*Journal of Pharmaceutical Research International*

***Volume 35, Issue 32, Page 1-13, 2023; Article no.JPRI.110577***
***ISSN: 2456-9119***
*(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)*

# Neuroimaging and Neuropsychological Performance in Parkinson's Disease Patients with Normal Cognition: 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/2023/v35i327467

**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/110577

***Systematic Review Article***

***Received: 04/10/2023***
***Accepted: 09/12/2023***
***Published: 14/12/2023***

## ABSTRACT

**Introduction:** Cognitive decline is one of Parkinson's disease's (PD) non-motor symptoms that is most frequently observed. Patients with PD exhibit quick cognitive decline in a variety of cognitive domains, particularly in the areas of executive functions, attention, language, memory, and visuospatial abilities. The scope of PD patients with normal cognition (PD-NC) and its relationship to specific regions of the brain as shown by neuroimaging, have not received much attention in the literature.
**Objective:** This review was to summarise the existing literature that explored cognitive performance in PD-NC using different neuroimaging techniques.
**Methods:** A comprehensive search was conducted on PubMed and Web of Science databases. This review focused on papers that investigated neuroimaging and neuropsychological performance in patients with PD. A total of 17 articles have met the criteria.

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**Results:** The findings of this review were that executive functions appear to be the most critical cognitive domain to be damaged in PD-NC. Global cognitive ability was found to have insignificant decline overall between PD-NC and healthy controls (HC). Attention and executive functions were associated with the prefrontal cortex. Memory was mainly associated with hippocampal atrophy. Language was associated with cerebrospinal fluid and grey matter. Visuospatial ability was associated with the anterior cingulate cortex.

**Conclusion:** This review illustrated that PD-NC seemed to experience different cognitive patterns and neuroanatomical changes compared with HC. These results suggested that PD-NC may develop specific cognitive impairments associated with specific brain regions. Therefore, it indicated that PD-NC may need to have specific treatments tailored to their needs.

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

## 1. INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's and it is characterised as a movement disorder (Parkinson's Disease Foundation, n.d.). It is known to be a neurodegenerative disease that is chronic and progressive. (Parkinson's Disease Foundation, n.d.). According to the Parkinson's disease foundation, approximately one million individuals in the U.S. are living with PD, 90,000 cases are diagnosed each year, and there are more than 10 million individuals worldwide living with PD diagnosis. Parkinson's disease affects 1-2% of individuals over the age of 65, and its prevalence is rapidly increasing as population ages [1]. The prevalence of PD-related cognitive impairment varies across studies [2]. Cognitive decline is common between patients with PD. It is usually gradual, but it can be rapid in some cases. Recently, the emphasis has shifted to early cognitive changes, where executive function and visuospatial impairments are common and can be accompanied by memory loss [3].

Some studies have investigated the association between cognitive performance and brain regions using different neuroimaging techniques in PD patients with normal cognitive ability (PD-NC). A functional magnetic resonance imaging (fMRI) study investigating their behavioural performance and neural activity, constructed regions-of-interest as in the dorsolateral prefrontal cortex (DLPFC) concluded that patients with PD-NC have significantly decreased functional connectivity of DLPFC with other task-related neurons [4]. Whereas a study using positron emission tomographic (PET) investigated the association between the dopaminergic function and the cognitive performance of patients with PD-NC have found evidence that reduced dopaminergic activity in the right caudate nucleus was associated with impaired performance in the frontal lobe function [5]. Another study investigating grey matter (GM) changes in PD-NC patients using voxel-based morphometry (VBM) has found a considerable decrease in GM, particularly in the frontal and parieto-occipital regions [6]. In another study, they found that decreased dopaminergic function in the caudate nucleus was associated with poor performance on measures of the frontal lobe [5,7]. The vast majority of PD patients experience neuropsychiatric symptoms such as depression, anxiety, and apathy. These three symptoms strongly indicated a low quality of life. These symptoms can manifest before or after the onset of PD [8]. The prevalence of neuropsychiatric symptoms in PD patients is up by 80% such as depression, anxiety, and apathy [9]. Whereas, depression are the most common symptoms 38% [10]. Symptoms such as low mood, loss of pleasure, and feelings of worthlessness are more frequent in PD than in non-PD [8]. A Longitudinal study by Meng et al. [11] illustrated the evolution of neuropsychiatric impact on several cognitive domains. They discovered that PD patients with depression and anxiety performed worse on measures of attention-processing speed, memory, visuospatial ability, and executive function. Apathy was also linked to a gradual drop in processing speed and attentiveness.

Neuroimaging and neuropsychological evaluation have aided in the identification of particular brain regions associated with cognitive decline. Prior research, however, demonstrated inconsistency due to the diverse methods of participant selection and the range of criteria inclusions and exclusions.

To our knowledge, there were no literature reviews exploring the neuroimaging and cognitive functions in PD-NC patients. Previously, there have been four review articles,

the first one explored executive function using fMRI in PD-NC, which concluded that there was insufficient information to determine a specific neural correlation of executive dysfunction with PD-NC [12]. The second review explored cognitive dysfunction in patients with PD-NC using only structural MRI. The findings have shown indications of structural changes in the brain associated with cognitive impairment in patients with PD-NC [13]. The third review, mainly focused on the correlation between the hippocampal and episodic memory. They provided evidence for the significance of the hippocampus's structural and functional integrity in episodic memory impairment in PD-NC [14]. While the fourth literature review explored the neuroimaging correlation between PD-NC patients and Mild Cognitive Impairment (PD-MCI). The results of the review demonstrated that there were differences between PD-MCI patients and PD-NC, specific brain regions were associated with specific cognitive domains. For example, global cognitive ability was associated with the frontal lobe, basal ganglia, parahippocampal gyrus, occipital lobe, and cerebellum [15]. Therefore, this systematic review is an extension to our previous review (Alanadas et al, 2022), we used the same inclusion and exclusion criteria (See the method section). However, in this review we focused on articles that included PD-NC patients only. All the three previous review articles did not take into consideration the stages of PD patient's cognitive condition, and the existence of neuropsychiatric symptoms. Except our previous study by Alanadas et al, 2022 and this current review. However, in comparison with this review and our previous article, this review explored PD-NC patients while the previous review focuses on PD-MCI patients. Prior research had established evidence relating neuropsychiatric symptoms to the cognitive impairment by patients with early PD-NC. Therefore, it was imperative that these symptoms be excluded from the review [16,17]. The purpose of this study was to summarise the existing studies on cognitive function in PD-NC patients using a variety of neuroimaging techniques, with a particular aim of determining whether there were specific brain regions associated with cognitive performance in early-stages of PD-NC without neuropsychiatric symptoms.

## 2. METHODS

In this review, the articles were collected using thorough research on PubMed and Web of Science databases. The objective of this search was to find articles that investigated the association between cognitive performance and neuroimaging data among patients with early-stage in PD-NC. 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 included articles until March. 2023. No time span was specified during the search. The initial search identified 4276 titles and abstracts, 3080 of them were duplicates, and 1017 were excluded according to the present inclusion and exclusion criteria. The full text of the remaining articles, 179 was retrieved. Based on the inclusion and exclusion criteria, 17 articles remained. Exclusion criteria were as follows: (1) review articles, (2) no neuropsychological assessment, (3) neuropsychiatric symptoms, (4) foreign language, (5) reports only published in abstract format (6) participants with other neurological conditions, (7) case reports (8) moderate and severe Parkinson's disease (9) cognitive impairments (see Fig. 1). A total of 17 articles have met our inclusion criteria which included a sample of participants with early PD, used neuropsychological assessment and linked it with the used neuroimaging techniques and focused on cognition.

## 3. RESULTS

Seventeen studies were eligible for the analysis, four studies used fMRI, seven studies used MRI, three studies used PET scans, and three studies used more than on techniques e.g., fMRI and MRI. All the studies explored one or more cognitive domains. Three studies only explored one cognitive domain and the rest of the studies explored more than one cognitive domain. Below is a summary of the results of each study in association with specific cognitive domains. We observed that most of the articles focused on exploring the executive functions.

### 3.1 Global Cognitive Ability

Research by Brück et al., [18], found that the global cognitive abilities for PD-NC patients did not deteriorate as the overall performance on the Mini-Mental State Examination (MMSE) was 26.7. Additionally, a study by Compta et al., [19],

performed a longitudinal study on early-stage PD, found that these patients converted to PD with dementia at 11 months follow-up, had lower scores than PD-NC, however their scores within normal range on measures of global cognitive ability. Whereas, another study by Wen et al., [20], reported that no statistical significance was found between PD-NC patients and HC on global cognitive ability measures. Furthermore, a study by Duncan et al., [21] found that PD patients had insignificant differences on measures of global cognitive ability compared to HC.

### 3.2 Attention and Executive Functions

A study by Brück et al., [5], found that with PD-NC patients there was a clear negative correlation between performance on frontal lobe measures Stroop test, Wisconsin Card Sorting Test (WCST) and Fluorodopa (FDOPA) uptake of the right caudate, which indicated that the weak dopaminergic activity was related to poor performance on measures that requires suppressing attention. Moreover, no correlation was found between WCST and FDOPA uptake in the caudate nucleus or the putamen. However, interestingly, the right caudate was significantly more impaired than any other striatal region for PD-NC patients. Furthermore, Lewis et al., [22], used the Tower of London (ToL) planning task to identify executive impairments during fMRI scanning. This study found that there was a significant decrease during the working-memory paradigm in specific regions of the basal ganglia and frontal cortex in patients with early PD-NC. Furthermore, Brück et al., [18], found that patients with PD-NC had atrophy in the right and left prefrontal cortex, which correlated with impairments in vigilance and sustained attention. In another study by Jokinen et al., [7] found that frontal lobe functions were associated with atrophy in the prefrontal cortex. Moreover, Nagano-Saito et al., [23], used the ToL as a measure of cognitive function. Intriguingly, the HC and the early-stage PD-NC displayed deactivation in the ventral medial prefrontal cortex (vmPFC) and amygdala. In another study by Picco et al., [24], found significantly lower [18F]-Fluoro-L-dopa (18F-DOPA) uptake in PD-NC patients than in HC in the bilateral striatum, the right hemisphere, and the right temporal region. This study also found a significantly positive correlation between executive functions and 18F-DOPA uptake in the bilateral Anterior Cingulate Cortex (ACC) and the middle frontal gyrus.

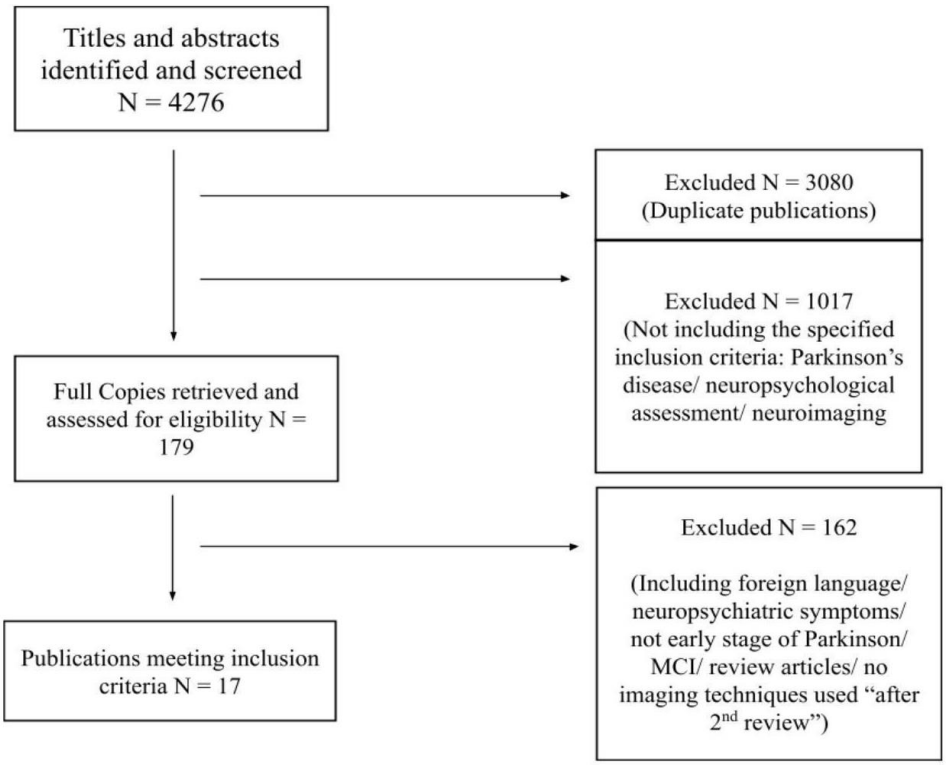


**Fig. 1. Flow chart of the study selection process**

**Table 1. Summary of reviewed articles**

| Study | Participants | | Age [years] | Cognitive Domains Studied | Neuropsychological Tests | Imaging Technique | Results |
|---|---|---|---|---|---|---|---|
| Brück et al., [5] | 10 | PD=10 | 48.3 | Global cognitive ability, executive functions, memory, naming, and visuomotor performance. | WCST and MMSE. | PET | The impaired dopaminergic function of the caudate nucleus is related to the impairment in the frontal lobe. |
| Lewis et al., [22] | 30 | HC = 10<br>PD NC = 10<br>PD MCI = 10 | 50-70<br>40-70<br>44-66 | Global cognitive ability, executive functions, memory, naming, and visuomotor performance. | MMSE, VFT, PRM, SRM, TOL. | MRI | Patients with cognitive impairments showed significant reduction during working memory tasks in specific areas: the striatal and frontal lobe areas. |
| Brück et al., [18] | 42 | HC = 22<br>PD = 20 | 65.7<br>61.3 | Global cognitive ability, executive functions, memory, language, and visuospatial ability. | CERAD, WMS-R, and a vigilance test. CERAD consisted of nine different tasks, namely: verbal fluency, modified Boston naming, MMSE, WLM, WLR, , Word-List Savings, Word-List Recognition, VIM, and delayed memory, VEM, VIM, Praxis Recall, and Praxis Savings, vigilance test. | MRI | Patients with PD exhibited more atrophy in the hippocampus and frontal cortex in comparison to the control. |
| Jokinen et al., [7] | 40 | HC = 21<br>PD = 19 | 62.6 | Global cognitive ability, executive functions, memory language, and visuospatial ability. | CERAD, WMS-R, WAIS-R (subtests: block design, digit symbol and similarities), TMT-A, TMT-B, ATT/C, FAB, WCST, MMSE, CERAD subtests, and GDS. | MRI | Patients with PD showed an overall cognitive impairment when compared to the healthy control group. Moreover, patients with PD showed hippocampal and prefrontal cortex atrophy. |
| Nagano-Saito et al., [23] | 12 | HC = 6<br>PD = 6 | 49 - 66<br>52 - 69 | Executive functions | TOL | PET | They found that nigrostriatal, mesolimbic and mesocortical dopamine systems were all impaired in patients with PD. |

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| vito et al., [25] | 62 | HC = 31<br>PD = 31 | 67.9<br>64.4 | Executive functions | FAB | fMRI | They found that PD patients performed worse on the FAB tasks indicating executive function impairment. Moreover, PD patients performed worse on the future thinking task, which indicates executive function impairments over memory impairments. |
| Compta et al., [19] | 27 | PD = 27 | 69 [64-75] | Global cognitive ability, executive functions, memory language, and visuospatial ability. | MMSE, RAVLT, F-A-S, BNT, visual object and space subtests. | MRI | It was found that lower CSF amyloid-b, worse verbal learning, semantic fluency and visuoperceptual scores, and thinner superior-frontal/anterior cingulate and precentral regions were significant baseline dementia predictors. PD patients without these predictors at baseline were not found to progress to dementia. |
| Lee et al., [6] | 80 | HC = 40<br>PD = 40 | 58<br>59 | Processing speed, executive functions, set shifting, spontaneous flexibility, language, learning, memory, spatial cognition, attention, and working memory. | GPB, The colour subtest from D-KEFS, the symbol search subtest (WMS), CWInt (switch, inhibition, and word subtests), VVLT, BNT, BVMT-R, HVLT-R, JoLO, DRS-2 (construction subtest), DS, and LNS. | MRI | PD patients showed cortical structure in the frontal and parietal occipital regions. |
| Gallagher et al., [26] | 15 | PD = 15 | 60.3 | language, verbal memory, and executive functions. | BNT, HVLT, WCST, TMT-B, and WSCT. | MRI/ PET | No neuropsychological differences were found. |
| Picco et al., [24] | 25 | HC = 10<br>PD = 15 | 68.5<br>66.8 | verbal learning, delayed recall, working memory, attention, cognitive flexibility, language, abstraction, and visuospatial abilities. | Digit span, CBTT, WCST, CWST, DSST, TMT A/B, Vasoconstriction, F-A-S, CVFT, and RAVLT. | PET | Results showed that PD patients had significantly lower Dopaminergic uptake in the bilateral striatum, which was more pronoun in the right hemisphere, and in the right temporal region. There was a positive correlation between executive factor and Dopaminergic uptake in the bilateral ACC and the middle frontal gyrus. |
| Trujillo et al., [4] | 271 | HC = 35<br>PD = 16 | 56<br>58 | Working Memory | Visuospatial version of the n-back task. | fMRI | PD patients showed significantly decreased accuracy during the assessment. Moreover, there was an increased activity in the left DLPFC, a |

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| | | | | | | | trend-significant increase in activity of the right DLPFC, left caudate nucleus, and left IPC. |
| Wen et al., [20] | 42 | PD = 42 | 62.5 | Global cognitions, attention and working memory, executive function, memory, language, visuospatial ability. | MOCA, DS, CTT, FAB, CDT, Word list test, word recognition test, Object Naming test, Receptive speech test, figure copy test, Maze test. | MRI | White matter reduction can be an indicator for conversion to PD-MCI in PD asymptomatic patients. The decreased volume of WM was mainly in the frontal areas. Moreover, baseline GM and WM volumes of the frontal and parietal regions were associated with frontal cognitive changes. |
| Cohn et al., [30] | 28 | HC = 13<br>PD = 15 | 53.9<br>59.1 | IQ, Attention/processing speech, executive function, memory, visuoperceptual and visuospatial skills, language | WTAR, SDMT-oral, C-TMTA, C-TMTB, WCST-64, Phonemic verbal fluency, Matrix Reasoning from (WASI-II), HVLT-R, BVMT-R, Object Decision, number location and Cube analysis subtests of VOSP, animal catelry verbal fluency and WASI-II vocabulary subtest and ARM. | fMRI | ARM performance for PD patients was lower than the control group's performance, and correlated with verbal memory measures; however, not with attention or executive functions. Hippocampal activation was reduced in PD. |
| Duncan et al., [21] | 175 | HC = 50<br>PD = 125 | 65.8<br>66 | Global cognitive function, attention, memory, executive function, | MMSE, MOCA, Tests from the Cognitive Drug Research battery, SRM, PRM, and paired associates learning subsets from CANTAB, Phonemic fluency, semantic fluency, and TOL. | MRI | Increased mean diffusivity was observed bilaterally in PD patients, which was associated with performance on the semantic fluency and TOL tasks in frontal and parietal white matter tracts, including the cingulate, superior longitudinal fasciculus, inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus. Gray matter volume reduction in the bilateral frontal and parietal regions was associated with reduced performance on measures of Executive function in PD patients. |
| Lucas-Jimenez et al., [27] | 53 | HC = 16<br>PD = 37 | 56.1<br>67.9 | Processing speed, verbal fluency, verbal and visual learning and memory, visual | TMT-A, SLCT, semantic & phonetic fluency test, learning & long-term recall performance on HVLT, learning & long-term recall performance on the brief | fMRI/ MRI | Reduced functional connectivity was observed between the posterior cingulate and medial temporal lobe in PD. Lower cognitive performance, grey matter loss in the posterior, medial temporal and parietal |

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| | | | | abilities and executive function | visual memory test, the drawing test, visual objects and space perception battery, WAIS-III Indirect digits and WCST. | | areas, and fractional anisotropy reduction in the white matter adjacent to DMN regions were also observed in PD patients. |
| Poston et al., [28] | 47 | HC = 23<br>PD = 24 | 61.1<br>65.33 | Global cognitive ability, executive function, memory language, visuospatial ability | BNT, BVMT-R, CVLT, verbal fluency, HVOT, MMSE, MOCA, SDMT, SVF, WCST, TMT A&B, and WAIS-IV-digit total. | fMRI/ MRI | Results showed an activation in the bilateral putamen, anterior dorsal insula, supplementary motor area, and ACC dependent on Working memory. The PD-OFF group showed hyperactivation in the putamen and posterior insula; however, PD-On did not show this effect. Moreover, loss of compensatory hyperactivation on dopaminergic medication correlated with slower performance on the working memory task and slower cognitive speed on the symbol digit modality test. |
| Zhou et al., [29] | 102 | HC = 32<br>PD = 70 | 59.9<br>62.3 | Visuospatial function, memory, attention and working memory, executive function | BJLO, HVLT-R, SDMT, LNS, and SVF. | MRI | Early atrophy in the temporal lobes and frontal lobes may act as an indicator of the progression of PD and cognitive decline. |

*WCST: The Stroop Color and Word Test; MMSE: Mini-Mental State Examination; PET: Positron emission tomography; MRI: Magnetic resonance imaging; fMRI: functional Magnetic resonance imaging; VFT: Category Verbal Fluency Test; PRM: pattern recognition memory; SRM: spatial recognition memory; TOL: Tower of London; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; WMS-R: Wechsler Memory Scale-Revised; WLM: Word-List Memory; WLR: Word-List Recall; VEM: WMS-R test for verbal memory; VIM: WMS-R test for visual memory; WMS-R: Wechsler Memory Scale-Revised; WAIS-R: Wechsler Adult Intelligence Scale-Revised; TMT-A/B: Trail Making Test A and B; ATT/C: Attention/Concentration; FAB: frontal assessment battery; GDS: Geriatric Depression Scale; RAVLT: Rey Auditory Verbal Learning Test (immediate and delayed recall); BNT: Boston Naming test; F-A-S: phonemic verbal fluency; GPB: The grooved Pegboard Test; D-KEFS: The Delis–Kaplan Executive Function System; CWInt: color-word interference test; VVLT: Visual Verbal Learning Test; BVMT-R: Brief Visuospatial Memory Test-Revised; HVLT-R: Hopkins Verbal Learning Test Revised; DRS-2: Dementia Rating Scale - Second Edition; DS: Digit Span; LNS: Letter–Number Sequencing; HVLT: Hopkins verbal learning test; WSCT: Wisconsin Card Sorting Test; CBTT: Corsi block-tapping task; DSST: Digit symbol substitution test; CVFT: categorical verbal fluency test; MOCA: Montreal Cognitive Assessment; CTT: The Color Trails Test; CDT: The Clock Drawing Test; WTAR: Wechsler Test of Adult Reading; SDMT-oral: Oral symbol digit modalities test; C-TMTA: color trail making test A; C-TMTB: color trail making test A; WCST-64: Wisconsin Card soring test -64; HVLT-R: Hopkins Verbal Learning Test-Revised; BVMT-R: Brief Visual Memory Test-Revised; ARM: Associative reinstatement memory task; VOSP: visual object and space perception battery; SRM: Spatial recognition memory; PRM: pattern recognition memory; CANTAB: Cambridge Neuropsychological Test Automated Battery; SLCT: Salthouse Letter Comparison Test; HVLT: Hopkins Verbal Learning Test; CVLT: California verbal learning test; BVMT-R: brief visuospatial memory test-revised; HVOT: Hooper visual organisation test; SDMT: Symbol Digit Modalities Test; SVF: Semantic word fluency test; BJLO: Benton Judgment of Line Orientation Test; LNS: Letter-Number Sequencing.*

Moreover, Vito et al., [25], found that PD-NC patients performed worse than HC on the Frontal Assessment Battery (FAB), which assessed executive functions. In research done by Lee et al., (2013), PD-NC patients showed significant loss of GM volume in areas of the frontal and parieto-occipital brain regions. PD-NC patients seemed to perform significantly worse on both fine motor speed and set-shifting. However, no significant differences were found on tasks of processing speed, spontaneous flexibility, and attention. In addition, a study by Gallagher et al., [26] also found that there were no significant differences in executive functions' assessment in the early stages of PD-NC, although lower dopamine ratios in the anterior cingulate were associated with behavioural changes.

Furthermore, Trujillo et al., [4] investigated working memory impairments in PD-NC patients compared to HC via a visuospatial working memory task. They found that PD-NC patients demonstrated a significantly decreased in task accuracy, and a significant increase in task-related activity in the left DLPFC, as well as, a significant increase in activity of the right DLPFC, left caudate nucleus and left Inferior Parietal Cortex (IPC). Wen et al., [20], reported that statistically significant differences were found between PD-NC patients and HC in frontal lobe-related functions, including attention/working memory and executive functions in patients with PD-NC that converted to MCI after a longitudinal study. They also found that converters had a more longitudinal reduction in White Matter (WM), but not GM. The decreased volume of WM was mostly localised in the frontal areas. Cohen et al., (2016), investigated hippocampal function in PD-NC patients using an experimental memory task called Associative Reinstatement Memory (ARM) -that may be beneficial for examining hippocampus- during fMRI scanning. They found that ARM was not correlated with attention or executive function measures. Another study done by Lucas-Jimenez et al., [27] found significantly lower performance on processing speed and executive function measures in PD-NC patients in comparison to HC. Additionally, Poston et al., [28], found that PD-NC patients and HC groups demonstrated working memory activation in the bilateral putamen, anterior dorsal insula, supplementary motor area, and ACC. However, PD patients off-medication showed increased activation in the bilateral putamen and posterior insula, whereas, PD patients on-medication (PD-ON) showed less activation in putamen, caudate, dorsolateral PFC, and hippocampus. This loss of dopaminergic activation in PD-ON, was correlated with working memory tasks and slower cognitive speed on the symbol digit modality test. Moreover, the loose dopaminergic activation was due to dopamine suppression; the results suggested the dopamine played a crucial role in cognitive processing and that its suppression can have a negative effect on cognitive speed.

Moreover, Zhou et al., [29] found among the three groups, PD-NC. PD who converted to MCI, and HC a right temporal atrophy and significant interaction effect in bilateral frontal lobes. Additionally, they found significantly lower striatal binding ratio in PD-NC patients compared to HC. However, during follow-up, no significant GM volume alteration was found in the PD-NC patients and HC.

### 3.3 Memory

Research by Brück et al., [18] studied hippocampal atrophy in patients with early PD-NC and found that they had right and left hippocampus atrophy. Left hippocampus atrophy in PD-NC patients was correlated with verbal memory. Jokinen et al., [7], found similar results, which showed that caudate FDOPA correlated positively with the performance of verbal and visual memory, which was related to hippocampus atrophy. This positive correlation indicated the weaker the dopaminergic activity, the poorer the cognitive performance in patients with PD-NC.

However, contrary to this, Vito et al., [25], showed that there were no deficits in the immediate or delayed memory tests in PD-NC patients. In addition, Lee et al, [6] showed that PD-NC patients did not differ from HC on their learning and memory tasks. In another study, Gallagher et al., [26] found that there were no significant differences on verbal memory assessment in early-stage PD-NC. Picco et al., [24], found an insignificant correlation between 18F-DOPA uptake and verbal memory or working memory.

Moreover, Wen et al., [20], reported that there were no significant differences between PD-NC patients and controls on memory-related measures. Cohn and his colleagues [30], did not find a correlation between ARM, attention, and executive functions. However, they found a difference in hippocampal activation, as ARM was worse in PD-NC patients when compared to

HC and this had an effect on verbal memory measures. In addition, Lucas-Jimenez et al., [27], found that the functional neural connectivity between the Posterior Cingulate Cortex (PCC) and the left Medial Temporal Lobe (MTL) correlated with lower verbal and visual memory. This connectivity is related to cognition, brain GM structure and white matter integrity and diffusivity in PD-NC patients.

### 3.4 Language

An MRI study by Compta et al., [19], found decreased Cerebrospinal Fluid (CSF) amyloid-b, worsened verbal learning, and semantic fluency which were significant indicators of dementia in PD-NC patients was associated with left inferior parietal GM volume reduction. Furthermore, Duncan et al., [21], found that reduced GM volume in frontal, parietal, and temporal areas by using MRI in PD-NC patients was associated with poorer performance on the semantic fluency task. In addition, Lucas-Jimenez et al., [27], found a significant decline in the performance of PD-NC patients on verbal fluency using fMRI compared to HC was related with lower functional connectivity. Additionally, Picco et al., [24], they found through the use of PET a significantly positive correlation in PD-NC patients compared with HC between verbal fluency and 18F-DOPA uptake in the left medial frontal gyrus and the bilateral striatum. On the other hand, a study by Gallagher et al., [26] by the use of PET they found that there were no significant differences on language assessment in early-stage PD-NC patients compared with HC. Moreover, Lee et al, (2013), by using MRI they showed that PD-NC patients' performance did not differ from HC on language tasks. Moreover, an MRI study by Wen et al., [20], reported that there were no statistically significant differences found between PD-NC patients and HC on language-related measures.

### 3.5 Visuospatial and Visuo-Perceptual Abilities

A study by, Compta et al., ([19]), found that lower visuo-perceptual scores and thinner superior-frontal/anterior cingulate and perceptual regions were significant indicators of dementia in the PD-NC patients who converted to dementia. On the other hand, Lee et al, (2013), showed that PD-NC patients did not differ from HC on tasks of spatial cognitions. In addition, Picco et al., [24], found a significantly positive correlation in PD-NC patients between visuospatial abilities and the 18F-DOPA uptake in the left ACC and bilateral striatum.

Furthermore, Lucas-Jimenez et al., [27], found that the lower Default Mode Network (DMN) functional connectivity correlated with lower verbal, visual memory, and visual abilities performance in PD-NC patients compared with HC. Functional Connectivity between the PCC and the right MTL correlated with visual abilities. In addition, Zhou et al., [29] found neuropsychological differences amongst PD-NC patients that converted to MCI on measures of visual-spatial abilities, that MCI scored lower.

## 4. DISCUSSION

This review aimed to develop a rigorous criterion to exclude any confounding variables that may affect cognitive deterioration. The goal of this exclusion criterion was to examine the cognitive domain pattern in PD-NC. Most of the articles in this review reported differences in cognitive domains in PD-NC in detail.

Our previous review with PD-MCI [15] showed the overall global cognitive ability was associated with frontal lobe, basal ganglia, parahippocampal gyrus, occipital lobe and cerebellum, however, our present review PD-NC found, there was no deterioration in their global cognitive ability. Attention and executive functions in our previous review PD-MCI [15] were associated with different brain regions as in the insula network and the parietal and frontal regions, whereas, in our present review PD-NC was associated with prefrontal atrophy, bilateral frontal cortex, right caudate, basal ganglia, vmPFC, amygdala, bilateral ACC, middle frontal gyrus, DLPFC, left IPC, left caudate nucleus, bilateral putamen, anterior and posterior dorsal insula. Memory in our previous review PD-MCI [15] was associated with GM atrophy and right cingulate gyrus and the limbic lobe, whereas in the present review PD-NC was associated with bilateral hippocampal atrophy, PCC, and ML. Language in our previous review PD-MCI was associated with frontal cortex, precuneus, and anterior cingulate gyrus, however, in the present review PD-NC were associated with CSF and reduced GM in frontal, parietal, and temporal. Visuospatial ability in our previous review PD-MCI was associated with different brain regions such as Salience network (SN) and White Matter Hyperintensity (WMH), whereas, in the present review PD-NC were associated with left ACC, bilateral striatum, DMN, PCC, and MTL.

Therefore, it seems that PD-NC has different cognitive patterns compared to PD-MCI. These differences can be explained by the neuropathology of this disease.

The results of this literature review showed that most of the reviewed studies examined executive functions, attention, and working memory. It appears as if executive functions are the most sensitive cognitive domain that begins to be impacted in PD patients with NC. The strength of this literature review was that the evaluation focused on the early stage of PD-NC based on MMSE scores and no indications of neuropsychiatric illnesses, or any other neurological diseases. We also considered different neuroimaging techniques to provide a clear overview of the brain regions that may contribute to cognitive function in this group of patients. We acknowledge some limitations to our study. As considering systematic reviews and relying on the strength of the articles reviewed. We have not searched for age differences or drug on/off states.

## 5. CONCLUSION

In conclusion, our findings indicated that PD-NC patients seem to experience different cognitive patterns and different neuroanatomical changes compared with PD-MCI. These results suggested that although PD-NC have normal scores on MMSE, they may develop specific cognitive impairments that are associated with specific brain regions. Therefore, this finding indicated that PD-NC patients may need to have specific treatments tailored to fit their needs. Moreover, this review can have diagnostic and treatment implications for this group of patients. These findings also can provide a better understanding of cognitive performance and it is associated with brain regions in early PD-NC.

## 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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