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ORIGINAL RESEARCH

# Brain degeneration in Parkinson's disease patients with cognitive decline: a coordinate-based meta-analysis

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## Abstract

Cognitive decline in Parkinson's disease (PD) is a common sequela of the disease, with its severity increasing as the neurodegenerative process advances. The present meta-analysis used anisotropic effect size seed-based *d* mapping software to perform analyses using both functional and structural brain imaging data. The analyses were between PD patients with mild cognitive impairment (PD-MCI) and PD patients with dementia (PDD) compared to PD cognitively unimpaired patients (PD-CU) and PD patients without dementia (PD-ND) respectively. Thirty-four studies were found and split into three analyses: 405 PD-MCI patients compared to 559 PD-CU patients from 1) 15 studies with structural imaging modalities and 2) eight studies with functional imaging modalities, as well as 178 PDD patients compared to 278 PD-ND patients (which includes both PD-CU and PD-MCI) in 3) 11 studies with structural imaging modalities. Statistical threshold was set to uncorrected $p < 0.001$. We found several brain regions that differed between PD-MCI and PD-CU patients: the left insula, bilateral dorsolateral prefrontal cortex, left angular gyrus, midcingulate cortex, and right supramarginal gyrus. The brain regions identified in the PD-MCI analyses are associated with the somatosensory network and executive processing. In PDD patients, the bilateral insula and right hippocampus were found as regions of structural atrophy. The insula was found in both structural analyses of PD-MCI and PDD, with unilateral insula involvement in PD-MCI extending to bilateral insula involvement in PDD. The results found both a spectrum of increasing brain atrophy in PD cognitive impairment and supports the existence of sub-typing in PD-MCI.

**Keywords** Parkinson's disease · Cognitive decline · Neuroimaging · Meta-analysis · Mild cognitive impairment · Parkinson's disease dementia

## Introduction

Cognitive decline is a common sequela of Parkinson's disease (PD), with up to 60% of PD patients being impaired in one or more cognitive domains (Aarsland et al. 2011). The cognitive domains affected include: executive function, attention, language skills, visuospatial function and memory (Litvan et al. 2012). There is growing evidence that PD with mild cognitive impairment (PD-MCI) is one of the strongest predictors of later conversion to PD dementia (PDD) (Gomperts et al.

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2013; Janvin et al. 2006; Aarsland et al. 2007). Janvin et al. (2006) found that 62% of PD-MCI patients progressed to dementia within 4 years of MCI diagnosis, with PD-MCI patients who have multi-domain impairments being the most vulnerable groups. However, not all PD-MCI patients are PDD converters and there is growing interest what protective factors may contribute to this long-term cognitive sparing.

Recent studies have suggested that PD-MCI may be composed of different subtypes with unique pathologies and PDD conversion outcomes. For instance, Williams-Gray et al. (2009) performed a longitudinal study of PD patients and found that PD-MCI patients with frontal-executive dysfunction were less likely to convert to PDD long-term over 5 years than PD-MCI patients with posterior brain impairments (i.e. visuospatial function and memory). Frontal-executive dysfunction was proposed to be related to dopaminergic dysregulation while posterior parietal-occipital impairments related to cholinergic dysregulation (Kehagia et al. 2010; Williams-Gray et al. 2007). Non-amnestic PD-MCI with dysexecutive symptoms is the most common subtype, however more longitudinal data is needed to discover which subtypes are most vulnerable to PDD conversion (Kalbe et al. 2016).

Neuroimaging studies have found both structural atrophy and functional impairments (i.e. metabolic and blood flow reduction) in the brains of PD-MCI and PDD patients compared to PD patients without MCI or dementia. Gonzalez-Redondo et al. (2014) acquired both structural magnetic resonance imaging (MRI) and [$^{18}$F]fludeoxyglucose positron emission tomography (FDG-PET) scans in PD-MCI and PDD patients. They found that areas of functional impairment in PD-MCI patients were also areas of structural abnormality in PDD patients. They hypothesized that areas in the brain with hypometabolism may evolve into structural atrophy as PD cognitive decline progresses. Functional changes in the brains of PD-MCI patients have been found both in frontal-temporal (Tang et al. 2016; Garcia-Garcia et al. 2012) and posterior cortical regions (Lyoo et al. 2010; Hosokai et al. 2009), with inconsistency in the present literature. Similarly, structural brain changes in PD-MCI patients compared to PD cognitively unimpaired (PD-CU) patients have found PD-MCI atrophy in many parts of the brain: frontal-temporal areas (Beyer et al. 2007; Danti et al. 2015), right middle frontal areas (Song et al. 2011; Noh et al. 2014), left precuneus (Pereira et al. 2014; Noh et al. 2014), right temporal pole, posterior cingulate gyrus (Noh et al. 2014), left hippocampus and thalamus (Chen et al. 2016), and left insula (Danti et al. 2015). Gratwicke et al. (2015) suggested that a more comprehensive neural network approach is needed to understand cognitive decline in PD-MCI and PDD due to the heterogeneity of the symptoms.

In the current study, we investigated the differences between PD-MCI and PDD compared to PD-CU and PD patients without dementia (PD-ND) respectively by performing a meta-analysis using the anisotropic effect size seed-based *d* mapping (AES-SDM) software (Radua et al. 2012) to pool together data from the current neuroimaging literature of cognitive impairment in PD. AES-SDM is a fully validated coordinate based meta-analysis software that has been used successfully in other recent neuroimaging studies (Radua et al. 2010; Nakao et al. 2011; Wise et al. 2016). AES-SDM adopted and combined many of the features found in previous coordinate based meta-analysis tools such as Activation Likelihood Estimation and Multi-Level Kernel Density Analysis. AES-SDM added improvements to the meta-analysis methodology such as the inclusion of effect-sizes to improve statistical power, weighing calculations to offset intra-study variance, and the use of specific masks and correlation templates for functional MRI (fMRI), PET and gray matter/white matter (Radua et al. 2012).

Previous meta-analyses which explored structural changes in PD-MCI and PDD patients found unilateral grey matter volume (GMV) reduction the left superior temporal lobe, left insula and left superior frontal lobe in PD-MCI patients. They also found GMV reductions bilaterally in the superior temporal lobe extending to the hippocampus and left superior frontal lobe in PDD patients (Xu et al. 2016). The medial temporal lobe was consistently found as an area of structural atrophy in PDD patients (Xu et al. 2016; Pan et al. 2013). To date however, no meta-analysis has looked at the breadth of information regarding PD-MCI and PDD from both structural and functional modalities. Our study aimed to explore both the structural and functional differences in PD-MCI and PDD patients compared to PD-CU and PD patients without dementia respectively, and to see how the brain changes as PD cognitive impairment progresses in severity. We performed three sets of analyses looking at: 1) functional changes between PD-MCI and PD patients who are cognitively unimpaired (PD-CU), 2) structural changes between PD-MCI and PD-CU and 3) structural changes between PDD and PD-ND. PD-ND includes both PD-MCI patients as well as PD-CU patients, with all but two included studies not distinguishing between PD-MCI and PD-CU in the PD-ND group. The objective of this meta-analysis was to discover if these brain differences were unique to PD-MCI and PDD respectively, or if these changes overlapped and progressed along a gradient of increasing PD pathology.

## Methods

### Literature search

We acquired the data for this meta-analysis by performing an exhaustive search of the PubMed and Web of Science databases for papers published between January 1st, 1999 and May 31st, 2017. Two sets of keywords were used to find experiments, with '(Parkinson or PD) AND fMRI OR

(functional magnetic resonance imaging) OR PET OR (Positron emission tomography) OR MRI OR (Magnetic resonance imaging)' being common in both search queries. The first query added 'MCI OR (Mild cognitive impairment)' to find articles related to PD-MCI while 'PDD OR (Parkinson's disease dementia)' was added for the second query to find articles related to PDD. The reference lists of relevant articles were then searched for any potential missed studies.

### Study selection and meta-analysis using AES-SDM

The inclusion criteria for the experiments were as follows: 1) resting state fMRI, structural MRI and [$^{18}$F]FDG-PET 2) idiopathic PD patients 3) paper published in English 4) 3D coordinates reported in stereotactic space (Montreal Neurologic Institute [MNI] or Talairach), and 5) statistical significance reported. The structural changes were examined using either voxel-based morphometry (VBM), a parametric approach of mapping GMV changes in the brain, or through cortical thickness (CTh) measures. VBM and CTh studies provide complementary results that are very consistent with each other when examining an aging population as is the case in PD (Hutton et al. 2009). The functional changes were examined using [$^{18}$F]FDG-PET, which uses a radiotracer to measure glucose metabolism in the brain, and through fMRI which uses the blood-oxygen-level dependent signal to measure the brain's oxygen consumption, with higher oxygen needs in those areas with greater neuronal demand. There is convincing evidence that [$^{18}$F]FDG-PET and the blood-oxygen-level dependent signal are correlated to each other and measure similar physiological markers (La Fougere et al. 2010; Riedl et al. 2014). The included fMRI studies used different data analysis methods, independent component analysis and seed-based correlation analysis, but both methods are assumed to be representative of brain functional abnormalities in PD patients.

The flow diagram illustrating the study selection process used is shown in Fig. 1 and the imaging modality and statistical information for the included studies is shown in Table 1. Seventy-nine papers were excluded because they were either task-based fMRI studies, compared PD patients to healthy controls, did not use FDG-PET or the papers were not in English. A total of 34 studies were identified and included in this meta-analysis, split into 3 different comparisons (Table 2). Diagnostic classification of subjects into patient groups was done with a variety of different diagnostic measures by the included studies which were specified in Table 2.

The meta-analysis was performed using AES-SDM software (version 5.12 http://www.sdmproject.com). Talairach coordinates were converted to MNI space using the Brett transform (Lancaster et al. 2007). Statistical significance was set an uncorrected $p$ value <0.001, number of randomizations = 500, anisotropy = 1, isotropic FWHM (mm) = 20, with a gray matter mask and correlation template, peak height threshold = 1, and extent threshold = 10. Radua et al. (2012) found using empirical validation that an uncorrected $p = 0.005$ using the AES-SDM software is approximately equivalent to a corrected $p = 0.025$. The maps of the AES-SDM values were superimposed on the Collin brain atlas (Laird et al. 2005) using the MRIcron software (http://people.cas.sc.edu/rorden/mricron/install.html). Functional imaging data from [$^{18}$F]FDG-PET and fMRI were grouped together and structural imagining data from both VBM and cortical thickness analyses were grouped together to increase statistical power.

### Jackknife sensitivity analysis

Whole-brain jackknife sensitivity analysis was performed on each of the three analyses to assess the replicability of the results. This is done by systemically running the statistical analysis for each result several times, once for each included study in that analysis, and not including one of the experiments from the analysis each time it is run (i.e. in our PD-MCI vs. PD-CU analysis, there are 15 included experiments and so jackknife sensitivity ran 15 times with 14 included experiments each time). If a brain region remains significant after running jackknife sensitivity in all or most of the combinations, then it can be concluded that the finding is highly replicable (Radua and Mataix-Cols 2009).

## Results

The demographics of the present meta-analysis are summarized in Table 3. As expected, significant differences were found between PD-MCI and PD-CU patients in age, unified Parkinson's disease rating scale part III - motor evaluation (UPDRS-III) score and mini-mental state examination (MMSE) score. Similarly, significant differences were found as well between PDD and PD-ND patients in UPDRS-III score, MMSE score and Hoehn and Yahr stage (H-Y) score. As expected, these differences were due to the more aggressive nature of PDD disease pathology. We conducted the following comparisons to measure: 1) structural and functional changes in PD-MCI vs. PD-CU, 2) structural changes of the brain in PDD vs. PD-ND. There were insufficient studies looking at the functional changes of PDD vs. PD-ND, and thus this comparison was not included in the meta-analysis.

### PD-MCI vs PD-CU

In the PD-MCI vs. PD-CU comparison investigating the structural changes, a total of 405 PD-MCI patients and 559 PD-CU patients from 15 MRI experiments were included. Of the 15

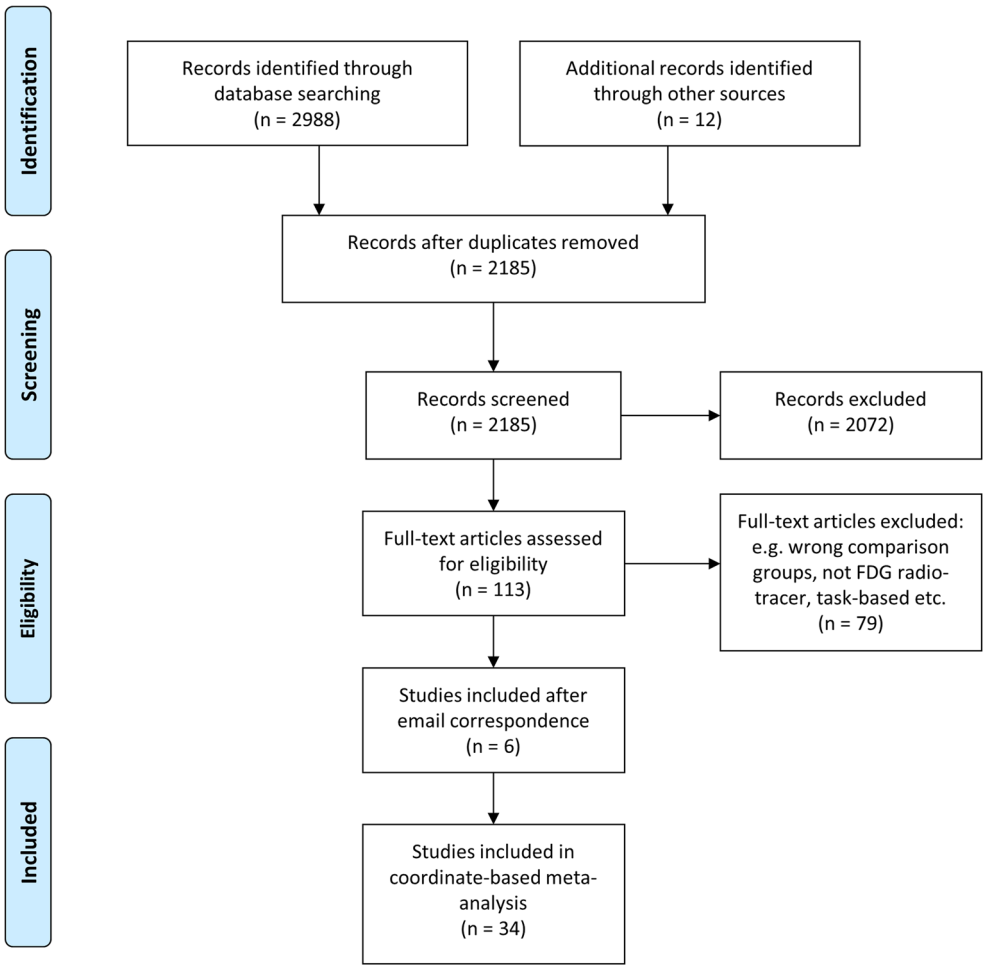


**Fig. 1** PRISMA flow diagram showing study selection process

experiments, eight investigated GMV changes using VBM and seven looked at cortical thickness. Brain areas with reductions in gray matter were found in the left posterior insula, right supramarginal gyrus, and the midcingulate cortex (MCC) (Table 4, Fig. 2a). Jackknife sensitivity analysis revealed that both the right supramarginal gyrus and the left posterior insula were found in 14 of the 15 combinations, while the mid-cingulate was found in 13 of the 15 combinations, suggesting that these findings were robust.

In the comparison of PD-MCI vs. PD-CU patients investigating the functional imaging changes, a total of 172 PD-MCI patients and 237 PD-CU patients from 8 experiments were included. Of the eight experiments, five were PET imaging studies using [$^{18}$F]FDG-PET and three were fMRI studies. Brain areas with functional changes were found in the left angular gyrus and bilaterally in the dorsolateral prefrontal cortex (DLPFC) (Table 4, Fig. 2b). Jackknife sensitivity analysis revealed that these results were robust, with the left angular gyrus and right dorsolateral prefrontal cortex found in all eight combinations, while the left dorsolateral prefrontal cortex was found in six of the eight combinations.

### PDD vs PD-ND

In the PDD vs. PD-ND comparison that examined the structural changes, a total of 178 PDD patients and 278 PD-ND patients from 11 experiments were included. All 11 experiments were done using MRI with VBM. Two brain areas with significant reductions in gray matter were found: one large area encompassing the right insula and right hippocampus and a second brain area was found in the left insula (Table 4, Fig. 2c). After performing jackknife sensitivity analysis, the right insula was found in all 11 combinations, while the left insula was found in 8 of the 11 experiments, suggesting our findings were robust and replicable.

## Discussion

We found structural and functional regional changes in PD-MCI patients and PDD patients. As expected, structural changes in PDD patients compared to PD-ND patients revealed much larger areas of degeneration. In the PD-MCI patients, the brain areas most affected with structural and functional changes included: the left insula, bilateral DLPFC, left

**Table 1** Scanning methods, data analysis and equipment used in the 34 studies included in this meta-analysis

| First Author | Year | Manufacturer | Sequence | Field, T (coil, channels) | Thickness (mm) | Voxel Size (mm) | Matrix Size | FOV (mm) | FWHM (mm) | No. of Foci | Modality | Threshold $p <$ (cor or uncor) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PD-MCI | | | | | | | | | | | | |
| *Baggio* | 2015 | Siemens | MPRAGE | 3 (8) | 3 | NA | NA | 256 | 6 | 2 | fMRI | 0.05 (cor) |
| *Beyer* | 2007 | Philips | Fast SPGR | 1.5 (NA) | 1.6 | NA | 256 × 256 × 192 | NA | 8 | 6 | MRI (VBM) | 0.001 (uncor) |
| *Chen* | 2016 | Siemens | MPRAGE | 3 (NA) | 1.33 | NA | 256 × 256 × 192 | 256 | 8 | 1 | MRI (VBM) | 0.01 (cluster level cor) |
| *Danti* | 2015 | Siemens | MPRAGE | 1.5 (birdcage) | 1 | 1 | 256 × 256 × 256 | 256 | 5 | 3 | MRI (CTh) | 0.05 (cor) |
| *Duncan* | 2016 | Siemens | MPRAGE | 3 (8) | 1.2 | 1.15 | NA | 240 | 8 | 3 | MRI (VBM) | 0.05 (cor) |
| *Garcia-Garcia* | 2012 | Siemens ECAT EXAT HR+ | Filtered Back Projects - ECAT | NA | 2.06 | 2.016 | 128 × 128 × 128 | 187 × 250 | 8 | 5 | PET ([$^{18}$F]FDG) 370 MBq | 0.001 (uncor) |
| *Hanganu* | 2014 | Siemens | MPRAGE | 3 (12) | NA | 1 | 256 × 256 × 240 | 256 × 240 | 10 | 6 | MRI (CTh) | 0.001 (uncor) |
| *Hanganu* | 2013 | Siemens | Gradient-echo | 3 (12) | NA | 1 | 256 × 256 × 240 | 256 × 256 × 240 | 20 | 4 | MRI (CTh) | 0.05 (cor) and 0.005 (uncor) |
| *Hosokai* | 2009 | Siemens | NA | NA | 2.0 | 1.33 × 1.33 | 256 × 256 × 256 | NA | 10 | 8 | PET ([$^{18}$F]FDG) 185–218 MBq | 0.001 (uncor) |
| *Hou* | 2016 | Siemens | EPI | 3 (8) | 1 | 1 × 1 × 1 | 256 × 256 × 256 | 256 × 256 × 256 | 6 | 2 | fMRI | 0.001 (uncor) |
| *Huang* | 2008 | General Electric | NA | NA | NA | 2 × 2 × 4 | 128 × 128 × 35 | NA | 8 | 6 | PET ([$^{18}$F]FDG) | 0.001 (uncor) |
| *Lyoo* | 2010 | Philips Medical System | NA | NA | NA | NA | NA | NA | 10 | 28 | PET ([$^{18}$F]FDG) 5.18 MBq/kg | 0.05 (cor) |
| *Mak* | 2014b | General Electric | MPRAGE | 3 (NA) | NA | 1 × 1 × 1 | 256 × 256 × 256 | 256 × 256 | 8 | 3 | MRI (VBM) | 0.001 (uncor) |
| *Mak* | 2015 | Philips Medical System | MPRAGE | 3 (NA) | 1.2 | 1.15 × 1.15 | NA | 240 × 240 | 15 | 3 | MRI (CTh) | 0.05 (cor) |
| *Melzer* | 2012 | General Electric | SPGR | 3 (8) | 1 | 0.98 × 0.98 × 1 | 256 × 256 × 170 | 250 | 10 | 14 | MRI (VBM) | 0.001 (uncor) |
| *Noh* | 2014 | Philips | T1-TFE | 3 (NA) | 1.2 | 0.98 × 0.98 × 1.2 | 256 × 256 × 256 | 220 | 6 | 4 | MRI (VBM) | 0.001 (uncor) |
| *Pagonabarraga* | 2013 | Philips | MPRAGE | 3 (NA) | NA | 0.889 × 0.889 × 1.2 | 288 × 288 × 170 | NA | 10 | 7 | MRI (CTh) | 0.001 (uncor) |
| *Peraza* | 2017 | Philips | MPRAGE | 3 (NA) | 1 | NA | NA | 240 × 240 | 6 | 17 | fMRI | 0.05 (cor) |
| *Pereira* | 2014 | Siemens | MPRAGE | 3 (NA) | NA | 1 × 1 × 1 | 256 × 256 × 256 | NA | 15 | 1 | MRI (CTh) | 0.05 (cor) |
| *Segura* | 2014 | Siemens | Axial FLAIR | 3 (NA) | NA | 1 × 1 × 1 | 256 × 256 × 256 | 256 | 15 | 2 | MRI (CTh) | 0.05 (cor) |
| *Song* | 2011 | Philips | 3 (NA) | TFE | NA | 0.98 × 0.98 × 1.2 | 224 × 256 × 256 | 256 × 256 | 6 | 1 | MRI (VBM) | 0.05 (cor) |
| *Tang* | 2016 | Siemens | NA | NA | NA | NA | NA | NA | 10 | 5 | PET ([$^{18}$F]FDG) 185 MBq | 0.01 (uncor) |
| *Zhang* | 2015 | General Electric | T2WI-PR-OPELLER & axial DWI | 3 (8) | 6 & 6 | 1 × 1 × 1 | 352 × 352 × 352 & 128 × 128 × 128 | 240 & 240 | 8 | 7 | MRI (VBM) | 0.005 (NA) |
| PDD | | | | | | | | | | | | |
| *Beyer* | 2007 | Philips | Fast SPGR | 1.5 (NA) | 1.6 | NA | 256 × 256 × 192 | NA | 8 | 31 | MRI (VBM) | 0.05 (cor) |
| *Burton* | 2004 | General Electric | Fast SPGR | 1.5 (NA) | 1.6 | 0.78 × 0.78 × 0.78 | 256 × 256 × 256 | 200 | 8 | 3 | MRI (VBM) | 0.001 (uncor) |
| *Compta* | 2012 | Siemens | MPRAGE | 3 (NA) | NA | 1 × 1 × 1 | 256 × 256 × 256 | NA | 8 | 6 | MRI (VBM) | 0.05 (cor) |
| *Gee* | 2017 | Siemens | MPRAGE | 1.5 (NA) | 1.5 | 1 × 1 × 1.5 | 256 × 256 × 256 | 256 | 8 | 3 | MRI (VBM) | 0.05 (cor) |

**Table 1** (continued)

| First Author | Year | Manufacturer | Sequence | Field, T (coil, channels) | Thickness (mm) | Voxel Size (mm) | Matrix Size | FOV (mm) | FWHM (mm) | No. of Foci | Modality | Threshold $p$ < (cor or uncor) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Goldman* | 2014 | General Electric | MPRAGE | 1.5 (NA) | 1.2 | NA | 192 × 192 × 192 | 240 | 8 | 28 | MRI (VBM) | 0.01 (uncor) |
| *Lee* | 2013 | Philips | T1-TFE | 1.5 (NA) | 1.3 | 0.86 × 0.86 × 1.3 | 256 × 256 × 256 | 220 | 8 | 7 | MRI (VBM) | 0.001 (uncor) |
| *Melzer* | 2012 | General Electric | SPGR | 3 (8) | 1 | 0.98 × 0.98 × 1 | 256 × 256 × 170 | 250 | 10 | 17 | MRI (VBM) | 0.001 (uncor) |
| *Nagano-Saito* | 2005 | Toshiba | Field Echo | 1.5 (NA) | 1.3 | 1 × 1 × 1 | NA | NA | 8 | 9 | MRI (VBM) | 0.001 (cor) |
| *Song* | 2011 | Philips | T1-TFE | 3 (SENSE) | NA | 0.98 × 0.98 × 1.2 | 224 × 224 × 256 | 220 | 6 | 5 | MRI (VBM) | 0.001 (uncor) |
| *Summerfield* | 2005 | General Electric | 3D IR SPGR | 1.5 (NA) | 1.5 | NA | NA | 240 | NA | 2 | MRI (VBM) | 0.001 (uncor) |
| *Xia* | 2013 | General Electric | Fast SPGR | 3 (8) | 1.2 | 0.47 × 0.47 × 1.2 | 256 × 256 × 256 | 240 | 8 | 10 | MRI (VBM) | 0.001 (uncor) |

*MRI* = magnetic resonance imaging; *fMRI* = functional magnetic resonance imaging; *VBM* = voxel-based morphometry; *CTh* = cortical thickness; *PET* = positron emission tomography; *FDG-PET* = [$^{18}$F]fludeoxyglucose positron emission tomography; *cor* = corrected; *uncor* = uncorrected; *NA* = datum not available

angular gyrus, MCC, and right supramarginal gyrus. These results suggest a strong relationship between cognitive decline in PD and structural and functional decline in the frontal-temporal regions, illustrating area-specific regions of atrophy and hypometabolism in the brain.

In the structural analysis of PD-MCI patients compared to PD-CU patients, three brain regions were found with significant differences: the left posterior insula, right supramarginal gyrus and MCC. These regions are all part of a network involved in the somatosensory processing (Klein et al. 2013; Cauda et al. 2011). Often PD patients have been documented to experience deficits in sensory perceptions of their body (Koller 1984). The supramarginal gyrus has been found to be functionally connected to the insula, with lowered connectivity between the two brain regions in patients suffering from somatosensory perception (Su et al. 2016). The MCC has been found to be functionally connected to the posterior insula and the supplemental motor area (SMA) (Deen et al. 2011; Taylor et al. 2009) and is involved in multisensory orientation of the body in space, specifically with the direction and force of movement (Vogt 2016). The posterior insula appears to act as a hub region, as it is connected to both the supramarginal gyrus cluster and the MCC cluster along with dorsal/posterior striatum (Klein et al. 2013; Cauda et al. 2011; Christopher et al. 2014). A previous meta-analysis on the role of the insula in PD found that the mid-insula was an area of significant convergence for experiments which examined sensorimotor tasks, providing convincing evidence for the middle/posterior insula being an important hub region in sensorimotor tasks (Criaud et al. 2016). Specific to PD-MCI, Okada et al. (2016) found a strong correlation between cognitive impairment in PD patients and increased dysfunction in pain processing, which is an important aspect of the somatosensory network. Dysfunction in this brain region could contribute to the somatosensory impairments experienced by PD patients.

When comparing PD-MCI patients to PD-CU patients using functional imaging modalities, three brain areas of significance were found: the left angular gyrus and bilateral involvement of the DLPFC. The DLPFC is a brain region that has been shown to be important for higher cognitive functions such as executive functions, (Lara and Wallis 2015; Miller and Cohen 2001). The DLPFC is heavily innervated through the mesocortical dopaminergic pathway from the ventral tegmental area to the prefrontal cortex (Alcaro et al. 2007; Wagner et al. 2001). Consistent with our observations, several imaging studies in PD patients have reported reduced activation in the DLPFC during working memory tasks compared to healthy controls (Masdeu et al. 2014; Monchi et al. 2006). The angular gyrus has been found to act as a hub region, wherein multisensory information is converged and integrated together (Seghier 2013). The left angular gyrus specifically has been implicated in speech processing (Frost et al. 1999). Speech deficits with hypophonia are a common feature in PD and it

**Table 2** Characteristics of the 34 included studies of this meta-analysis for both the PD-MCI papers and PDD papers

| First Author | Year | Sample (female) | Age[a] | | Disease Duration (years)[a] | | Education (Years)[a] | |
|---|---|---|---|---|---|---|---|---|
| | | | PD-MCI /PDD | PD-CU /PD-ND | PD-MCI /PDD | PD-CU/ PD-ND | PD-MCI /PDD | PD-CU /PD-ND |
| PD-MCI | | | | | | | | |
| *Baggio* | 2015 | *PD-MCI 22 (8) – PD-CU 43 (20)* | 66.1 (12.2) | 64 (9.8) | 9.3 (5.5) | 6.1 (4.4) | 8.8 (4) | 10.8 (5.1) |
| *Beyer* | 2007 | *PD-MCI 8 (5) – PD-CU 12 (6)* | 77.4 (7.4) | 69 (8) | 10.8 (3.7) | 14.1 (7.1) | 8.4 (1.5) | 12.5 (3.6) |
| *Chen* | 2016 | *PD-MCI 18 (4) – PD-CU 19 (4)* | 62.83 (5.38) | 61.21 (6.75) | 6.62 (4.55) | 5.73 (3.45) | 9.55 (3.63) | 10.47 (3.63) |
| *Danti* | 2015 | *PD-MCI 18 (4) – PD-CU 18 (3)* | 66.5 (6.7) | 60.6 (9.0) | 1.66 (1.17) | 1.5 (0.83) | 9.7 (3.4) | 9.9 (3.6) |
| *Duncan* | 2016 | *PD-impaired semantic fluency 19 - PD-CU 101* | NA | N/A | NA | NA | NA | NA |
| *Garcia-Garcia* | 2012 | *PD-MCI 28 (14) – PD-CU 21 (6)* | 71.5 (3.8) | 67 (7.1) | 14.1 6) | 12.4 (3.8) | 9.9 (3.1) | 11.7 (3.6) |
| *Hanganu* | 2014 | *PD-MCI 17 (6) – PD-CU 15 (7)* | 64.01 (5.36) | 60.98 (3.83) | 5.35 (2.96) | 5.09 (4.90) | 13.47 (3.37) | 14.36 (2.37) |
| *Hanganu* | 2013 | *PD-MCI 18 (5) – PD-CU 19 (7)* | 64.7 (4.5) | 59.9 (4.2) | 3.7 (2.8) | 5.4 (3.8) | 13.4 (3.2) | 14.7 (2.1) |
| *Hosokai* | 2009 | *PD-MCI 13 (1) – PD-CU 27 (15)* | 67.6 (5.5) | 65.7 (5.1) | 6.1 (5.8) | 4.1 (3.0) | 13.4 (1.9) | 11.6 (2.4) |
| *Hou* | 2016 | *PD-MCI 14 (9) – PD-CU 18 (9)* | 54.56 (8.13) | 53.61 (8.68) | 1.24 (1.05) | 1.53 (1.22) | 7.21 (2.05) | 11.5 (3.22) |
| *Huang* | 2008 | *PD-MCI 18 (7) – PD-CU 18 (6)* | 62.4 (8.7) | 59.0 (9.3) | 9.2 (1.4) | 9.5 (1.0) | 14.2 (3.1) | 15.1 (2.3) |
| *Lyoo* | 2010 | *PD-MCI 18 – PD-CU 20* | 65.5 | 62.0 | 2.0 | 3.0 | NA | NA |
| *Mak* | 2014a, 2014b | *PD-MCI 24 (10) – PD-CU 66 (25)* | 68.99 (6.09) | 63.48 (7.53) | 4.83 (2.70) | 5.32 (4.27) | 9.4 (3.52) | 10.88 (3.1) |
| *Mak* | 2015 | *PD-MCI 39 (10) – PD-CU 66 (25)* | 69.4 (8.8) | 62.9 (9.9) | 2.08 (0.29) | 2.02 (0.29) | 11.6 (3.5) | 13.8 (3.5) |
| *Melzer* | 2012 | *PD-MCI 23 (9) – PD-CU 57 (18)* | 70.8 (8.0) | 64.3 (8.7) | 7.2 (5.0) | 3.8 (3.3) | NA | NA |
| *Noh* | 2014 | *PD-MCI 24 (10) – PD-CU 28 (16)* | 67.2 (7.4) | 67.9 (10.1) | 2.14 (4.1) | 1.6 (1.59) | 8.9 (4) | 7 (4) |
| *Pagonabarraga* | 2013 | *PD-MCI 26 (11) – PD-CU 26 (12)* | 73.3 (7) | 71.5 (4) | 6.8 (4) | 7.3 (4) | 9.2 (4) | 9 (5) |
| *Peraza* | 2017 | *PD-MCI 37 (9) – PD-CU 65 (25)* | 70.4 (9.13) | 62.77 (10.83) | 0.48 (0.38) | 0.54 (0.4) | 10.97 (3.24) | 14.32 (3.9) |
| *Pereira* | 2014 | *PD-MCI 33 (13) – PD-CU 90 (35)* | 63.4 (7.6) | 59.4 (10.0) | 0.52 (0.58) | 0.57 (0.61) | 14.6 (3.4) | 15.5 (2.6) |
| *Segura* | 2014 | *PD-MCI 47 (23) – PD-CU 43 (29)* | 67.72 (9.71) | 60.77 (10.51) | 9.73 (6.37) | 6.23 (4.05) | 9.19 (5.24) | 12.02 (5.05) |
| *Song* | 2011 | *PD-MCI 27 (12) – PD-CU 23 (14)* | 71.3 (6.0) | 69.1 (6.1) | 3.91 (5.29) | 1.41 (1.23) | 9.2 (5.3) | 10.8 (4.5) |
| *Tang* | 2016 | *PD-MCI 20 (10) – PD-CU 30 (14)* | 61.9 (6.7) | 61.9 (6.3) | 5.7 (4.5) | 3.6 (3.2) | 11.2 (3.6) | 12.9 (3) |
| *Zhang* | 2015 | *PD-MCI 21 (7) – PD-CU 14 (9)* | 63.8 (5.58) | 58.5 (9.22) | 5.24 (3.30) | 3.23 (2.35) | 8.38 (2.8) | 8.78 (3.92) |
| PDD | | | | | | | | |
| *Beyer* | 2007 | *PDD 16 (6) – PD-ND 20 (11)* | 73.5 (6.5) | 72.5 (8.5) | 12.3 (7.5) | 12.0 (6.3) | 10.2 (3.6) | 11 (3.6) |
| *Burton* | 2004 | *PDD 26 (10) – PD-ND 31 (8)* | 72.3 (5.2) | 75.2 (5.2) | 6.8 (5.05) | 3.63 (2.85) | NA | NA |
| *Compta* | 2012 | *PDD 15 (10) – PD-ND 18 (6)* | 73 | 69 | 9 | 10 | 8 | 8 |
| *Gee* | 2017 | *PDD 10 (3) – PD-ND 23 (11)* | 71.6 (2.7) | 69.4 (3.3) | 9.8 (4.2) | 7.7 (4.3) | 13.2 (1.5) | 14.7 (3.6) |
| *Goldman* | 2014 | *PDD – PD-ND – 50* | NA | NA | NA | NA | NA | NA |
| *Lee* | 2013 | *PDD 16 (14) – PD-ND 16 (13)* | 69.9 (6.5) | 68.3 (7.2) | 4.0 (1.4) | 2.8 (1.9) | NA | NA |
| *Melzer* | 2012 | *PDD 16 (6) – PD-CU 57 (18)* | 73.3 (7.0) | 64.3 (8.7) | 12.9 (8.8) | 3.8 (3.3) | NA | NA |
| *Nagano-Saito* | 2005 | *PDD 9 – PD-ND 17* | 67.3 (5.4) | 61.8 (8.1) | 9.3 (5.4) | 3.5 (3.4) | NA | NA |
| *Song* | 2011 | *PDD 18 (9) – PD-CU 23 (14)* | 72.0 (6.0) | 69.1 (6.1) | 4.73 (3.43) | 1.41 (1.23) | 5.7 (6.3) | 10.8 (4.5) |
| *Summerfield* | 2005 | *PDD 16 – PD-ND 13* | 70.06 (7.88) | 72.77 (4.90) | 12.94 (5.36) | 10.61 (7.41) | 6.62 (4.53) | 8.15 (5.27) |
| *Xia* | 2013 | *PDD 12 (8) – PD-ND 12 (4)* | 69.25 (11.12) | 65.58 (8.32) | 7.83 (4.08) | 4.83 (2.48) | 6.92 (5.4) | 11.75 (3.33) |

| First Author | H-Y Stage[a] | | MMSE[a] | | UPDRS-III[a] [ON/OF] | | PD-MCI Diagnosis Criteria/PDD Diagnosis Criteria |
|---|---|---|---|---|---|---|---|
| | PD-MCI /PDD | PD-CU /PD-ND | PD-MCI /PDD | PD-CU /PD-ND | PD-MCI /PDD | PD-CU /PD-ND | |
| PD-MCI | | | | | | | |
| *Baggio* | 2.05 | 1.58 | 28.50 (1.22) | 29.35 (0.47) | 18.2 [ON] | 14.1 [ON] | Other: Z-Score below 1.5 on 2+ tests in 1+ domains |
| *Beyer* | 2.6 (0.8) | 2.3 (0.4) | 25.9 (2.9) | 29.4 (0.5) | NA [ON] | NA [ON] | Petersen et al. (2001) |
| *Chen* | 2.44 (0.98) | 1.89 (0.74) | 27.83 (1.54) | 29.42 (0.84) | 24.00 (10.98) [NA] | 17.74 (9.68) [NA] | Other: MoCA score less than 26 |
| *Danti* | 1.6 (0.4) | 1.3 (0.4) | 26.4 (2.1) | 28.7 (1.8) | 16.4 (7.0) [OFF] | 10.7 (4.5) [OFF] | Litvan et al. (2012) |

**Table 2** (continued)

| First Author | H-Y Stage[a] | | MMSE[a] | | UPDRS-III[a] [ON/OF] | | PD-MCI Diagnosis Criteria/PDD Diagnosis Criteria |
|---|---|---|---|---|---|---|---|
| | PD-MCI /PDD | PD-CU /PD-ND | PD-MCI /PDD | PD-CU /PD-ND | PD-MCI /PDD | PD-CU /PD-ND | |
| *Duncan* | NA | NA | NA | NA | NA [ON] | NA [ON] | Other: Below 1.5 SD on semantic fluency task |
| *Garcia-Garcia* | 2.9 (0.7) | 2.6 (0.8) | 28 | 29.5 | 17.7 (9.1) [ON] | 16.4 (7.1) [ON] | Litvan et al. (2012) |
| *Hanganu* | NA | NA | NA | NA | 30.5 (10.2) [OFF] | 26.4 (8.04) [OFF] | Litvan et al. (2012) |
| *Hanganu* | NA | NA | NA | NA | 29.5 (9.9) [OFF] | 28.1 (7.1) [OFF] | Litvan et al. (2012) |
| *Hosokai* | 2.7 (0.3) | 2.5 (0.5) | 27.1 (2.3) | 27.9 (2.0) | 22.4 (6.4) [OFF] | 18.5 (7.8) [OFF] | Other: Clinical Dementia Rating score of 0.5 |
| *Hou* | 1.93 | 1.56 | NA | NA | 17.78 (8.46) [OFF] | 15.35 (5.58) [OFF] | Litvan et al. (2012) |
| *Huang* | 3.6 (0.6) | 3.1 (1.1) | 27.1 (1.9) | 28.2 (1.4) | 34.9 (16.7) [OFF] | 29.2 (16.9) [OFF] | Other: 1.5 SD below on at least 1 of 4 domains |
| *Lyoo* | 2.3 | 2.3 | 27.0 | 29.0 | 25.5 [OFF] | 22.0 [OFF] | Modified Petersen et al. (1999) with Korean MMSE |
| *Mak* | 1.81 (0.44) | 1.91 (0.37) | 26.91 (2.47) | 28.36 (1.62) | 19.96 [ON] | 17.44 [ON] | Litvan et al. (2012) |
| *Mak* | 2.1 (0.6) | 1.9 (0.7) | 28.1 (1.4) | 29.1 (0.8) | 29 (10.9) [ON] | 25.3 (10.9) [ON] | Litvan et al. (2012) |
| *Melzer* | 2.5 | 2 | 27.7 (1.5) | 29.4 (0.5) | 35.7 (18.7) [ON / NAIVE] | 25.9 (14.2) [ON / NAIVE] | Other: 1.5 SD below on at least 2 of 4 domains |
| *Noh* | 2.25 (0.51) | 2.33 (0.62) | NA | NA | 20.3 (9.5) [OFF] | 17.2 (8.0) [OFF] | Litvan et al. (2012) |
| *Pagonabarraga* | 2 (0.6) | 2.2 (0.4) | NA | NA | 21 (9) [ON] | 24 (8) [ON] | Other: Clinical Dementia Rating score of 0.5 |
| *Peraza* | NA | NA | 28.18 (1.48) | 29.01 (0.93) | 28.86 (10.97) [ON] | 24.59 (10.39) [ON] | Litvan et al. (2012) |
| *Pereira* | 2 | 2 | NA | NA | 21.5 (8.2) [OFF] | 19.6 (8.9) [OFF] | Litvan et al. (2012) |
| *Segura* | 2.06 | 1.70 | 28.68 (1.29) | 29.47 (0.74) | 17.79 (11.07) [ON] | 13.16 (7.67) [ON] | Litvan et al. (2012) |
| *Song* | NA | NA | 25.8 (2.8) | 28.6 (1.1) | 18.6 (10.9) [NA] | 16.9 (11.8) [NA] | Modified Petersen et al. (1999) with Seoul Neuropsych-ological screening battery |
| *Tang* | 2.1 (1.1) | 1.8 (0.8) | NA | NA | 30.0 (17.4) [OFF] | 23.0 (8.1) [OFF] | Litvan et al. (2012) |
| *Zhang* | 1.77 (0.98) | 1.42 (0.57) | 28.85 (1.06) | 29.07 (1.07) | NA [OFF] | NA [OFF] | Petersen et al. (1999) |
| PDD | | | | | | | |
| *Beyer* | 3.0 (0.6) | 2.4 (0.6) | 19.4 (4.6) | 28.2 (2.1) | NA [ON] | NA [ON] | DSM III or IV & Dementia Rating Scale |
| *Burton* | NA | NA | 18.9 (5.80 | 26.4 (1.9) | 36.4 (10.5) [NA] | 25.8 (11.1) [NA] | McKeith et al. (1996) |
| *Compta* | 4 | 3 | NA | NA | 32 [OFF] | 28.5 [OFF] | Emre et al. (2007) & DSM-IV |
| *Gee* | NA | NA | 27.3 (2.2) | 28.9 (1.2) | 14.4 (8.7) [ON] | 15.3 (6.3) [ON] | DSM-IV |
| *Goldman* | NA | NA | NA | NA | NA | NA | Emre et al. (2007) |
| *Lee* | 2.6 (0.6) | 1.7 (0.6) | 19.6 (2.4) | 27.3 (1.3) | 22.3 (7.3) [OFF] | 15.6 (5.8) [OFF] | DSM-IV & MMSE <24 |
| *Melzer* | 4 | 2 | 23.9 (3.1) | 29.0 (1.2) | 48.9 (15.7) [ON/ NAÏVE] | 25.9 (14.2) [ON/ NAÏVE] | Emre et al. (2007) |
| *Nagano-Saito* | 3.3 (0.7) | 2.3 (0.9) | 16.1 (5.7) | 28.4 (1.9) | 45.7 (10.9) [NA] | 25.5 (16.1) [NA] | DSM-IV |
| *Song* | NA | NA | 18.1 (5.1) | 28.6 (1.1) | 32.1 (10.9) [NA] | 16.9 (11.8) [NA] | Seoul Neuropsychological screening battery |
| *Summerfield* | 3.37 (1.02) | 2.73 (0.72) | 17.33 (5.51) | 28.54 (1.05) | 36.33 (13.81) [NA] | 24.50 (12.04) [NA] | DSM-IV & MMSE <23 and CDR = 1 |
| *Xia* | 3.0 (0.83) | 1.8 (0.62) | 23.42 (3.37) | 28.08 (1.39) | 44.04 (14.26) [ON] | 14.25 (9.08) [ON] | MMSE <25 & MoCA <17 & ADL >30 |

*PD-MCI* = Parkinson's disease with mild cognitive impairment; *PD-CU* = Parkinson's disease without cognitive impairment; *PDD* = Parkinson's disease dementia; *PD-ND* = Parkinson's disease without dementia; *LEDD* = levodopa equivalent daily dose; *MMSE* = mini-mental state examination; *UPDRS-III* = unified Parkinson's disease rating scale part III; *ON* = on medication at time of scan; *OFF* = off medication or drug-naïve at time of scan; NAÏVE = off medication and drug naïve at time of scan; *H-Y stage* = Hoehn and Yahr scale stage; *MRI* = magnetic resonance imaging; *fMRI* = functional magnetic resonance imaging; *VBM* = voxel based morphometry; *CTh* = cortical thickness; *PET* = positron emission tomography; *FDG-PET* = [$^{18}$F]fludeoxyglucose; *MoCA* = Montreal Cognitive Assessment; *SD* = standard deviation; *DSM* = Diagnostic and statistical manual of mental disorders; *CDR* = Clinical dementia rating scale; *ADL* = activities of daily living; *NA* = datum not available

[a] mean (standard deviation)

**Table 3** Participant demographic and clinical characteristics for PD-MCI and PDD

| Population | Number of Subjects | Age | Disease Duration (years) | UPDRS-III | H-Y Stage | MMSE | LEDD (mg/day) | Education (years) |
|---|---|---|---|---|---|---|---|---|
| PD-CU | 796 | 62.88 (3.41) | 3.87 (3.05) | 20.43 (4.75) | 1.98 (0.35) | 28.93 (0.44) | 296.21 (300.92) | 12.37 (2.26) |
| PD-MCI | 577 | 67.23* (4.03) | 5.26 (3.74) | 23.73* (5.80) | 2.22 (0.43) | 27.68* (0.90) | 558.18 (361.03) | 10.56 (2.02) |
| PD-ND | 278 | 67.90 (4.34) | 5.30 (3.20) | 22.69 (4.88) | 2.29 (0.37) | 28.25 (0.85) | 322.29 (181.82) | 10.99 (2.33) |
| PDD | 178 | 71.50 (1.74) | 8.75 (3.16) | 34.84† (9.44) | 3.33† (0.51) | 20.14† (3.02) | 570.54 (201.30) | 8.12 (2.36) |

Demographic information population sample, number of subjects, and the weighted average and weighted standard deviation of: age, disease duration in years, Unified Parkinson's Disease Rating Scale – Category III (UPDRS-III), Hoehn and Yahr scale stage (H-Y stage), Mini-Mental State Examination score (MMSE), Levodopa equivalent daily dose (LEDD), and the numbers of years of education. PD-MCI = Parkinson's disease patients with mild cognitive impairment, PD-CU = Parkinson's disease patients without any measurable cognitive impairment, PDD = Parkinson's disease patients with dementia, PD-ND = Parkinson's disease patients without dementia

* means this value had statistically significant differences in the independent samples t-test between PD-MCI and PD-CU with $p < 0.05$

† means this value had statistically significant differences in the independent samples t-test between PDD and PD-ND with $p < 0.05$

is likely dysfunction in the left angular gyrus may contribute to this symptom. The structural PD-MCI findings within the somatosensory network were not observed in the functional PD-MCI results. Somatosensory deficits are an early

**Table 4** Results of the three different analyses for PD-MCI and PDD

| Location | Local peak (MNI) | | | BA | *p*-value, uncorrected | Z-Score | Voxels | Cluster Breakdown (No. of voxels) [Largest 3 Clusters] |
|---|---|---|---|---|---|---|---|---|
| | x | y | z | | | | | |
| Structural analysis PD-MCI vs. PD-CU | | | | | | | | |
| L Insula / L Heschl gyrus | −42 | −18 | 12 | 48 | 0.00008 | −2.953 | 293 | L heschl gyrus, BA 48 (87)<br>L rolandic operculum, BA 48 (82)<br>L insula, BA 48 (80) |
| R Supramarginal gyrus / R Postcentral gyrus | 62 | −20 | 30 | 43 | 0.00002 | −3.160 | 229 | R supramarginal gyrus, BA 48 (100)<br>R postcentral gyrus, BA 43 (43)<br>R supramarginal gyrus, BA 2 (40) |
| Midcingulate / L Paracingulate gyri | −4 | −12 | 44 | 23 | 0.00005 | −3.021 | 142 | median cingulate / paracingulate gyri, BA 23 (73)<br>median cingulate / paracingulate gyri (31)<br>L supplementary motor area (18) |
| Functional analysis PD-MCI vs. PD-CU | | | | | | | | |
| L Angular gyrus | −50 | −60 | 28 | 39 | 0.000009 | −2.413 | 1106 | L angular gyrus, BA 39 (361)<br>L inferior parietal (excluding supramarginal and angular) gyri, BA 40 (142)<br>L supramarginal gyrus, BA 40 (103) |
| L Dorsolateral prefrontal.cortex | −38 | 16 | 46 | 9 | 0.000008 | −2.419 | 283 | R middle frontal gyrus, BA 9 (117)<br>R middle frontal gyrus, BA 44 (68)<br>R middle frontal gyrus, BA 46 (39) |
| R Dorsolateral prefrontal cortex | 42 | 22 | 44 | 9 | 0.00008 | −2.120 | 286 | L middle frontal gyrus, BA 9 (103)<br>L precentral gyrus, BA 6 (64)<br>L middle frontal gyrus, BA 6 (51) |
| Structural analysis PDD vs. PD-ND | | | | | | | | |
| R Insula / R superior temporal gyrus / R Hippocampus | 54 | 2 | −10 | 38 | 0.000001 | −3.849 | 4639 | R insula, BA 48 (775)<br>R temporal pole, superior temporal gyrus, BA 38 (370)<br>R rolandic operculum, BA 48 (303) |
| L Insula / L middle temporal gyrus | −40 | −8 | −16 | 20 | 0.00025 | −2.454 | 334 | L middle temporal gyrus, BA 21 (41)<br>L insula, BA 48 (26)<br>L temporal pole, superior temporal gyrus, BA 38 (25) |

L = left; R = right; BA = Brodmann area; MNI = Montreal Neurological Institute coordinates

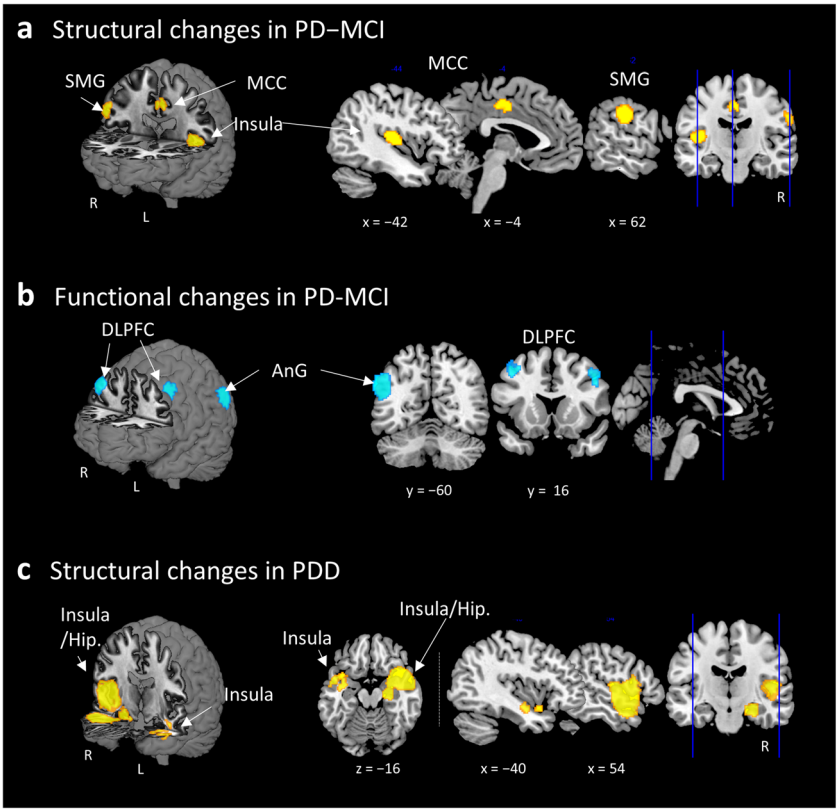


**Fig. 2** Brain regions of significance found when thresholded to $p < 0.001$. (**a**) Structural changes in patients with Parkinson's disease with mild cognitive impairment vs. Parkinson's disease without cognitive impairment (**b**) Functional changes in patients with Parkinson's disease with mild cognitive impairment vs. Parkinson's disease without cognitive impairment (**c**) Structural changes in patients with Parkinson's disease dementia vs. Parkinson's disease patients without dementia. SMG = supramarginal gyrus, MCC = midcingulate cortex, DLPFC = dorsolateral prefrontal cortex, AnG = angular gyrus, Hip. = hippocampus

symptom of PD, and the brain regions responsible for these symptoms are likely atrophied, affecting functional imaging data (Conte et al. 2013). Taken together with the results of Gonzalez-Redondo et al. (2014), we hypothesize that structural atrophy in the somatosensory network may occur at the same time as PD-MCI manifesting, with PD-CU patients only having functional impairments in those brain areas. Thus, when comparing PD-MCI to PD-CU as our included studies have done, the somatosensory network deficit may not be visualized with functional imaging because the somatosensory brain areas in the PD-MCI group may have already developed structural atrophy with no functional imaging signal to be detected. The differences can only be visualized when using structural brain imaging comparing PD-MCI to the PD-CU group, the latter group not yet having structural impairments in those areas.

In the current study, we found GMV atrophy in the left insular cortex in PD-MCI patients and to a larger degree with involvement of the bilateral insula as well as of the right hippocampus in PDD patients. This seems to suggest a possible progression of the atrophy as PD progressed from PD-MCI to PDD. As described earlier, while the posterior insula is related more to sensorimotor processing and bodily awareness, the anterior insula is generally related to attentional processing, cognitive control and decision making (Chang et al. 2013; Klein et al. 2013; Christopher et al. 2014). There is strong evidence of the bilateral involvement of the insula in the non-motor symptoms of PD (Criaud et al. 2016; Christopher et al. 2014). Criaud et al. (2016) performed a meta-analysis which found clusters of significant convergence in both the anterior and posterior insula confirming that the insula is indeed a key region affected by cognitive decline in PD. The involvement of the insula bilaterally when comparing PD-MCI to PDD led us to believe the importance of this brain region in cognitive deterioration.

Our study found the right hippocampus to be a significant site of gray matter atrophy in the PDD patients compared to PD-ND patients, confirming the results of the previous studies (Pan et al. 2013; Xu et al. 2016). The hippocampus is heavily involved in procedural and declarative memory and learning (Eichenbaum 2000), and growing evidence suggests that the dopaminergic system may facilitate synaptic plasticity in the hippocampus, thus contributing to memory formation (Rocchetti et al. 2015; Etter and Krezel 2014; Nyberg et al. 2016). Zarei et al. (2013) found that hippocampal volume and cortical thinning predicted PDD with 80% accuracy in a sample of PD patients. Thus, confirming previous reports that found that neurodegeneration of the hippocampus in PDD follows a pattern of beginning at the head of the anatomical structure and then later spreading to the tail Ibarretxe-Bilbao et al. (2008). The lack of evidence of parietal-occipital degeneration in the PDD group analysis may be due to the fact that several of the PDD studies specifically excluded patients who had dementia with Lewy bodies, which have a characteristic

deficit in the occipital regions when scanned with FDG-PET (Mak et al. 2014a). Further research of PD cognitive impairment, especially regarding sub-typing of PD-MCI and PDD conversion, is important for providing better patient care and symptom management.

### Limitations

There are some limitations to make note of in our study. We pooled together different imaging analyses and methodologies into the same meta-analysis group. This was done for structural studies including VBM and cortical thickness. This might have reduced the sensitivity of the current findings on structural changes of subcortical regions, such as the basal ganglia. However, VBM and cortical thickness studies have been shown to have very consistent and complementary results in an aging population as is the case with PD (Hutton et al. 2009). Lastly, we included fMRI studies that utilized seed-based or independent component analysis. For the purposes of our study, we assumed that any brain region found through either seed-based or independent component analyses are both representative of functional abnormalities in PD patients, as the present meta-analysis focused on the brain activity differences and not connectivity changes. While we believe these groupings are valid for our meta-analysis, some caution should be taken when interpreting these imaging techniques together.

## Conclusion

In summary, within the limitations intrinsic to a meta-analysis, our results indicate that the structural and functional changes in the brains of PD patients occur at different rates and in different brain regions, suggesting that different processes are responsible for the decline. The progression of atrophy in PD-MCI and PDD strongly suggests that cognitive decline in PD occurs along a spectrum, with increasing grey matter loss and functional impairment as the disease progresses, leading to greater cognitive decline. Our study found structural brain atrophy unique to PD-MCI pathophysiology in the MCC and right supramarginal gyrus, as well as brain atrophy in areas common with PDD in the left insula, spreading to bilateral insular involvement in PDD. Coupled with the brain changes in the DLPFC found in the functional analysis of PD-MCI, it is likely that these three analyses captured distinct aspects of PD cognitive impairment. Our results support the hypothesis that PD-MCI is made up of different subtypes with unique pathologies and further research should be conducted to elucidate these PD-MCI subtypes to provide better long-term prognosis.

### Glossary

**PD:** Parkinson's disease.
**MCI:** mild cognitive impairment.
**PD-MCI:** Parkinson's disease with mild cognitive impairment.
**PDD:** Parkinson's disease dementia.
**PD-CU:** Parkinson's disease without any cognitive impairment.
**PD-ND:** Parkinson's disease without dementia.
**AES-SDM:** anisotropic effect size seed-based *d* mapping.
**PET:** positron emission tomography.
**FDG:** [$^{18}$F]fluodeoxyglucose.
**MRI:** magnetic resonance imaging.
**fMRI:** functional magnetic resonance imaging.
**GMV:** grey matter volume.
**MNI:** Montreal Neurological Institute.
**VBM:** voxel-based morphometry.
**CTh: c**ortical thickness.
**UPDRS-III:** Unified Parkinson's Disease Rating Scale Part III.
**MMSE:** Mini-Mental State Examination.
**H-Y:** Hoehn-Yahr staging.
**DLPFC:** dorsolateral prefrontal cortex.
**MCC:** midcingulate cortex.

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### Compliance with ethical standards

**Conflicts of interest** The authors declare they have no conflict of interest with this study.

**Ethical approval** This article does not contain any studies with human participants performed by any of the authors.

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