



Neuroimaging and Neuropsychological Performance in Parkinson's Disease Patients with Mild Cognitive Impairment: A Systematic Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2022/v34i31A36087

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/84956>

Systematic Review Article

Received 01 February 2022

Accepted 05 April 2022

Published 13 April 2022

ABSTRACT

Introduction: One of the most common non motor symptoms of Parkinson's disease (PD) is cognitive decline. Scientific evidence has demonstrated that patients with PD experience rapid cognitive decline in multiple cognitive domains, specifically executive functions, attention, visuospatial, language and memory. However, the extent of cognitive decline with its correlation to brain regions on neuroimaging have not been reviewed extensively in the literature.

Objective: The objective of this review is to summarize the existing literature that explores cognitive performance in patients with PD with mild cognitive impairment (MCI) using different neuroimaging techniques.

Methods: A comprehensive search was conducted on PubMed and Web of Science databases. This review is focused on articles that explored neuroimaging and neuropsychological performance in patients with Parkinson's disease. We screened articles and excluded those that did not fit the criteria of this study, and a total of 13 articles have met the criteria.

Results: Overall, PD-MCI patients experienced more cognitive decline than PD patients without MCI. Global cognitive ability was associated with frontal lobe, basal ganglia, para-hippocampal gyrus, occipital lobe, and the cerebellum. In addition, some specific cognitive domains were associated with specific brain regions. Attention and executive functions were associated with insula network and the parietal and frontal regions. Learning and memory were associated with grey

matter atrophy and right cingulate gyrus and the limbic lobe. Language was associated with frontal cortex, precuneus, and anterior cingulate gyrus. Visuospatial ability was associated with Salience network (SN) and White Matter Hyperintensity (WMH).

Conclusion: This review of the literature showed that PD-MCI patients display different cognitive impairment as well as different neuroanatomical changes when compared to PD-Normal Cognition (NC). These findings may suggest that cognitive impairment in PD-MCI patients require different clinical treatment and care. This review also can have diagnostic and treatment implications for this group of patients.

Keywords: Parkinson's disease; neuroimaging; cognition; executive function; attention; memory.

1. INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease, which is characterized as a movement disorder. The global of neurological diseases reported that the incidence and prevalence of PD has increased worldwide [1,2]. It has been characterized as the fastest growing neurological condition worldwide [1,3]. One of the most common symptoms of PD is cognitive decline [4-7]. Scientific evidence has demonstrated that patients with PD experience rapid cognitive decline in multiple cognitive domains, specifically executive functions, attention, visuospatial, language and memory [8]. Moreover, Mild Cognitive Impairment (MCI) is identified in 40% of newly diagnosed PD patients [9].

Some studies have investigated cognitive performance in PD using different neuroimaging techniques. A magnetic resonance imaging (MRI) study investigating cognitive decline in PD concluded that patient with PD and mild cognitive impairment (PD-MCI), have cortical thinning in the parietotemporal regions, global atrophy, and cognitive decline in memory, executive, visuospatial and visouperceptual domains [8]. Whereas a study using positron emission tomography (PET) scan to investigate cognitive decline in patient with PD has identified impairments in cognitive domains related to memory (in the hippocampus) and attention (in the prefrontal cortex) [10]. Another MRI study found cognitive impairment in domains of memory and executive functions (located in the hippocampus and the frontal lobe) [11].

Neuroimaging and neuropsychological assessment have helped associate specific brain regions with cognitive decline. However, due to the different methods of selection of participants and the variety of criteria inclusions and exclusions, results of prior studies showed discrepancy.

To our knowledge, there are only three review articles up to date that explored neuroimaging correlation to cognitive decline in patients with PD. The first is a meta-analysis that was focused exclusively on functional imaging and executive functions in PD, which concluded that there is a lack of evidence in the literature to associate specific neural pathways with executive dysfunction in patients with PD [12]. The second literature review explored the brain correlations relating to cognitive dysfunction in patients with PD; however, it focused only on one type of neuroimaging, which is structural MRI technique [13]. The aforementioned study concluded that there is evidence of structural changes detected by MRI associated with cognitive decline in patients with PD [13]. The third literature review focused only on the correlation between the hippocampal and episodic memory [14]. All review articles did not take into consideration the stages of PD, the cognitive status of the participants, and the presence of neuropsychiatric symptoms. The exclusion of neuropsychiatric symptoms is crucial as previous studies found evidence supporting the role of neuropsychiatric symptoms to the cognitive decline experienced by patients with PD [15-22].

The objective of this study is to summarize the existing literature that explores cognitive performance in patients with PD using different neuroimaging techniques, aiming specifically to identify if there are common specific brain regions associated with cognitive performance in early stages of PD with MCI without neuropsychiatric symptoms.

2. METHODS

A comprehensive search was conducted on PubMed and Web of Science databases. The search was aimed at finding articles that explored neuroimaging and neuropsychological performance in patients with Parkinson's disease. The key terms used in this search were:

Parkinson, Memory, Cognition, Executive function, Abstract reasoning, Cognitive performance, Learning and attention, Visual-construction, Language, Neuroimaging, Voxel-Based Morphometry (VBM), Positron Emission Tomography (PET), Single-Photon Emission Computed Tomography (SPECT), Magnetic Resonance Imaging (MRI) and functional MRI. The search includes articles until September, 2021. No time span was specified during the search. The initial search identified 4087 titles and abstracts, 3003 of them were duplicates, and 905 were excluded according to the inclusion and exclusion criteria. The full text of the remaining articles, 179 were retrieved. Based on the inclusion and exclusion criteria, 13 articles remained. Exclusion criteria was as follows: (1) review articles, (2) no neuropsychological assessment, (3) neuropsychiatric symptoms, (4) non English language studies, (5) reports published only in abstract format (6) participants with other neurological conditions, (7) case reports (8) moderate and severe Parkinson's patients (9) non-MCI (see Fig. 1). A total of 13

articles have met our inclusion criteria which included a sample of participants with Early Parkinson's Disease, used neuropsychological assessment and linked it with the used neuroimaging techniques and focused on cognition.

3. RESULTS

Thirteen studies were eligible after applying the review criteria, published between 2014 and 2021. All of them included patients with mild Parkinson's disease and mild cognitive impairment and were without neuropsychiatric symptoms. Nine studies used MRI, two study used fMRI and two studies used PET scan. Studies used various neuropsychological assessment tools, and almost all measured global cognitive ability except for one. Other cognitive domains were measured such as, attention, executive function, learning and memory, language and visuospatial abilities. Below is a summary of the results based on cognitive domains.

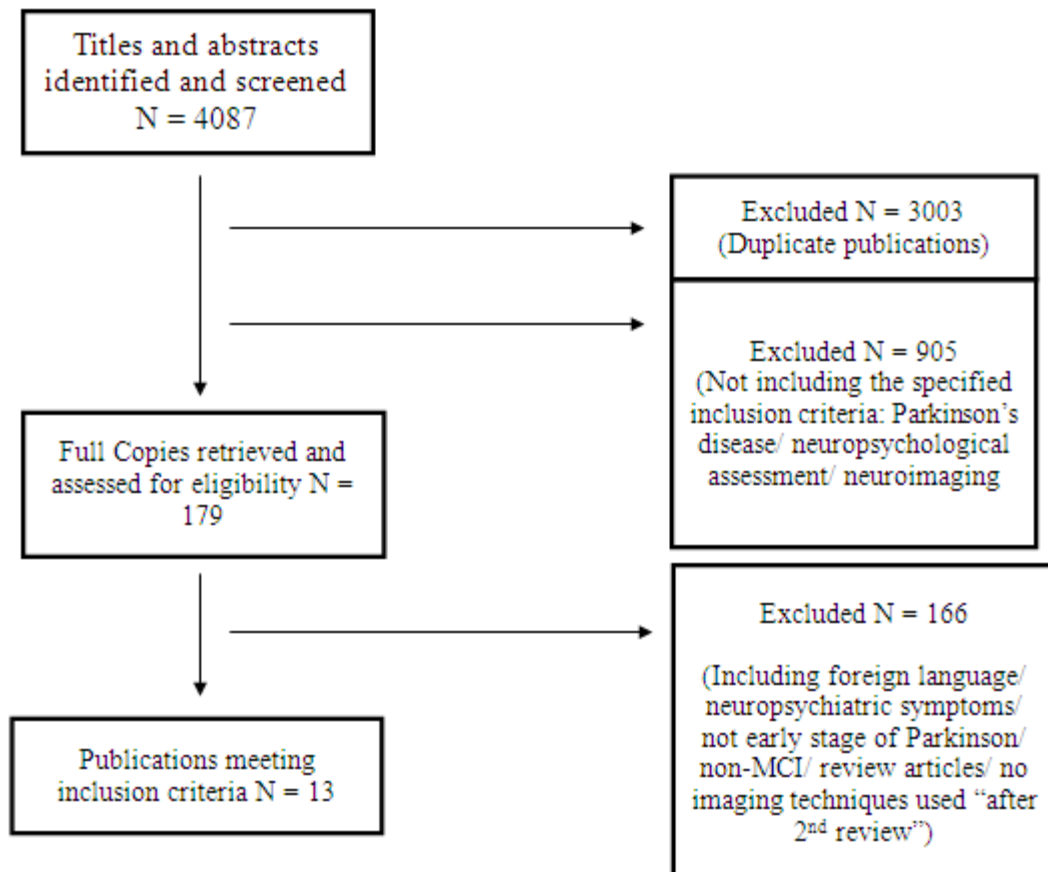


Fig. 1. Flow chart of the study selection process

3.1 Global Cognitive Ability

Global cognitive ability was measured in most of the articles reviewed except for one. Overall, patients with PD and MCI demonstrated a decrease in their global cognitions compared to patients with PD without MCI [23-26]. Research found that changes in the Salience network (SN) hub correlated with impairment in global cognitive function. Whereas, another study [23] found that PD-MCI group displayed lower grey matter regions that correlated with Montreal Cognitive Assessment (MoCA) score (mainly non-memory related) including the frontal lobe, basal ganglia, parahippocampal gyrus, occipital lobe, and the cerebellum.

On the other hand, other research group [13] have found no significant difference between patients with PD-MCI and PD-NC on measures of global cognitions. However, they found that PD-MCI have higher A β amyloids in the anterior cingulate than PD patients with normal cognition. They concluded that global measures are insensitive to A β amyloids in patients with PD.

Another study [25] reported that PD-MCI group performed significantly worse on measures of global cognitive ability. Moreover, study [10] also found that PD-MCI group performed worse on measures of global cognition than the patients with PD and without MCI.

Furthermore, a study [10] reported that PD-MCI group had greater motor severity and fewer years of education than patient with PD-without MCI. Whereas Huang et al. [31] noted that PD patients with MCI were noticeably older than PD with normal cognition.

Overall, changes in the Salience network hub [6], lower grey matter in the frontal lobe, basal ganglia, parahippocampal gyrus, occipital lobe, and cerebellum correlated with decline in global cognitive abilities [1,23].

3.2 Executive Function and Attention

Previous articles [27] have found significant cognitive impairment in executive functions in the PD-MCI group in comparison to PD without MCI. On the other hand, a research paper [27] demonstrated lower performance in PD-MCI patients than in PD-NC on tasks of planning. It is reported that [28] showed that PD-MCI converters showed severe cognitive deficits in the attention domain. A study done by [25] found

that PD-MCI group performed significantly worse on assessments of executive functions and attention. A study by [10] also found that PD-MCI group performed worse on measures of attention and executive function than the patient with PD and without MCI.

Moreover, Peraza and his group [24] investigated intra and inter-connectivity in in early PD and PD-MCI using fMRI and found differences in the insula network in comparison to PD-NC. The insula network is especially important for orienting attention. One study [29] reported an interesting pattern. They found that the stroop colors test significantly correlates with left superior parietal and frontal regions in PD-NC patients; however, a clear pattern of such was not observed in PD-MCI patients. Instead, they observed a widespread pattern in the anterior and posterior regions that correlates with Trail Making Test Part A (TMT-A) and Stroop Color Test.

Additionally, a paper by Huang et al. [31] investigated periventricular White Matter Hyperintensity (WMH) in early PD patients in association to cognitive decline. The study found that WMH burden was significantly associated with PD-MCI, which is also associated with worse executive function and visuospatial function [27]. Aracil-Bolaños et al. [6] found that changes in the Salience network (SN) hub correlated with impairment in executive function tasks [6].

3.3 Learning and Memory

The study by Nagano-Saito et al. [27] found that PD-MCI patients performed worse on measures of learning than PD non-MCI patients [27]. They also found that hippocampal activity is correlated with memory scores. Several studies have reported a lower performance in PD-MCI patients. Specifically, Schneider et al. [25] found that PD-MCI group had lower performance in relation to memory related assessments [25]. As well as, Firbank et al. [10] found that PD-MCI group performed worse on measures of memory than the patient with PD and without MCI patient with PD and without MCI [10].

Foo et al. [11] and Segura et al. [8] reported significant cognitive impairment in memory among the PD-MCI group in comparison to PD without MCI. Moreover, Research [23] found that grey matter atrophy was correlated with lower scored on the Mini Mental State Examination

(MMSE) especially memory related questions, including the right cingulate gyrus and the limbic lobe. Study by [26], found that higher brain connectivity was linked to a better episodic memory.

3.4 Language

One study showed that PD MCI patients had lower performance on measures of language than the PD non-MCI patient [27]. Akhtar et al. [13] reported that A β amyloid in the frontal cortex, precuneus, and anterior cingulate gyrus correlate with language performance. Moreover, memory and naming in MCI depends on regional A β amyloids [13]. A study reported that PD-MCI group performed significantly worse all the neuropsychological assessments except for Bosting naming test [25]. Another article also reported that PD-MCI group performed worse in measures of language than the patients with PD and without MCI [10].

3.5 Visuospatial Ability

Segura et al. [8] found significant cognitive impairment in visuospatial and visuoperceptual domains in the PD-MCI group in comparison to PD without MCI [8]. Another study found that PD-MCI group performed significantly worse on tasks measuring visuospatial ability [25].

Aracil-Bolaños et al. [6] found that changes in the Salience network (SN) hub correlated with impairment in visuospatial tasks [6]. whereas, Huang et al. [31] investigated periventricular White Matter Hyperintensity (WMH) in early PD patients in association to cognitive decline [31]. The study found that WMH burden was significantly associated with PD-MCI, which is also associated with worse visuospatial function.

3.6 Neuroimaging Outcomes (Comparison between PD-MCI and PD without MCI)

A study found that older age is associated with thinner cortex in various brain regions, especially in the frontal and temporal cortex bilaterally. They concluded that overall, cortical thickness did not differ between PD-NC and PD-MCI. However, the hippocampal volume is smaller in PD-MCI [25]. On the other hand, another study showed that PD-NC patients and PD-MCI

differed significantly in the progression of cortical thinning in posterior regions, where PD-MCI patients showed significantly greater cortical thinning in left lateral occipital and inferior parietal regions, and in right medial temporal regions [30]. Moreover, Segura et al. [8] have found that patients with MCI displayed regional cortical thinning in parietotemporal regions, increased global atrophy: global cortical thinning, gray matter reduction, and ventricular enlargement [8]. A study showed that PD-MCI group demonstrated thalamus atrophy and progressive atrophy in the thalamus, caudate nucleus, hippocampal atrophy, and presubiculum atrophy.

Another group of researchers argued that PD-MCI group displayed significantly less gray matter in the bilateral precuneus and the posterior cingulate cortex than patients with PD-NC [6]. Moreover, increasement in gray matter was not observed in the PD-MCI group compared to PD-NC. Furthermore, a study found that PD-MCI patients displayed grey matter atrophy in the frontal lobe, limbic lobe, basal ganglia and cerebellum [23]. When compared to the PD-NC patients, patient with PD-MCI displayed grey matter atrophy in the left side middle temporal gyrus, inferior temporal gyrus and frontal lobe.

Akhtar et al. [13] reported that the overall A β amyloid value did not significantly differ between PD-NC and PD-MCI [1]. However, there were regional difference between the groups. Hence, PD-MCI patients demonstrated A β amyloid in the posterior Cingulate more the PD-NC. While, Firbank et al. [10] pointed that patient with PD-MCI, had reduced metabolism in the inferior parietal and posterior temporal regions [10]. And have not found any other difference in any region between the PD-MCI and PD-NC. Furthermore, Park et al. [28] discussed that examining visible perivascular space (PVS) in the basal ganglia region can be a predictor of cognitive decline in PD-MCI patients, they also found lower scores of MMSE to be a predictor of cognitive decline [28]. Another paper reported that patients with MCI has reduced activity in the cognitive corticostriatal loop, which includes the caudate nucleus and prefrontal cortex. However, patients without MCI did not exhibit such pattern. Instead, Patients without MCI demonstrated a pattern similar to healthy participants.

Table 1. Summary of reviewed articles

Study	# Participants	Age [years]	Cognitive Domains Studied	Neuropsychological Tests	Imaging Technique	Results
Nagano-Saito, Atsuko, et al [27]	33 PD patients without MCI = 19 PD patients with MCI = 14	SD, 61.0 5.3 years	Global cognitive ability, executive function and attention, learning and memory, language, and visuospatial ability.	MoCA, DST, TMT/B, SCWT, TOL, BSAT, VFL: orthographic criteria subtest of the protocole MEC, Logical memory subtest of WMS-III, RAVLT, BNT, VFL: semantic criteria subtest of the MEC, Vocabulary subtest of WASI-II, HVOT, Clock-drawing subtest of MoCA, and ROCF/copy.	fMRI	It was found that the higher the participants (non-MCI) scored on Brixton, the more activity was found in the caudate head and body. As well as, higher scores on (non-MCI) RAVLT correlated with an activity increase in the hippocampus. And, the higher the errors made on WCST (MCI), the less individual activation in the caudate.
Segura, Bárbara, et al. [8]	122 PD non MCI = 43 PD MCI = 47 HC = 32	60.77 ± 10.51 67.72 ± 9.71 64.69 ± 8.63	Global cognitive ability, executive function and attention, learning and memory, language, and visuospatial ability.	MMSE, TMT, SDMT, DST, SCWT, BNT, SFT, RAVLT, JLO, and VFD.	MRI	PD patients with MCI scored significantly worse than the other two groups on all test except on Digit Span which measures attention and executive functions. They also exhibited a posterior pattern of atrophy shown through a cortical thinning in the bilateral superior parietal and supramarginal regions and in the inferior temporal area, parahippocampal gyrus, fusiform gyrus, and precuneus.
Akhtar, Rizwan S., et al., [13]	61 PD-NC = 42 PD-MCI = 19	age at scan time was 67.0 (64.9 to 69.0) years	Global cognitive ability, executive function and attention, learning and memory, language, and visuospatial ability.	DRS-2, BNT, TMT, SDGMT, HVLT-R, IDFR, LNST, VFL, F-A-S, and SFT.	PET	Significant differences between patients with PD-MCI and PD-NC were found on measures of global cognitions. They concluded that global measures are insensitive to AB amyloids in patients with PD. And that AB amyloid in the frontal cortex, precuneus, and anterior cingulate gyrus correlate with language performance, and that memory and naming in MCI depend on regional AB amyloids.
Firbank, Michael J., et al [10]	99 Control = 20 PD-NC = 38 PD-MCI = 41	71.9 (9.7) 72.3 (6.4) 74.2 (4.8)	Global cognitive ability, executive function and attention, learning and memory,	MMSE, MoCA, PRM, SRM, and PAL from CANTAB.	PET	Significant correlation was found in the FDG angular gyrus/cerebellum uptake ratio which predicted both of MMSE and MoCA at 18 months in the PD-MCI group. Significant correlation was also found in the lateral

Study	# Participants	Age [years]	Cognitive Domains Studied	Neuropsychological Tests	Imaging Technique	Results	
			language, and visuospatial ability.			parietotemporal–occipital region.	
Foo, H., et al [11]	65	PD-NCI = 54 PD-MCI = 11	63.39 ± 6.86 69.45 ± 10.19	Global cognitive ability, executive function and attention, learning and memory, language, and visuospatial ability.	MMSE, MoCA, word-list delayed and recognition recall, CDT, DST, Maze test and constructional praxis and animal fluency.	MRI	Memory performance was significantly correlated with the left thalamus in the PD-MCI group.
Gao, Yuyuan, et al. [23]	67	Control = 21 PD-NC = 23 PD-MCI = 23	63.76 ± 5.42 62.35 ± 7.73 65.09 ± 8.71	Global cognitive ability, executive function and attention, learning and memory, language, and visuospatial ability.	MMSE, MoCA.	MRI/ VBM	MMSE scores were linked to brain structural changes in PD-MCI. This group also suffered from grey matter atrophy in the frontal lobe, limbic lobe, basal ganglia and cerebellum.
Peraza, Luis R., et al. [24]	129	HC = 30 PD-NC = 62 PD-MCI = 37	64.05 (7.92) 62.77 (10.83) 70.40 (9.13)	Global cognitive ability.	MMSE, MoCA, Power of Attention, DVT, PRM, SRM, TOL, ANT, Language total score and PAL.	MRI	SRM variable and cluster FPN-20 had a significant relation, which demonstrated a disconnection between the frontal pole network and the right middle frontal gyrus. There was also a significant positive relation between this inter-network connectivity and PAL.
Schneider , Christine B., et al. [25]	68	PD = 31 PD-MCI = 32	67.7 (7.5) 68.3 (6.8)	Executive function and attention, learning and memory, language, and visuospatial ability.	CERAD, Word list learning, Word list recall, Word list recognition, MCST, Categories, Nonperseverative errors, Perseverative errors, VFL, Animal, Words with S, TMT, SCWT, Words, Colors, Interference, LPS subtest 7, LPS subtest 9, CERAD constructional praxis, and BNT.	MRI	This study suggests accelerated aging-related decline in hippocampal volume for patients with PD-MCI.

Study	# Participants	Age [years]	Cognitive Domains Studied	Neuropsychological Tests	Imaging Technique	Results	
Garcia-Diaz, Anna I., et al [29]	64	HC = 20	65.50 ± 8.00	Global cognitive ability and visuospatial ability.	PCT, JLOT, VFDT, FRT, and SDMT.	MRI	They found that the stroop colors test significantly correlates with left superior parietal and frontal regions in PD-NC patients; however, a clear pattern of such was not observed in PD-MCI patients. Instead, in the PD-MCI group they observed a widespread pattern in the anterior and posterior regions that correlates with TMT-A and stroop colors test.
		PD-NC = 28	59.50 ± 9.58				
		PD-MCI = 16	64.63 ± 9.67				
Aracil-Bolaños, Ignacio, et al [6]	53	PD-NC = 34	65.8 ± 6.7	Global cognitive ability, executive function and attention, learning and memory, language, and visuospatial ability.	TMT/B, ROCFT, VOSP; number location, BNT and Token Test, and FCSRTR.	MRI	They found that changes in the Saliency network (SN) hub correlated with impairment in global cognitive ability, executive function, and visuospatial tasks. (in which group?)
		PD-MCI = 19	73 ± 4.5				
Park, Yae Won, et al [28]	271	PD-IC (intact cognition) = 106 PD-MCI = 165		Global cognitive ability, executive function and attention, learning and memory, language, and visuospatial ability.	MMSE and SNSB.	MRI	Results showed that PD-MCI converters showed severe cognitive deficits in the attention domain.
Huang, X., et al [31]	175	PD-MCI = 94	52 (55.3%)	Global cognitive ability, executive function and attention, learning and memory, language, and visuospatial ability.	ADAS, ROCF, JLO, WAIS-IV, DST, WMS- IV; symbol span, BNT, WAIS-IV similarities, Fruit Fluency and FAB.	MRI	Study found that periventricular and deep-subcortical WMH (White Matter Hyperintensity) burden was significantly associated with PD-MCI, which is also associated with worse executive function and visuospatial function. There are significant differences between patient with PD-MCI and NC-PD in total brain WMH and periventricular WMH.
		PD-NC = 81	47 (58.0%)				
Wang, Qingguan g, et al.	46	HC = 13 PD-NC = 13	70.2±7.1 70.4±6.4	Global cognitive ability, episodic memory,	MMSE, AVALT, ROCF, TMT A&B, VFT, DSST, and CDT.	fMRI	It was found that PD-MCI performed significantly worse on global cognition, episodic memory, visuospatial function,

Study	# Participants	Age [years]	Cognitive Domains Studied	Neuropsychological Tests	Imaging Technique	Results
[26]	PD-MCI = 20	72.6±6.1	visuospatial function, information processing speed and executive function.			information processing speed, and executive function. Compared with the HCs, PD-NC and PD-MCI showed significantly decreased Functional Connectivity within bilateral precuneus (BPcu).

Key: MMSE: Mini Mental Status Examination; TMT: Trail Making Test; SDMT: Symbol Digit Modalities Test; DST: Digit Span Test; SCWT: Stroop Color and Word Test; BNT: Boston Naming Test; JLO: Benton's Judgement of Line Orientation; VFD: Visual Form Discrimination Tests; DRS-2: The Dementia Rating Scale-2; SDGMT: Symbol-Digit Modalities Test; HVL-R: Hopkins Verbal Learning Test-R; IDFR: Immediate & delayed free recall; LNST: Letter-Number Sequencing Test; VFL: Verbal Fluency; F-A-S: The F-A-S Test assesses phonemic verbal fluency by requesting an individual to orally produce words that begin with the letters F, A and S; SFT: Semantic Fluency Test; MoCA: The Montreal Cognitive Assessment; TOL: Tower of London; BSAT: Brixton Spatial Anticipation Test; VFL: Verbal fluency test orthographic criteria subtest of the MEC; WMS-III: Wechsler Memory Scale; RAVLT: Rey Auditory Verbal Learning Test; BNT: Boston Naming Test; VFL: Verbal fluency: semantic criteria subtest of the MEC; WASI-II: Vocabulary subtest of the Wechsler Abbreviated Scale of Intelligence; HVOT: Hooper Visual Organization; ROCF: Rey-Osterrieth figure copy; PRM: Pattern Recognition Memory; SRM: Spatial Recognition Memory; PAL: Paired Associates Learning from (CANTAB); CANTAB: Cambridge Neuropsychological Test Automated Battery; CDT: 10-point clock drawing and frontal assessment battery; DVT: Digit Vigilance Accuracy; ANT: Animal naming; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; MCST: Modified card sorting test; PCT: Pentagon Copying Test; JLOT: Judgment of Line Orientation Test; VFDT: Visual Form Discrimination Test; FRT: Facial Recognition Test; SDMT: Symbol Digit Modalities Test; VOSP: Visual Object and Space Perception Battery; FCSRTR: Free and Cued Selective Reminding Test; SNSB: Seoul Neuropsychological Screening Battery; ADAS: Alzheimer's Disease Assessment Scale; WAIS-IV: Wechsler Adult Intelligence Scale-Fourth Edition; WMS- IV: Wechsler Memory Scale-Fourth Edition; FAB: Frontal Assessment Battery. WMH: White Matter Hyperintensity; AVL: Auditory Verbal Learning Test; DSST: Digital Symbol Substitution Test; CDT; Clock Drawing Test

4. DISCUSSION

Most of the articles in this review reported difference in cognitive domains in PD-MCI patients in comparison to PD-NC patients. A pattern of lower education and older age was observed in PD-MCI patients. Overall, global cognitive ability was associated with frontal lobe, basal ganglia, parahippocampal gyrus, occipital lobe and cerebellum. In addition, some specific brain regions were associated with specific cognitive domains. Attention and executive functions were associated with insula network and the parietal and frontal regions. Learning and memory were associated with grey matter atrophy and right cingulate gyrus and the limbic lobe. Language was associated with frontal cortex, precuneus, and anterior cingulate gyrus. Visuospatial ability was associated with SN and WMH.

This review attempted to establish a rigorous criterion to exclude any confounding variables that may influence cognitive decline. The purpose of this excluding criteria to investigate the cognitive domains pattern in PD-MCI in comparison to PD-NC.

The strengths of this study include rigorous criterion to exclude confounding variables such psychiatric illnesses which was not taken into consideration in previous literature reviews [31,32]. We also defined “early stage” and only included articles that examined PD in early stages in comparison to cognitive functions. Furthermore, we included all neuroimaging techniques to have broad picture about the brain areas that may contribute to cognitive performance in this group of patients.

We acknowledge some limitations to our study. It has the drawbacks of conducting systematic reviews and its dependence on the quality of the studies reviewed. We have not looked for on or off state of dopaminergic medications.

5. CONCLUSION

In conclusion, our findings indicate that PD-MCI patients display different cognitive impairment, as well as, different neuroanatomical changes when compared to PD-NC. These findings suggest that cognitive impairment in PD-MCI patients requires different clinical treatment and care. This review also can have diagnostic and treatment implications for this group of patients. Providing an understanding of the extent of cognitive

decline in early stages of PD as well as an earlier picture of the nature of this disease.

CONSENT

It is not applicable.

ETHICAL APPROVAL

This project was approved by the Institutional Review Board of the Research Center, King Fahad Medical City, Riyadh, Saudi Arabia.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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