p_{1b} = 0.010$, $R_{1c} = 0.69$, $p_{1c} = 0.014$). The SBM component 2 (C2) exhibited a GMV loss in occipital regions (Fig. 2a) and differentiated AD from HC (M-W test; $p = 0.0013$). This component correlated with attention domain z-scores in the AD group (Fig. 2b, $R = -0.46$, $p = 0.003$). The SBM component 8 (C8) showed a hippocampal and temporal lobe atrophy (Fig. 3a), which correlated with all cognitive z-scores (Fig. 3b) (M-W test; $p = 0.0047$). Surface-based analysis was not performed in the AD group because of too small sample size (n = 10 after removing data from two subjects, see also above). For detailed results, see Table 4.

HC Versus aMCI

The aMCI patients showed more atrophy than HC in both the anterior and posterior cingulate (see Fig. 4) according to VBM. SBM revealed a temporo-fronto-parietal atrophy (see Fig. 5) in aMCI (M-W test; $p = 0.0083$) when compared to HC (Component C1). Various fronto-occipital areas were affected in aMCI compared to HC (see Fig. 6a, b) using surface-based analysis. For detailed results, see Table 5.

HC Versus PD-NC

Only surface-based analysis revealed differences between HC and PD-NC: PD-NC displayed cortical thinning in the frontal and temporal areas, and in the precuneus (see Fig. 7). For detailed results, see Table 6.

HC Versus PD-MCI

Using VBM, we observed GMV differences between PD-MCI and HC in the left precuneus and bilateral orbitofrontal cortex (see Fig. 8). The SBM component 9 (C9) displayed a temporo-fronto-parietal atrophy (see Fig. 9) in PD-MCI compared to HC (M-W test; $p = 0.0203$). Using CT measures, PD-MCI differed from HC by cortical thinning in the right superior frontal gyrus (Fig. 10). For detailed results, see Table 7.

AD Versus aMCI

Using VBM, the aMCI and AD patients differed in the GMV of the left hippocampus (lower in AD than in aMCI, see Fig. 11a), the GMV of this structure correlated with

Table 4 HC versus AD

Method	Cluster size	X_1	Y_1	Z_1	$Area_1$
VBM	464,216	−28	−6	−20	l. + r. Hippocampus
	2215	−14	48	38	l. Superior frontal gyrus
SBM	16,358 (C2)	4.5	−70.5	6	Cuneus, precuneus, calcarine fissure, lingual gyrus
	10,602 (C8)	39	−7.5	−37.5	ITG, MTG, STG, fusiform gyrus, hippocamus, uncus, parahipocampal gyrus
	7113 (C8)	−40.5	−13.5	−34.5	ITG, MTG, STG, fusiform gyrus, hippocamus, uncus, parahipocampal gyrus
	1338 (C8)	16.5	−87	25.5	Posterior cerebellar lobe
CT	Not performed				

C2 component 2, *C8* component 8, *STG* superior temporal gyrus, *MTG* medial temporal gyrus, *ITG* inferior temporal gyrus, X_1, Y_1, Z_1 MNI coordinates of cluster maximum intensity, $Area_1$ brain region according to automated anatomical labeling (Tzourio-Mazoyer et al. 2002)

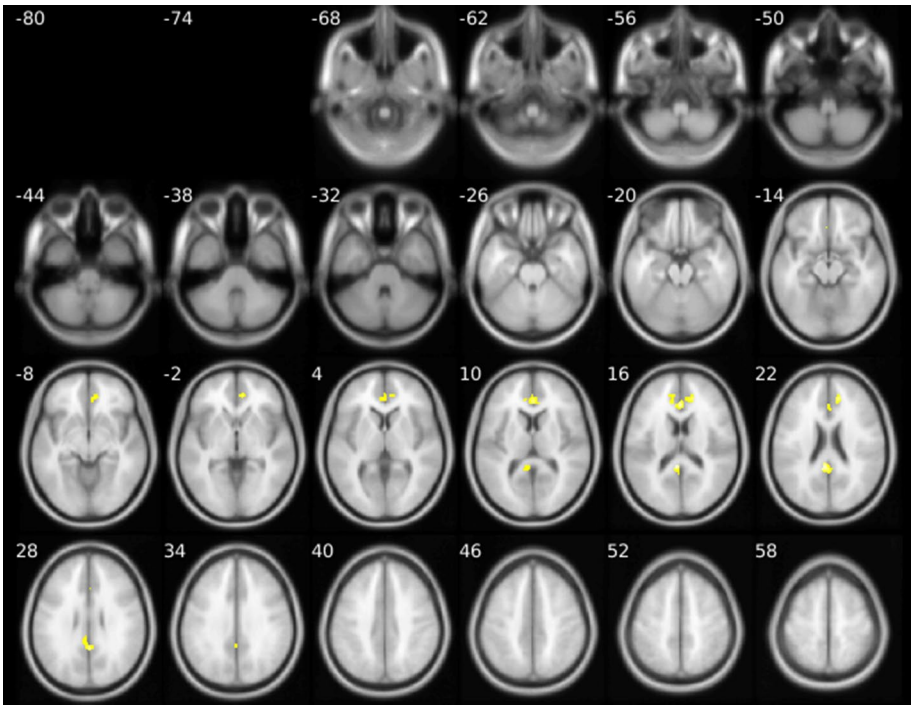


Fig. 4 VBM analysis HC versus aMCI

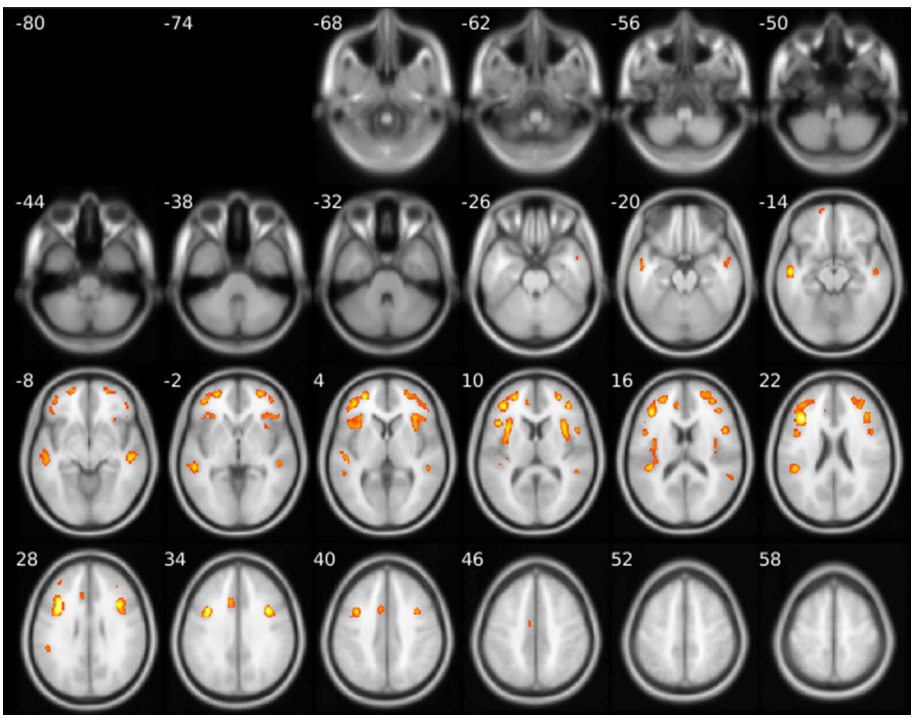


Fig. 5 SBM analysis HC versus aMCI versus AD—component 1

all cognitive domains except for visuospatial functions in the AD group (see Fig. 11b; for R and p values, see Table 8.) Surface-based analysis was not performed due to a small sample size of the AD group. For detailed results, see Table 9.

PD-NC Versus PD-MCI

Lower GMV was found in the left orbitofrontal cortex in PD-MCI than in PD-NC (see Fig. 12a) when VBM was employed. The GMV of this region correlated with memory z-scores in PD-MCI (Fig. 12b, $R = 0.42$, $p = 0.003$).

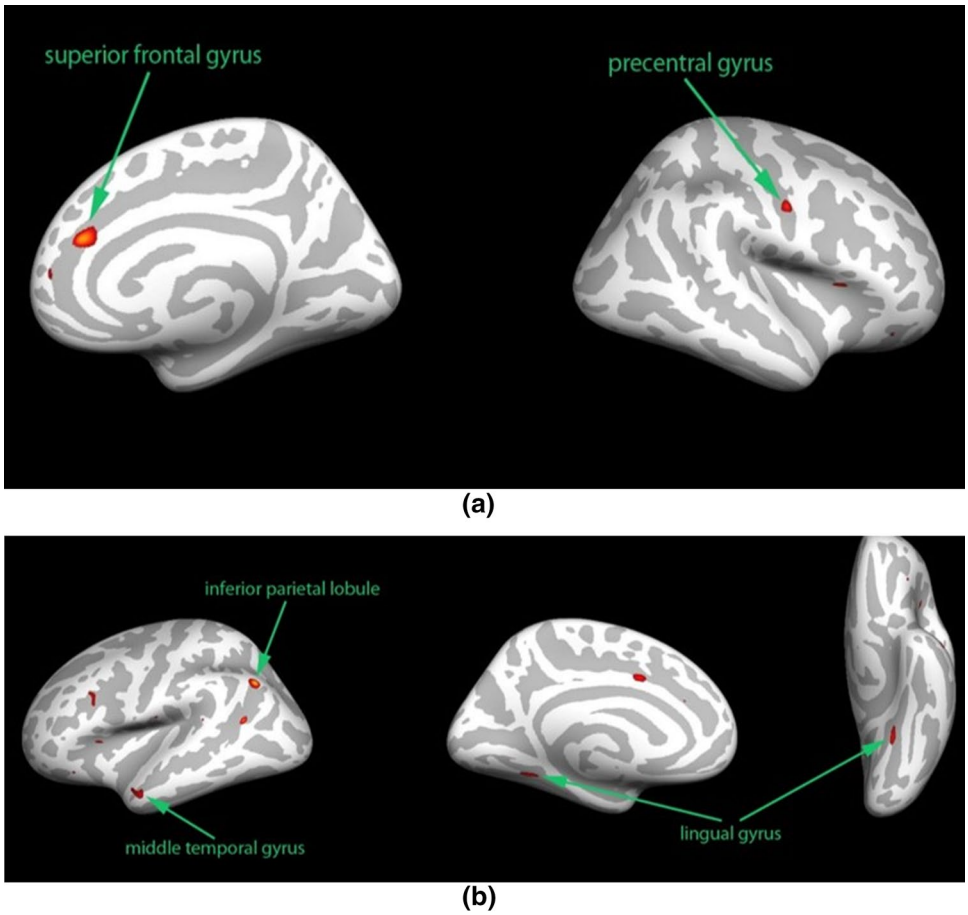


Fig. 6 **a** Cortical thickness analysis HC versus aMCI. **b** Cortical thickness analysis HC versus aMCI

Table 5 HC versus aMCI

Method	Cluster size	X_1	Y_1	Z_1	$Area_1$
VBM	1978	−4	−44	18	l. + r. Posterior cingulate
	4588	15	42	20	l. + r. Anterior cingulate
	2156	18	16	−12	r. Gyrus rectus
SBM	697 (C1)	51	−22.5	−7.5	STG, MTG
	893 (C1)	−52.5	−15	−12	MTG
	6025 (C1)	−37.5	21	25.5	SFG, MFG, IFG, Inferior parietal lobule, insula
	4163 (C1)	36	7.5	36	MFG, SFG, insula
	563 (C1)	−9	21	33	Anterior cingulate
	Size (mm^2)	X_2	Y_2	Z_2	$Area_2$
CT	126.84	−51.3	−1.7	−22.7	l. Middle temporal gyrus
	117.55	−40.4	−62.7	39.6	l. Inferior parietal lobule
	49.72	−30.8	−51.6	−3.2	l. Lingual gyrus
	98.84	14.9	34.5	16.4	r. Superior frontal gyrus (ACC)
	47.55	45.5	−5.8	26.4	r. Precentral gyrus

C1 component 1, *STG* superior temporal gyrus, *MTG* medial temporal gyrus, *SFG* superior frontal gyrus, *MFG* medial frontal gyrus, *IFG* inferior frontal gyrus, X_1, Y_1, Z_1 MNI coordinates of cluster maximum intensity, $Area_1$ brain region according to automated anatomical labeling (Tzourio-Mazoyer et al. 2002), X_2, Y_2, Z_2 Talairach coordinates of vertex with maximum p value, $Area_2$ brain region designated according to Desikan–Killiany atlas (Desikan et al. 2006), *r./l.* right/left, *ACC* anterior cingulate cortex

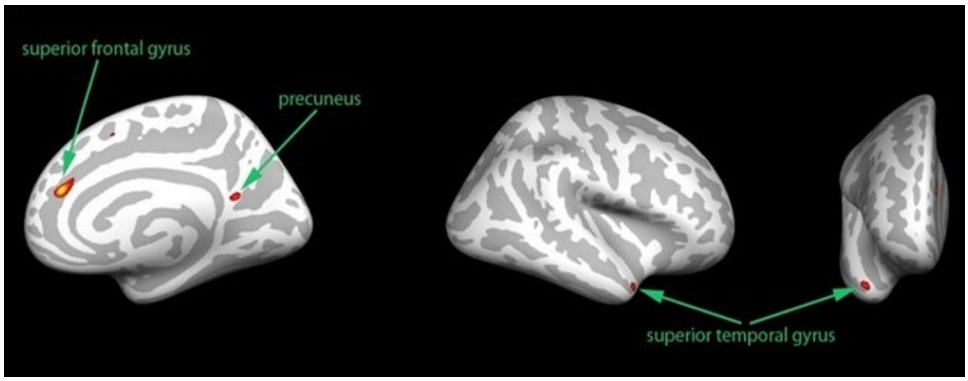


Fig. 7 Cortical thickness analysis HC versus PD-NC

Table 6 HC versus PD-NC

Method					
VBM	No significant difference				
SBM	No significant difference				
	Size (mm^2)	X_2	Y_2	Z_2	$Area_2$
CT	84.54	15.1	36.2	15.2	r. Superior frontal gyrus (ACC)
	66.35	45.6	13.9	− 23.1	r. Superior temporal gyrus
	41.57	7.2	− 55.4	16.5	Precuneus

X_2, Y_2, Z_2 Talairach coordinates of vertex with maximum p value, $Area_2$ brain region designated according to Desikan–Killiany atlas (Desikan et al. 2006), *r./l.* right/left, *ACC* anterior cingulate cortex

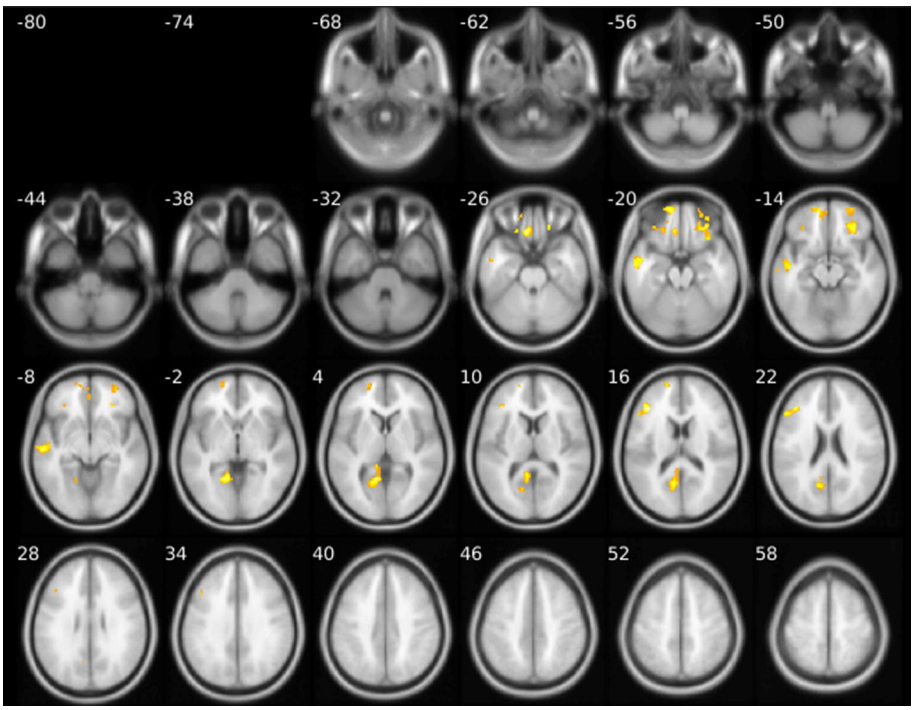


Fig. 8 VBM analysis HC versus PD-MCI

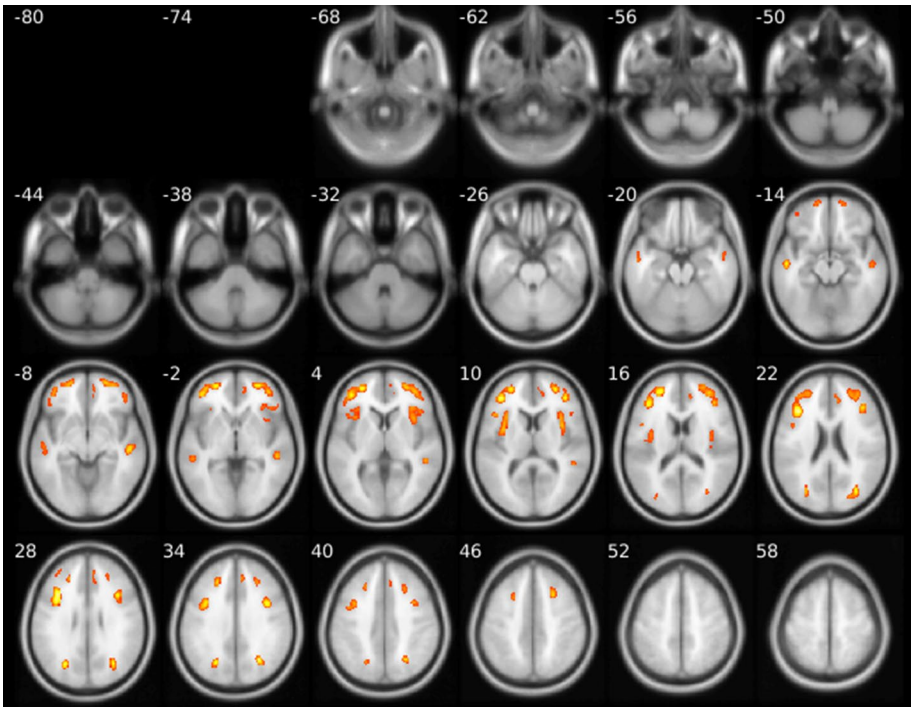


Fig. 9 SBM analysis HC versus PD-MCI versus aMCI—component 9

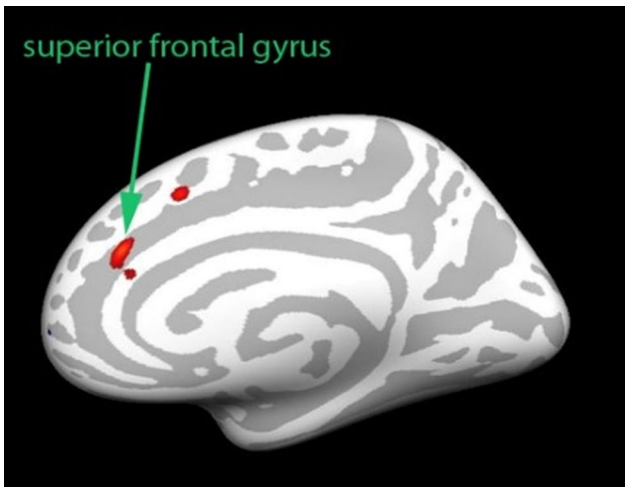


Fig. 10 Cortical thickness analysis HC versus PD-MCI

Moreover, PD-MCI showed a parietal cortical thinning when compared to PD-NC (see Fig. 13). For detailed results, see Table 10.

aMCI Versus PD-MCI

No method was able to detect any differences between aMCI a PD-MCI groups.

Discussion and Conclusion

Our study is the first one comparing multiple techniques of GM atrophy assessment in different stages of AD and PD. We looked at specific between-group differences in GM volumes using both VBM and SBM. We were particularly interested in comparing two groups with MCI caused by different brain pathologies (i.e. AD and PD pathologies). CT measures were additionally employed since some authors have asserted that CT is the most sensitive technique for describing subtle GM alterations in the early stages of neurodegenerative brain diseases (Lehericy et al. 2017; Duncan et al. 2013). Thus altogether three different approaches were used and their complementarity was assessed. VBM was used as the gold standard method for assessing localized GM changes between group pairs in a voxel-wise manner. SBM is a multivariate method which uses independent component analysis in order to target more widespread patterns of cortical atrophy, i.e. structural components of cortical regions with related GMV changes (Rektorova et al. 2014). The method makes it possible to evaluate GM alterations among multiple groups of subjects. As mentioned in "Introduction", "Methods", and "Results" sections above, cortical thickness analysis was additionally performed in all groups except for AD patients.

Using both VBM and SBM, we were able to distinguish between AD and HC. GMV loss was recorded in the temporal lobes and both hippocampi (C3), regions typically

Table 7 HC versus PD-MCI

Method	Cluster size	X_1	Y_1	Z_1	$Area_1$
VBM	1102	33	39	− 16	r. Orbitofrontal cortex
	1437	− 8	30	− 26	l. Orbitofrontal cortex
	1486	− 10	− 56	3	l. Precuneus
SBM	736 (C9)	51	− 24	− 6	STG, MTG
	527 (C9)	− 52.5	− 13.5	− 13.5	MTG
	3749 (C9)	37.5	6	36	SFG, MFG, IFG
	4628 (C9)	− 37.5	21	25.5	SFG, MFG, IFG
	538 (C9)	10.5	36	24	MFG
	1112 (C9)	34.5	16.5	7.5	Insula, IFG
	866 (C9)	− 36	0	12	Insula, IFG
	505 (C9)	− 27	− 67.5	30	Superior parietal lobule, precuneus
	772 (C9)	33	− 73.5	21	Superior parietal lobule, precuneus
	Size (mm^2)	X_2	Y_2	Z_2	$Area_2$
CT	63.83	14.7	33.3	21.1	r. Superior frontal gyrus (ACC)

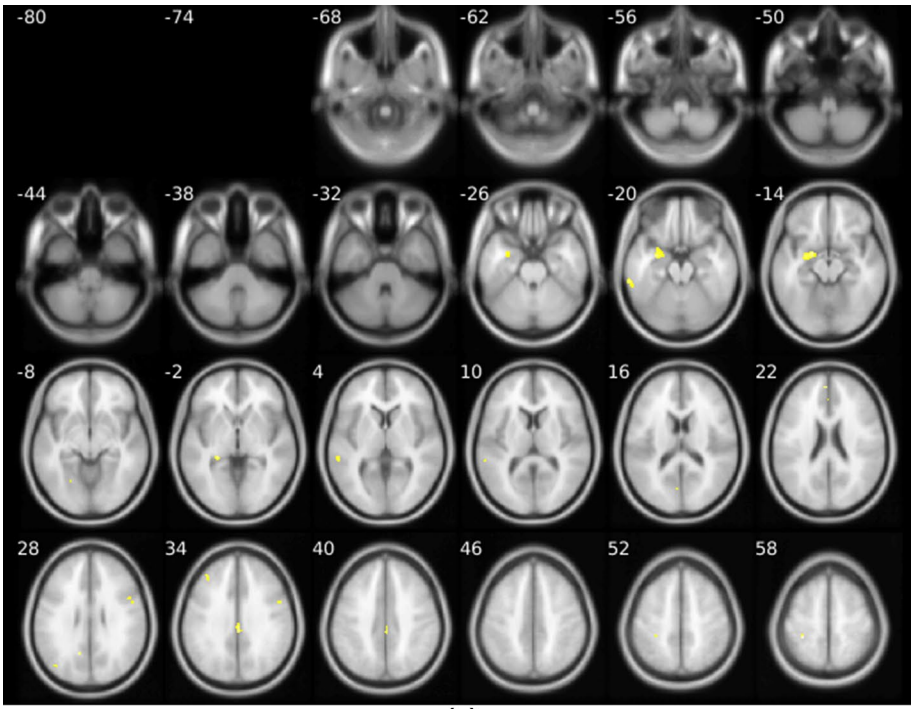
C9 component 9, *STG* superior temporal gyrus, *MTG* medial temporal gyrus, *SFG* superior frontal gyrus, *MFG* medial frontal gyrus, *IFG* inferior frontal gyrus, X_1, Y_1, Z_1 MNI coordinates of cluster maximum intensity, $Area_1$ brain region according to automated anatomical labeling (Tzourio-Mazoyer et al. 2002), X_2, Y_2, Z_2 Talairach coordinates of vertex with maximum p value, $Area_2$ brain region designated according to Desikan–Killiany atlas (Desikan et al. 2006), *r./l.* right/left, *ACC* anterior cingulate cortex

associated with Alzheimer pathology (Jack et al. 2013). This GM atrophy correlated with cognitive outcomes in each cognitive domain. Greater atrophy in the occipital lobes was seen in the AD group than in HC (C2). The latter pattern of GM loss is also in congruence with published research (Thompson et al. 2003) and was associated with lower scoring in attention domain. These regions are crucial for processing visual information; intact visual processing is required for spatial orientation, which is known to be particularly impaired in AD (Quental et al. 2013; Binetti et al. 1996).

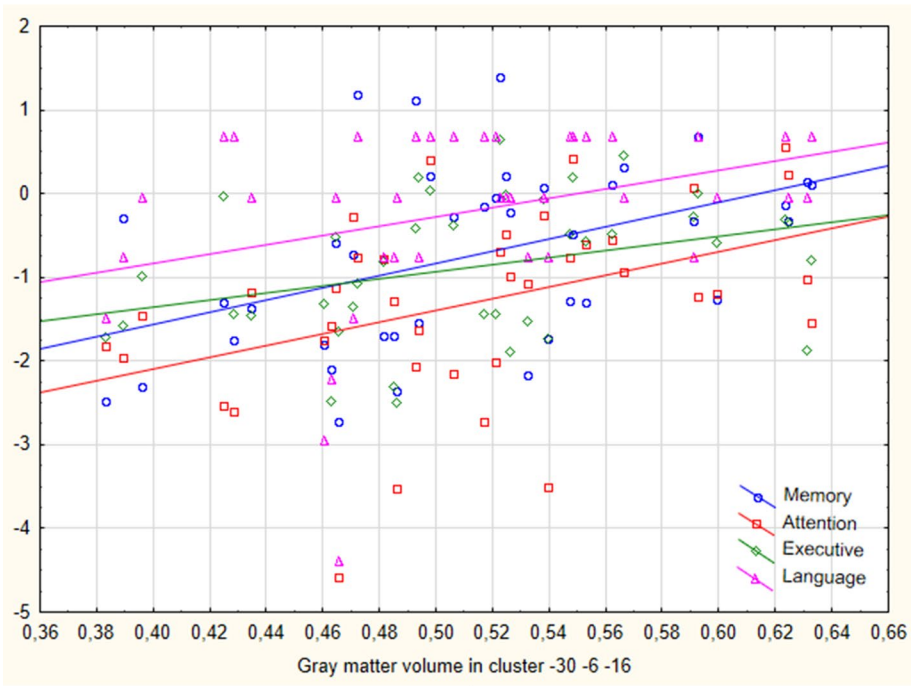
Both VBM and SBM methods were able to detect GMV atrophy in our aMCI patients as compared to HC. VBM detected GMV loss in the limbic region within the anterior and posterior cingulate cortex. Using SBM, we observed temporo-fronto-parietal atrophy (C1) that differentiated aMCI from HC, while CT revealed additional changes in temporo-parieto-occipital regions in the aMCI group. These results are in accordance with previous findings that showed similar patterns of atrophy in the medial temporal, lateral temporoparietal, and midline parietal regions, with variable findings in frontal regions using CT (e.g. Petersen et al. 2001; Du et al. 2007) as well as using VBM and similar techniques (e.g. Apostolova et al. 2007; Whitwell et al. 2008).

Only cortical thickness measures were useful in identifying differences between HC and PD-NC. This was probably because the cortical thickness measure is more sensitive to cortex changes, possibly because it is less dependent on cortical folding and the overall brain size than VBM and SBM (Hutton et al. 2009). We found GM changes in the anterior cingulate cortex/superior frontal gyrus, right anterior temporal gyrus ,and precuneus. Previous CT studies are in line with our current data with described changes in the parietal cortices (Madhyastha et al. 2015), and in the anterior cingulate and the superior frontal gyrus (Ye et al. 2017). Moreover, longitudinal studies show that PD patients who later develop dementia have reduced cortical thickness in the right precentral and superior frontal gyri as well as in the ACC (Compta et al. 2013). Atrophy of the temporal and posterior cortical areas also seem to be predictive of cognitive decline in PD (Mak et al. 2015; Weintraub et al. 2011; Camicioli et al. 2003; Song et al. 2011; Lee et al. 2013; for review, see; Rodriguez-Oroz et al. 2015).

VBM and SBM both found a greater GMV loss in PD-MCI than in HC. VBM showed a more localized atrophy in the precuneus and orbitofrontal cortex, i.e. regions involved in visual processing and attention, memory, visuospatial functions, and other cognitive functions (Cavanna and Trimble 2006; Sack 2009). Additional atrophy was observed in the orbitofrontal cortex in PD-MCI patients as compared to HC. These GMV changes were related to declines in memory domain z-scores (Preston and Eichenbaum 2013). Using SBM we recorded GMV loss in temporo-fronto-parietal regions (C9); and using CT, in the right superior frontal region. Many authors as well as recent reviews (Pereira et al. 2014; Hanganu et al. 2014; Mak et al. 2015; Nagano-Saito



(a)



(b)

Fig. 11 **a** VBM analysis AD versus aMCI. **b** Correlation of cognitive z-scores in AD versus aMCI VBM analysis

et al. 2005; Summerfield et al. 2005; Beyer et al. 2007; Song et al. 2011; Melzer et al. 2012 for review; see also; Duncan et al. 2013; Rodriguez-Oroz et al. 2015) point out that PD-MCI patients exhibit rather heterogeneous areas of GM atrophy. similar to those in PD-dementia but to a lesser extent. The GM atrophy is particularly found in orbitofrontal and other prefrontal regions, the superior temporal and parietal

Table 8 AD versus aMCI difference in GMV: correlations with cognitive domain z-scores

Domain	R-value	p-value
Memory	0.49	< 0.01
Attention	0.48	< 0.01
Executive	0.36	0.03
Language	0.34	0.03

Table 9 AD versus aMCI

Method	Cluster size	X_1	Y_1	Z_1	$Area_1$
VBM	1382	− 30	− 6	− 16	l. Hippocampus
SBM	No significant difference				
CT	Not performed				

X_1, Y_1, Z_1 MNI coordinates of cluster maximum intensity, $Area_1$ brain region according to automated anatomical labeling (Tzourio-Mazoyer et al. 2002)

neocortex, occipital areas, medial temporal regions, and the precuneus. Prefrontal and temporo-parietal atrophy has been the most consistent finding (Burton et al. 2004; Compta et al. 2012; Xu et al. 2016; Gasca-Salas et al. 2017; Pereira et al. 2014; Hanganu et al. 2014; Mak et al. 2015).

Neither VBM nor SBM found differences in GMV between aMCI and PD-MCI. CT did not reveal any difference between these two entities either. This result of our study supports earlier published VBM and SBM MRI data

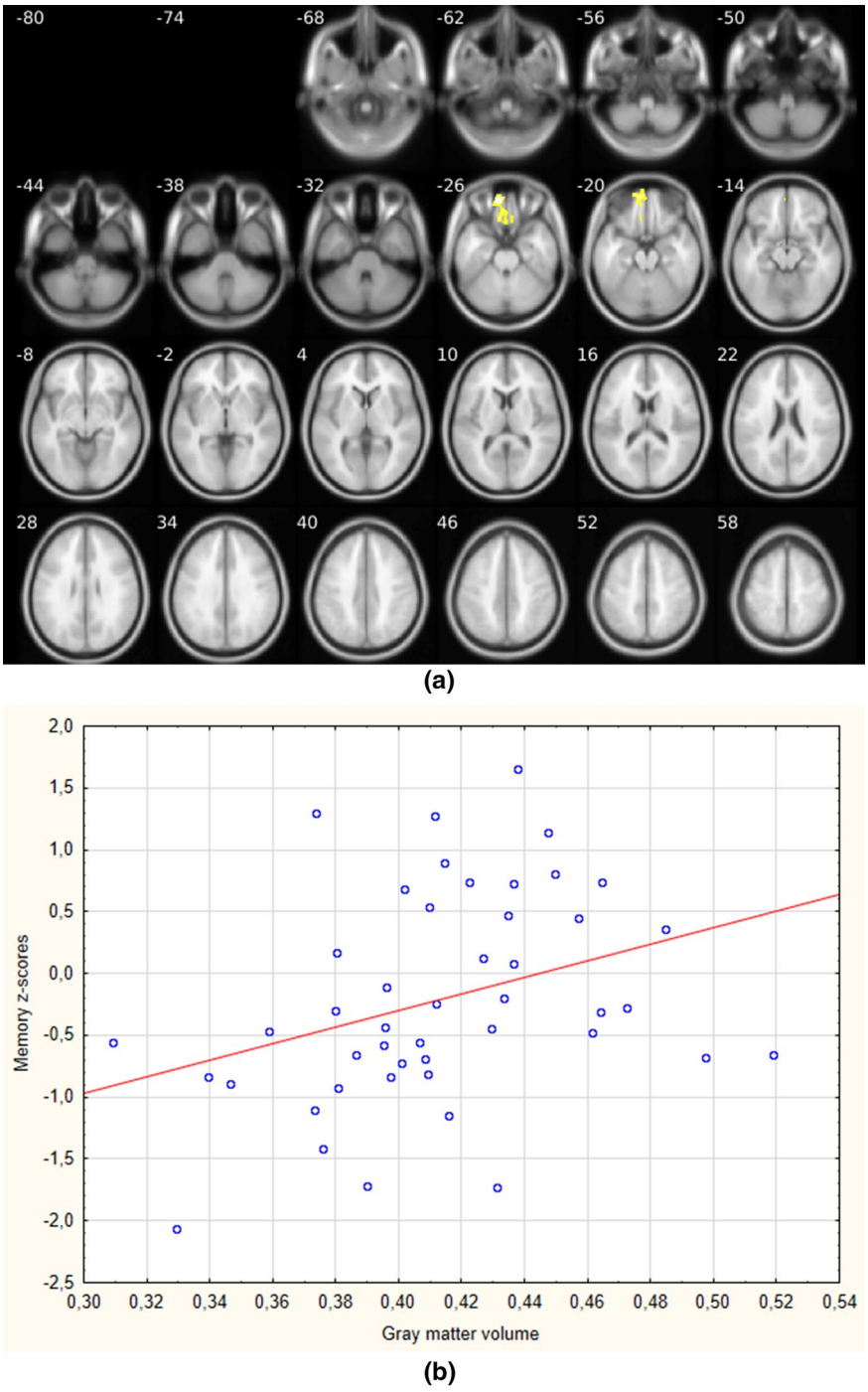


Fig. 12 **a** VBM analysis PD-NC versus PD-MCI. **b** Correlation of cognitive z-scores in PD-NC versus PD-MCI VBM analysis

(Weintraub et al. 2011; Rektorova et al. 2014) as well as functional MRI results (Anderkova et al. 2017; Nemcova-Elfmarkova et al. 2017); the result suggests that even though AD and PD are two different clinical entities (Besser et al. 2016), the distinct pathology underlying the neurodegenerative process responsible for cognitive decline development in both diseases might share a common structural pattern (Jellinger et al. 2002; Irwin et al. 2012, 2013; Compta et al. 2011, 2012; Pan et al. 2013). In this regard, a recent study showed that AD and PD cognition-related metabolic patterns as assessed by ^{18}F-fluorodeoxyglucose PET (Mattis et al. 2016) might be more sensitive than structural or functional MRI in differentiating the two patient groups.

We are aware of several limitations of our study, mainly uneven group samples and age differences between participants. We tried to minimize the impact of these discrepancies by using age, education duration, sex and GDS as covariates in second-level statistical analysis. We lacked CSF or amyloid PET biomarkers in our aMCI subjects and this may be quite a heterogenous group with respect to brain pathology and progression rates. Subjects with aMCI that lack amyloid pathology based on biomarker assessment are referred to as "SNAPs" (suspected non-Alzheimer pathology). In some, the cognitive impairment is caused by PART (primary age-related tauopathy) (Jack et al. 2016; Vos et al. 2013; Jack 2014). This entity does not progress to dementia as fast as aMCI due to typical AD pathology, but individuals with PART have increased levels of tau pathology and still bear a significant risk to dementia conversion as compared to healthy age-matched individuals (Burnham et al. 2016). Nevertheless, it was shown that 12% of all aMCI subjects progress to typical AD dementia every year and 80% of them convert into AD dementia within 6 years (Petersen et al. 2001).

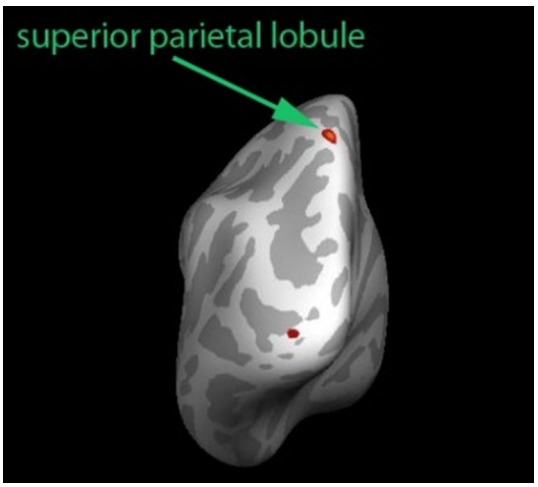


Fig. 13 Cortical thickness analysis PD-NC versus PD-MCI

In conclusion, we found distinct limbic and fronto-temporo-parietal neocortical atrophy in both MCI groups compared to HC with no specific differences between them. AD subjects displayed a typical pattern of major temporal lobe atrophy which was associated with deficits in all cognitive domains. VBM and CT were more sensitive than SBM for identifying distinct frontal limbic and superior parietal lobule atrophy in PD-MCI as compared to PD-NC. Only CT measures revealed some subtle differences between HC and PD-NC.

Our data support the notion that the results of studies using different analytical methods cannot be directly compared (Duncan et al. 2013) and may show slightly different results when comparing the same groups of subjects. CT measures seem to depict early GM changes more sensitively than VBM or SBM; all methods identify the well described spatial patterns of GM atrophy in advanced brain neurodegeneration. Further longitudinal studies should show which analytical methods are best suited for monitoring disease progression and potential treatment effects.

Table 10 PD versus PD-MCI

Method	Cluster size	X_1	Y_1	Z_1	$Area_1$
VBM	3826	−8	56	−22	l. Orbitofrontal cortex
	1091	−4	48	33	l. Superior frontal gyrus
SBM	No significant differences				
	Size (mm^2)	X_2	Y_2	Z_2	$Area_2$
CT	68.56	−13.2	−59.2	59.3	l. Superior parietal lobule

X_1, Y_1, Z_1 MNI coordinates of cluster maximum intensity, $Area_1$ brain region according to automated anatomical labeling (Tzourio-Mazoyer et al. 2002), X_2, Y_2, Z_2 Talairach coordinates of vertex with maximum p value, $Area_2$ brain region designated according to Desikan–Killiany atlas (Desikan et al. 2006), *r./l.* right/left

Acknowledgements The authors acknowledge and deeply thank our participants for their commitment to our research project. We acknowledge also the core facility MAFIL of CEITEC supported by the MEYS CR (LM2015062 Czech-BioImaging funded by Ministry of Education, Youth and Sports of the Czech Republic).

Funding The work was supported by the EU Joint Programming initiative within Neurodegenerative Diseases, funded by the Norwegian Strategic Research Council (JPND, APGeM—Preclinical genotype-phenotype predictors of Alzheimer's disease and other dementias, Grant Agreement Number 3056-00001) and by the 15-33854A Grant from the Czech Ministry of Health (Ministerstvo Zdravotnictví Ceské Republiky).

Compliance with Ethical Standards

Conflict of interest All author declares that they have no conflict of interest to disclose.

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