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Review Article

Visuospatial and Executive Deficits in Parkinson's Disease: A Review

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disorder. Although it is classically defined by motor symptoms, non-motor symptoms including cognitive impairment (CI) are often even more disabling for patients. CI may happen in one or multiple cognitive domains, resulting in diverse profiles. Executive dysfunction and visuospatial impairment are two prominent and early cognitive symptoms. Visuospatial deficits are typically associated with atrophy in the parieto-temporal or parieto-frontal areas, precuneus, and hippocampus that may progress to dementia. Executive dysfunction in PD is typically associated with atrophy in the frontal (especially superior frontal gyrus) and parietal areas (especially temporoparietal areas), as well as white matter, changes cingulum, and parieto-frontal areas.

Inconsistencies remain in understanding many factors that affect the manifestation of different PD-CI profiles. These factors include the relationship between neuropsychological tests and neuroimaging measures, as well as atrophy of brain areas such as the putamen or caudate nucleus, and the neural profile of different executive function or visuospatial symptoms. Factors related to disease severity, onset, and duration may play a role. In addition, the relationship between PD-CI and the multiple neurotransmitters involved in PD is not clear.

PD is a heterogeneous disease, especially in terms of cognitive dysfunction. Diversity of manifested symptoms (i.e. different PD profiles) may be due to which cortico-subcortical pathways have been involved, or how severely they have been damaged and how far the disease has spread through those pathways. More neuroimaging studies with different analysis methods and focus on subdivisions of subcortical structures are required.

Keywords: Parkinson's Disease; Executive Function; Visuospatial; Cognitive Impairment; Cortico-Subcortical Circuits; Neurotransmitter; Dopamine; Norepinephrine; Freezing of Gait

Abbreviations

ACC: Anterior Cingulate Cortex; CI: Cognitive Impairment; DMN: Default Mode Network; DMN: Default Mode Network; DTI: Diffusion Tensor Imaging; DLPFC: Dorsolateral Prefrontal Cortex; FDG-PET: Fluorodeoxyglucose; FA: Fractional Anisotropy; FA: Fractional Anisotropy; FOG: Freezing of Gait; fMRI: Functional Magnetic Resonance Imaging; LC-NE: Locus-Coeruleus-Subcoeruleus-Norepinephrine; MD: Mean Diffusivity; MMSE: Mini-Mental State Examination; Moca: Montreal Cognitive Assessment; M: Motor Impairment Only; NMS: Non-Motor Symptoms; OFC: Orbitofrontal Cortex; OH: Orthostatic Hypotension; PD: Parkinson's Disease; PD-CI: Parkinson's Disease with Cognitive Impairment; PD-OH: Patients with Parkinson's Disease and Orthostatic Hypotension; PDD: PD Patients with Dementia; M/EF: PD with Motor and Executive Function Impairment; M/CI: PD with Motor and Other CI; PDCP: PD-Related Cognitive Pattern; FDOPA: PET Using 6-[18F] Fluoro-L-Dopa; PET: Positron Emission Tomography; F-18 FP-CIT: Fluorinated N-3-Fluoropropyl-2β-Carbomethoxy-3β-4-Iodophenyl: Nortropane; PCC: Posterior Cingulate Cortex; SPECT: Single Photon Emission Computed Tomography; SMA: Supplementary Motor Area; UPDRS: Unified Parkinson's Disease Rating Scale; VBM: Voxel-Based Morphometry; Wmhs: White Matter Hyperintensities

Introduction

Motor and non-motor symptoms in Parkinson's disease (PD)

Until relatively recently, Parkinson's disease (PD) was conceptualized primarily as a motor disorder with classic symptoms including bradykinesia, tremor, rigidity, and postural instability [1].

Nevertheless, PD is often accompanied by early non-motor symptoms (NMS), which may even manifest prior to motor symptoms. NMSs are diverse and can include autonomic dysfunction, hyposomia, behavioral impairments, speech disorders, and cognitive dysfunction [1,2]. The focus of this review is on conditions commonly associated with later stages of PD but that may be detectable as early as the time of diagnosis. The pathophysiologic underpinnings of PD cognitive dysfunction are not completely understood, but converging evidence suggests a combination of structural-, functional-, and neurotransmitter-based pathology.

Cognitive impairment (CI) in PD

The overall prevalence of non-motor symptoms in PD can be over 90%. However, manifestations of NMSs are not homogenous or predictable, either between or within patients [3]. For example, some symptoms such as anxiety (66%) and bradyphrenia (58%) are reported to have higher incidence [4], while a wide range of incidences has been reported for orthostatic hypotension. Significant cognitive dysfunction is frequent, occurring in up to 80% of PD patients over the course of their disease [3]. Cognitive impairment (CI) has been referred to as the most disabling NMS in PD [3] and even in early stages of PD, NMSs can be more disabling than motor symptoms and often dominate the quality of life later in the illness [5]. Furthermore, CI in PD has been significantly associated with further development of dementia as the disease progresses [6]. Thus, CI is an important NMS with significant impact across the PD timeline.

In PD, CI classically includes individual or combined deficits in executive function, working memory, memory, learning, visuospatial processing, and language, which can manifest at different PD stages. Furthermore, CI in PD may or may not respond to dopaminergic therapies, complicating its understanding. In an attempt to better describe PD-CI, Barker and Williams-Gray [7] argued that it would be an oversimplification to label all PD patients with cognitive deficit as PD-CI. Taking a neuropathological-etiological approach, they proposed at least two distinct profiles for PD-CI: a frontostriatal executive dysfunction syndrome and a cognitive deficit syndrome evolving to dementia. Barker and Williams-Gray [7] suggested that the former is primarily dopaminergic-related and includes working memory deficits. But the latter is less dopamine-dependent and includes visuospatial deficit and semantic impairment involving posterior cortical regions [7]. Similarly, Kalbe and colleagues [8] divided PD-CI into subtypes of single and multiple domains of amnestic and non-amnestic CI with different incidences at baseline (6.4% to 39.4%). The International Parkinson and Movement Disorder Society guidelines for PD-MCI diagnosis [9] endeavor to include this broad array of cognitive symptoms in PD. To avoid confusion with such cognitive subtype diagnosis and to ensure an appropriate overview of the broad range of impaired cognition in PD, in this review "PD-CI" (PD patients with CI) includes both mild cognitive impairment and dementia.

Overlap versus dissociation between CI and motor impairment in PD

In PD, CI and motor deficits may or may not be associated. Results from positron emission tomography (PET) studies demonstrate two topographically distinct patterns for motor and executive dysfunction [10], which suggests different aspects of cortico-subcortical processing for bradykinesia and executive dysfunction in PD [11]. Furthermore, dopamine transporter PET data also provide evidence that NMS severity (as measured by the Non-Motor Symptoms Scale) is not clearly correlated with striatal binding ratio patterns, and motor and non-motor symptoms show negative correlation at early stages of PD [12]. Distinct Fluorinated N-3-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (F-18 FP-CIT) binding uptake patterns have been observed in four groups of PD patients: PD with motor impairment only (M), PD with motor and executive function impairment (M/EF), PD with motor and other CI (M/CI) and healthy controls. The authors argue that the caudate nucleus and not the putamen shows a reduced dopaminergic activity related to executive function [13]. The putamen is classically considered integral in the motor circuit, whereas the caudate nucleus is theorized to be more involved in three classical cortico-subcortical circuits that are involved in executive function. Dissociation of NMS and motor symptoms in regards with resting-state functional connectivity has been reported [14]. While, there is a positive correlation between the dynamic functional connectivity of the Default Mode Network (DMN) and cognitive functions, there is no correlation with these networks and other symptoms [14].

Despite such evidence for a separate anatomical substrate for motor and CIs in PD, functional magnetic resonance imaging (fMRI), studies with humans and monkeys have shown that some brain regions affected in PD (such the dorsal premotor cortex, lateral prefrontal cortex, pre-supplementary motor area, and caudate nucleus) have both executive and motor function roles [15]. Further, studies of freezing of gait (FOG) suggest a significant correlation between motor and executive dysfunction including task switching, verbal fluency, as well as interference control/memory, and balance gait [16]. In PD patients with FOG, as compared with PD patients without FOG and healthy controls, reduced resting-state functional networks of executive function (in the right middle frontal gyrus and the angular gyrus) and vision (in the right occipitotemporal gyrus) have been reported. Patients with FOG also perform worse on putative tests of frontal lobe function [17]. Further, atrophy of frontal and parietal lobes involved in executive function correlates with the presence of FOG, Mini-Mental State Examination (MMSE) scores, and inhibitory tasks [18]. Besides, studies of PD fallers and

non-fallers suggest that motor and/or CI may be associated with atrophy of areas involved in executive function in fallers [19,20]. Lastly, PD executive dysfunction and motor impairment are reported to be correlated with the same functional and structural changes [11,16,19,20], although there may be conflicting results [10,11,20].

Overall, the discrepancy between results of studies showing executive dysfunction/motor deficit overlap and dissociation in PD, along with the above detailed heterogeneity in PD-CI phenomenology, neuroanatomy, and pathophysiology, call for thorough review of the current understanding of functional and structural neuroanatomic substrates of CI (highlighting common and debilitating executive and visuospatial dysfunction) in PD.

Approach

In this review, I will focus on the neuroanatomy of visuospatial and executive dysfunction in PD, which are involved in a wide range of cognitive processes and thus daily activities. Furthermore, visuospatial deficit and executive dysfunction commonly occur early in the process of PD and are among the most prominent NMS [21]. Therefore, a better understanding of these two aspects of cognition may improve the understanding and management of CI in PD more broadly.

I also examine the current understanding of anatomical and functional changes relevant for executive dysfunction and visuospatial deficits in patients with PD, focusing particularly on neuroimaging studies to date. First, we discuss visuospatial deficits, including PD-associated visual hallucinations, followed by executive dysfunction. In each section, we first briefly review the underlying anatomical pathways. Then, PET studies emphasizing metabolic- and perfusion-based studies as well as molecular neurotransmitter-based studies are discussed. PET studies are followed by structural MRI studies, including investigations of cortical thickness, volume measurements and white matter changes. Finally, fMRI studies are considered emphasizing functional connectivity, which provides putative information regarding functional changes in brain networks. The framework of this approach enables a logically consistent and coherent review of the current understanding of CI in PD as it relates to functional and structural neuroanatomic correlates.

Discussion

Visuospatial dysfunction in PD

Studies of visuospatial function in PD have largely focused on visual hallucination, perception, attention, and neglect given the common occurrence of related symptoms in the disease. Visuospatial perception permits the recognition and interpretation of information regarding many aspects of the visual world and is distinct from visuospatial attention, which is specific to directing attention to a particular location in space. Visuospatial deficit has been associated with dysfunction of several brain regions including occipital lobe, parietal lobe, frontal lobe, thalamus, and the superior longitudinal fasciculus [22].

Cortico-subcortical pathways associated with visuospatial processing

Classically, cortical visual pathways have been divided into the dorsal stream and the ventral streams. The dorsal stream (occipitoparietal) supports processing object information, and the ventral stream (occipitotemporal), supports spatial processing. For a summary of visuospatial pathways (See table 1). Furthermore, it has been suggested that the right hemisphere is more heavily involved in visuospatial tasks [22]. Recently, it has been proposed that there are at least three pathways that originate from the occipitoparietal region. For a summary of these cortical pathways (See table 2).

	Visuospatial pathways (VSP)		**Motor pathways (MP)**	
Pathway	**Dorsal Stream**	**Ventral Stream**	**Direct Pathway (DP)**	**Indirect Pathway (IP)**
Areas	Occipito-parietal	Occipito-temporal	SMA PMC MC BG Thalamus	
Cognitive Functions	Object information	Spatial Processing	Voluntary movements - Initiation - Execution	

Table 1: The visuospatial pathways.

SMA: Supplementary Motor Area; PMC: Pre Motor Cortex; MC: Motor Cortex; BG: Basal Ganglia.

	Pathways originating from the Occipitoparietal region		
	Pathway 1	**Pathway 2**	**Pathway 3**
Name of the pathway	Parieto-prefrontal	Parieto-premotor	Parieto-medial temporal (3)
Regions that are connected	Parietal gyrus to frontal cortex	Occipito-parietal region to premotor cortex	Occipito-parietal region to posterior cingulate cortex (PCC) and Retrosplenial cortex (RSC)
Functions supported by this pathway	- Spatial working memory - Executive control of visuospatial processing	-Visually guided actions (e.g. reaching, grasping)	- Shifting - Selection - Spatial attention

Table 2: The pathways originating from the occipitoparietal region supporting visuospatial processing.

The visuospatial cortical pathways are linked to subcortical regions anatomically through two key frontal-subcortical circuits: the oculomotor circuit and the lateral orbitofrontal circuit. The oculomotor circuit is purported to be primarily involved in visual, spatial, and working memory along with the execution of movement, while the lateral orbitofrontal circuit is suggested to be important in executive function including decision-making, planning, and reasoning. These two pathways are summarized in figure 1 (the oculomotor circuit) and figure 2 (the lateral orbitofrontal circuit).

Figure 1: Frontal-subcortical circuits: The oculomotor circuit.

Figure 2: Frontal-subcortical circuits: The lateral orbitofrontal circuit.

PET studies

Evidence from fluorodeoxyglucose (FDG)-PET shows that visuospatial impairment in PD patients without CI correlates with significant topographic patterns of lower metabolic activity in parietooccipito-temporal and medial temporal brain regions, and higher metabolic activity in subcortical areas (putamen, globus pallidus, thalamus and pons) and the cerebellum. However, FDG-PET studies suggest that PD patients with visual hallucination show higher cerebral glucose metabolic rate in the left superior frontal gyrus [23,24], and a significant reduction in uptake values in the right caudate nucleus [25] as compared to patients without hallucinations. Although controversial, visuospatial deficit has been also associated with dopaminergic dysfunction [26]. Much work in this area has been performed in animal models of dopamine depletion, which limits the interpretability of dysfunction in PD that involves much more diffuse pathology. In humans, there is evidence that the subthalamic nucleus and its cortical projections influence the networks involved in visuospatial orientation and attention, which is consistent with the presence of neglect in PD patients [27]. PET using 6-[^{18}F] fluoro-l-dopa (FDOPA) and FDG has showed a positive correlation between visuospatial testing, the left hippocampus, the left middle frontal gyrus, and right retrosplenial cortex, suggesting damage to the frontoparietal-hippocampal network [28]. However, most studies investigating dopamine depletion in PD have focused on executive dysfunction rather than visuospatial impairment.

Structural MRI studies: Cortical thickness

Structural MRI studies using cortical thickness suggest PD patients with visuospatial deficits show cortical thinning in parietal and temporal areas. Specifically, global cortical thinning and thinning of parieto-temporal regions have been reported in PD as compared with healthy controls and associated with visuospatial and visuoperceptual domain test scores [24]. Also, cortical thinning has been reported in the left occipital and parietooccipital (pericalcarine gyrus, cuneus, precuneus and lingual), inferior parietal, bilateral rostral middle frontal cortex, and the right cuneus in PD [29]. Cortical thinning of the temporoparietal and superior frontal regions has been associated with the worsened visuospatial performance [30]. However, color discrimination tests and the cortical thickness measures are not correlated [31].

Structural MRI studies: Volume measurements

Studies that have measured the changes to the volume of cortical and subcortical structures report a volume reduction in patients with PD. Voxel-based morphometry (VBM) comparison of healthy controls and PD patients with dementia (PDD) for gray matter density has demonstrated atrophy in the anterior cingulate gyrus and hippocampus as well as the temporal lobe, dorsolateral prefrontal cortex (DLPFC), thalamus, and caudate nucleus

[32]. However, the association of cortical and subcortical atrophy with visuospatial deficits is controversial. One study reported total gray matter volume reduction and ventricular enlargement in PD as compared with healthy controls, but it argued that no differential pattern of atrophy had been observed in association with any specific visuospatial or visuoperceptual tests [23]. However, in other studies, cortical and subcortical atrophy has been associated with visuospatial deficits. In one study, atrophy in the DLPFC and parahippocampal gyrus has been correlated with visuospatial and executive dysfunction performance [32]. In another study, authors compared PD patients to matched healthy controls, observed decreased cortical surface area in the left pars triangularis, and reported a correlation between surface area and volume of the frontal cortex and visuospatial memory performance [29]. Structural neuroimaging has also been used to compare gray matter density between demented PD patients or amnestic PD-CI, amnestic CI, and healthy controls. Amnesic PD-CI patients show decreased VBM of gray matter density in the precuneus and left prefrontal and primary motor areas relative to controls. The decreased VBM in these areas is correlated to visuospatial function. Specifically, amnestic PD-CI patients perform worse on visuospatial processing tasks as compared to amnestic-MCI and healthy controls [33]. Furthermore, verbal and visual recognition memory in amnestic PD-CI shows correlation with reduced gray matter density in the bilateral precuneus, left primary motor, and right parietal areas, as compared to amnestic-MCI [33]. Other studies have reported decreased volume of frontoparietal regions as the only difference observed between PD patients with dementia (PDD) and healthy controls or PD-CI. However, the reduction of hippocampus size has been observed in both groups [34].

In sum, these results suggest that PD patients manifest a deficit in visuospatial processing that is correlated with atrophy of occipitoparietal areas. Furthermore, VBM evidence demonstrates that PD with visual hallucination is correlated with grey matter reduction in parietooccipital areas and hippocampal head, and that this group is prone to developing dementia associated with progressive atrophy in limbic, paralimbic, and neocortical areas [35].

Structural MRI studies: White matter changes

Diffusion tensor imaging (DTI) has revealed white matter changes in brain areas implicated both in PD motor and visuospatial dysfunction [36]. Only a limited number of studies have used DTI to measure the correlation between white matter changes and visuospatial processing tests in PD and PD-CI patients. However, to this date, the results of these studies are conflicting. Some studies have not found any association between visuospatial skills and DTI measures [37,38]. While, other studies have reported decreased visuospatial function associated with reduced fractional anisotropy (FA) in the fronto-occipital connections [39-41], anterior corona radiata, anterior thalamic radiation, and pathways supporting visuospatial attention (i.e. the right optic radiation, right posterior thalamus, and right medial precuneus white matter) [42]. In PD-CI patients, color discrimination test scores have been correlated with visuospatial abilities and executive function scores, suggesting some perceptual involvement. The color discrimination test scores show a correlation with higher mean and radial diffusivity values in the right posterior white-matter structures [31].

Functional MRI studies

Functional MRI has been extensively used to investigate functional changes underlying cognitive dysfunction in PD. However, investigations specific to visuospatial dysfunction are far less common. Further, although existing results are intriguing, conclusions are conflicting for the most part. Specifically, fMRI evidence suggests decreased activity of areas involved in visuospatial processing in non-demented PD patients without visuospatial impairment or hallucinations, as compared to healthy controls. These areas included the right insula, left putamen, bilateral caudate, and right hippocampus, as well as over-activation of the right dorsolateral prefrontal and posterior parietal cortices, particularly in the right hemisphere [35,43-45].

Functional connectivity maps including resting-state fMRI emphasize distributed network function in correlation with PD-CI. Evidence from longitudinal resting-state functional connectivity suggests that impairment of visuospatial skill is correlated with stronger coupling between the dorsal caudate and the rostral anterior cingulate cortex, but motor impairment is associated with weaker links between anterior putamen and midbrain including the substantia nigra. These results suggest that CI and motor deficit are associated with different functional networks [46]. Focal lower functional striatal connectivity in visual areas is observed in patients with advanced PD compared with age-matched healthy controls [47]. Results of resting-state fMRI using graph theory reveal that PD-CI is associated with decreased connectivity in long-range connections and an increased local interconnectedness, which tends to correlate negatively with cognitive performance in visuospatial and visuo-perception tests [48].

Visuospatial dysfunction in PD: Summary

Neuroimaging studies of visuospatial deficit in PD have demonstrated a variety of neuroanatomical correlates. Commonalities among results of the current literature using different neuroimaging techniques suggest that visuospatial deficits are typically associated with atrophy in parieto-temporal, parieto-occipital, or parieto-frontal areas, as well as the hippocampus. These areas match the brain regions that are involved in the oculomotor circuit

(See figure 1). Reports of structural MRI studies are controversial regarding whether atrophy of these brain regions is associated with specific neuropsychological tests, however. Resting-state functional connectivity studies reflect a decreased functional connectivity between distant brain areas and an increased connectivity between local regions. However, inconsistencies remain in correlation of specific neuropsychological tests with neuroimaging measures, disease severity, disease onset and disease duration. Furthermore, it is unclear if atrophy of other brain regions such as the putamen or the caudate nucleus is related to visuospatial deficit. Future studies should focus on how different neural profiles-e.g. PET, single photon emission computed tomography (SPECT), fMRI activation patterns-correlate with specific visuospatial symptoms. Moreover, future studies should investigate how different patterns are visuospatial symptoms, and how neural profiles associate with different PD-CI profiles. For a summary of studies on visuospatial skills in patients with PD (See table 3).

Importantly, while visuospatial deficits may be accompanied by deficits in executive function in PD, visuospatial and executive dysfunction seem to be two distinct deficits: Kehagia, Barker and Robbins [49] review their studies in PD over the course of 20 years and conclude that executive deficits and visuospatial impairment belong to two distinct PD profiles. They suggest that visuospatial deficit is an early sign of dementia, whereas executive dysfunction is dopaminergically mediated and is associated with fronto-striatal damage [49]. In the following section, we will elaborate on executive dysfunction in patients with PD.

Executive dysfunction in PD

The most common form of CI in patients with PD is executive dysfunction [21]. It has been estimated that 93% of PD patients show executive dysfunction [50], which can start at early stages of the disease and can be detected even in newly diagnosed, un-medicated patients [51]. Patients with PD who show executive dysfunction are characterized primarily by an inability to maintain or switch (control) attention and inhibition and have impairment in multitasking, planning, and decision-making [52]. Thus, impairment manifests in all three main processes of executive function: initiation, shifting, and inhibition [50].

Cortico-subcortical pathways associated with executive function

Executive function has been linked to the frontal lobes including DLPFC, left inferior frontal cortex and right middle frontal gyrus [53-55], premotor area and the supplementary motor area (SMA) [15,56], anterior cingulate cortex (ACC) and caudate nucleus [57,58]. Based on neuroanatomical studies, we know that the frontal lobes and the caudate nuclei are important regions in the five classic frontal-subcortical circuits. Cortico-subcortical circuits include the dorsolateral prefrontal circuit (involved in short-term memory, verbal fluency, and sustained attention) and anterior cingulate circuit (involved in error detection, motivation, and conflict monitoring), which are known to be involved in executive function [59], as well as the motor circuit that is involved in motor processing. Figure 3 to 5 summarize the classic frontal-subcortical circuits.

Figure 3: Frontal-subcortical circuits: The dorsolateral prefrontal circuit.

Figure 4: Frontal-subcortical circuits: The anterior cingulate circuit.

The cortico-subcortical circuits are linked to the cerebellum via the thalamus. The cerebellum receives noradrenergic, serotonergic, and dopaminergic inputs from brainstem nuclei [60]. The cerebellum is involved in movement and sensorimotor processing, as well as cognitive control and executive function [60,61]. Impairment of executive function as a result of cerebellar damage has been demonstrated in tasks such as verbal fluency, planning, response shifting, divided attention, and spatial attention [61]. In PD,

Authors/Year	Study Type	Participants N: (age)	Cognitive processing measured/NP tests	Findings
Kiferle., *et al*. 2014	PET	PD: 18 (70.5) PD-VH: 18 (69.5)	Visual hallucination	PD-VH show frontal impairment reported and is associated with right caudate dysfunction: points to damage to cortico-subcortical loops
Nagano-Saito., *et al*. 2005	PET	PD: 28 (62.6)	Raven's Colored Progressive Matrices	A positive correlation between visuospatial test and the left hippocampus and the left middle frontal gyrus and right retrosplenial cortex, suggesting damage to the frontoparietal–hippocampal network
Caproni., *et al*. 2014	fMRI	11: (65) T: Right sided onset, no visual or visuospatial impairment	Visuoperceptual visuospatial	PD showed Less activity: R insula, L putamen, bilateral caudate, right hippocampus + over activation of over-activation of R dorso-lateral prefrontal, R posterior parietal c.
Segura., *et al*. 2014	Cortical Thickness and Volumetric	HC: 32 (64.69) PD: 43 (60.77) PD-CI: 47 (67.72)	Attention and working memory, executive functions, memory, language, and visuoperceptual-visuospatial functions.	PD-CI>PD>HC: - Global cortical thinning, - Thinning of parieto-temporal, - Total gray matter volume reduction, - Ventricular enlargement, - No correlation with NP tests.
Pereira., *et al*. 2014	Cortical Thickness	HC: 56 (58) PD: 90 (59.4) PD-CI: 63.4 (33)	Memory, Executive and Visuospatial performance	- In PD-CI: CT of temporal, parietal, frontal, occipital areas - In non-CI-PD: CT of R infer-temporal cortex - In all: CT of temporoparietal and superior frontal associated with memory, executive and visuospatial performance
Gerrits., *et al*. 2016	Volumetric Measures	HC: 93 (27-88) PD: 45 (47-77)	6 NP tasks	In PD: - CT of L pericalcarine gyr. cuneus, precuneus and lingual areas and L inferior parietal C., bilateral rostral middle frontal C., - Correlation between FC and visuospatial memory
Rektorova., *et al*. 2014	Volumetric Measures	HC: 25 (57.8) PD: 75 (64.2) PD-CI: 27 (67) PDD: 22 (70.7)	NA	In PDD: reduction of frontoparietal regions In all PD: reduction of hypocampus
Nagano-Saito., *et al*. 2005	VBM of ROI	HC: 31(63.5) PD: 58 (62.5) PDD:9 (67.5)	Raven Colored Progressive Matrices	Atrophy in anterior cingulate gyrus, hippocampus, temporal lobe, dorsolateral prefrontal c., thalamus, caudate, correlated with Raven Colored Progressive Matrices scores
Lee., *et al*. 2010	VBM	HC: 21 (70.7) PD-CI: 78 (70.5) PDD: 41 (71.3)	Visuospatial processing	PD-CI < MCI on visuospatial processing but NOT on verbal and visual memory PD-CI vs HC: GM density reduction in precuneus, L prefrontal, PMA PD-CI vs MCI: GM density reduction in bilateral precuneus, L PMA, R parietal areas
Manza., *et al*. 2016	L-RSFC	HC: 178 (?) $PD_{un\ med}$: 39 (60.5) $PD_{Drug\text{-}naïve}$: 23 (38.04)	Visuospatial and memory	Motor deficits correlated with weaker links between anterior putamen and SN Deteriorating by time VS impairment of visuospatial and memory correlated with stronger dorsal caudate and rostral ACC coupling

Hacker., *et al.* 2012	RSFC	HC: 13 (65.8) Advanced PD: 19 (63.4)	NA	PD: lower striatal correlations with thalamus, midbrain, pons, cerebellum FC in supramarginal gyrus, sensori-motor, visual areas In both groups, FC in posterior Putamen > anterior Putamen > caudate
Baggio., *et al.* 2014	RSFC	HC: 36 (63.4) PD: 43 (64) PD-CI: 23 (66.7)	Memory, Visuospatial and visuo-perception tests	Decreased FC in long-range connections, Increased local interconnectedness, Correlated negatively with Visuospatial and visuo-perception tests and memory functions

Table 3: Visuospatial Deficits in Parkinson's disease.

L: Longitudinal; fMRI: Functional Magnetic Resonance; FC: Functional Connectivity; RSFC: Resting State Functional Connectivity; N: Number of Participants; DD: Disease Duration; S: Disease Severity; T: Type of Patients: PD: Parkinson Disease, No Cognitive Impairment Reported; PDD: Parkinson's Disease with Dementia; PD-CI: Parkinson's Disease with Cognitive Impairment; HC: Healthy Control; NP: Neuropsychological; CT: Cortical Thinning; VBM: Voxel Based Morphometry; ROI: Region of Interest; GM: Gray Matter; PMA: Primary Motor Areas; ACC: Anterior Cingulate Cortex.

structural changes to the cerebellum [62,63]. Altered connectivity for the cerebellum in the Levodopa-Off condition [64], changes to cortico-cerebral pathways [65] and changes to functional connectivity at rest have been reported in PD as well [66]. Structural or functional changes in some cases have been correlated with PD-CI [67-69]. It has been argued that cerebellum plays a role in cognitive processing, and damage to cerebellum causes deficits of cognitive control, visuospatial perception, and most frequently executive dysfunction [70].

Figure 5: Frontal-subcortical circuits: The motor circuit.

PET studies

Metabolic PET studies

Metabolic PET studies bring evidence for two distinct patterns: a decrease metabolic activation in cortical and subcortical structures including the caudate and the putamen, and an increase of metabolic activation in the cerebellum. Specifically, evidence supports neural connectivity between the caudate nucleus and frontal cortex, and that decreased dopaminergic function is related to executive function [13]. Other studies have demonstrated an association between executive function and pathways including the frontal lobe and anterior cingulate [71]. PET measuring regional glucose metabolism in patients with different PD profiles (i.e. multiple-domain CI, single-domain CI, no CI) has yielded two different patterns in PD-CI as compared to PD: decreased prefrontal and parietal metabolism, as well as increased brainstem/cerebellar metabolism [72]. In addition, FDG-PET data analyzed using distributed network spatial covariance analysis demonstrated that PD patients with executive dysfunction (as tested by tests of strategy, planning, and working memory) have shown a distinct network. This network is characterized by increased metabolic activity in the left pallidum and mediodorsal thalamus and a decrease in ventromedial frontal regions and striatum bilaterally and in the left hippocampal gyrus [11]. This pattern is different from the network associated with motor impairment in PD patients [11,72]. Further, correlated with executive function measures, a significant covariance pattern characterized by metabolic reductions in frontal and parietal association areas and relative increases in the cerebellar vermis and dentate nuclei has been identified using FDG PET and a voxel-based network modeling approach [72].

These studies confirm two different metabolic networks for a PD-related pattern and PD-related cognitive pattern (PDCP), suggesting that dysfunction in different neural systems underlies the observed dysfunction.

Perfusion SPECT studies

Executive dysfunction observed in patients with PD has been linked to the neurodegeneration of certain brain structures, such as the ACC or other cortical areas such as the prefrontal and the parietal areas, by the evidence coming from metabolic and perfusion studies. Proton magnetic resonance spectroscopy has been used to identify the role of anterior cingulate in executive dysfunction in

PD. Most PD patients with executive dysfunction have damage to their DLPFC circuit rather than to their ACC or orbitofrontal cortex (OFC) circuits [73]. Also, PD-CI patients show perfusion changes in cortical areas, especially in temporal and parietal areas. For example, a 1-year longitudinal study reported a decrease in perfusion in the frontal lobe (Brodmann area 10; involved in executive dysfunction) in PD patients but not healthy controls [74]. Other SPECT studies have also shown that the right frontal and prefrontal lobes are significantly correlated with executive function measures, associated with executive function tests, a reduced striatal ratio of the caudate [75,76], as well as the putamen and the caudate uptake in the more affected hemisphere [76], have also been documented in PD-CI, as compared to PD, patients.

Association of executive dysfunction with impairment of certain brain structures, such as the ACC or other cortical areas (prefrontal and parietal lobes), in metabolic and perfusion studies may point to damage of the relevant circuits in PD patients with executive dysfunction.

Structural MRI studies

Structural MRI studies: Cortical thickness

Structural MRI studies that have compared the cortical thickness and neuropsychological evaluations of PD and PD-CI patients to healthy controls report cortical thinning of fronto-temporo-parietal areas correlated with global cognition and tests of executive function and visual-spatial processing. Precisely, when compared to controls, PD-CI patients show cortical thinning in bilateral precentral gyri, left enthorhinal cortex, superior frontal gyrus, and the right inferior frontal gyrus. Bilateral postcentral gyri get thinner only in PD-CI [77]. The atrophy of frontotemporal areas has shown association with cognition in PD-CI and PD-D, as compared to healthy controls. There is a correlation between attention/working memory, executive function, memory, language, and visuospatial function with a priori assumption of neuroanatomical bases of relevant cognitive processes including areas involved in fronto-striatal cognitive-control, medial temporal memory, dorsal spatial-based, ventral object-based, and cerebellar areas. Interestingly, executive function test scores can well predict atrophy in fronto-striatal and ventral areas [78]. The results of studies on cortical thickness in PD patients with executive dysfunction may be taken as evidence of damage to either the dorsolateral prefrontal circuits or lateral orbitofrontal circuits. However, functional connectivity studies to corroborate this hypothesis are lacking.

Structural MRI studies: Volume measurements

Earlier studies reported no significant correlation between the volume of brain structures and executive function measures. No atrophy was observed in PD or PD-D patients [79-81]. Caudate volume did not show correlation with global cognitive function, executive performance, or processing speed [80]; however, the putamen was correlated with motor deficit. A negative correlation was observed between ventricular enlargement and performance on a verbal learning test and certain executive function measures (i.e. Stroop), but no correlation with visuospatial, visual attention, task switching (Trial Making Test), or phonemic verbal fluency tests was observed [80].

However, more recent studies have found a measurable relationship between brain atrophy and executive function in PD. These studies report that patients who score lower in visuospatial/executive function items in the Montreal Cognitive Assessment (MoCA) have smaller volumes of bilateral temporal, frontal, and insular lobes [82,83], as well as the caudate nucleus [58].

Structural MRI studies: White matter changes

White matter, gray matter association

There is conflicting evidence in regards to the white matter-gray matter association in PD patients with cognitive decline. While some studies did not find any correlations between the volume of the caudate and the severity of white matter changes [57], other studies reported an association of executive dysfunction with changes of cortical thickness and white matter hyperintensities (WMHs) in the frontal areas [84]. Cognitive decline and WMHs in frontal [20,36] parietal and occipital regions have also been associated with greater volumes of periventricular and deep subcortical structures.

White matter networks and hyperintensities

Neurodegeneration of the white matter includes fractional anisotropy (FA) and mean diffusivity (MD), as well as WMHs. CI in PD seems to be associated with changes to the white matter, in terms of FA and MD. Typically, FA and MD are thought to reflect white matter density by means of axon diameter, myelination, or fiber density. Results have shown that white matter microstructural abnormalities associate with executive dysfunction in PD [37,57,61]. Microstructural white matter changes detected by DTI show an increased mean diffusivity in bilateral frontal and parietal white matter tracts [81] and cingulum [37].

Unlike convergent results regarding changes to the anisotropy and diffusivity of the white matter in PD-CI, results regarding WMHs are divergent.

Specifically, in an older study, newly diagnosed PD and PD-CI patients, as well as healthy controls, were compared on total volume and spatial distribution of WMHs and association with performance on attention and executive function in drug-naïve PD patients,

PD-CI patients, and healthy controls. No significant differences were observed between any of the groups in total volume or spatial distribution of WMH, nor between WMHs and attention or executive function [81,82]. The authors argued that these results provide evidence that executive dysfunction is not due to white matter changes. However, their results might reflect that the tasks used in this study were not sensitive to white matter changes. In fact, other studies have reported that white matter changes in PD are correlated with performance on executive function tests. Precisely, lower executive function test scores show correlation with high-grade deep WMHs [84] in all regions, especially in the parietal lobe [85] and show correlation with higher Unified Parkinson's Disease Rating Scale (UPDRS) gait, posture, and postural stability sum, as well as reduced velocity in non-demented PD patients. However, the white matter changes of the parietal lobe alone are not correlated with motor speed. This may suggest that slower velocity occurs as a result of changes to the global network and not local white matter changes [85]. The white matter fibers are not the only way brain regions connect. Many brain networks are not detectable by fiber tracts. They are functional.

fMRI studies

PD has also been associated with functional changes in numerous brain regions and networks. Functional neuroimaging has been used to examine the function of brain areas involved in tasks that measure a cognitive domain, such as Wisconsin Card Sorting or Tower of London that measure executive function. PD patients may vary in their performance on subsections measuring different cognitive skills, despite equal total score on different neuropsychological tests that measure CI, such as the MoCA or MMSE.

Scanning patients with similar total cognitive scores, but with different executive function scores and visuospatial subdomains (as measured by Tower of London), revealed reduced activity in the striatum as well as the ventrolateral and dorsolateral prefrontal cortices [86-88]. The striatum and the prefrontal cortex have been reported to activate in both PD patients without CI and healthy controls while performing the Wisconsin task, another task that measures executive function. However, there is no evidence of co-activation of the striatum and the prefrontal cortex [89,90], which may suggest that executive dysfunction in PD is not related only to striatal dopamine depletion, but also related to the mesocortical dopaminergic substrate [90]. However, co-activation of prefrontal areas may reflect damage to the dorsolateral prefrontal circuit or the lateral orbitofrontal circuit.

Functional connectivity

Task-based studies have analyzed the pattern of functional connectivity between the cortex and the striatum in PD patients. Compared to healthy controls, medicated PD patients with executive dysfunction show lower functional connectivity in brain areas related to tasks measuring inhibition. These areas include the inferior parietal lobule and DLPFC [91]. Further, strong evidence for the association of executive dysfunction in PD patients with damage to cortico-subcortical circuits come from a meta-analysis of 126 fMRI and PET studies [92]. This meta-analysis concludes that co-activation of the three parts of the striatum with different cortical areas is consistent with the predictions of the parallel loop [95]. Furthermore, network expression for PDCP has been measured and compared across groups of PD patients with CI in different domains. Network values for PDCP show an increase in multiple-domain PD-CI as compared to PD, but no difference can be observed between single-domain PD-CI and either group [96]. These networks have been studied using resting-state functional connectivity, which yielded similar results.

Resting-state functional imaging investigates functional brain networks at rest, not at a task. Brain regions interact even when not focusing on a task. The default mode network (DMN) is one of several major identifiable cognitive networks at rest. Another well-defined network is the salient network, which is involved in switching from the DMN to a task-related network [95]. It has been proposed that CI, including impairment of executive function, psychomotor speed and verbal memory, may be due to more positive salience network/default-mode network coupling [96]. Resting-state functional connectivity shows different patterns in PD patients and PD patients with CI and dementia. Compared to healthy controls, PD patients present an altered pattern of functional connectivity of the caudate nucleus and the putamen, which correlates with atrophic changes to these subcortical structures as well as slower speed in performing tasks and perceptual deficits. Patients with PD-CI and PD-dementia show different patterns of resting-state functional connectivity pattern in the posterior cingulate cortex (PCC). While patients with PD-CI show an increase in PCC connectivity, those with PD-dementia show a decrease [97]. The PCC is known for its involvement in executive function and cognitive control [98]. However, another study reported a decrease in resting-state functional connectivity between the vermis and DLPFC in PD patients with CI, which also shows correlation with CI in general and attention deficit and executive dysfunctions in particular [99]. In general, resting-state functional connectivity studies confirm the parallel loop hypothesis [100]. However, resting-state studies do not implicate any specific tasks, and they may not provide sufficient evidence to confirm damage to a particular cortico-subcortical pathway.

Executive function deficit in PD: Summary

Neuroimaging evidence suggests that symptoms of motor and/or CI in PD manifest depending on which brain region has been affected, disconnected from the network, endured atrophy, or who-

se function is impaired. Executive dysfunction in PD is associated with both structural and functional changes because of progressive neuron loss, brain tissue changes and changes to functional and white matter networks. Results from structural and functional neuroimaging addressing executive dysfunction in PD patients point in particular to damage in frontal/prefrontal areas, as well as subcortical structures, and may be associated with presumed early axonal damage, which is not coupled with significant gray matter volume loss. These results are in line with cortical and subcortical structures involved in the dorsolateral prefrontal, lateral orbitofrontal, and anterior cingulate circuits. However, more precise task-based functional connectivity studies are required to corroborate damage to specific pathways. For a summary of studies on executive function in patients with PD (See table 4).

Authors/ Year	Study Type	Participants n (age)	Cognitive processing measured	Findings
Picco., *et al*. 2015	Metabolic PET	PD: 15 (66.8) Essential Tremor: 10 (68.5)	EF VS Speed Attention	The medial frontal lobe, anterior cingulate and left BA 46 are the main cortical are correlated with executive and language functions.
Huang., *et al*. 2008	Metabolic PET	PD: 18(59.0) PD-SD-CI: 15 (62.1) PD-MD-CI: 18 (62.4)	EF VS Verbal learning	Decreased prefrontal and parietal metabolism in PD-MD-CI>PD-SD-CI>PD
Firbank., *et al*. 2005	SPECT	HC: 30 (76) PD: 30 (76)	MMSE CAMCOG	Involvement of the frontal lobe in EF
Nobili., *et al*. 2010	SPECT	PD: 30(68) Essential Tremor: 15 (70.3)	EF Visual Apraxia Episodic Verbal Memory	EF associated with reduced striatal ratio of the caudate in both sides and the putamen of the more affected side
Pellecchia., *et al*. 2015	SPECT	PD: 19 (60.4) PD-CI: 15 (63.1)	EF VS	Striatal dopamine depletion may contribute to CI
Lewis., *et al*. 2012	Proton magnetic resonance spectroscopy	HC: 20 (65.1) PD: 20 (62.3)	EF Visual hallucination	Lower NAA/Cr ratios in ACC, Correlated with worse EF and visual hallucination
Galantucci., *et al*. 2016	Cortical thickness	HC: 41 PD: 54	GC Visuospatial EF	-CT of FTP correlated with GC, visuospatial and EF tests -In PD-CI: CT in bi. precentral gyri, L enthorinal C., SFG, R IFG -PD_CI vs PD: Thinner Bi. postcentral gyri
Almeida., *et al*. 2003	Volumetric measures	HC: 35 (74.9) PD: 28 (75.5) PDD: 20 (73) AD: 27 (77.5)	GC EF Processing speed	-No atrophy in PD, PDD, HC -No correlation between caudate volume and GC, EF or processing speed
Xia., *et al*. 2013	VBM	HC: 32 (51-87) PD: 25 (53-79)	MMSE MoCA	-PD: lower scores in VS and EF subtests of MoCA, -Smaller volumes of bi temporal, occipital, parietal, frontal, insular lobes, parahippocampal gyrus, amygdala, R uncus, posterior cerebellum
Mak., *et al*. 2013	VBM	PD: 66 (63.4) PD-CI: 24 (68.9)	MMSE MoCA	-PD-CI <PD: EF, attention, memory, language -Smaller volumes of L insular, SFG, MTG

Duncan., *et al.* 2016	Volumetric measures DTI	HC: 50 (65.8) PD: 125 (66)	NP tests: semantic fluency Tower of London tasks	-No difference between groups -No correlation between GM and NP -Increased MD correlated with NP and frontal and parietal WM in the cingulum, superior longitudinal fasciculus, inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus.
Macfarlane., *et al.* 2013	L Volumetric measures	66 (73.2) PD at baseline vs 3 years		-Caudate volume correlated with poorer EF at baseline and at 3 years; -Not correlated with WM changes.
Ham., *et al.* 2015	WMHs topography	Low: 28 (67.7) Moderate: 30 (68.4) High: 29 (70.3)	EF	-WMHs associated with GC and CT of entire frontal areas and restricted temporoparietal areas -Lower EF scores correlated with high-grade deep WMHs -No correlation between Periventricular white matter hyperintensities and frontal CT
Kandiah., *et al.* 2013	WMH	PD: 24 (68.9) PD-CI: 67 (63.39)	NP tests	-Greater volumes of WMH in frontal, parietal, occipital regions -Above associated with lower performance on EF, memory and language
Murray., *et al.* 2010	WMH Topography	PD: 148 (73-91)	EF	-EF correlated negatively with UPDRS -EF correlated with WM changes in the parietal lobe
Gallagher., *et al.* 2013	DTI	HC: 15 (60.3) PD: 15 (62.7)	EF	-EF associated with WM changes -WM microstructural abnormalities contribute to EF deficits
Zheng., *et al.* 2014	DTI VBM	PD: 16 (62.2)	EF attention	-EF correlated with frontal FA (positively) and MD (negatively) -Attention correlated with FA and MD of cingulum, -VS tests did not correlate with DTI
Dalaker., *et al.* 2009	Volumetric measures WM hyperintensity	HC: 102 (65.7) PD: 133 (65.5) PD-CI: 30 (66.2) MCI: 30 (69.4)	EF attention	-No significant differences between PD vs PD-CI -No correlation between EF or attention and WM hyperintensity
Tessitore., *et al.* 2012	RSFC	HC: 15 (65.5) PD: 13 (66.3) PD-FG: 16 (66.9)	EF freezing- gait Vision	-Reduced EF in R middle frontal gyrus and in the angular gyrus
Brugger., *et al.* 2015	VBM	PD: 18 (61) PD-FG: 20 (61.5)	MMSE	-FG correlated with atrophy in MFG superior/MOG, SPL, IPL (precuneus and supramarginal gyrus), SFG, R MTG -MMSE correlated with atrophy in the frontal lobe (SFG, SMA, L IFG, L SPG, bil. IFG, R MFG -Conjunction analysis: Overlapping in R MFG corresponding to the DLPFC
Walton., *et al.* 2015	VBM	HC: 10 (63.9) PD: 11(65.7) PD-FG:15 (68)	Antisaccade task	Atrophy of bil. Visual and Fronto-parietal regions

Kelly., *et al*. 2015		PD (mixed profiles) 783 (67.3)		In fallers: -Lower GM volume in the caudate head, (but not in the posterior putamen) -Increased FC in posterior partial regions of the central executive network, -Correlation between FG and EF, VS, memory PD vs PD-Fallers vs HC: -No difference within the sensorimotor network
Alegret., *et al*. 2001	MRI	Advanced PD: 14 (60.4)	Rey's Auditory-Verbal Learning test (RAVLT), Stroop Benton's Line Orientation Trail Making, Phonemic verbal fluency.	-Correlation between ventricular enlargement and performance on Purdue Pegboard, Rey's Auditory-Verbal Learning test (RAVLT), and Stroop -Correlation between atrophy in the Putamen and motor deficit -No correlation with Benton's Line Orientation, Trail Making, phonemic verbal fluency. -No correlation between caudate atrophy and cognitive deficits

Table 4: Executive deficits in Parkinson's disease.

ACC: Anterior Cingulate Cortex; CAMCOG: Cambridge Cognitive Examination; CT: Cortical Thinning; DLPFC: Dorsolateral Prefrontal Cortex; EF: Executive Functions; FA: Fractional Anisotropy; FG: Freezing Gait; FTP: Frontotemporoparietal; GC: Global Cognition; IFG: Inferior Frontal Gyrus; IPL: Inferior Parietal Lobule; MD: Mean Diffusivity; MFG: Middle Frontal Gyrus; MOG: Middle Orbital Gyrus; MTG: Middle Temporal Gyrus; NAA/Cr: N-acetyl Aspartate/Creatine; NP: Neuropsychological; OFC: Orbitofrontal Cortex; PD-FG: Patients with Parkinson's Disease and Freezing of Gait; RoI: Regions-of-interest; SFG: Superior Frontal Gyrus; SFG: Superior Frontal Gyrus; SPG: Superior Parietal Gyrus; SPL: Superior Parietal Lobule; VS: Visuospatial; WM: White Matter; WMHs: White Matter Hyperintensities.

Conclusion

PD is a neurodegenerative disease that has a wide variety of motor, behavioral, and cognitive manifestations. It remains unclear whether these symptoms stem from the same or distinct neural correlates and whether or not similar symptoms would manifest throughout the course of the disease for all or certain patients. Disease severity, which is typically rated based on motor symptoms, seems to be an important factor in the manifestation of certain neural or symptomatic profiles [57,86]. Disease duration is another important factor in distinguishing disease profiles. There is evidence that more than half of PD patients with no CI at the onset of the disease will develop cognitive deficits within 6 years and that PD-CI patients will develop dementia after 5 years. Nonetheless, evidence from event-related fMRI reveals distinct activation patterns in PD-CI as compared with patients without CI [87], suggesting that some PD patients may never show CI. These results are in line with different neural profiles reported for PD and PD-CI in studies using a variety of structural neuroimaging techniques [34,83,92].

CI symptoms seem to be more prominent in two types of patients: patients who show signs of executive dysfunction at the early stages of the disease, and patients who get diagnosed with PD at older ages [21,87]. On the other hand, in the latter patients, the motor symptoms are seen to be less severe. Nevertheless, some studies have demonstrated a significant correlation between balance impairment and executive dysfunction, as well as between CI and functional mobility [16]. Similarly, functional and structural neuroimaging evidence support common pathophysiology/neural correlates for executive and motor dysfunction by demonstrating correlation between visuospatial/parietal dysfunction and motor symptoms, such as postural stability, as well as association between freezing of gait or falls with deficits in executive function [16,20,37]. These results may suggest that the presence or absence of certain cognitive or motor impairments may be related to what brain area is affected. Further, different PD profiles may vary because the disease may take different neuroanatomical paths to spread.

While both gray and white matter studies in patients with visuospatial and executive dysfunction point to structural as well as functional changes in the parietal, temporal and frontal lobes [17,24,29,32,35,43,77,83] (See table 3 and 4 for summary). It is not possible to draw firm conclusions at this time. Some authors suggest that there is no one-to-one correlation with deficit of executive function in PD and damage to the frontal lobe [54]. However, there is direct and indirect evidence that executive functions are associated with the DLPFC. In addition to functional association, there is at least eight studies showing an association between white matter changes and executive function, memory and language and three studies report no correlation between white matter changes and cognition [31,36,38,39,41,42,58,81].

In early stages of PD, dopamine depletion is thought to be primarily limited to the putamen and the dorsal caudate nucleus but spreads to the more ventral parts of the striatum, limbic, and cortical areas as the disease progresses [89]. This argument is consistent with the results of both functional neuroimaging and post-mortem studies. Autopsy-based investigations in PD suggest pathological changes in Lewy neurites and Lewy bodies initiate from the lower brainstem and progress to more rostral parts and the cortex. In other words, PD spreads to the basal ganglia, basal forebrain, medial temporal lobe and finally discrete cortical regions [47]. This hypothesis, although not fully internally consistent nor fully accepted in the field is broadly consistent with the results of neuroimaging studies indicating that PD spreads through networks. Thus, atrophy patterns generated by deformation-based morphometry and independent component analysis on images provided by the PPMI includes the midbrain, basal ganglia, basal forebrain, medial temporal lobe, and discrete cortical regions. This pattern overlaps the intrinsic networks in healthy participants and the amount of atrophy in brain areas associated with the disease severity and its distance from substantia nigra.

Involvement of cortical areas partly explains CI in PD-CI. Although CI in PD appears to involve damage to the frontostriatal circuit [73] particularly early in the disease, nevertheless details remain unclear. Particularly, damage to a single circuit cannot justify different manifestations of PD-CI involving different cognitive processes. PD-CI patients may manifest impairment in different cognitive domains, which may or may not be shared across profiles. Different cognitive processes are executed by distributed cortical regions and are known to be part of different and potentially functionally overlapping/interacting cortico-subcortical pathways (e.g. at least five cortico-subcortical pathways, three cortical pathways, and two visuospatial pathways; see figure 1 to 5). The current literature suggests that PD may spread through one or more cortico-subcortical pathways, causing different profiles. Diversity of manifested symptoms (i.e. different PD profiles) may be due to which pathways are involved or how severely they are damaged and how far the disease has spread through those pathways.

Results of different neuroimaging studies discussed in this review (See table 3 to 4) suggest that at least three profiles can be distinguished. Typically, patients who show motor deficits show damage to the motor circuit, and patients with deficits of visuospatial function show damage to areas that are part of the visuospatial ventral or dorsal streams, parieto-prefrontal, parieto-premotor, or parieto-medial temporal cortical pathway, and/or the oculomotor circuit. Patients with executive dysfunction typically show pathologic changes to the areas that are part of the parieto-medial temporal cortical pathway and/or to the areas that are part of the cortico-subcortical pathways including the dorsolateral, and/or the lateral orbitofrontal and/or the anterior cingulate circuits. In the case of executive dysfunction, it is not easy to distinguish which of the three executive function cortico-subcortical pathways may have been damaged. All three cortico-subcortical pathways that encompass brain areas implicated in executive function involve similar brain structures and can be distinguished by subdivisions. However, the neuroimaging techniques currently used in the literature do not often address subdivisions of structures. Moreover, dopaminergic, noradrenergic, serotonergic, and cholinergic cell groups support communication between the subcortical and cortical circuits [65,66,94,100]. However, our understanding in regards to the dysfunction of neurotransmitters, particularly norepinephrine, in PD is limited.

Limits of the Current Literature and Future Avenues of Investigation

Despite the frequent occurrence of executive dysfunction and visuospatial deficits in PD [21], there is lack of consistency in patterns of these CIs across investigations, and PD-CI subtypes are not easily distinguished in either cross-sectional or longitudinal fashion. Discrepancies can be explained, at least in part, by different patient samples in regards to age, age of onset, disease duration, and disease severity, in addition to methodological limitations. Definition of executive function and the best way to measure it is still under discussion as well [54] and many tasks that aim to measure executive function have a visuospatial nature and thus inevitably measure both skills (e.g. Simon Task, Stroop Task, Tower of London, Go-No Go). Furthermore, in many tasks it is not easy to fully disentangle visual perception from motor execution related to visual perception or spatial processing or relevant executive function. In many studies, global terms (e.g. mild CI, or MCI) have been used instead of more precise terms (e.g. impairment of executive function) [52], which makes the interpretation of relevant literature even more difficult. Nevertheless, evidence from neuroimaging studies suggests that patients with visuospatial deficits and those with impairment of executive function may have different disease profiles. More standardized imaging studies with more focused and standardized neuropsychological approaches are required to address subdivisions of brain structures and cortico-subcortical pathways involved in PD-CI (See figure 1 to 5). Also, there is a need for more longitudinal studies addressing executive function and visuospatial deficits in PD, which will be vital to understand how each profile evolves. Furthermore, expanded studies are required to examine the impact of neurotransmitter dysfunction on pathways in regards to executive function and visuospatial deficits in PD.

Highlights

- Over ½ PD patients develop cognitive impairment (CI). CI shows different profiles.
- It is unclear if motor and cognitive symptoms of PD have the same neuronal roots.
- Neuroimaging suggests 3 profiles based on damage to distinct neuronal networks.
- Networks are Motor, Visuospatial or Executive Function (EF). EF has 3 routes.
- Damage to each network (and/or routes) roots subdivisions of different PD profiles.

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Conflict of Interest

The author has no conflict of interest to report.

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