Neuroimaging outcomes associated with mild cognitive impairment subtypes in Parkinson's disease: A systematic review.

Quentin Devignes, Renaud Lopes, Kathy Dujardin

Version of Record: https://www.sciencedirect.com/science/article/pii/S1353802022000396
Manuscript_708f9b177cf328a42946969e5beb8e0f

Neuroimaging outcomes associated with mild cognitive impairment subtypes in Parkinson's disease: a systematic review

Quentin Devignes[a*], Renaud Lopes[a,c], Kathy Dujardin[a,b]

[a] Univ. Lille, Inserm, CHU Lille, Lille Neurosciences and Cognition, F-59000 Lille, France

[b] Neurology and movement disorders department, Lille University Medical Centre, F-59000 Lille, France

[c] Univ. Lille, CNRS, Inserm, CHU Lille, Institut Pasteur de Lille, US 41 – UMS 2014 – PLBS, F-59000 Lille, France

Running title: Neuroimaging and PD-MCI subtypes

Word counts
Abstract: 220/250 words
Manuscript: 4,219/4,000 words
Running title: 32 characters
Illustrations: 5 tables and 3 figures
Supplemental material: supplementary material includes additional figures and tables

Declarations of interest: None
Funding source: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

[*]Correspondence to Quentin DEVIGNES, PhD

Université de Lille, Faculté de médecine – Pôle Recherche, Département de pharmacologie médicale, 1 place de Verdun, F-59045 Lille cedex, France

Tel. : +33 635-219-381 ; e-mail: qdevignes@gmail.com

Abstract

Background – Mild cognitive impairment in Parkinson's disease (PD-MCI) is heterogenous and cognitive subtypes have been identified. However, the anatomo-functional bases of each subtype remain partly unknown.

Objective – To propose a description of the current literature on neuroimaging findings associated with cognitive subtypes of PD-MCI.

Methods – PubMed/Medline, Embase, PsycINFO and the Cochrane Library databases were searched (until April 2021). Studies comparing PD-MCI cognitive subtypes with healthy controls (HC) and PD patients with normal cognition (PD-NC) on any neuroimaging outcome were included.

Results – Ten studies met the inclusion criteria. Six used structural MRI methods, two functional MRI methods, one electroencephalography and five positron or single-photon emission tomography. Most studies (n=8) determined PD-MCI subtypes based on memory impairment and two based on executive impairment. Compared with HC and/or PD-NC, brain modifications were found in PD patients (a) with amnestic MCI and, to a lesser extent, non-amnestic MCI in occipital, parietal and temporal regions, (b) with executive MCI in frontal and striatal regions and (c) with non-executive MCI in posterior cortical regions.

Conclusions – Very few neuroimaging studies have considered cognitive heterogeneity that exists within PD-MCI, making it difficult to draw robust conclusions regarding brain modifications associated with specific subtypes. Given the promising potential of neuroimaging methods in both clinical practice and research, further studies are needed to overcome the limitations of the current literature.

Keywords: magnetic resonance imaging; electroencephalography; positron-emission tomography; single photon emission computed tomography; cognitive dysfunction; memory; executive function

1. Introduction

Parkinson's disease (PD) is a neurodegenerative pathology characterized by both motor and non-motor symptoms including cognitive impairment. Mild cognitive impairment in Parkinson's disease (PD-MCI) refers to significant cognitive deficits in PD patients without global cognitive decline and with preserved independence for the main activities of daily living [1,2]. This concept corresponds to a transitional state between normal cognition for age and education and Parkinson's disease dementia (PDD). International consensus diagnostic criteria have been published [3] as well as recommendations for the assessment of five main cognitive domains that can be affected individually or in various combination [1,3,4]. The estimated mean prevalence of PD-MCI is 27% [5] but varies according to the studies [2]. PD-MCI patients have a higher risk of developing PDD [6] but some also revert to normal cognition [7,8]. Moreover, PD-MCI is heterogenous. PD-MCI subtypes have been identified with data-driven [9–11] or *a priori* approaches [12–14]. Using a data-driven approach, Williams-Gray et al. reported that PD patients who converted to PDD after a 5-year follow-up had poorer baseline performance on visuospatial and semantic fluency tests than PD patients who did not [15]. These results were confirmed at the 10-year follow-up of the same cohort [16]. This finding led to the formulation of the dual syndrome hypothesis that suggests the existence of two cognitive subtypes in PD-MCI [17]: a frontostriatal one, characterized by attention/working memory and executive deficits, and a posterior cortical one, characterized by visuospatial, memory and language deficits and which is associated with a higher risk of developing PDD. This model is more and more accepted in the scientific literature [18–21]. Identifying cognitive subtypes in PD-MCI is of critical interest to improve both therapeutic care and understanding of the underlying physiopathological mechanisms. Several studies have reported various anatomical and functional alterations in PD-MCI compared to healthy controls (HC) and, to a lesser extent, to PD patients with normal cognition (PD-NC)

[2,22,23]. Although systematic reviews have been conducted regarding neuroimaging changes in PD-MCI, none has been interested in cognitive subtypes in PD-MCI. Therefore, the aims of this systematic review were (a) to propose a description of the current literature on neuroimaging findings associated with cognitive subtypes in PD-MCI and (b) to identify the brain modifications associated with these subtypes.

2. Methods

The protocol of the present systematic study adhered to the recommendations proposed by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [24,25] and has been registered at PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=243408).

2.1 Inclusion and exclusion criteria

A literature search was performed in PubMed/Medline, Embase, PsycINFO and the Cochrane Library. We determined an optimal search strategy for PubMed/Medline database (**Table 1**) according to previous recommendations [26], and then modified it to match the specificity of each other database (**Supplementary Material Tables 1, 2 and 3**). To reduce the number of results, we used filters whenever possible. The search was conducted across the entire time span until April 12, 2021. We included studies (a) with PD patients that assessed PD-MCI and identified distinct cognitive subtypes, (b) using any method of neuroimaging such as structural or functional MRI, electroencephalography (EEG), positron emission tomography (PET) or single-photon emission computed tomography (SPECT), (c) comparing HC and/or PD-NC with PD patients with specific cognitive impairment on imaging parameters. To ensure the inclusion of all relevant studies, a broad definition of PD-MCI was adopted, namely specific cognitive deficits at neuropsychological tests without global

cognitive decline and impact on main activities of daily living, regardless of the diagnostic criteria used for PD-MCI. Moreover, there was no specific criteria regarding the cognitive categorization procedure as long as we were able to identify distinct cognitive subtypes. The exclusion criteria were: (a) review/methodological articles reporting no original data or preclinical studies, (b) studies dealing with other diseases than PD, (c) studies without assessment of PD-MCI or without cognitive subtyping of PD-MCI, (d) studies without comparison of PD-MCI subtypes with HC and/or PD-NC, (e) studies without neuroimaging, (f) studies not in English, (g) case reports.

2.2 *Data selection and extraction*

Eligibility was determined independently by two authors (QD and KD). Firstly, duplicates were removed from the research results. Then, screening of the title and abstract was performed, followed by the screening of the entire article to confirm the inclusion. Discrepancies were resolved in a consensus meeting and a third specialist (RL) was consulted if no consensus was reached. Finally, two authors (QD and KD) extracted data. The following information was extracted from each study: the first author, the year of publication, the journal name, the sample nature and size, demographic characteristics (age, sex, educational level), clinical characteristics (disease duration, disease severity (Hoehn and Yahr stage), antiparkinsonian medication (levodopa equivalent daily dose), motor symptoms severity (assessed with either the Unified Parkinson's disease rating scale – part III [27] or the Movement Disorders Society (MDS) version [28]), neuropsychiatric measures), the performance on global cognitive efficiency tests, the neuropsychological assessment, the cognitive categorization procedure. Regarding neuroimaging data, we extracted the MRI sequence used, the magnetic field strength, the number of electrodes for EEG, the name of the manufacturer, the neuroimaging method, the neuroimaging outcomes and the statistical

analysis. Regarding the imaging results, we extracted the localization labels, the peak coordinates of the significant brain areas in the Montreal Neurological Institute space and the statistical values when available. When needed, we converted coordinates in the Talairach space into coordinates in the Montreal Neurological Institute space. For visualization purpose, we used BrainNet toolbox [29] to project peak coordinates (when available) of significant results between HC/PD-NC and PD-MCI cognitive subtypes on a brain representation for each neuroimaging approach.

2.3 *Quality assessment*

To assess the risk of bias in individual studies, the approach proposed by Wolters et al. [30] was used. It corresponds to nine items (**Supplementary Material Table 4**) that were rated for each selected study by two independent authors (QD and KD). Each item could score 0, 0.5 or 1 point. An overall score of ≥7.5 was considered as good quality, 4–7.5 as moderate quality, and ≤4 as poor quality [30]. Discrepancies were discussed until consensus was reached. If no consensus could be reached, a third specialist was consulted (RL).

3. Results

3.1 Research results

The PRISMA flowchart of the study selection procedure is presented in **Figure 1**. Ten neuroimaging studies met the inclusion criteria. Some studies used several neuroimaging methods. Six studies used structural methods [31–36], two functional methods [34,36], one EEG [37], three analyzed neurotransmitter/transporter activity [32,36,38], one brain glucose metabolism [39] and one brain perfusion [40]. In total, these studies gathered data from 204 HC, 170 PD-NC patients and 355 PD-MCI patients. Within PD-MCI patients, two main approaches were used to determine cognitive subtypes: eight studies subtyped PD-MCI

according to the presence of memory impairment, distinguishing amnestic subtype (PD-aMCI) and non-amnestic subtypes (PD-naMCI) [31–36,39,40], while two studies subtyped PD-MCI according to the presence of executive impairment, distinguishing executive (PD-exMCI) and non-executive (PD-nexMCI) subtypes [37,38]. One study also distinguished a PD-MCI subtype with impairment in multiple cognitive domains (PD-MCI multiple) [39]. Finally, two studies also included a group of non-PD MCI patients (nonPD-aMCI) [31,40]. Demographic and clinical characteristics are presented in **Table 2**. It is noteworthy that the criteria used to identify PD-MCI and the subtyping methods were heterogenous (for details, see **Table 2**). The MDS international criteria [3] were used in five studies [32,34–36,38], a modified version of Petersen's criteria [41] in three studies [31,39,40] and two studies used other criteria [33,37]. Moreover, various cut-off scores were applied: six studies used a cut-off of ≤-1.5 standard deviations [32–35,38,40], three studies a cut-off of ≤16th percentile, which represents a cut-off of ≤-1 standard deviation [31,36,39], and one study a cut-off of <70 for a standardized score, which represents a cut-off of ≤-2 standard deviations [37]. Finally, the number of tests or cognitive variables considered to identify PD-MCI patients also varied between studies.

Regarding the quality assessment, two studies had a good quality total score [32,35] and eight a moderate one [31,33,34,36–40] (**Supplementary Material Tables 5 and 6** for details).

From now on, we only focus on significant results between HC/PD-NC and PD-MCI cognitive subtypes (PD-aMCI, PD-naMCI, PD-exMCI and PD-nexMCI).

3.2 Structural studies

The six studies using structural methods [31–36] included 149 HC, 89 PD-NC patients, 146 PD-aMCI and 84 PD-naMCI. Regarding neuroimaging methods, detailed results are

presented in **Table 3** and showed that two studies used voxel-based morphometry [31,34], two cortical thickness [32,36], one hippocampal volume [36] and three white matter integrity [33,35,36]. Voxel-based morphometry studies reported reduced volume of the left amygdala, right rectal gyrus, right middle occipital gyrus, left middle frontal gyrus, left precentral gyrus and right precuneus in PD-aMCI compared with HC. There was no significant difference between PD-naMCI and HC/PD-NC. One study analyzing cortical thickness revealed cortical thinning in PD-aMCI in left frontotemporal regions compared with HC [36], while the other did not report any significant difference [32]. The hippocampal volumes were not significantly different between HC, PD-aMCI and PD-naMCI [36]. Studies analyzing white matter integrity showed reduced fractional anisotropy in PD-aMCI compared with PD-NC in several cortical and subcortical regions, including the corpus callosum, the bilateral cingulate gyri, the bilateral posterior thalamic radiation, the bilateral posterior corona radiata, the left superior corona radiata, the right tapetum, the bilateral superior and inferior longitudinal fascicles, the bilateral inferior fronto-occipital fascicles and the left fornix [35]. Compared with HC, PD-aMCI and PD-naMCI also showed reduced fractional anisotropy in bilateral fronto-temporo-parietal regions and corpus callosum [36]. Finally, one study used the graph theory approach to analyze white matter structural connectivity and reported reduced mean node strength and mean path length in a network including 82 brain areas in PD-aMCI compared with HC [33]. In all selected studies, there was no significant structural difference between PD-aMCI and PD-naMCI. **Figure 2** represents brain areas with significant volumetric or diffusion MRI difference between PD-MCI subtypes and HC/PD-NC in studies providing peak coordinates.

3.3 Functional MRI studies

The two studies using functional methods [34,36] analyzed functional connectivity strength based on the blood-oxygen-level-dependent signal. They both subtyped PD-MCI according to the presence of memory impairment and included 54 HC, 28 PD-NC patients, 70 PD-aMCI and 74 PD-naMCI. Detailed results are presented in **Table 4**. PD-aMCI showed reduced functional connectivity in the central executive network and the dorsal attentional network compared with HC and in the default-mode network compared with HC, PD-NC and PD-naMCI. PD-naMCI showed reduced functional connectivity in the default-mode, the dorsal attentional and the central executive networks compared with HC, in the visual network compared with HC and PD-NC, in the cerebellum network compared with HC and PD-aMCI. PD-aMCI also had increased functional connectivity in the salience network compared with HC. There was no significant result regarding increased functional connectivity in PD-naMCI compared with HC. For studies providing peak coordinates, **Figure 2** represents brain areas with significant connectivity difference in functional MRI between PD-MCI subtypes and HC/PD-NC.

3.4 EEG study

One study used quantitative EEG and included 25 PD-NC and 7 PD-exMCI patients [37]. The authors analyzed the spectral ratio (defined as the sum of the absolute power values for alpha and beta frequency bands divided by the sum of the absolute power values for delta and theta) at six brain locations and showed that this ratio was a significant predictor of executive impairment in the frontal cortex and the frontal pole. Data from left and right electrodes were averaged since there was no significant difference between both hemispheres. Results are presented in **Table 4**.

3.5 PET/SPECT studies

The five studies using PET/SPECT methods [32,36,38–40] included 99 HC, 67 PD-NC patients, 86 PD-aMCI, 71 PD-naMCI, 38 PD-exMCI and 24 PD-nexMCI. Regarding neuroimaging methods, three studies analyzed striatal and/or cortical dopaminergic transporter/receptors or striatal vesicular monoamine transporter (i.e. a marker for dopaminergic neuron integrity) [32,36,38]. One of them showed that (a) PD-aMCI had reduced dopaminergic receptor availability in the right parahippocampal gyrus, the bilateral insula and the bilateral anterior cingulate cortex compared with HC and, to a lesser extent, with PD-NC and PD-naMCI; (b) PD-naMCI had reduced dopaminergic receptor availability in the bilateral insula and the right parahippocampal gyrus compared with HC and PD-NC; (c) PD-aMCI had also reduced striatal vesicular monoamine transporter binding in the associative striatum compared with PD-NC [32]. Another study found no significant difference regarding striatal dopamine active transporter binding potential between PD-aMCI/PD-naMCI and HC/PD-NC [36]. Finally, one study analyzed the cortical and striatal dopamine active transporter binding potential and reported: (a) reduced binding in the bilateral frontal, temporal and parietal cortices, the cerebellum, the midbrain and the putamen in PD-exMCI compared with HC and PD-NC; (b) reduced binding in the bilateral occipital, temporal, parietal, posterior cingulate cortices and the bilateral lentiform nuclei in PD-nexMCI compared with HC; (c) reduced binding in the bilateral caudate nuclei in PD-exMCI compared with PD-NC and PD-nexMCI.

Furthermore, one study analyzed brain perfusion and reported reduced perfusion in PD-aMCI in several parietal, occipital and precuneus areas compared with HC [40]. Finally, one study analyzed cerebral glucose metabolism and found hypometabolism in the right precentral, the right superior temporal, the right postcentral, the left middle temporal, the left angular, the left cuneus and the left middle occipital areas in PD-naMCI compared with HC [39]. There was no significant difference between HC/PD-NC and PD-aMCI regarding brain

glucose metabolism. Detailed results are presented in **Table 5**. For studies providing peak coordinates, **Figure 2** represents brain areas with significant difference between PD-MCI subtypes and HC/PD-NC identified with PET and SPECT methods.

4. Discussion

The aim of this systematic review was to determine whether distinct cognitive subtypes in PD-MCI were associated to specific brain modifications. Ten studies were included and the results showed that (a) only very few neuroimaging studies have considered the cognitive heterogeneity that exists within PD-MCI, (b) most focused on memory performance to determine cognitive subtypes in PD-MCI and (c) brain modifications have been reported in these subtypes.

4.1 Cognitive heterogeneity of PD-MCI is little considered in neuroimaging studies

Only very few neuroimaging studies have considered the cognitive heterogeneity that exists within PD-MCI. We used a broad search strategy including a large number of terms to refer to cognitive deficits/subtypes and neuroimaging methods in order to minimize the risk of missing a relevant paper. Moreover, we defined PD-MCI with a broad definition to include as many studies as possible. However, out of 3,575 articles, only ten met the inclusion criteria of this review. Interestingly, 231 articles dealing with PD-MCI were excluded because they did not determine PD-MCI subtypes. This result highlights a gap in the scientific literature regarding PD-MCI subtyping in neuroimaging studies. However, a growing body of evidence shows that cognitive heterogeneity is a key aspect in PD-MCI [1,5,19,21]. Neuroimaging approaches are powerful and promising tools to help identify patients who are at higher risk of developing severe cognitive impairment and to help decipher the pathophysiological mechanisms associated with distinct cognitive subtypes [42]. It is thus of crucial interest to

promote neuroimaging studies of cognitive subtypes in PD-MCI. The small number of studies considering cognitive heterogeneity in PC-MCI raises questions. Despite awareness of cognitive deficits in PD, studies focused for a long time on dementia. The concept of PD-MCI was only introduced in 2007 [1] and diagnostic criteria published in 2012 [3]. It is noteworthy that these criteria considered subtyping based on the number of impaired cognitive domains (single versus multiple domain) but not depending on the nature of the deficits. Nevertheless, they provided a framework for a more standardized and comprehensive neuropsychological assessment convenient for subtyping. Since then, neuroimaging studies mainly focused on comparing PD-MCI versus HC and/or PD-NC, with inconsistent results [2,18]. Although cognitive heterogeneity was mentioned since the introduction of the concept of MCI in PD [1], studying the neuroimaging correlates associated with distinct subtypes has started only recently, with half of the studies included in this review published in the last four years. Finally, we did not include data-driven studies in the present systematic review. Although these studies found interesting results and may reveal cognitive clusters similar to the PD-MCI subtypes identified in this review, it is difficult to determine whether patients in these clusters had PD-MCI according to consensus criteria [43–47].

4.2 PD-MCI subtypes are associated with brain modifications

The selected studies reported brain modifications in PD-MCI subtypes. Indeed, compared with HC and/or PD-NC, PD-aMCI patients displayed changes mainly in parietal, occipital and temporal regions with either structural [31,33–36], functional [34,36] or PET/SPECT [32,40] approaches. Similar results were also found in PD-naMCI patients but to a lesser extent [32,34,36,39]. **Figure 3** summarizes brain modifications between HC/PD-NC and PD-aMCI or PD-naMCI regardless of the neuroimaging approach. However, two studies did not report any significant differences between PD-aMCI or PD-naMCI and HC/PD-NC

regarding cortical thickness [32] and striatal dopamine availability [36]. Besides, the voxel-based morphometry analyses only revealed small significant clusters in PD-aMCI compared with HC [31,34]. These results demonstrate the great heterogeneity in neuroimaging outcomes associated with PD-MCI subtypes. Data-driven studies also reported inconsistent results. Indeed, Bayram et al. found cortical atrophy in PD patients with weak memory/learning performance compared to PD-NC patients [44], whereas Crowley et al. showed no significant difference between PD patients with low memory performance compared to HC and PD-NC regarding cortical and subcortical volumes, but reduced structural connectivity between the hippocampus and the entorhinal cortex in both hemispheres in these patients compared to HC [43]. Interestingly, both functional MRI studies included in this review reported significant hypoconnectivity in the default-mode in PD-aMCI and PD-naMCI patients [34,36], which is in line with a recent metanalysis reporting that this specific network was associated with cognitive decline in PD [30].

Furthermore, two studies distinguished PD-MCI subtypes according to executive impairment and showed that (a) PD-exMCI patients has a slowing of EEG in frontal regions [37] and reduced dopamine availability mainly in frontal and striatal regions compared with HC and in posterior regions compared with PD-NC [38] and (b) PD-nexMCI patients had reduced dopamine availability mainly in posterior cortical regions compared with HC [38]. Moreover, no study included in this review has applied structural and functional MRI approaches in PD-exMCI and PD-nexMCI patients. However, using a data-driven approach, Crowley et al. showed recently that PD patients with low executive performance displayed cortical and subcortical alterations as well as structural connectivity changes between the dorsolateral prefrontal cortex and the caudate nucleus and between the hippocampus and the entorhinal cortex in the right hemisphere compared to HC, PD-NC and/or PD patients with low memory performance [43].

Taken together, these results suggest that amnestic PD-MCI patients have brain modifications mainly in posterior cortical regions, while no robust conclusions can be drawn for non-amnestic, executive and non-executive PD-MCI subtypes given the small number of studies identifying these subtypes. Finally, it is noteworthy that if the nature of cognitive deficits must be considered, their severity must also be taken into account. Indeed, several studies reported structural, functional and EEG alterations associated with more severe cognitive deficits in PD [45–47].

4.3 Cognitive subtyping in neuroimaging studies is mainly focused on memory impairment

Out of the ten studies included in the present systematic review, eight distinguished cognitive subtypes in PD-MCI according to the presence of memory impairment and two according to the presence of executive impairment. The high rate of subtyping on memory performance is partly due to the origin of the concept of MCI. Indeed, this concept was developed to refer to a transitional state between cognitive changes in normal aging and Alzheimer's disease, a neurodegenerative pathology cognitively characterized mainly by memory impairment [41]. Thereafter, it has been applied in PD to refer to a pre-dementia state [1]. However, the consideration of memory as the key cognitive function to distinguish cognitive subtypes in PD can be questioned. Indeed, if memory impairment has been associated with a higher risk of PDD [36,48], deficits in other cognitive domains have also been, especially visuospatial functions and semantic fluency [15,16,48]. Moreover, some studies reported that patients with cognitive impairment in multiple domains are at higher risk of developing PDD [48], suggesting that the number of impaired cognitive domains is also crucial. It is noteworthy that most PD-MCI patients in the included studies had deficits in multiple domains. Given these limitations, the dual syndrome hypothesis [17] appears to be a relevant model to distinguish cognitive subtypes because (a) it does not focus on one specific

cognitive domain but combines several domains together within two subtypes, (b) it has a predictive potential, namely posterior cortical deficits are associated with a higher risk of developing dementia, and (c) it is applicable in clinical practice and research. Although this hypothesis is more and more cited in the scientific literature [18–21,49], at time of this systematic review, we did not find any study using this hypothesis *per se* to determine cognitive subtypes in any neuroimaging studies of PD-MCI. Recently, we published a paper in which we distinguished frontostriatal and posterior cortical PD-MCI subtypes and showed for the first time that, compared with PD-NC, PD patients with posterior cortical deficits, isolated or not, had more abundant and more extensive structural alterations than PD patients with isolated frontostriatal deficits [14]. However, this study was published after the literature search on which the present systematic review was based. Further studies are needed to confirm our findings and analyze the predictive potential of these alterations regarding the risk of developing PDD.

4.4 Strengths and limitations

The main strength of the present review was to use a broad search strategy and apply it in four databases in order to minimize the risk of missing a relevant paper. We also included a large number of neuroimaging methods. This review provides therefore a description of the current scientific literature dealing with neuroimaging outcomes in PD-MCI subtypes. Moreover, we performed this review according to international recommendations. We also published the protocol on Prospero to ensure a total transparency.

The main limitation of the present systematic review is the high heterogeneity of the selected studies, concerning in particular the definition of PD-MCI, the subtyping method and the neuroimaging technique. This heterogeneity prevents from drawing robust conclusions regarding the brain modifications associated with PD-MCI subtypes. Indeed, the diagnostic

criteria used to identify PD-MCI subtypes were heterogenous. Even among the six studies published after the publication of the diagnostic criteria for PD-MCI [3], one did not use them to identify PD-MCI patients [33] and only a small subset [32,35,36] used at least two tests *per* cognitive domain (level II) as recommended for establishing PD-MCI subtypes [3]. Moreover, the cut-off scores used to determine that a cognitive test/variable was failed, were heterogenous, ranging from -1 to -2 standard deviations. Therefore, one can wonder whether the different populations can be compared, including from a pathophysiological point of view, as the cut-off score has a direct impact on the severity of cognitive impairment. Therefore, it is of critical interest to promote the utilization of the consensus diagnostic criteria [3] to identify PD-MCI patients and to develop standardized subtyping methods to improve inter-studies comparability.

Furthermore, several other limitations have to be considered. Although the PD-aMCI subtype may appear as having extended and abundant brain modifications, this may be explained by the high frequency of studies basing subtyping only on memory impairment (80%) and by the absence of contrast with a PD-naMCI subtype in half of these studies. Results regarding PD-exMCI and PD-nexMCI patients have to be interpreted with caution given the small number of studies using this cognitive categorization and the small sample sizes. In general, it is noteworthy that the sample size of the PD-MCI subgroups was smaller than 20 in six out of the ten studies included in this review, which raises question about the statistical power of these studies. Moreover, all PD-MCI patients had deficits in several cognitive domains, except in one study which considered a single-domain amnestic MCI group [39].

Finally, limitations specific to each study may be noticed and are detailed in **Supplementary Material Table 6**. Demographic data like sex ratio or educational level and clinical data such as levodopa equivalent daily dose or Hoehn and Yahr stage, were missing in

some studies. As these variables are of critical interest, we recommend a more rigorous characterization of study groups, including at least the following variables: age, sex, level of education, disease duration, levodopa equivalent daily dose, severity of the motor symptoms. Besides, only four studies controlled for neuropsychiatric symptoms [32,33,38,40]. Given the high prevalence of such disorders in PD and their impact on cognition [50,51], it is essential to systematically assess them for inclusion as covariates in statistical analysis. Regarding neuroimaging analysis, some data were missing or not explicitly stated, especially the (pre)processing steps, the quality control measures of imaging data or the application of a statistical correction for multiple comparisons. At last, the spatial coordinates of the significant brain areas were often missing, preventing any accurate localization of the results.

4.5 Conclusions and perspectives

The present systematic review shows that neuroimaging approaches could provide a promising support to decipher the mechanisms of cognitive heterogeneity in PD-MCI. However, the current scientific literature on this particular topic is still very limited. With the publication of international criteria for PD-MCI diagnosis and the growing body of evidence showing how crucial it is to consider cognitive heterogeneity in PD-MCI, further neuroimaging studies using consensus diagnostic criteria and well-defined subtyping methods should be particularly promoted.

Abbreviations

EEG	electroencephalography
HC	healthy controls
MCI	mild cognitive impairment
MDS	Movement Disorder Society
PD	Parkinson's disease
PD-aMCI	PD patients with amnestic MCI
PDD	Parkinson's disease dementia
PD-exMCI	PD patients with executive MCI

PD-naMCI PD patients with non-amnestic MCI
PD-nexMCI PD patients with non-executive MCI

References

[1] J.N. Caviness, E. Driver-Dunckley, D.J. Connor, M.N. Sabbagh, J.G. Hentz, B. Noble, V.G.H. Evidente, H.A. Shill, C.H. Adler, Defining mild cognitive impairment in Parkinson's disease, Mov. Disord. Off. J. Mov. Disord. Soc. 22 (2007) 1272–1277. https://doi.org/10.1002/mds.21453.

[2] D.M. Cammisuli, S.M. Cammisuli, J. Fusi, F. Franzoni, C. Pruneti, Parkinson's Disease-Mild Cognitive Impairment (PD-MCI): A Useful Summary of Update Knowledge, Front. Aging Neurosci. 11 (2019) 303. https://doi.org/10.3389/fnagi.2019.00303.

[3] I. Litvan, J.G. Goldman, A.I. Tröster, B.A. Schmand, D. Weintraub, R.C. Petersen, B. Mollenhauer, C.H. Adler, K. Marder, C.H. Williams-Gray, D. Aarsland, J. Kulisevsky, M.C. Rodriguez-Oroz, D.J. Burn, R.A. Barker, M. Emre, Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines, Mov. Disord. Off. J. Mov. Disord. Soc. 27 (2012) 349–356. https://doi.org/10.1002/mds.24893.

[4] B.J. Lawrence, N. Gasson, A.M. Loftus, Prevalence and Subtypes of Mild Cognitive Impairment in Parkinson's Disease, Sci. Rep. 6 (2016) 33929. https://doi.org/10.1038/srep33929.

[5] I. Litvan, D. Aarsland, C.H. Adler, J.G. Goldman, J. Kulisevsky, B. Mollenhauer, M.C. Rodriguez-Oroz, A.I. Tröster, D. Weintraub, MDS Task Force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI, Mov. Disord. Off. J. Mov. Disord. Soc. 26 (2011) 1814–1824. https://doi.org/10.1002/mds.23823.

[6] A. Nicoletti, A. Luca, R. Baschi, C.E. Cicero, G. Mostile, M. Davì, L. Pilati, V. Restivo, M. Zappia, R. Monastero, Incidence of Mild Cognitive Impairment and Dementia in Parkinson's Disease: The Parkinson's Disease Cognitive Impairment Study, Front. Aging Neurosci. 11 (2019) 21. https://doi.org/10.3389/fnagi.2019.00021.

[7] M.E. Domellöf, U. Ekman, L. Forsgren, E. Elgh, Cognitive function in the early phase of Parkinson's disease, a five-year follow-up, Acta Neurol. Scand. 132 (2015) 79–88. https://doi.org/10.1111/ane.12375.

[8] K.F. Pedersen, J.P. Larsen, O.-B. Tysnes, G. Alves, Natural course of mild cognitive impairment in Parkinson disease: A 5-year population-based study, Neurology. 88 (2017) 767–774. https://doi.org/10.1212/WNL.0000000000003634.

[9] K. Dujardin, A.J.H. Moonen, H. Behal, L. Defebvre, A. Duhamel, A.A. Duits, L. Plomhause, C. Tard, A.F.G. Leentjens, Cognitive disorders in Parkinson's disease: Confirmation of a spectrum of severity, Parkinsonism Relat. Disord. 21 (2015) 1299–1305. https://doi.org/10.1016/j.parkreldis.2015.08.032.

[10] L. Alonso-Recio, P. Martín-Plasencia, M. Ruiz, J.M. Serrano, Differences in cognitive performance in nondemented Parkinson's disease: A latent profile analysis of cognitive subtypes, J. Clin. Exp. Neuropsychol. 40 (2018) 777–789. https://doi.org/10.1080/13803395.2018.1432570.

[11] D. Pourzinal, J.H.J. Yang, G.J. Byrne, J.D. O'Sullivan, L. Mitchell, K.L. McMahon, D.A. Copland, N.N. Dissanayaka, Identifying subtypes of mild cognitive impairment in Parkinson's disease using cluster analysis, J. Neurol. 267 (2020) 3213–3222. https://doi.org/10.1007/s00415-020-09977-z.

[12] I.N. Miller, S. Neargarder, M.M. Risi, A. Cronin-Golomb, Frontal and posterior subtypes of neuropsychological deficit in Parkinson's disease, Behav. Neurosci. 127 (2013)

175–183. https://doi.org/10.1037/a0031357.
[13] C. Kormas, I. Zalonis, I. Evdokimidis, E. Kapaki, C. Potagas, The severity of executive dysfunction among different PD-MCI subtypes, Appl. Neuropsychol. Adult. (2020) 1–5. https://doi.org/10.1080/23279095.2020.1786832.
[14] Q. Devignes, R. Viard, N. Betrouni, G. Carey, G. Kuchcinski, L. Defebvre, A.F.G. Leentjens, R. Lopes, K. Dujardin, Posterior Cortical Cognitive Deficits Are Associated With Structural Brain Alterations in Mild Cognitive Impairment in Parkinson's Disease, Front. Aging Neurosci. 13 (2021). https://doi.org/10.3389/fnagi.2021.668559.
[15] C.H. Williams-Gray, J.R. Evans, A. Goris, T. Foltynie, M. Ban, T.W. Robbins, C. Brayne, B.S. Kolachana, D.R. Weinberger, S.J. Sawcer, R.A. Barker, The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort, Brain J. Neurol. 132 (2009) 2958–2969. https://doi.org/10.1093/brain/awp245.
[16] C.H. Williams-Gray, S.L. Mason, J.R. Evans, T. Foltynie, C. Brayne, T.W. Robbins, R.A. Barker, The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort, J. Neurol. Neurosurg. Psychiatry. 84 (2013) 1258–1264. https://doi.org/10.1136/jnnp-2013-305277.
[17] A.A. Kehagia, R.A. Barker, T.W. Robbins, Cognitive impairment in Parkinson's disease: the dual syndrome hypothesis, Neurodegener. Dis. 11 (2013) 79–92. https://doi.org/10.1159/000341998.
[18] O. Monchi, A. Hanganu, P. Bellec, Markers of cognitive decline in PD: The case for heterogeneity, Parkinsonism Relat. Disord. 24 (2016) 8–14. https://doi.org/10.1016/j.parkreldis.2016.01.002.
[19] M. Bailey, J.G. Goldman, Characterizing Cognitive Impairment in Parkinson's Disease, Semin. Neurol. 37 (2017) 167–175. https://doi.org/10.1055/s-0037-1601894.
[20] R. Biundo, L. Weis, E. Fiorenzato, A. Antonini, Cognitive Rehabilitation in Parkinson's Disease: Is it Feasible?, Arch. Clin. Neuropsychol. 32 (2017) 840–860. https://doi.org/10.1093/arclin/acx092.
[21] J.C. Greenland, C.H. Williams-Gray, R.A. Barker, The clinical heterogeneity of Parkinson's disease and its therapeutic implications, Eur. J. Neurosci. 49 (2019) 328–338. https://doi.org/10.1111/ejn.14094.
[22] E. Mak, L. Su, G.B. Williams, J.T. O'Brien, Neuroimaging correlates of cognitive impairment and dementia in Parkinson's disease, Parkinsonism Relat. Disord. 21 (2015) 862–870. https://doi.org/10.1016/j.parkreldis.2015.05.013.
[23] S. Sasikumar, A.P. Strafella, Imaging Mild Cognitive Impairment and Dementia in Parkinson's Disease, Front. Neurol. 11 (2020) 47. https://doi.org/10.3389/fneur.2020.00047.
[24] D. Moher, L. Shamseer, M. Clarke, D. Ghersi, A. Liberati, M. Petticrew, P. Shekelle, L.A. Stewart, PRISMA-P Group, Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement, Syst. Rev. 4 (2015) 1. https://doi.org/10.1186/2046-4053-4-1.
[25] L. Shamseer, D. Moher, M. Clarke, D. Ghersi, A. Liberati, M. Petticrew, P. Shekelle, L.A. Stewart, the PRISMA-P Group, Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation, BMJ. 349 (2015) g7647–g7647. https://doi.org/10.1136/bmj.g7647.
[26] J.A. Salvador-Oliván, G. Marco-Cuenca, R. Arquero-Avilés, Errors in search strategies used in systematic reviews and their effects on information retrieval, J. Med. Libr. Assoc. JMLA. 107 (2019) 210–221. https://doi.org/10.5195/jmla.2019.567.
[27] S. Fahn, R. Elton, Members of the UPDRS Development Committe, Unified Parkinson's disease rating scale, in: S. Fahn, C.D. Marsden, M. Goldstein (Eds.), Recent Dev. Park. Dis., Fahn, Macmillan Health Care Information, Florham Park, NJ, 1987: pp. 153–163, 293–304.

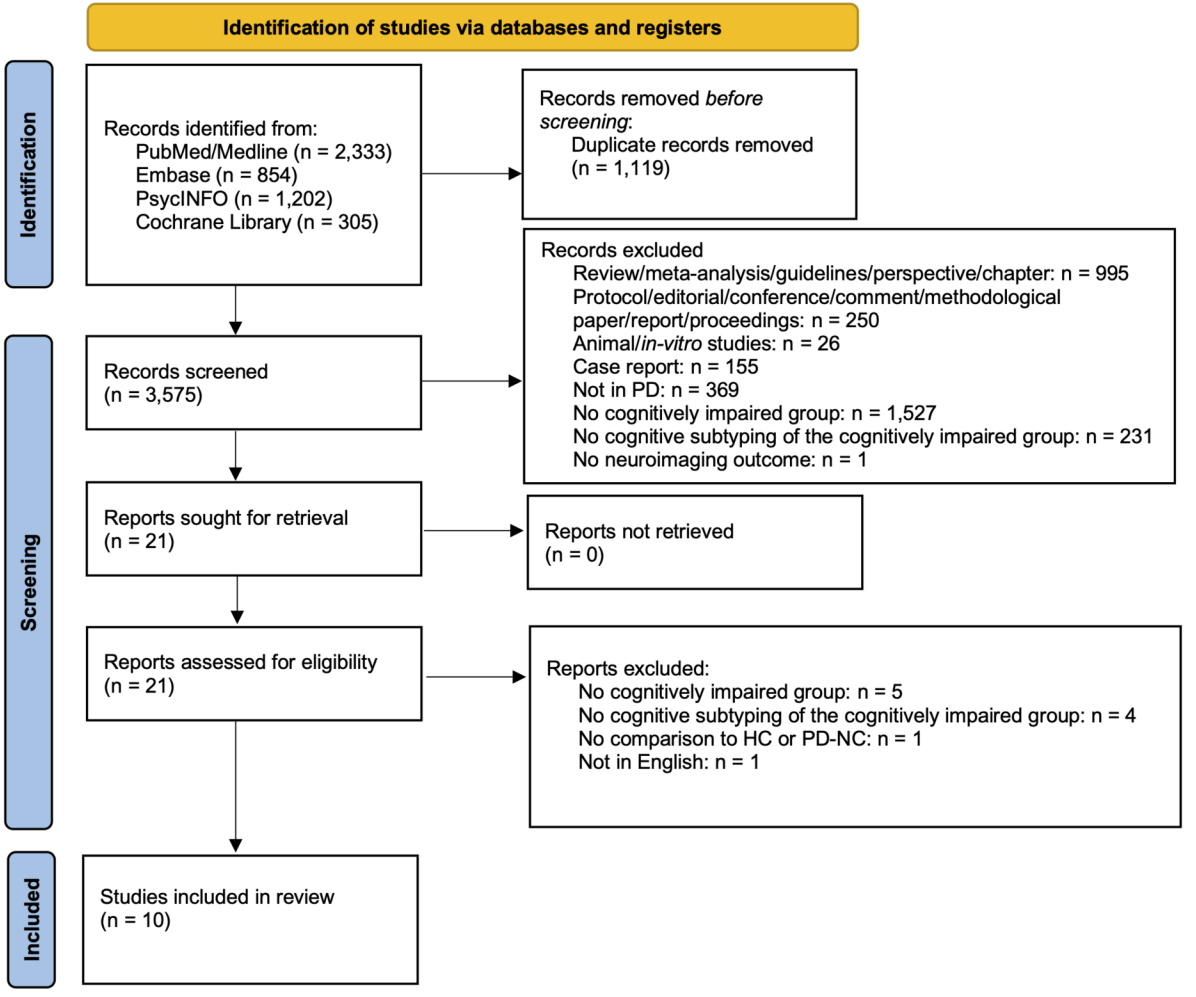
[28] C.G. Goetz, B.C. Tilley, S.R. Shaftman, G.T. Stebbins, S. Fahn, P. Martinez-Martin, W. Poewe, C. Sampaio, M.B. Stern, R. Dodel, B. Dubois, R. Holloway, J. Jankovic, J. Kulisevsky, A.E. Lang, A. Lees, S. Leurgans, P.A. LeWitt, D. Nyenhuis, C.W. Olanow, O. Rascol, A. Schrag, J.A. Teresi, J.J. van Hilten, N. LaPelle, Movement Disorder Society UPDRS Revision Task Force, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results, Mov. Disord. Off. J. Mov. Disord. Soc. 23 (2008) 2129–2170. https://doi.org/10.1002/mds.22340.
[29] M. Xia, J. Wang, Y. He, BrainNet Viewer: a network visualization tool for human brain connectomics, PloS One. 8 (2013) e68910. https://doi.org/10.1371/journal.pone.0068910.
[30] A.F. Wolters, S.C.F. van de Weijer, A.F.G. Leentjens, A.A. Duits, H.I.L. Jacobs, M.L. Kuijf, Resting-state fMRI in Parkinson's disease patients with cognitive impairment: A meta-analysis, Parkinsonism Relat. Disord. 62 (2019) 16–27. https://doi.org/10.1016/j.parkreldis.2018.12.016.
[31] J.E. Lee, H.-J. Park, S.K. Song, Y.H. Sohn, J.D. Lee, P.H. Lee, Neuroanatomic basis of amnestic MCI differs in patients with and without Parkinson disease, Neurology. 75 (2010) 2009–2016. https://doi.org/10.1212/WNL.0b013e3181ff96bf.
[32] L. Christopher, S. Duff-Canning, Y. Koshimori, B. Segura, I. Boileau, R. Chen, A.E. Lang, S. Houle, P. Rusjan, A.P. Strafella, Salience network and parahippocampal dopamine dysfunction in memory-impaired Parkinson disease, Ann. Neurol. 77 (2015) 269–280. https://doi.org/10.1002/ana.24323.
[33] L.M. Colon-Perez, J.J. Tanner, M. Couret, S. Goicochea, T.H. Mareci, C.C. Price, Cognition and connectomes in nondementia idiopathic Parkinson's disease, Netw. Neurosci. Camb. Mass. 2 (2018) 106–124. https://doi.org/10.1162/NETN_a_00027.
[34] K. Kawabata, H. Watanabe, K. Hara, E. Bagarinao, N. Yoneyama, A. Ogura, K. Imai, M. Masuda, T. Yokoi, R. Ohdake, Y. Tanaka, T. Tsuboi, T. Nakamura, M. Hirayama, M. Ito, N. Atsuta, S. Maesawa, S. Naganawa, M. Katsuno, G. Sobue, Distinct manifestation of cognitive deficits associate with different resting-state network disruptions in non-demented patients with Parkinson's disease, J. Neurol. 265 (2018) 688–700. https://doi.org/10.1007/s00415-018-8755-5.
[35] F. Chen, T. Wu, Y. Luo, Z. Li, Q. Guan, X. Meng, W. Tao, H. Zhang, Amnestic mild cognitive impairment in Parkinson's disease: White matter structural changes and mechanisms, PloS One. 14 (2019) e0226175. https://doi.org/10.1371/journal.pone.0226175.
[36] S.J. Chung, Y.-H. Park, H.J. Yun, H. Kwon, H.S. Yoo, Y.H. Sohn, J.-M. Lee, P.H. Lee, Clinical relevance of amnestic versus non-amnestic mild cognitive impairment subtyping in Parkinson's disease, Eur. J. Neurol. 26 (2019) 766–773. https://doi.org/10.1111/ene.13886.
[37] S. Kamei, A. Morita, K. Serizawa, T. Mizutani, K. Hirayanagi, Quantitative EEG analysis of executive dysfunction in Parkinson disease, J. Clin. Neurophysiol. Off. Publ. Am. Electroencephalogr. Soc. 27 (2010) 193–197. https://doi.org/10.1097/WNP.0b013e3181dd4fdb.
[38] H.J. Son, Y.J. Jeong, H.J. Yoon, J.W. Kim, G.-E. Choi, J.H. Park, D.-Y. Kang, Parkinson disease-related cortical and striatal cognitive patterns in dual time F-18 FP CIT: evidence for neural correlates between the caudate and the frontal lobe, Q. J. Nucl. Med. Mol. Imaging Off. Publ. Ital. Assoc. Nucl. Med. AIMN Int. Assoc. Radiopharmacol. IAR Sect. Soc. Of. 63 (2019) 379–386. https://doi.org/10.23736/S1824-4785.17.02976-4.
[39] C.H. Lyoo, Y. Jeong, Y.H. Ryu, J.O. Rinne, M.S. Lee, Cerebral glucose metabolism of Parkinson's disease patients with mild cognitive impairment, Eur. Neurol. 64 (2010) 65–73. https://doi.org/10.1159/000315036.
[40] F. Nobili, G. Abbruzzese, S. Morbelli, R. Marchese, N. Girtler, B. Dessi, A. Brugnolo,

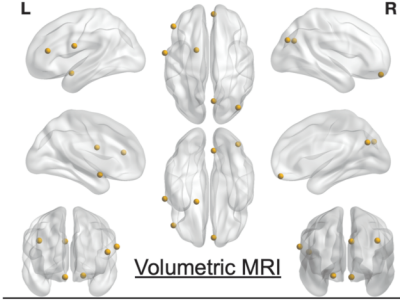
C. Canepa, G.C. Drosos, G. Sambuceti, G. Rodriguez, Amnestic mild cognitive impairment in Parkinson's disease: a brain perfusion SPECT study, Mov. Disord. Off. J. Mov. Disord. Soc. 24 (2009) 414–421. https://doi.org/10.1002/mds.22381.
[41] R.C. Petersen, Mild cognitive impairment as a diagnostic entity, J. Intern. Med. 256 (2004) 183–194. https://doi.org/10.1111/j.1365-2796.2004.01388.x.
[42] J.H. Lanskey, P. McColgan, A.E. Schrag, J. Acosta-Cabronero, G. Rees, H.R. Morris, R.S. Weil, Can neuroimaging predict dementia in Parkinson's disease?, Brain J. Neurol. 141 (2018) 2545–2560. https://doi.org/10.1093/brain/awy211.
[43] S.J. Crowley, G. Banan, M. Amin, J.J. Tanner, L. Hizel, P. Nguyen, B. Brumback, K. Rodriguez, N. McFarland, D. Bowers, M. Ding, T.A. Mareci, C.C. Price, Statistically Defined Parkinson's Disease Executive and Memory Cognitive Phenotypes: Demographic, Behavioral, and Structural Neuroimaging Comparisons, J. Park. Dis. 11 (2021) 283–297. https://doi.org/10.3233/JPD-202166.
[44] E. Bayram, B. Bluett, X. Zhuang, D. Cordes, D.R. LaBelle, S.J. Banks, Neural correlates of distinct cognitive phenotypes in early Parkinson's disease, J. Neurol. Sci. 399 (2019) 22–29. https://doi.org/10.1016/j.jns.2019.02.013.
[45] R. Lopes, C. Delmaire, L. Defebvre, A.J. Moonen, A.A. Duits, P. Hofman, A.F.G. Leentjens, K. Dujardin, Cognitive phenotypes in parkinson's disease differ in terms of brain-network organization and connectivity, Hum. Brain Mapp. 38 (2017) 1604–1621. https://doi.org/10.1002/hbm.23474.
[46] M. Hassan, L. Chaton, P. Benquet, A. Delval, C. Leroy, L. Plomhause, A.J.H. Moonen, A.A. Duits, A.F.G. Leentjens, V. van Kranen-Mastenbroek, L. Defebvre, P. Derambure, F. Wendling, K. Dujardin, Functional connectivity disruptions correlate with cognitive phenotypes in Parkinson's disease, NeuroImage Clin. 14 (2017) 591–601. https://doi.org/10.1016/j.nicl.2017.03.002.
[47] A.F. Wolters, A.J.H. Moonen, R. Lopes, A.F.G. Leentjens, A.A. Duits, L. Defebvre, C. Delmaire, P.A. Hofman, F.C. van Bussel, K. Dujardin, Grey matter abnormalities are associated only with severe cognitive decline in early stages of Parkinson's disease, Cortex J. Devoted Study Nerv. Syst. Behav. 123 (2020) 1–11. https://doi.org/10.1016/j.cortex.2019.09.015.
[48] J. De Roy, R.B. Postuma, M. Brillon-Corbeil, J. Montplaisir, D. Génier Marchand, F. Escudier, M. Panisset, S. Chouinard, J.-F. Gagnon, Detecting the Cognitive Prodrome of Dementia in Parkinson's Disease, J. Park. Dis. 10 (2020) 1033–1046. https://doi.org/10.3233/JPD-191857.
[49] S. Martinez-Horta, J. Kulisevsky, Mild cognitive impairment in Parkinson's disease, J. Neural Transm. Vienna Austria 1996. 126 (2019) 897–904. https://doi.org/10.1007/s00702-019-02003-1.
[50] C. Mueller, A.P. Rajkumar, Y.M. Wan, L. Velayudhan, D. Ffytche, K.R. Chaudhuri, D. Aarsland, Assessment and Management of Neuropsychiatric Symptoms in Parkinson's Disease, CNS Drugs. 32 (2018) 621–635. https://doi.org/10.1007/s40263-018-0540-6.
[51] A. Nagy, A. Schrag, Neuropsychiatric aspects of Parkinson's disease, J. Neural Transm. Vienna Austria 1996. 126 (2019) 889–896. https://doi.org/10.1007/s00702-019-02019-7.

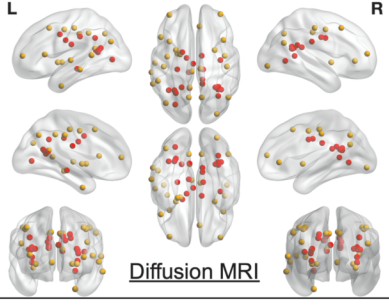
Figure 1 – PRISMA flowchart
Some studies used several neuroimaging methods. HC = healthy controls; PD = Parkinson's disease; PD-NC = Parkinson's disease – normal cognition.

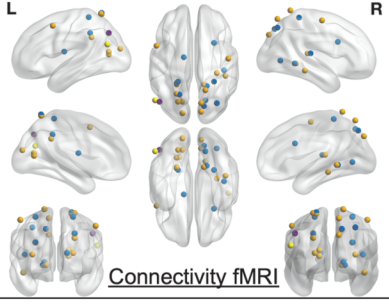
Figure 2 – Significant brain areas according to the neuroimaging approach
For studies showing significant between-group differences, the peak coordinates of the significant brain areas, when provided, were projected on a smoothed MNI template, with colors representing the between-group comparisons. No study subtyping PD-MCI patients according to the presence of an executive impairment provided the peaks coordinates. Therefore, these studies could not be represented. It should be noted that the MNI coordinates for the significant results of Colon-Perez et al. were provided by the first author after we contacted him to obtain the supplementary material file that was not available online. In each panel, the brain views are as follows: lateral (top-left and top-right), medial (middle-left and middle-right); anterior (bottom-left); posterior (bottom-right); superior (top-center); inferior (bottom-center). HC = healthy controls; L = left; MCI = mild cognitive impairment; MNI = Montreal Neurological Institute; (f)MRI = (functional) magnetic resonance imaging; PET = positron emission tomography; PD = Parkinson's disease; PD-aMCI = PD patients with amnestic MCI; PD-naMCI = PD patients with non-amnestic MCI; PD-NC = PD patients with normal cognition; R = right; SPECT = single-photon emission computed tomography.

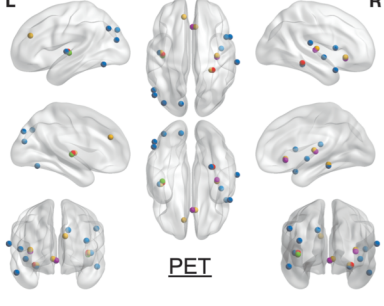
Figure 3 – Significant brain modifications in PD-aMCI and PD-naMCI regardless of the neuroimaging approach
For studies showing significant differences between HC/PD-NC and PD-aMCI or PD-naMCI, the peak coordinates of the significant brain areas, when provided, were projected on a smoothed MNI template, with colors representing the between-group comparisons. As no study subtyping PD-MCI patients according to the presence of an executive impairment provided the peaks coordinates, a similar figure could not be represented for these subtypes. In each panel, the brain views are as follows: lateral (top-left and top-right), medial (middle-left and middle-right); anterior (bottom-left); posterior (bottom-right); superior (top-center); inferior (bottom-center). HC = healthy controls; L = left; MCI = mild cognitive impairment; MNI = Montreal Neurological Institute; PD = Parkinson's disease; PD-aMCI = PD patients with amnestic MCI; PD-naMCI = PD patients with non-amnestic MCI; PD-NC = PD patients with normal cognition; R = right.

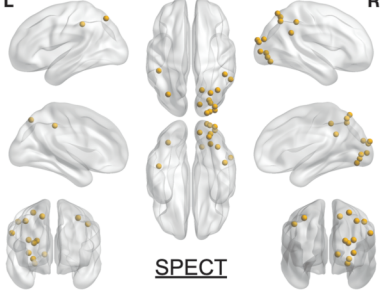

Identification of studies via databases and registers
Identification
Records identified from:
PubMed/Medline (n = 2,333)
Embase (n = 854)
PsycINFO (n = 1,202)
Cochrane Library (n = 305)
Records removed *before screening*:
Duplicate records removed
(n = 1,119)
Screening
Records screened
(n = 3,575)
Records excluded
Review/meta-analysis/guidelines/perspective/chapter: n = 995
Protocol/editorial/conference/comment/methodological paper/report/proceedings: n = 250
Animal/*in-vitro* studies: n = 26
Case report: n = 155
Not in PD: n = 369
No cognitively impaired group: n = 1,527
No cognitive subtyping of the cognitively impaired group: n = 231
No neuroimaging outcome: n = 1
Reports sought for retrieval
(n = 21)
Reports not retrieved
(n = 0)
Reports assessed for eligibility
(n = 21)
Reports excluded:
No cognitively impaired group: n = 5
No cognitive subtyping of the cognitively impaired group: n = 4
No comparison to HC or PD-NC: n = 1
Not in English: n = 1
Included
Studies included in review
(n = 10)

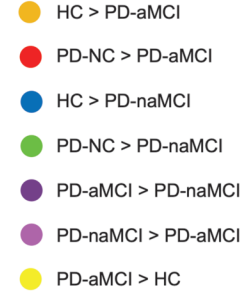

L
R
Volumetric MRI


L
R
Diffusion MRI


L
R
Connectivity fMRI


L
R
PET


L
R
SPECT


HC > PD-aMCI
PD-NC > PD-aMCI
HC > PD-naMCI
PD-NC > PD-naMCI
PD-aMCI > PD-naMCI
PD-naMCI > PD-aMCI
PD-aMCI > HC

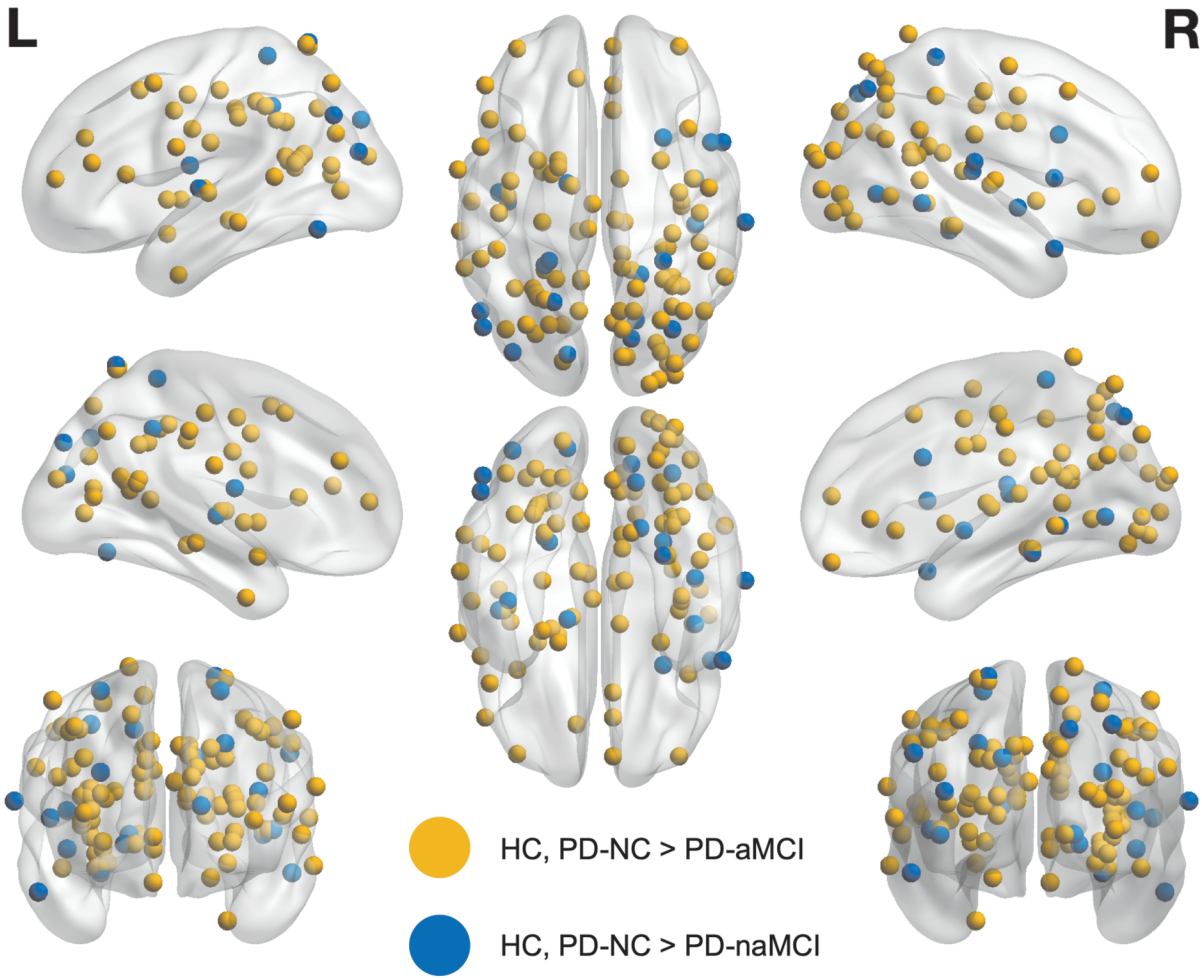

L
R
HC, PD-NC > PD-aMCI
HC, PD-NC > PD-naMCI

Table 1 – Search strategy for PubMed/Medline database

1. parkinson's disease[MeSH Terms]	33. functional neuroimaging[MeSH Terms]
2. parkinson[Title/Abstract]	34. brain cortical thickness[MeSH Terms]
3. #1 OR #2	35. "cortical thickness"[Title/Abstract]
4. cognitive dysfunction[MeSH Terms]	36. mri[Title/Abstract]
5. "cognitive dysfunction"[Title/Abstract]	37. dti[Title/Abstract]
6. "cognitive impairment"[Title/Abstract]	38. fmri[Title/Abstract]
7. mild cognitive impairment[MeSH Terms]	39. structural[Title/Abstract]
8. "mild cognitive impairment"[Title/Abstract]	40. anatomic*[Title/Abstract]
9. "PD-MCI"[Title/Abstract]	41. volume*[Title/Abstract]
10. PDMCI[Title/Abstract]	42. "cortical thinning"[Title/Abstract]
11. "cognitive subtyp*"[Title/Abstract]	43. atrophy[Title/Abstract]
12. "dual syndrome hypothesis"[Title/Abstract]	44. "shape analys*"[Title/Abstract]
13. "striato-frontal"[Title/Abstract]	45. "functional connectivity"[Title/Abstract]
14. frontostriatal[Title/Abstract]	46. "resting-state"[Title/Abstract]
15. "fronto-striatal"[Title/Abstract]	47. network*[Title/Abstract]
16. "posterior cortical"[Title/Abstract]	48. electroencephalography[MeSH Terms]
17. visuospatial[Title/Abstract]	49. electroencephalogra*[Title/Abstract]
18. memory[MeSH Terms]	50. eeg[Title/Abstract]
19. memory[Title/Abstract]	51. qeeg[Title/Abstract]
20. amnestic[Title/Abstract]	52. positron emission tomography[MeSH Terms]
21. language[MeSH Terms]	53. "positron emission tomography"[Title/Abstract]
22. language[Title/Abstract]	54. pet[Title/Abstract]
23. semantic*[Title/Abstract]	55. tomography, emission computed, single photon[MeSH Terms]
24. attention[MeSH Terms]	56. "single-photon emission tomography"[Title/Abstract]
25. attention*[Title/Abstract]	57. spect[Title/Abstract]
26. executive function[MeSH Terms]	58. susceptibility[Title/Abstract]
27. "executive function"[Title/Abstract]	59. r2[Title/Abstract]
28. #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	60. "quantitative susceptibility mapping"[Title/Abstract]
29. magnetic resonance imaging[MeSH Terms]	61. qsm[Title/Abstract]
30. "magnetic resonance imaging"[Title/Abstract]	62. #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61
31. diffusion tensor imaging[MeSH Terms]	63. #3 AND #28 AND #62
32. "diffusion tensor imaging"[Title/Abstract]	Filters: Journal article, Humans, English

Table 2 – Demographic and clinical characteristics of participants included in the selected studies

Study	Size	Age (in years)	Sex (F/M)	Education (in years)	Disease duration (in years)	Hoehn and Yahr stage (/5)	LEDD (mg/day)	MDS-UPDRS-III (/132) / #UPDRS-III (/108)	Neuropsychiatric measures	Cognition		Cognitive subtyping method
										MMSE/ #MoCA	Other tests	
Chen et al. (2019)									None		Battery of tests (RBANS) assessing immediate memory, delayed memory, language, attention, visuospatial function	MDS level II criteria[1] Amnestic MCI = performance ≤-1.5 SD below the mean of normative data on at least two tests in the immediate and/or delayed memory domains
HC	20	59.5 (6.2)	4/16	9.3 (2.2)	NC	NC	NC	NC		29.5 (0.4)		
PD-NC	19	61.3 (6.9)	4/15	10.3 (3.3)	5.9 (3.4)	1.5 (0.8)	917.0 (144.6)	17.7 (9.7)		29.4 (0.8)		
PD-aMCI	17	64.9 (5.9)	2/15	9.6 (3.8)	7.6 (4.9)	1.9 (0.8)	942.2 (120.6)	24.4 (11.2)		28.5 (1.4)		
Christopher et al. (2015)									BDI		Battery of tests assessing memory, executive functions, attention/working memory, language, visuospatial functions	MDS level II criteria[1] MCI = performance ≤-1.5 SD below the mean of normative data on at least 2 cognitive variables Amnestic/non-amnestic MCI = mean z-score computed from scores at memory tests on all PD patients, then split into 2 groups using the median z-score
HC	14	67.5 (5.35)	11/3	17.1 (2.74)	NC	NC	NC	NC	4.0 (3.96)	#27.6 (2.21)		
PD-NC	11	68.8 (3.71)	8/3	15.7 (2.87)	6.32 (4.20)	NP	725.0 (570.85)	#23.3 (12.03)	5.91 (1.87)	#26.5 (1.81)		
PD-aMCI	9	68.3 (7.40)	2/7	16.6 (1.94)	6.11 (2.85)	NP	577.98 (245.00)	#36.1 (16.00)	5.78 (6.00)	#21.9 (3.40)*		
PD-naMCI	10	70.2 (8.27)	3/7	16.7 (1.12)	6.11 (3.10)	NP	611.17 (437.85)	#20.8 (12.86)	4.89 (3.89)	#24.0 (2.12)*		
Chung et al. (2019)									None		Battery of tests (SNSB) assessing attention, executive functions, visuospatial functions, language and memory	MDS level II criteria[1] Amnestic/non-amnestic MCI = performance on at least one memory test ≤16th percentile of normative data
HC	30	70.63 (5.38)	19/11	10.28 (5.98)	NC	NP	NP	NC		28.33 (1.42)		
PD-aMCI	50	69.12 (7.88)	22/38	8.42 (4.70)	2.62 (3.36)	NP	NP	#27.89 (10.73)		25.40 (2.37)		
PD-naMCI	50	69.52 (7.46)	30/20	8.83 (4.69)	2.58 (2.61)	NP	NP	#25.53 (10.90)		26.00 (2.49)		
Colon-Perez et al. (2018)									Controlled but data not provided	DRS > 130 but details not provided	Battery of tests assessing processing speed, working memory and memory	Amnestic MCI = memory composite score ≤-1.5 SD relative to HC
HC	40	68.18 (4.64)	NP	16.75 (2.35)	NC	NC	NC	#2.75 (3.36)				
PD-NC	31	67.30 (5.02)	NP	16.80 (2.91)	7.87 (5.60)	NP	NP	#18.20 (11.60)*				
PD-aMCI	9	69.40 (6.77)	NP	14.3 (2.74)*	6.22 (3.07)	NP	NP	#15.70 (7.25)*				
Kamei et al. (2010)									None		Battery of tests (BADS) assessing the executive functions (6 tests)	Executive MCI = standardized score <70
PD-NC	25	70.0 &(65-74)	NP	13.0 &(9-16)	5.2 &(1-15)	NP	188.8 &(0-500)	#36.5 &(20-66)		27.8 &(24-30)		
PD-exMCI	7	70.0 &(67-74)	NP	12.3 &(9-16)	6.8 &(2.5-3)	NP	292.9 &(0-450)	#46.3 &(36-80)		26.6 &(24-30)		
Kawabata et al. (2018)									None		Battery of tests (ACE-R) assessing attention/orientation, memory, fluency, language, visuospatial ability	MDS level I criteria[1] MCI = performance on at least one domain ≤-1.5 SD below the mean of data from 72 HC Amnestic/non-amnestic MCI = hierarchical cluster analysis (data-driven)
HC	24	68.7 (7.4)	12/12	13.8 (3.5)	NC	NC	NC	NC		29.5 (0.8)		
PD-NC	28	65.1 (9.0)	18/10	14.7 (3.3)	5.9 (2.9)	2.1 (0.4)	442.0 (269.0)	21.4 (9.9)		29.4 (0.8)		
PD-aMCI	20	71.6 (7.8)	9/11	13.0 (3.1)	5.8 (3.9)	2.4 (0.8)	497.0 (388.0)	31.7 (12.4)*		28.2 (1.0)*		
PD-naMCI	24	68.8 (6.5)	12/12	13.6 (3.1)	5.0 (3.0)	2.2 (0.8)	472.0 (359.0)	29.7 (13.6)		28.6 (1.2)*		
Lee et al. (2010)									None		Battery of tests (SNSB) assessing attention, language and related functions, visuospatial functions, verbal	Amnestic MCI = performance on at least one memory test <16th percentile of normative data
HC	21	70.7 (2.7)	NP	NP	NC	NC	NC	NC		≥28.0		
PD-aMCI	41	71.3 (6.3)	20/21	8.9 (4.7)	3.61	NP	205.9	#19.9		25.4 (3.4)		
nonPD-aMCI	78	70.5 (8.0)	46/32	9.4 (4.9)	NC	NC	NC	NC		25.1 (2.4)		

											memory, visual memory, executive functions	nonPD-amnestic MCI = performance on at least one memory test <16th percentile of normative data but without diagnosis of PD (Petersen's criteria[2])
Lyoo et al. (2010)									None		Battery of tests (SNSB) assessing language and related functions, visuospatial functions, verbal and visual memory, executive functions	Modified Petersen's criteria[2] Amnestic MCI single-domain = only performance on at least one memory test <16th percentile of normative data Non-amnestic MCI single-domain = only performance in one cognitive domain other than memory <16th percentile of normative data MCI multiple-domains = performance in at least two cognitive domains <16th percentile of normative data
HC	14	$61.0 (58.0-62.0)	NP	NP	NC	NC	NC	NC		NP		
PD-NC	20	$62.0 (55.8-73.0)	NP	NP	$3.0 (2.0-10.8)	$2.3 (2.0-4.0)	Data per group were not provided, but 33 patients had no antiparkinsonian medication, while the 28 remaining PD patients had a mean LEDD of 594.6	$#22.0 (15.5-46.0)		$29.0 (28.0-30.0)*		
PD-aMCI single	12	$65.5 (56.0-71.0)	NP	NP	$4.4 (2.6-13.0)	$2.5 (2.4-4.0)		$#27.5 (19.8-62.0)		$28.5 (26.8-30.0)*		
PD-naMCI single	11	$57.0 (54.0-72.0)	NP	NP	$3.0 (1.5-16.0)	$3.0 (2.5-4.0)		$#26.0 (20.5-53.0)		$28.0 (27.0-30.0)*		
PD-MCI multiple	18	$65.5 (60.3-69.0)	NP	NP	$2.0 (1.1-20.8)	$2.3 (2.0-4.0)		$#25.5 (21.0-54.0)		$27.0 (26.0-30.0)*		
Nobili et al. (2009)									GDS (frequencies of score >5)		Battery of tests assessing verbal episodic memory, categorical fluency, sustained attention, visuoconstruction abilities and logical reasoning. Some tests were performed only in a part of patients.	Amnestic MCI = performance on immediate and/or delayed recall ≤-1.5 SD below the mean of normative data nonPD-amnestic MCI = performance on immediate and/or delayed recall ≤-1.5 SD below the mean of normative data but without diagnosis of PD (Petersen's criteria[2])
HC	15	71.3 (6.1)	9/6	9.3 (4.3)	NC	NP	NP	NC	1 (6.67%)	29.5 (0.6)		
PD-NC	15	70.8 (5.0)	7/8	9.4 (4.7)	5.7 (2.7)	NP	NP	#15.3 (6.9)	4 (26.67%)	28.7 (1.2)		
PD-aMCI	15	71.5 (5.9)	5/10	8.5 (4.0)	7.6 (4.4)*	NP	NP	#22.9 (7.3)*	7 (46.47%)	27.3 (1.3)*		
nonPD-aMCI	15	73.7 (4.9)	12/3	73.7 (4.9)	NC	NP	NP	NC	2 (13.33%)	27.1 (1.8)*		
Son et al. (2019)									GDS / NPI		Battery of tests (SNSB) assessing language and related functions, visuospatial functions, verbal and visual memory, executive functions	MDS level I criteria[1] MCI = performance ≤-1.5 SD below the mean of normative data Executive MCI = performance on at least the executive test ≤-1.5 SD below the mean of normative data Non-executive MCI = performance in one or more cognitive domains other than executive functions ≤-1.5 SD below the mean of normative data
HC	26	NP	NP	NP	NC	NC	NC	NC	NP	NP		
PD-NC	21	$63.5 (54.8-72.0)	14/4	$9.0 (5.0-16.0)	$1.5 (0.4-5.0)	$2.0 (1.9-2.1)	$275.0 (150-450)	$#9.8 (8.0-13.4)	$11.0 (6.0-15.8) / $1.5 (0-2.5)*	$27.5 (25.8-28.0)*		
PD-exMCI	38	$74.0 (65.5-75.0)	21/15	$8.5 (6.0-12.0)	$3.0 (1.4-6.0)	$2.0 (2.0-2.6)	$375 (225-700)	$#11.3 (8.9-14.1)	$16.0 (5.5-21.8) / $2 (0-10)*	$26.0 (22.0-28.0)*		
PD-nexMCI	24	$63.5 (54.8-72)	14/10	$9.0 (5.0-16.0)	$1.5 (0.4-5.0)	$2.0 (1.9-2.1)	$300 (150-450)	$#9.8 (8-13.4)	$11.0 (6.0-15.8) / $1.5 (0-2.5)*	$27.5 (25.8-28.0)*		

Means (and standard deviations when available) are presented, unless otherwise specified ($medians (and interquartile range); &range (minimum-maximum)). [1]Litvan et al. (2012); [2]Petersen et al. (2004); ACE-R = Addenbrooke's cognitive examination – revised; BADS = behavioral assessment of the dysexecutive syndrome; BDI = Beck depression inventory; DRS = Dementia rating scale; GDS = geriatric depression scale; HC = healthy controls; LEDD = levodopa equivalent daily dose; MCI = mild cognitive impairment; MDS = Movement

Disorder Society; MDS-UPDRS III = Movement Disorder Society – Unified Parkinson's disease rating scale; MMSE = mini-mental state examination; MoCA = Montreal cognitive assessment; NC = not concerned; nonPD-aMCI = patients without PD but with amnestic MCI; NP = not provided; NPI = neuropsychiatric inventory; PD = Parkinson's disease; PD-aMCI = PD patients with amnestic MCI; PD-exMCI = PD patients with executive MCI; PD-naMCI = PD patients with non-amnestic MCI; PD-NC = PD patients with normal cognition; PD-nexMCI = PD patients with non-executive MCI; RBANS = repeatable battery for the assessment of neuropsychological status; SD = standard deviation; SNSB = Seoul neuropsychological screening battery; [#]To distinguish MDS-UPDRS III and UPDRS-III for motor symptoms or MMSE and MoCA for global cognitive efficiency; *significantly different.

Table 3 – Studies using MRI structural methods

Study	Size	Sequence, magnetic field strength and manufacturer	Outcome	Analysis	Localization	MNI coordinates (x/y/z)	Statistic values
Chen et al.		Diffusion tensor imaging sequence	FA, AD, RD (voxel-based)	ANCOVA (controlled for age, sex, disease duration)	<u>FA, AD, RD voxel-based</u>		
HC	20		FA (TBSS-based)		**PD-NC>PD-aMCI** (FA)		
PD-NC	19				R corpus callosum splenium	10/-39/20	*p*=0.04
PD-aMCI	17	3.0 Tesla		Threshold-free cluster enhancement (5,000 permutations)	R corpus callosum body	-3/-17/24	*p*=0.04
					L cingulum (cingulate gyrus)	-8/-51/16	*p*=0.04
		Siemens			L posterior thalamic radiation	-28/-56/17	*p*=0.03
				Family-wise error	L posterior corona radiata	-19/-50/33	*p*=0.04
				FSL	L tapetum	-29/-54/13	*p*=0.03
					R cingulum (cingulate gyrus)	10/-45/23	*p*=0.05
					R posterior thalamic radiation	33/-52/18	*p*=0.03
					R tapetum	32/-49/8	*p*=0.05
					R posterior corona radiata	32/-53/21	*p*=0.03
					R superior longitudinal fascicle	36/-53/18	*p*=0.04
					L superior corona radiata	-18/-1/38	*p*=0.04
					L fornix	-25/-25/-10	*p*=0.05
					<u>FA TBSS-based</u>		
					PD-NC>PD-aMCI		
					L cingulum body	-12/-9/30	*p*=0.03
					R cingulum body	11/-25/28	*p*=0.02
					L superior longitudinal fascicle	-37/-54/15	*p*=0.03
					R superior longitudinal fascicle	35/-12/34	*p*=0.04
					L cingulum (cingulate gyrus)	-9/-29/35	*p*=0.03
					R cingulum (cingulate gyrus)	9/-6/33	*p*=0.03
					L inferior longitudinal fascicle	-27/-58/19	*p*=0.03
					R inferior longitudinal fascicle	28/-50/19	*p*=0.03
					R inferior fronto-occipital fascicle	32/-62/1	*p*=0.04
					L inferior fronto-occipital fascicle	-28/-74/3	*p*=0.05
Christopher et al.		3-dimensional T1-weighted sequence	Cortical thickness	ANCOVA (controlled for age, UPDRS-III and levodopa equivalent daily dose)	No significant result		
HC	14						
PD-NC	11						
PD-aMCI	9	3.0 Tesla					
PD-naMCI	10			Monte Carlo simulation (10,000 iterations)			
		General Electric		Software NP			
Chung et al.		3-dimensional T1-weighted sequence	Hippocampal volume	ANCOVA (controlled for age, sex, years of education, total intracranial volume (except in TBSS))	<u>Cortical thickness</u>	NP	NP
HC	30		Cortical thickness		**HC>PD-aMCI**		
PD-aMCI	50	Diffusion-weighted imaging sequence	FA, MD (TBSS-based)		L frontotemporal regions		
PD-naMCI	50				<u>FA</u>		
		3.0 Tesla			**HC>PD-aMCI**		
					L frontotemporoparietal regions		
					R frontotemporoparietal regions		

		Philips		Random-field theory correction for cortical thickness Threshold-free cluster enhancement (5,000 permutations) and family-wise error correction for TBSS SurfStat	Corpus callosum **HC>PD-naMCI** L frontotemporoparietal regions R frontotemporoparietal regions Corpus callosum		
Colon-Perez et al. HC PD-NC PD-aMCI	 40 31 9	Diffusion tensor imaging sequence 3.0 Tesla Siemens	Graph theory metrics (graph density, node strength, clustering coefficient, path length, small-worldness) at two levels (global (i.e. for the entire network) and local (i.e. at each brain area (n=82) composing the network))	Mann-Whitney test (controlled for graph density) False non-discovery rate R software	<u>Global level</u> *Node strength* **HC>PD-aMCI** *Path length* **HC>PD-aMCI** <u>Local level</u> *Node strength* **HC>PD-aMCI** L putamen R putamen L caudal middle frontal R caudal middle frontal L inferior parietal R inferior parietal L postcentral R postcentral L posterior cingulate R posterior cingulate L precentral R precentral L precuneus R precuneus L pallidum L entorhinal cortex L isthmus cingulate L middle temporal L pars opercularis L banks of the superior temporal sulcus L supramarginal L rostral middle frontal L superior temporal R lateral occipital R rostral anterior cingulate R rostral middle frontal R superior parietal *Path length*	 NC NC -27/2/-1 27/2/-1 -36/14/47 39/16/47 -41/-72/28 46/-64/26 -44/-21/47 44/-21/47 -5/-28/39 7/-24/41 -39/-7/45 41/-6/45 -9/-64/39 9/-64/39 -21/-4/-1 -25/-3/-34 -8/-50/18 -61/-29/-11 -48/20/10 -59/-45/9 -52/-41/40 -36/51/8 -56/-16/2 30/-87/-6 6/35/1 35/52/11 NP	 p=0.004 p=0.014 p=0.043 p=0.002 p=0.018 p=0.040 p=0.031 p=0.019 p=0.017 p=0.045 p=0.043 p=0.006 p=0.017 p=0.019 p=0.019 p=0.043 p=0.021 p=0.004 p=0.027 p=0.016 p=0.003 p=0.019 p=0.002 p=0.003 p=0.006 p=0.029 p=0.019 p=0.007 p=0.040

					HC>PD-aMCI		
					L pars opercularis	-48/20/10	p=0.002
					R putamen	27/2/-1	p=0.001
Kawabata et al.		3-dimensional T1-weighted sequence	Voxel-based morphometry	Statistical method NP (controlled for age, sex and total intracranial volume) Family-wise error SPM	**HC>PD-aMCI**		
HC	24				L amygdala	-18/2/-16	p = 0.005
PD-NC	28				R rectal gyrus	6/52/-18	p = 0.034
PD-aMCI	20	3.0 Tesla			R middle occipital gyrus	40/-78/30	p = 0.030
PD-naMCI	24						
		Siemens					
Lee et al.		3-dimensional T1-weighted sequence	Voxel-based morphometry	ANCOVA (controlled for age and mini-mental state examination total score) Uncorrected p<0.001 with minimal cluster size of 50mm^3 SPM	**HC>PD-aMCI**		Z-values
HC	21				L middle frontal gyrus	-50/35/15	4.04
PD-aMCI	41				L precentral gyrus	-62/-2/22	3.37
nonPD-aMCI	78	3.0 Tesla			R precuneus	6/-69/29	4.76
		Philips					

Only significant results between HC/PD-NC and PD-MCI subtypes are presented. AD = axial diffusivity; ANCOVA = analysis of covariance; FA = fractional anisotropy; FSL = FMRIB software library; HC = healthy controls; L = left; MCI = mild cognitive impairment; MD = mean diffusivity; MNI = Montreal Neurological Institute; MRI = magnetic resonance imaging; NC = not concerned; nonPD-aMCI = patients without PD but with amnestic MCI; NP = not provided; PD = Parkinson's disease; PD-aMCI = PD patients with amnestic MCI; PD-naMCI = PD patients with non-amnestic MCI; PD-NC = PD patients with normal cognition; RD = radial diffusivity; R = right; SPM = statistical parametric mapping; TBSS = tract-based spatial statistics; UPDRS-III = Unified Parkinson's disease rating scale.

Table 4 – Studies using functional MRI or EEG methods

Study	Size	Sequence, magnetic strength field or number of electrodes, and manufacturer	Outcome	Analysis	Localization	MNI coordinates (x/y/z)	Statistic values
Functional MRI studies							
Chung et al.		T2*-weighted	Functional connectivity	ANCOVA (controlled	**HC>PD-naMCI**		T-values
HC	30	functional MRI	strength	for age, sex, years of	*Default-mode network*		
PD-aMCI	50	sequence	(BOLD signal)	education)	R postcentral gyrus	28/-42/62	4.705
PD-naMCI	50			Monte Carle simulation	L postcentral gyrus	-22/-42/62	4.898
		3.0 Tesla		(10,000 iterations)	R lingual gyrus	18/-48/-2	4.218
				AFNI	L posterior cingulate	-14/-8/14	4.402
		Philips			*Central executive network*		
					L superior parietal lobule	-20/-70/76	4.873
					R precuneus	14/-76/46	3.698
					R superior parietal lobule	32/-72/48	4.448
					Dorsal attentional network		
					R lingual gyrus	16/-68/2	4.813
					L cingulate gyrus	-24/-44/40	5.502
					R transverse temporal gyrus	42/-26/12	4.723
					R middle frontal gyrus	28/12/28	4.609
					HC>PD-aMCI		
					Default-mode network		
					R precentral gyrus	56/-10/64	4.104
					L superior parietal lobule	-24/-68/76	4.217
					R parahippocampal gyrus	14/-46/-2	4.514
					L cuneus	-16/-86/18	4.331
					L cuneus	-22/-70/14	4.277
					Central executive network		
					R precunues	10/-84/60	3.840
					L superior parietal lobule	-20/-70/76	4.088
					Dorsal attentional network		
					L cuneus	-16/-70/10	5.305
					L precuneus	-24/-46/34	5.688
					R precuneus	10/-84/38	4.195
					R transverse temporal gyrus	32/-30/12	4.975
					R parahippocampal gyrus	44/-34/-12	4.657
					R postcentral gyrus	16/-54/72	4.076
					L middle frontal gyrus	-52/8/50	3.662
					PD-aMCI>HC		
					Salience network		
					L middle temporal gyrus	-54/-74/24	-3.540
					PD-aMCI>PD-naMCI		

					Salience network L inferior parietal lobule	-48/-70/40	-3.331
Kawabata et al. HC PD-NC PD-aMCI PD-naMCI	 24 28 20 24	T2*-weighted functional MRI sequence 3.0 Tesla Siemens	(Mean regional) functional connectivity strength (BOLD signal)	Dual regression analysis (age and sex adjusted) on each resting-state network to assess intranetwork connectivity Permutation test (n=5000) Threshold-free cluster enhancement Family-wise error Steel-Dwass test or two-sample t-test for mean regional functional connectivity on networks significantly different between PD patients and HC (identified in the dual regression analysis) SPSS Matlab R software	<u>Resting-state network</u> **HC>PD-aMCI** *Ventral default-mode network* Precuneus Posterior cingulate cortex *Dorsal attentional network* L cuneus **PD-NC>PD-aMCI** *Ventral default-mode network* Precuneus Posterior cingulate cortex **PD-naMCI>PD-aMCI** *Ventral default-mode network* Precuneus Posterior cingulate cortex **HC>PD-naMCI** *Primary visual network* Lingual gyrus *Medial visual network* Lingual gyrus Calcarine gyrus **PD-NC>PD-naMCI** *Primary visual network* Lingual gyrus *Medial visual network* Lingual gyrus Calcarine gyrus **PDaMCI>PD-naMCI** *Cerebellum-brainstem network* Bilateral cerebellar lobule <u>Mean regional functional connectivity</u> **HC>PD-aMCI** *Ventral default-mode network* *Dorsal attentional network* **PD-NC, PD-naMCI>PD-aMCI** *Ventral default-mode network* **HC>PD-naMCI** *Primary visual network* *Medial visual network* *Cerebellum-brainstem network* **PD-NC>PD-naMCI** *Primary visual network*	NP	NP

				PD-aMCI>PD-naMCI *Cerebellum-brainstem network*		
EEG study						
Kamei et al. PD-NC PD-exMCI	 25 7	16 electrodes Nihon Kohden	Quantitative electroencephalography (resting-state) (alpha, beta, delta, theta bands for six locations: frontal pole, frontal, central, parietal, occipital, temporal) Spectral ratio = sum of absolute power values for alpha and beta waves divided by sum of absolute power values for delta and theta waves	Multiple logistic regression (dependent variable =group; independent variables =age, UPDRS score, spectral ratio) SPSS	**Significant predictors of executive deficit** Spectral ratio at the frontal pole Spectral ratio at the frontal location	NP *p*=0.031 *p*=0.048

Only significant results between HC/PD-NC and PD-MCI subtypes are presented. AFNI = analysis of functional Neuroimages; ANCOVA = analysis of covariance; BOLD = blood-oxygen level dependent; EEG = electroencephalography; HC = healthy controls; L = left; MCI = mild cognitive impairment; MNI = Montreal Neurological Institute; MRI = magnetic resonance imaging; NP = not provided; PD = Parkinson's disease; PD-aMCI = PD patients with amnestic MCI; PD-exMCI = PD patients with executive MCI; PD-naMCI = PD patients with non-amnestic MCI; PD-NC = PD patients with normal cognition; R = right; SPSS = statistical package for the social sciences; UPDRS-III = Unified Parkinson's disease rating scale.

Table 5 – Studies using PET or SPECT methods

Study	Size	Scan manufacturer	Outcome	Analysis	Localization	MNI coordinates (x/y/z)	Statistic values
Neurotransmission/neuromodulation studies							
Christopher et al.		Siemens	[^{11}C]FLB 457	ANCOVA	Cortical dopaminergic receptor		T-values (*p*-values)
HC	14		Cortical	(controlled for age,	**HC>PD-aMCI**		
PD-NC	11		dopaminergic	UPDRS-III and	R parahippocampal gyrus	28/-36/-12	4.13 (0.002)
PD-aMCI	9		receptor binding	levodopa equivalent	L insula	-42/-12/4	4.06 (0.005)
PD-naMCI	10		potential	daily dose)	R insula	36/-16/8	3.95 (0.007)
			[^{11}C]DTBZ	Family-wise error or	L anterior cingulate cortex	-10/38/26	3.38 (0.026)
			Striatal vesicular	Bonferroni	R anterior cingulate cortex	6/24/-4	3.16 (0.041)
			monoamine	correction	**HC>PD-naMCI**		
			transporter 2	SPM and SPSS	R insula	42/-6/-4	3.48 (0.021)
			binding potential		L insula	-44/-12/4	3.46 (0.022)
					R parahippocampal gyrus	28/-36/-14	3.31 (0.012)
					PD-NC>PD-aMCI		
					R insula	36/-18/6	3.83 (0.009)
					L insula	-40/-14/4	3.68 (0.013)
					R parahippocampal gyrus	30/-36/-12	2.45 (0.047)
					PD-NC>PD-naMCI		
					L insula	-40/-16/2	3.26 (0.034)
					PD-naMCI>PD-aMCI		
					R insula	36/-18/6	3.66 (0.028)
					R anterior cingulate cortex	2/24/-6	2.70 (0.042)
					Striatal vesicular monoamine transporter 2		
					HC>PD-aMCI, PD-naMCI		
					Associative striatum (anterior putamen and caudate nucleus)	NP	(*p*<0.0001)
					Sensorimotor striatum	NP	(*p*<0.0001)
					PD-NC>PD-aMCI		
					Associative striatum (anterior putamen and caudate nucleus)	NP	(*p*=0.016)
Chung et al.		General Electric	18F-FP-CIT PET	ANCOVA	No significant difference		
HC	30		Striatal dopamine	(controlled for age,			
PD-aMCI	50		active transporter	sex, years of			
PD-naMCI	50		binding potential	education)			
				SPSS			
Son et al.		Siemens	18F-FP-CIT PET	ANCOVA	Early measure	NP	NP
HC	26		Striatal and	(controlled for age	**HC>PD-exMCI**		
PD-NC	21		cortical dopamine	and disease	Bilateral inferior frontal		
PD-exMCI	38		active transporter	duration)	Bilateral medial frontal		
PD-nexMCI	24		binding potential	SPM	Bilateral middle frontal		
					Bilateral superior frontal		

			2 time points: early (10 minutes after injection) and delayed (2 hours after injection)		R parietal Bilateral temporal R limbic Bilateral putamen L midbrain Bilateral cerebellum **HC>PD-nexMCI** Bilateral occipital Bilateral temporal Bilateral parietal Bilateral posterior cingulate Bilateral lentiform nuclei **PD-NC>PD-exMCI** Bilateral inferior orbitomedial frontal Bilateral parietal Bilateral temporal Bilateral limbic Bilateral midbrain Bilateral cerebellum <u>Delayed measure</u> **PD-NC>PD-exMCI** R caudate nucleus L caudate nucleus **PD-nexMCI>PD-exMCI** R caudate nucleus L caudate nucleus		 *p*=0.001 *p*=0.014 *p*=0.001 *p*=0.005
<u>Metabolic/perfusion studies</u>							
Lyoo et al. HC PD-NC PD-aMCI single PD-naMCI single PD-MCI multiple	 14 20 12 11 18	Philips	FDG PET Cerebral metabolic rate for glucose	ANCOVA (controlled for age) Cluster-level correction SPM	**HC>PD-naMCI single** R precentral R superior temporal L middle temporal R postcentral L angular L cuneus L middle occipital	 49/10/9 54/10/-22 -38/-82/20 70/-25/16 -51/-71/36 -14/-83/34 -57/-66/-14	<u>T-values</u> 3.9 5.1 5.2 3.4 4.6 3.0 3.9
Nobili et al. HC PD-NC PD-aMCI nonPD-aMCI	 15 15 15 15	General Electric	99mTc-bicisate Regional cerebral blood flow	ANCOVA (controlled for age, depression score, UPDRS-III) False discovery rate SPM	**HC>PD-aMCI** L superior parietal lobule L inferior parietal lobule R inferior parietal lobule R occipital cuneus R occipital cuneus R middle occipital gyrus R inferior parietal lobule	 -32/-70/50 -45/-37/42 47/-42/45 12/-84/2 22/-96/20 26/-94/17 37/-64/46	<u>Z-values</u> (*p*-values) 4.77 (0.018) 4.29 (0.018) 4.53 (0.018) 4.26 (0.019) 4.20 (0.019) 4.13 (0.019) 4.11 (0.019)

	R supramarginal gyrus	55/-49/30	4.00 (0.020)
	R superior occipital gyrus	33/-87/21	3.86 (0.023)
	R precuneus	15/-64/52	3.73 (0.025)
	R superior parietal lobule	27/-68/57	3.48 (0.029)
	R middle occipital gyrus	27/-82/-4	3.38 (0.032)
	R lingual lobule	25/-78/-10	3.27 (0.036)
	R middle occipital gyrus	33/-92/4	3.08 (0.046)

Only significant results between HC/PD-NC and PD-MCI subtypes are presented. ANCOVA = analysis of covariance; HC = healthy controls; L = left; MCI = mild cognitive impairment; MNI = Montreal Neurological Institute; nonPD-aMCI = patients without PD but with amnestic MCI; NP = not provided; PD = Parkinson's disease; PD-aMCI = PD patients with amnestic MCI; PD-exMCI = PD patients with executive MCI; PD-naMCI = PD patients with non-amnestic MCI; PD-NC = PD patients with normal cognition; PD-nexMCI = PD patients with non-executive MCI; R = right; SPM = statistical parametric mapping; SPSS = statistical package for the social sciences; UPDRS-III = Unified Parkinson's disease rating scale.