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

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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 amnesic MCI and, to a lesser extent, non-amnesic 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 amnesic subtype (PD-aMCI) and non-amnesic 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 $\leq 16^{\text{th}}$ 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 amnesic PD-MCI patients have brain modifications mainly in posterior cortical regions, while no robust conclusions can be drawn for non-amnesic, 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 amnesic 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 amnesic 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

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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 amnesic MCI; PD-naMCI = PD patients with non-amnesic 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 amnesic MCI; PD-naMCI = PD patients with non-amnesic 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)

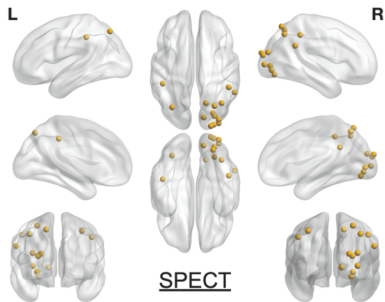
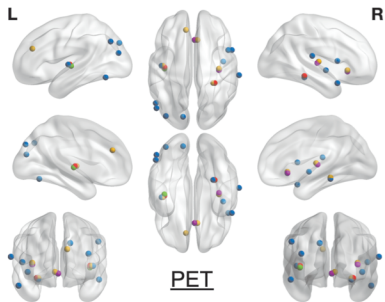
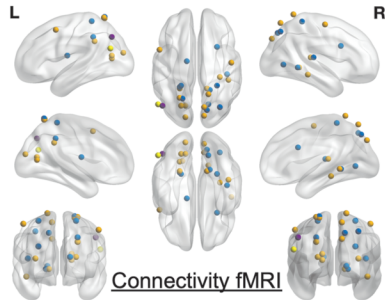
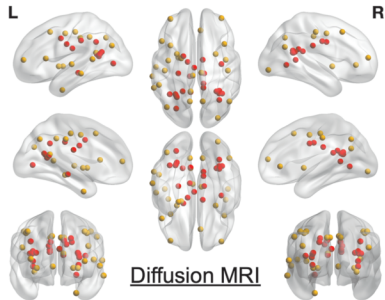
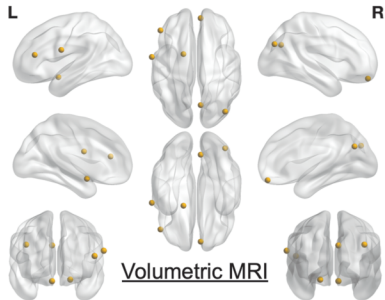
Reports not retrieved
(n = 0)

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)



- 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

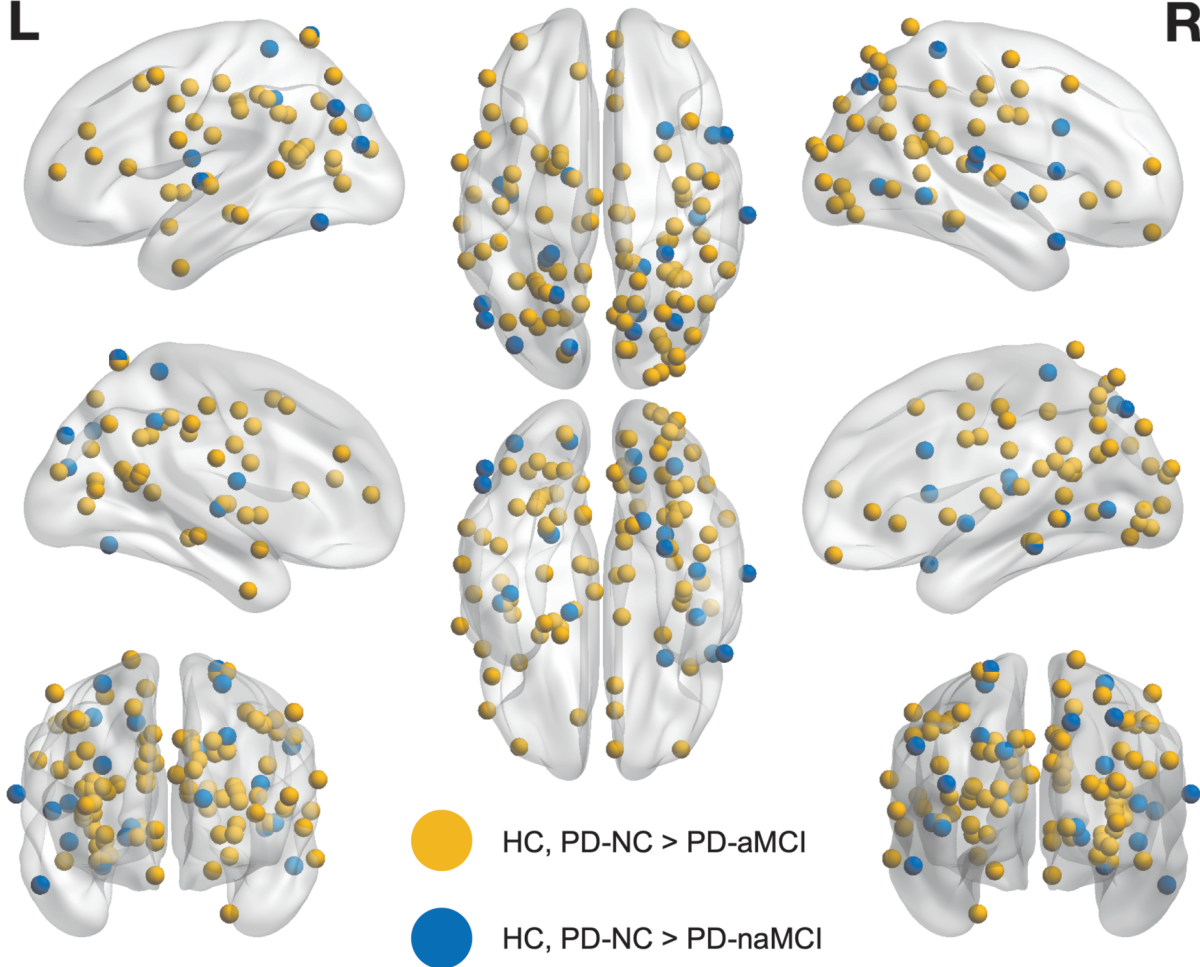
L**R**

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. amnesic[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			
HC	20	59.5 (6.2)	4/16	9.3 (2.2)	NC	NC	NC	NC		29.5 (0.4)	Battery of tests (RBANS) assessing immediate memory, delayed memory, language, attention, visuospatial function	MDS level II criteria ¹ Amnestic MCI = performance \leq -1.5 SD below the mean of normative data on at least two tests in the immediate and/or delayed memory domains
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			
HC	14	67.5 (5.35)	11/3	17.1 (2.74)	NC	NC	NC	NC	4.0 (3.96)	#27.6 (2.21)	Battery of tests assessing memory, executive functions, attention/working memory, language, visuospatial functions	MDS level II criteria ¹ MCI = performance \leq -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
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)*		
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	8.42 (4.70)		25.40 (2.37)	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 \leq 16 th percentile of normative data
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		
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			
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)	Battery of tests (BADS) assessing the executive functions (6 tests)	Executive MCI = standardized score <70
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			
HC	24	68.7 (7.4)	12/12	13.8 (3.5)	NC	NC	NC	NC		29.5 (0.8)	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 \leq -1.5 SD below the mean of data from 72 HC Amnestic/non-amnestic MCI = hierarchical cluster analysis (data-driven)
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)*		
HC	21	70.7 (2.7)	NP	NP	NC	NC	NC	NC		\geq 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-amnesic MCI = performance on at least one memory test <16 th percentile of normative data but without diagnosis of PD (Petersen's criteria ²)	
Lyoo et al. (2010)									None			
HC	14	[§] 61.0 (58.0-62.0)	NP	NP	NC	NC	NC	NC		NP	Battery of tests (SNSB) assessing language and related functions, visuospatial functions, verbal and visual memory, executive functions	Modified Petersen's criteria ²
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	[§] 22.0 (15.5-46.0)		[§] 29.0 (28.0-30.0)*		Amnesic MCI single-domain = only performance on at least one memory test <16 th percentile of normative data
PD-aMCI single	12	[§] 65.5 (56.0-71.0)	NP	NP	[§] 4.4 (2.6-13.0)	[§] 2.5 (2.4-4.0)	provided, but 33 patients had no antiparkinsonian medication, while the 28 remaining PD patients had a mean LEDD of 594.6	[§] 27.5 (19.8-62.0)		[§] 28.5 (26.8-30.0)*		Non-amnesic MCI single-domain = only performance in one cognitive domain other than memory <16 th percentile of normative data
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)*		MCI multiple-domains = performance in at least two cognitive domains <16 th percentile of normative data
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)									<u>GDS</u> (frequencies of score >5)			
HC	15	71.3 (6.1)	9/6	9.3 (4.3)	NC	NP	NP	NC	1 (6.67%)	29.5 (0.6)	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.	Amnesic MCI = performance on immediate and/or delayed recall ≤-1.5 SD below the mean of normative data
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)		nonPD-amnesic 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)
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)									<u>GDS / NPI</u>			
HC	26	NP	NP	NP	NC	NC	NC	NC	NP	NP	Battery of tests (SNSB) assessing language and related functions, visuospatial functions, verbal and visual memory, executive functions	MDS level I criteria ¹
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)*		MCI = performance ≤-1.5 SD below the mean of normative data
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)*		Executive MCI = performance on at least the executive test ≤-1.5 SD below the mean of normative data
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)*		Non-executive MCI = performance in one or more cognitive domains other than executive functions ≤-1.5 SD below the mean of normative data

Means (and standard deviations when available) are presented, unless otherwise specified ([§]medians (and interquartile range); [&]range (minimum-maximum)). ¹Litvan et al. (2012); ²Petersen 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 amnesic MCI; NP = not provided; NPI = neuropsychiatric inventory; PD = Parkinson’s disease; PD-aMCI = PD patients with amnesic MCI; PD-exMCI = PD patients with executive MCI; PD-naMCI = PD patients with non-amnesic 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. HC PD-NC PD-aMCI	20 19 17	Diffusion tensor imaging sequence 3.0 Tesla Siemens	FA, AD, RD (voxel-based) FA (TBSS-based)	ANCOVA (controlled for age, sex, disease duration) Threshold-free cluster enhancement (5,000 permutations) Family-wise error FSL	<u>FA, AD, RD voxel-based</u> PD-NC>PD-aMCI (FA) R corpus callosum splenium R corpus callosum body L cingulum (cingulate gyrus) L posterior thalamic radiation L posterior corona radiata L tapetum R cingulum (cingulate gyrus) R posterior thalamic radiation R tapetum R posterior corona radiata R superior longitudinal fascicle L superior corona radiata L fornix <u>FA TBSS-based</u> PD-NC>PD-aMCI L cingulum body R cingulum body L superior longitudinal fascicle R superior longitudinal fascicle L cingulum (cingulate gyrus) R cingulum (cingulate gyrus) L inferior longitudinal fascicle R inferior longitudinal fascicle R inferior fronto-occipital fascicle L inferior fronto-occipital fascicle	10/-39/20 -3/-17/24 -8/-51/16 -28/-56/17 -19/-50/33 -29/-54/13 10/-45/23 33/-52/18 32/-49/8 32/-53/21 36/-53/18 -18/-1/38 -25/-25/-10 -12/-9/30 11/-25/28 -37/-54/15 35/-12/34 -9/-29/35 9/-6/33 -27/-58/19 28/-50/19 32/-62/1 -28/-74/3	<i>p</i> =0.04 <i>p</i> =0.04 <i>p</i> =0.04 <i>p</i> =0.03 <i>p</i> =0.04 <i>p</i> =0.03 <i>p</i> =0.05 <i>p</i> =0.03 <i>p</i> =0.05 <i>p</i> =0.03 <i>p</i> =0.04 <i>p</i> =0.04 <i>p</i> =0.05 <i>p</i> =0.03 <i>p</i> =0.02 <i>p</i> =0.03 <i>p</i> =0.04 <i>p</i> =0.03 <i>p</i> =0.03 <i>p</i> =0.03 <i>p</i> =0.03 <i>p</i> =0.04 <i>p</i> =0.05
Christopher et al. HC PD-NC PD-aMCI PD-naMCI	14 11 9 10	3-dimensional T1-weighted sequence 3.0 Tesla General Electric	Cortical thickness	ANCOVA (controlled for age, UPDRS-III and levodopa equivalent daily dose) Monte Carlo simulation (10,000 iterations) Software NP	No significant result		
Chung et al. HC PD-aMCI PD-naMCI	30 50 50	3-dimensional T1-weighted sequence Diffusion-weighted imaging sequence 3.0 Tesla	Hippocampal volume Cortical thickness FA, MD (TBSS-based)	ANCOVA (controlled for age, sex, years of education, total intracranial volume (except in TBSS))	<u>Cortical thickness</u> HC>PD-aMCI L frontotemporal regions <u>FA</u> HC>PD-aMCI L frontotemporoparietal regions R frontotemporoparietal regions	NP	NP

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.	Diffusion tensor imaging sequence	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> <i>Node strength</i> HC>PD-aMCI <i>Path length</i> HC>PD-aMCI <u>Local level</u> <i>Node strength</i> HC>PD-aMCI		
HC	40				NC	<i>p</i> =0.004
PD-NC	31				NC	<i>p</i> =0.014
PD-aMCI	9	3.0 Tesla Siemens				
				L putamen	-27/2/-1	<i>p</i> =0.043
				R putamen	27/2/-1	<i>p</i> =0.002
				L caudal middle frontal	-36/14/47	<i>p</i> =0.018
				R caudal middle frontal	39/16/47	<i>p</i> =0.040
				L inferior parietal	-41/-72/28	<i>p</i> =0.031
				R inferior parietal	46/-64/26	<i>p</i> =0.019
				L postcentral	-44/-21/47	<i>p</i> =0.017
				R postcentral	44/-21/47	<i>p</i> =0.045
				L posterior cingulate	-5/-28/39	<i>p</i> =0.043
				R posterior cingulate	7/-24/41	<i>p</i> =0.006
				L precentral	-39/-7/45	<i>p</i> =0.017
				R precentral	41/-6/45	<i>p</i> =0.019
				L precuneus	-9/-64/39	<i>p</i> =0.019
				R precuneus	9/-64/39	<i>p</i> =0.043
				L pallidum	-21/-4/-1	<i>p</i> =0.021
				L entorhinal cortex	-25/-3/-34	<i>p</i> =0.004
				L isthmus cingulate	-8/-50/18	<i>p</i> =0.027
				L middle temporal	-61/-29/-11	<i>p</i> =0.016
				L pars opercularis	-48/20/10	<i>p</i> =0.003
				L banks of the superior temporal sulcus	-59/-45/9	<i>p</i> =0.019
				L supramarginal	-52/-41/40	<i>p</i> =0.002
				L rostral middle frontal	-36/51/8	<i>p</i> =0.003
				L superior temporal	-56/-16/2	<i>p</i> =0.006
				R lateral occipital	30/-87/-6	<i>p</i> =0.029
				R rostral anterior cingulate	6/35/1	<i>p</i> =0.019
				R rostral middle frontal	35/52/11	<i>p</i> =0.007
				R superior parietal	NP	<i>p</i> =0.040
				<i>Path length</i>		

					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)	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			Family-wise error SPM			
		Siemens					
Lee et al.		3-dimensional T1-weighted sequence	Voxel-based morphometry	ANCOVA (controlled for age and mini-mental state examination total score)	HC>PD-aMCI		<u>Z-values</u>
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		Uncorrected $p<0.001$ with minimal cluster size of 50mm ³	R precuneus	6/-69/29	4.76
		Philips		SPM			

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 amnesic MCI; NP = not provided; PD = Parkinson's disease; PD-aMCI = PD patients with amnesic MCI; PD-naMCI = PD patients with non-amnesic 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
<u>Functional MRI studies</u>							
Chung et al.		T2*-weighted functional MRI sequence	Functional connectivity strength (BOLD signal)	ANCOVA (controlled for age, sex, years of education)	HC>PD-naMCI		<u>T-values</u>
HC	30			Monte Carlo simulation (10,000 iterations)	<i>Default-mode network</i>		
PD-aMCI	50			AFNI	R postcentral gyrus	28/-42/62	4.705
PD-naMCI	50	3.0 Tesla			L postcentral gyrus	-22/-42/62	4.898
		Philips			R lingual gyrus	18/-48/-2	4.218
					L posterior cingulate	-14/-8/14	4.402
					<i>Central executive network</i>		
					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
					<i>Dorsal attentional network</i>		
					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		
					<i>Default-mode network</i>		
					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
					<i>Central executive network</i>		
					R precuneus	10/-84/60	3.840
					L superior parietal lobule	-20/-70/76	4.088
					<i>Dorsal attentional network</i>		
					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		
					<i>Saliency network</i>		
					L middle temporal gyrus	-54/-74/24	-3.540
					PD-aMCI>PD-naMCI		

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

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	<i>p</i> =0.031 <i>p</i> =0.048
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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 amnesic MCI; PD-exMCI = PD patients with executive MCI; PD-naMCI = PD patients with non-amnesic 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
<u>Neurotransmission/neuromodulation studies</u>							
Christopher et al.		Siemens	[¹¹ C]FLB 457	ANCOVA	<u>Cortical dopaminergic receptor</u>		<u>T-values (p-values)</u>
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)
					<u>Striatal vesicular monoamine transporter 2</u>		
					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	<u>Early measure</u>	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
Delayed measure
PD-NC>PD-exMCI
R caudate nucleus *p=0.001*
L caudate nucleus *p=0.014*
PD-nexMCI>PD-exMCI
R caudate nucleus *p=0.001*
L caudate nucleus *p=0.005*

Metabolic/perfusion studies

						<u>T-values</u>
Lyoo et al.	Philips	FDG PET	ANCOVA	HC>PD-naMCI single		
HC	14	Cerebral metabolic	(controlled for age)	R precentral	49/10/9	3.9
PD-NC	20	rate for glucose	Cluster-level	R superior temporal	54/10/-22	5.1
PD-aMCI single	12		correction	L middle temporal	-38/-82/20	5.2
PD-naMCI single	11		SPM	R postcentral	70/-25/16	3.4
PD-MCI multiple	18			L angular	-51/-71/36	4.6
				L cuneus	-14/-83/34	3.0
				L middle occipital	-57/-66/-14	3.9
Nobili et al.	General Electric	99mTc-bicisate	ANCOVA	HC>PD-aMCI		<u>Z-values (p-values)</u>
HC	15	Regional cerebral	(controlled for age,	L superior parietal lobule	-32/-70/50	4.77 (0.018)
PD-NC	15	blood flow	depression score,	L inferior parietal lobule	-45/-37/42	4.29 (0.018)
PD-aMCI	15		UPDRS-III)	R inferior parietal lobule	47/-42/45	4.53 (0.018)
nonPD-aMCI	15		False discovery rate	R occipital cuneus	12/-84/2	4.26 (0.019)
			SPM	R occipital cuneus	22/-96/20	4.20 (0.019)
				R middle occipital gyrus	26/-94/17	4.13 (0.019)
				R inferior parietal lobule	37/-64/46	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 amnesic MCI; NP = not provided; PD = Parkinson's disease; PD-aMCI = PD patients with amnesic MCI; PD-exMCI = PD patients with executive MCI; PD-naMCI = PD patients with non-amnesic 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.