The Functional Connectivity of the Caudate Nucleus is Correlated with Cognitive Performance in Parkinson's Disease Patients

By

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ABSTRACT:

Mild cognitive impairment (MCI) is common in Parkinson's disease (PD) patients. However, the underlying mechanism is not well understood. Moreover, no cognitive therapy has been approved for use in this population. Here, we recruited 15 PD patients; 7 PDNC (normal cognition PD; Montreal Cognitive Assessment (MoCA) $\geq$ 26), 8 PDLC (low cognition PD; MoCA < 26) and 10 age-matched healthy controls. All subjects were scanned with resting state functional magnetic resonance imaging (MRI) and perfusion MRI. First, we found a strong positive correlation between the functional connectivity of the right caudate nucleus and MoCA scores in PD (p = 0.011) but not in healthy controls. Interestingly, PDNC's functional connectivity of the right caudate was significantly higher than both PDLC and normal controls (p<0.02, Mann-Whitney), while PDLC and normal subjects were not significantly different from each other. Then we estimated how much each individual patient expressed an Alzheimer's disease (AD)-like metabolic/perfusion pattern. Previously, our group reported that PD patients with dementia also show AD-like metabolic/perfusion pattern. This pattern did not correlate with MoCA scores in PD, however, it negatively correlated with the right caudate functional connectivity. Our findings suggest that the increased caudate connectivity in PD is a compensatory mechanism for cognitive impairment found

in PD, and that it may be related to comorbid AD-like pathology, which is potentially related with dementia in PD.

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Abbreviations

AD	Alzheimer's Disease	MoCA	Montreal Cognitive Assessment Test
ASL	Arterial Spine Labelling	MRI	Magnetic Resonance Imaging
BC	Betweenness Centrality	pCASL	Pseudo-Continuous Arterial Spine Labelling
BDI	Beck Depression Inventory	PD	Parkinson's Disease
BOLD	Blood-Oxygen Level Dependent	PDD	Parkinson's Disease Dementia
GLM	General Linear Model	PDLC	PD With Low Cognitive Performance in MoCA
LEDD	Levodopa Equivalent Daily Dose	PDMCI	PD With Mild Cognitive Impairment
MCI	Mild Cognitive Impairment	PDNC	PD With Normal Cognitive Performance in MoCA
MDS-UPDRS	Movement Disorder Society – Unified Parkinson's Disease Rating Scale	rsfMRI	Resting State Functional MRI

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder, primarily related with dopaminergic neuronal degeneration of substantia nigra which projects to the basal nuclei (also known as basal ganglia) through the nigrostriatal pathway. This leads to dopaminergic depletion in these regions. The putamen, which is connected to the primary motor cortex, is the most affected and causes the emergence of the classical motor symptoms; tremors, bradykinesia, rigidity, and loss of balance[1]. PD is also associated with non-motor symptoms such as depression, sleep disorders and cognitive impairment, which is common in these patients and ranges from mild cognitive impairment (MCI) to sever Parkinson's disease dementia (PDD) [2]. MCI can present at time of diagnosis in about 35% of cases, and the majority (62%) of these subjects progress to PDD over 5 years[3]. Cognitive impairment in PD affects several cognitive domains, such as executive function and attention, visuospatial, memory and language[2]. And non-amnestic single domain MCI is the most common in PD[3]. However, cognitive impairments in PD vary between individuals; PD patients with MCI experience deficits in working memory and executive functions that are similar to those seen in patients with frontal lobe damage[4]. On the other hand, PDD patients are impaired in visuospatial function and it resembles deficits seen in patients with temporal lobe damage[5].

The underlying mechanism of cognitive impairment in PD is not yet well understood. There are several possible mechanisms that might be the cause of cognitive dysfunction. One of them is dopamine depletion in the caudate nucleus. Other possible causes are imbalance in neurotransmitters such as acetylcholine, serotonin and norepinephrine. Also, the presence of cortical Lewy bodies in the frontal cortex could contribute to this impairment[1].

Response to medications has been also reported to be different among cognitively impaired PD patients. While PDD is routinely treated with cholinesterase inhibitors, they are not used for treating PD patients with MCI[6].

The variety in the underlying mechanism, clinical picture, and response to pharmacological therapy has led to the emergence of the dual syndrome hypothesis[7]. This hypothesis differentiates cognitively impaired PD patients into two groups; patients with MCI, who experience impairment in executive functions that are similar to those seen in patients with frontal lobe damage. This impairment is thought to be due to dysfunction in the fronto-striatal network that involves the caudate nucleus and prefrontal cortex[7]. The second group is PDD who express more dysfunction in the visuospatial domain due to impairment in the posterior cortical and temporal lobe. While this group responds well to anti-Alzheimer's medications, the former group does not[7].

In the current study, we have explored the validity of this hypothesis with two imaging modalities; functional Magnetic Resonance Imaging (fMRI) and Arterial Spin Labeling (ASL). We recruited PD patients with MCI and investigated whether the functional connectivity of the caudate nucleus is related to their cognitive impairment. We also investigated if these patients express an AD-like brain metabolic/perfusion pattern that have been previously reported to be expressed in PDD patients[8]. We hypothesized that cognitive performance in PDMCI patients is separately related to the caudate nucleus connectivity and AD-like pathology.

The findings in this study support and complement the dual syndrome hypothesis. Moreover, we have reported some novel findings that added to this hypothesis and helped in understanding the mechanism of cognitive impairment in PD.

2. Background

2.1. Parkinson's Disease

The disease was first described by James Parkinson in 1817 and was known as "shaking palsy"[9]. PD is a progressive neurodegenerative disease that affects adults over 40 years old. It has been traditionally considered as a motor disorder. However, now it is recognized as a complex disease with diverse clinical features including neuropsychiatric, nonmotor, as well as the motor manifestations. The symptoms emerge as a result of decrease dopamine supply in the basal ganglia due to degeneration of the dopaminergic neurons in the substaintia nigra[9]. The disease is diagnosed clinically, and symptoms could be managed by medications.

2.1.1. Epidemiology of Parkinson's disease

Idiopathic PD is the most common movement disorder, and the second most common neurodegenerative disease after Alzheimer's disease (AD)[9]. It affects one in 100 people who are over 60 years old in industrialized countries[10], with a worldwide prevalence of approximately 0.3% of the population over 40 years old and an estimated incidence range from 8 – 18 per 100,000 person-years[10,11]. The prevalence rises with age and the presence of a family history of PD[12,13]. Additionally, men are more prone to get the disease than women[10,11,14]

Epidemiological studies have reported some factors that are associated with developing the disease. While cigarette smoking[12,15], caffeine intake[12,16],

exercise[17,18], medications (ibuprofen[12,19] and statin[20]) were associated with lower risk, other factors such as repetitive head trauma[21], high dietary intake of iron[22], obesity[23], higher education levels[24], history of low muscular strength[25], migraine with aura[26] and exposure to trichloroethylene[27] were found to increase the risk of developing PD.

2.1.2. **Etiology and pathology of Parkinson's disease**

PD is primary caused by neuronal degeneration in the substantia nigra. These neurons project to the basal nuclei, and thus neuronal degeneration leads to dopamine depletion in these regions. The exact cause of neurodegeneration is still unknown; however, it is most likely to be due to a combination of genetic and environmental factors, such as toxins and inflammation[11].

- ***Anatomy of the basal nuclei***

The basal nuclei (also known as the basal ganglia) are gray matter structures that are located deep within both cerebral hemispheres. The basal nuclei are comprised of the striatum (the caudate nucleus and the putamen, linked together through the fundus), the ventral striatum (the nucleus accumbens, and the most ventral parts of the caudate nucleus and the putamen), the globus pallidus (both internal and external, also referred to as medial and lateral), the substantia nigra, and the subthalamic nucleus. The basal nuclei structures play an important role in motor control, both in inhibiting or facilitating movements, and in different cognitive,

behavioral, and emotional functions[28]. While the putamen is generally implicated in motor functions, the caudate nucleus has shown greater association with cognition[12].

The cortico-striatal loops explain the relationship between the cerebral cortex and striatum[29]. The basal nuclei receive axons from different parts of the cortex, except for the primary visual, auditory, and olfactory cortices. The main input is to the caudate nucleus and putamen. Their neurons project axons back via the globus pallidus interna, through the thalamus, to discrete cortical regions. There are several main cortico-striatal loops; (i) the associative loop involves the head of caudate nucleus and rostral putamen, and receives input from the dorsolateral prefrontal cortex, pre-supplementary motor area, and posterior parietal cortex; (ii) The sensory motor loop consists of the caudal putamen and receives input from the primary and supplementary motor areas and somatosensory cortex; (iii) The limbic loop, which involves the ventral striatum, receives projections from the orbital and medial prefrontal cortex (Figure 1)[12].

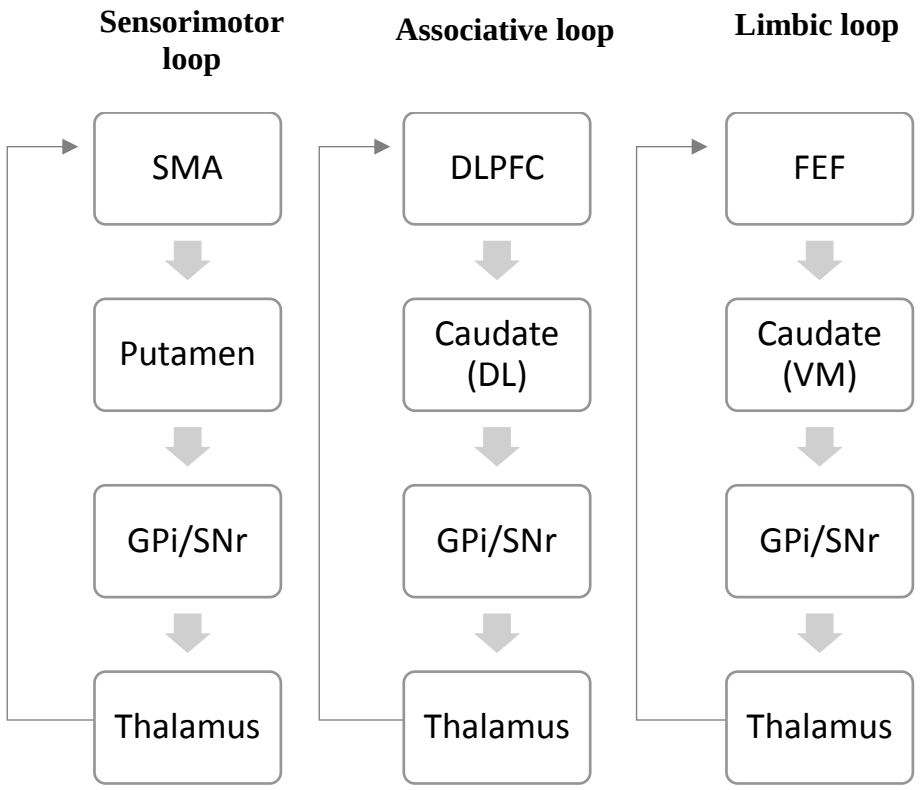

Figure 1: Different parts of the striatum are connected to discrete cortical regions in circuits. (Adopted from Alexander et al, 1986[27]) While the putamen plays a critical role in the motor loop, the caudate is a part of the cognitive and limbic circuits. SMA: supplementary motor area. DLPFC = dorsolateral prefrontal cortex. FEF = frontal eye field. GPi: globus pallidus (internal segment), SNr: substantia nigra pars reticulata. Caudate (DL) = dorsolateral caudate, Caudate (VM) = ventromedial caudate. (Adopted from Alexander et al, 1986[27])

2.1.3. **Clinical presentation of Parkinson's disease**

The disease is characterized by motor features: tremors, rigidity, bradykinesia postural instability. PD have been always considered as a motor disorder, however, other non-motor features are common. And they might even lead to disability more than the motor impairments and maybe more difficult to treat. These features include cognitive impairment and dementia, psychosis and hallucinations, mood disorders such as depression and anxiety, sleep disturbance, and autonomic

dysfunction[12]. Certain symptoms might even present before the motor impairment, such as depression, olfactory dysfunction and sleep disturbance[30]. In a survey that included over 1000 PD patients, almost all subjects (97%) complained of at least seven non-motor symptoms[31].

2.1.4. **Cognitive impairment in Parkinson's disease**

Cognitive functions are the intellectual processes that involve various domains such as learning and memory, attention, language, visuospatial, and executive functions. Executive functions refer to complex mental processes needed for planning, organizing, and evaluating behaviors necessary to achieve specific goals[32]. The three core executive functions are inhibition, working memory, and cognitive flexibility, and the dorsolateral prefrontal cortex plays an important role in controlling these functions[13]. Visuospatial functions refer to cognitive processes necessary to "identify, integrate, and analyze space and visual form, details, structure and spatial relations" in more than one dimension[33]. They are the skills needed for movement, depth and distance perception, and spatial navigation. Impairment in visuospatial functions can result in, for example, poor driving ability because distances are not judged correctly or difficulty navigating in space[33].
MCI is the loss of mental functioning that is abnormal for age but does not affect social or occupational life[34]. It is common in PD patients and can present at time of

diagnosis in about 35% of cases[14]. More than 60% of PDMCI patients (PD with mild cognitive impairment) convert to dementia (Parkinson's Disease Dementia; PDD) within 5 years. This results in increased mortality rate (5 times higher than normal elderly individuals, and 2 times higher than PD individuals without dementia)[15,2], nursing home admission[3], and burden of care[4]. Advanced age, disease duration, severity, and late onset of the disease are risk factors for MCI[1]. Different cognitive domains can be impaired in PD: executive functions[5], memory, attention[6], visuospatial[7] and/or language[8]. However, single-domain impairment is more prevalent than multiple domain, and non-amnestic single domain MCI is more common than amnestic single-domain MCI[1].

Several mechanisms for cognitive dysfunction in PD have been proposed. Some studies have attributed cognitive dysfunction in PD to dopamine depletion, which leads to an interruption in the normal transmission of information through the fronto-striatal circuitry, and affects the expression of frontal lobe functions[16,17,18]. Animal experiments have also found that damage to the caudate nucleus produces deficits that resemble the effects of prefrontal cortex damage[19]. Moreover, studies that showed executive functions in PD are sensitive to L-dopa withdrawal lend support to this hypothesis[20], as well as functional connectivity studies that reported significant modulations in the cognitive and motor networks of the cortico-striatal pathway with L-dopa administration in healthy individuals[21].

Another mechanism that could explain cognitive impairment in PD is the involvement of the mesocortical pathway, leading to decreased dopamine supply in the prefrontal cortex itself[23]. Furthermore, the disturbance of other neurotransmitters such as acetylcholine, serotonin, and norepinephrine, as well as the presence of cortical Lewy bodies in the prefrontal cortex could also contribute to cognitive impairment[22, 23,24].

2.1.5. **Diagnosis of Parkinson's disease**

Parkinson's disease is clinically diagnosed by an expert clinician based on the criteria from the Movement Disorder Society[35]. Bradykinesia with either tremor or rigidity must be present in order to confirm the diagnosis. Postural instability is also a feature of PD but usually does not appear until later in the course of the disease. Moreover, good dopaminergic therapy is an important supportive feature for establishing the diagnosis. There is no radiological or laboratory test to confirm the diagnosis. Nevertheless, MRI might be done in some rare cases to exclude other possible causes such as stroke. The gold standard for definitive diagnosis is the presence of neuronal degeneration in the substantia nigra in the neuropathological exam.

- **Clinical evaluation and diagnosis of cognitive impairment in Parkinson's disease**

Although neuropsychological testing is the gold standard for assessing cognitive status, it is also time consuming. Hence, the use of more practical screening tests is crucial, such as the Montreal Cognitive Assessment test (MoCA) and the Mini-Mental State Examination (MMSE). These screening tests have been widely used, as they are quick and easy to administer. The MoCA is a sensitive and specific tool for the detection of MCI in early stages. It is superior to MMSE as it has higher sensitivity (90% as compared to 18% for MMSE). The MoCA also provides more executive function-demanding tasks than the MMSE, which makes the MoCA more suitable for detecting cognitive impairment in PD patients, especially in the early disease stages[25].

The MoCA test (https://www.mocatest.org/) is accessible online and is available in several languages. It is a one-page 30-points test that can be administered in about 10 minutes. It assesses 5 cognitive domains. Visuospatial domain is assessed using clock- drawing task (3 points) and a three- dimensional cube copy (1 point). Executive functions are tested using Trail Making Test B (1 point), a phonemic fluency task (1 point), and a two- item verbal abstraction task (2 points). The short- term memory recall task (5 points) involves two learning trials of five nouns and delayed recall after approximately five minutes. Attention, concentration, and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and

backward (2 points). Language is assessed using a three- item confrontation naming task with low- familiarity animals (3 points), repetition of two syntactically complex sentences (2 points), and the aforementioned fluency task. Finally, orientation to time and place is evaluated (6 points)[26].

Because depression is common in PD and might be the cause or contribute to cognitive impairment, screening is highly recommended[36]. One of the questionnaires that is used for this purpose is the Beck Depression Inventory test (BDI)[36]. It has a high one-week test–retest reliability. It is a 21-question multiple-choice self-report inventory. Each answer being scored on a scale value of 0 to 3. Higher total scores indicate more severe depressive symptoms. The standardized cut-off scores are as follow: 0–13: minimal depression, 14–19: mild depression, 20–28: moderate depression, 29–63: severe depression.

- **MDS Task Force diagnostic criteria of MCI in PD patients**[37]

  The diagnosis of PDMCI requires the presence of all of the following:

  - A firmly established diagnosis of PD
  - Gradual decline, in the context of established PD, in cognitive ability reported by either the patient or informant, or observed by the clinician
  - Cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities

- Cognitive deficits are not sufficient to interfere with functional independence.
- Excluding other causes of cognitive impairment (eg, delirium, stroke, major depression, metabolic abnormalities, adverse effects of medication, or head trauma)
- Other PD-associated comorbid conditions (e.g. motor impairment or severe anxiety, depression, excessive daytime sleepiness, or psychosis) have not significantly influenced cognitive testing, in the opinion of the clinician

- **MDS Task Force diagnostic criteria of Parkinson's disease dementia (PDD)**[37]
  - A firmly established diagnosis of PD
  - Cognitive impairment with insidious onset and slow progression, developing in the context of established PD
  - Impairment in more than one cognitive domain (attention, executive function, visuospatial function, memory)
  - Decline from a premorbid level
  - Deficits severe enough to impair daily life (social, occupational, or personal care)

2.1.6. **Management of Parkinson's disease**

There is no cure for PD, but it can be managed, and the symptoms can be controlled. Treatment options include medications and surgery[38]. The medical therapy, which is the most common approach, aims to restore the balance of the neurotransmitters; dopamine and acetylcholine. However, some patients are good candidates for the surgical intervention which involves the implantation of a deep brain stimulator.

The drugs that are widely used for controlling the motor symptoms of PD are: Levodopa (the first drug of choice), dopamine agonists, Monoamine Oxidase (MAO) B inhibitors, anticholinergic agents, amantadine, and Catechol-O-methyl transferase (COMT) inhibitors[38].

- **Management of cognitive impairment in Parkinson's disease**

Before starting the treatment, treatable causes such as hypothyroidism, vitamin B12 or folate deficiencies, renal or liver failure, anemia, and viral infections should be excluded first. Structural MRI should be considered in the context of sudden onset cognitive impairment to rule out vascular events.

Although dementia in PD is an important aspect since it brings an additional burden of functional impairment and cognitive deterioration, research on clinical management of cognitive impairment is still scarce. Medical therapy has been used just to provide symptomatic relive. Although dopamine replacement therapy helps

with the motor symptoms, its effect on cognition is inconsistent between studies (ranging from deleterious to beneficial effects)[39]. Some studies showed more impairment with medications among those with severe symptoms, while others showed that medications improve performance[40]. Another study examined the effect of medications in restoring normal activity in the cognitive and motor circuits, and they reported that L-dopa restored the normal pattern of activity in the motor corticostriatal loop but not the cognitive loop[41]. Similar findings were reported in a PET study, they found that unlike PD related motor pattern, the PD related cognitive pattern was not normalized by antiparkinsonian medications[42]. This response to dopaminergic medication could be explained by the dopaminergic overdosing hypothesis[7]. This hypothesis proposes that dopamine replacement therapy could help in restoring neurotransmission function in the severely affected dorsal striatum but putatively overdose relatively less affected ventral striatum. Which results in improvement in the planning, executive functions and working memory alongside deterioration in reward processing and learning[43,44].

For PDD, cholinesterase inhibitors[6,45]and/or memantine[46,47] are used to control the symptoms while monitoring for side effects and tapering if no improvement or side effects develop.

Other therapeutic interventions might be incorporated in a multidisciplinary therapy program, such as cognitive training and brain stimulation. A meta-analysis

of several recent studies have found that cognitive training had small but significant effects on multiple domains of cognitive function often impaired in PD, including executive function, processing speed, working memory, and overall cognitive performance[48]. One of the brain stimulation modalities that has been used in research to improve cognition is transcranial Direct Current Stimulation (tDCS). When targeting the prefrontal cortex, some tDCS studies have reported an improvement in executive functions[49] and working memory[50].

2.2. **The dual syndrome hypothesis**

Cognitive impairments in PD vary between individuals from the clinical aspect, response to pharmacological treatment and tendency to progress to dementia. PD patients with MCI experience deficits in working memory and executive functions that are similar to those seen in patients with frontal lobe damage[4]. On the other hand, PDD patients' cognitive impairment resembles deficits seen in patients with temporal lobe damage[5].

Also, different response to medications was observed in many studies. L-dopa withdrawal caused a deterioration in working memory but not visuospatial learning[51]. And memory deficits were observed following long term administration of anticholinergic medications in PD[52], in addition to detrimental effect on

memory[53] and visual learning task[54] caused by the administration of muscarinic antagonists in PD patients but not in matched control group.

The dual syndrome hypothesis helps to understand the heterogeneity of cognitive impairment in PD. This hypothesis differentiates between two syndromes: (i) PD patients with tremor-dominant phenotype, MCI in the tests of planning, working memory and executive functions that reflect fronto-striatal dysfunction, and are amenable to dopaminergic amelioration but susceptible to overdosing effect; and (ii) PD patients with pronounced gait disturbance and early deficit in visuospatial and semantic fluency tests indicative of posterior cortical and temporal lobe dysfunction (AD-like), who progress rapidly to dementia and respond well to cholinergic medications[7].

That being said, it is worth mentioning that there is some degree of overlap between the two syndromes; cholinergic and noradrenergic imbalance may also contribute to executive dysfunction. Additionally, PDD cannot exist in the absence of significant dopaminergic disturbance, and the mesocortical pathway also innervates areas of the parietal and temporal lobes and could contribute to posterior cortical deficit[55,56]. However, the lack of response to dopaminergic medications is against this possibility (Figure 2).

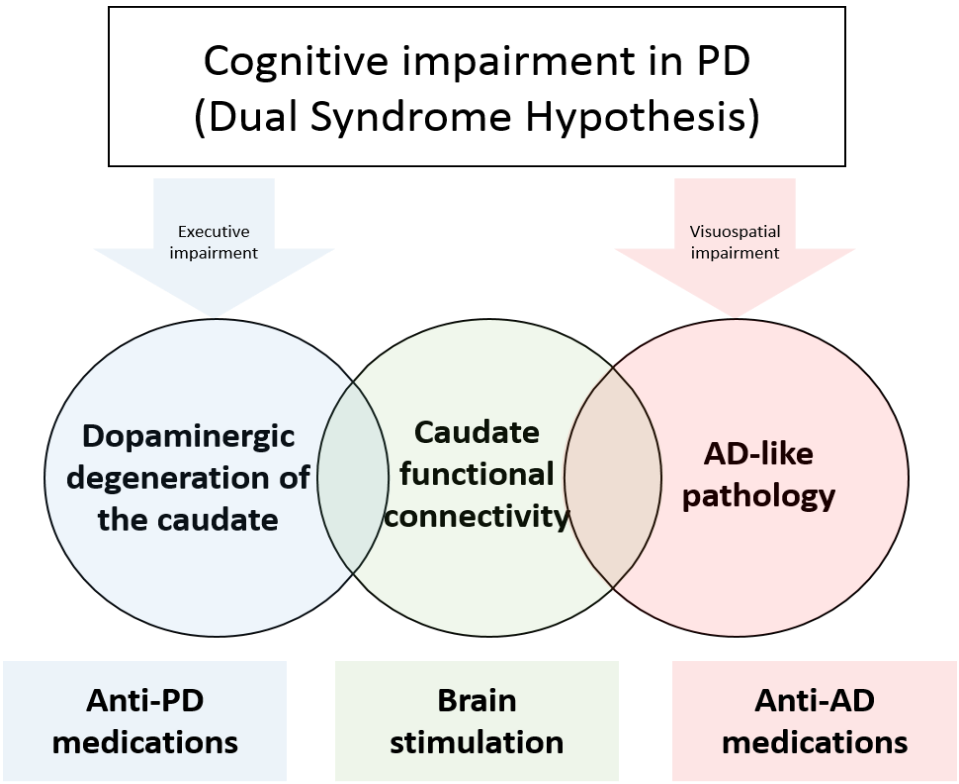

Figure 2: the dual syndrome hypothesis: Cognitive impairment in PD patients fits under two categories; Alzheimer's like, with an impairment in the visuospatial domain. And fronto-striatal dysfunction, which is impairment in executive functions. Unlike patients with AD-like impairment, patients with the dopaminergic degeneration of the caudate do not respond well to anticholinergic medications. Moreover, can not be controlled by dopaminergic medications since they are tittered for motor symptoms.

2.3. **Imaging methods**

2.3.1. **Resting State Functional Magnetic Resonance Imaging (rsfMRI)**

Functional imaging refers to a number of MRI applications, such as cardiac function and joint functions. However, the term functional MRI (fMRI) refers specifically to neuronal function. While conventional brain MRI is used to study the structure of the brain, fMRI is the method of choice for examining the neuronal activity in the human brain. It is a non-invasive, powerful tool with relatively high

temporal and spatial resolution(1-3 seconds and 3-5mm)[57]. Therefore, it has been used in research for many decades.

FMRI can be acquired while the subject is performing a task (cognitive, sensory, or motor) or to investigate network functional connectivity while the subject is at rest (rsfMRI). One of the functional connectivity networks that have been identified in healthy individuals is the cortico-striatal network, involving the caudate nucleus and prefrontal cortex, which plays an important role in understanding cognitive dysfunction in PD patients[58].

- **Hemodynamic response**

Functional MRI is based on acquiring MR images at different states of function. However, it does not measure brain activity directly. Rather, it relies on the concept that regional cerebral blood flow reflects neuronal activity (the neurovascular coupling hypothesis)[59].

Blood hemoglobin is diamagnetic when bound to oxygen (having a very weak magnetic effect because it does not contain unpaired electrons), but is paramagnetic (stronger magnetic effect, with four unpaired electrons) when not bound to oxygen. Thus, the magnetic field in blood vessels can be altered depending on the blood oxygenation level, which gives rise to the BOLD contrast[60].

BOLD contrast measures heterogeneities in the magnetic field due to changes in the oxygen level. An increase in neuronal activity is accompanied by an increase in local perfusion. This surge in perfusion exceeds oxygen demand due to neuronal activation, resulting in more oxygen in the tissue and a local reduction of the deoxyhemoglobin[59]. As the BOLD signal relies on deoxyhemoglobin as an endogenous parametric contrast agent, changes in the local deoxyhemoglobin concentration alter the signal intensity of the MRI; a low deoxygenated hemoglobin level results in an increase in the BOLD signal[57]. This makes BOLD contrast useful for functional brain mapping.

2.3.2. **Graph Theory Analysis**

One of the strategies to analyze fMRI data and study whole-brain functional connectivity is graph theory analysis. This method has been used in many studies to illustrate the topographical changes associated with brain disorders (e.g. depression, PD, AD, multiple sclerosis)[61].

In graph theory analysis, anatomical brain regions are considered as nodes (vertices) that are linked via “edges”, representing the functional connectivity (BOLD signal fluctuation) between nodes. A network is defined as a set of nodes and the edges between them.

Various measures are used to describe the topology of a graph and determine network integration and segregation. These measures can be divided into centrality measures (e.g. degree centrality, betweenness centrality, eigenvector centrality), global network metrices (e.g. global efficiency, characteristic path length, clustering coefficient, local efficiency).

Relevant measures of graph theory analysis are defined as follows[62]

Global efficiency measures the ability of a network to transmit the information at a global level.

Characteristic path length is defined as the average of the shortest distance between any pair of nodes in a network (number of edges that must be traversed to get from one node to any other node in the network). It is inversely correlated with global efficiency.

Clustering coefficient is the proportion of the number of connections with the nearest neighbors to a node, compared to the maximum number of possible connections. A cluster is formed when the nearest neighbors of a node are directly connected to each other. Clustering coefficient reflects the density of connections between a node's neighbors. It is a segregation measure for the network, whereas characteristic path length is a measure for global integration of the network. The mean clustering coefficient and characteristic path length determine whether the network is organized in a random or small-world order.

Small-worldness is a description for a network that is characterized by high clustering coefficient and low characteristic path length. Therefore, small-world networks transfer information efficiently both locally and globally (Figure 3)[62]

Betweenness centrality (BC) indicates the importance of a node in the network. It is defined as the number of shortest paths between any two other nodes, which pass through the given node. Nodes with high centrality are crucial to efficient communication and considered to be hubs of transmission.

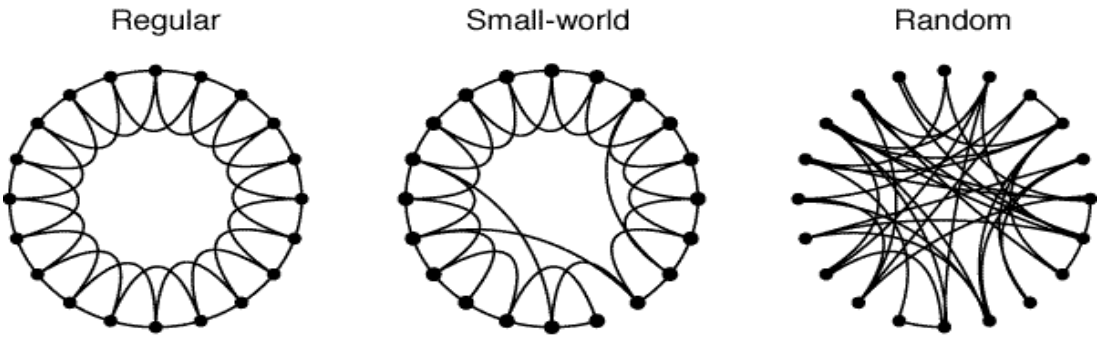

Figure 3: The graph theory metrics: A small-world organization is intermediate between that of random networks, the short path length and a low level of local clustering, and that of regular networks, the high-level of clustering of which is accompanied by a long path length. (Adopted from Bullmore E, et al, 2009) [62]

2.3.3. **Arterial Spin Labeling**

Arterial Spin Labeling (ASL) is a safe, non-invasive MRI modality to quantify regional blood perfusion. ASL is used to measure blood flow and brain tissue perfusion without contrast; an endogenous perfusion assessment method[63]. This technique uses water molecules in the cerebral arteries as a contrast. To generate

the perfusion image, two images are needed; the labeling image and the control image. The protons of the arterial water are magnetically labeled and used as an endogenous tracer. The labeled molecules then migrate via the arterial vessels towards the brain tissue and pass from the capillaries to the extravascular compartment and the images are acquired (labeling images). After a certain delay, to allow labelled protons to wash away from the vasculature and exchanged by unlabeled water, other MR images are acquired (control images). The perfusion images then can be generated by subtracting the labelled images from the control ones[64] (Figure 4).

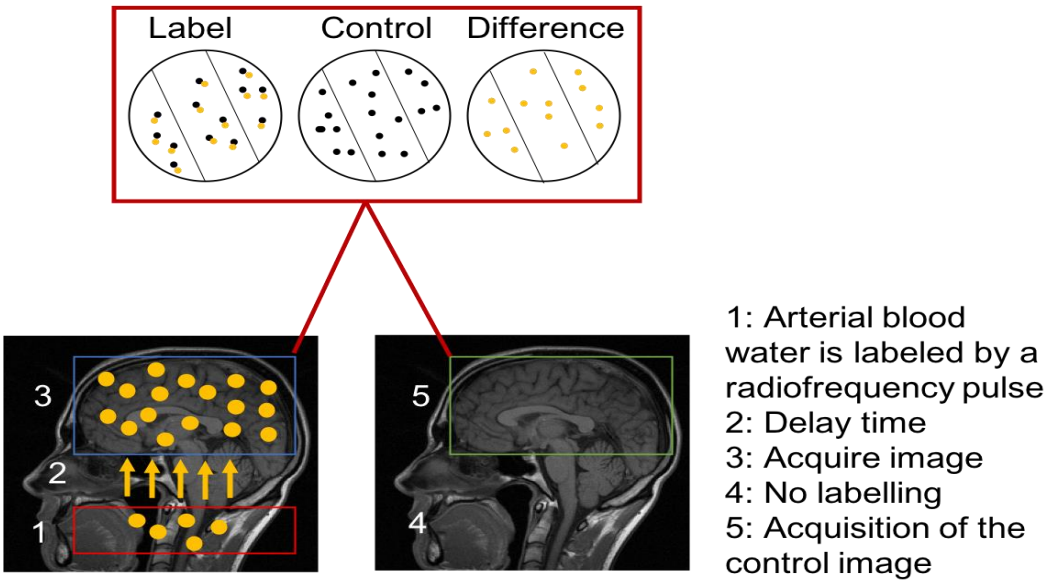

Figure 4: Basic principles of Arterial Spin Labelling. Arterial blood water is labeled by radiofrequency pulse. After a delay time between labelling and image acquisition, labeled spins reach capillaries and pass into brain tissue where they alter the local tissue's magnetization. After a certain delay, to allow labelled protons to wash away, another image is acquired without labelling. The static tissue signal is identical in both images **(labeled and control image)**, but magnetization of inflowing blood is different; this difference is **perfusion signal**.

2.3.4. ^{18}F - Fluorodeoxyglucose Positron Emission Tomography (FDG PET)

FDG PET is a brain imaging technique that estimates regional glucose metabolism to provide diagnoses of various medical conditions such as AD, tumors, and metastasis. It is invasive and involve exposure to ionizing radiation. After ^{18}F-FDG is injected into a patient, a PET scanner can form two-dimensional or three-dimensional images of the distribution of ^{18}F-FDG within the body.

In our previous study[8], we compared the performance of classification algorithms (general linear model (GLM), scaled subprofile modeling (SSM) and support vector machine (SVM)) to differentiate AD patients from normal subjects using FDG PET. SVM was found to be the best classification method to distinguish AD affected and unaffected individuals, also to predict the future development of AD from MCI. We also investigated the expression of AD-like metabolic pattern in PD. When SVM was used, PDND and PDMCI were rarely classified as AD, while the majority of PDD exhibited AD-like metabolic pattern and were classified as AD. When the GLM method was used, the majority of PDMCI patients were also classified as AD, potentially suggesting that the GLM is more sensitive to the earlier stage of cognitive deterioration.

2.4. **Imaging in Parkinson's disease cognition**

Several studies have been in line with the dual syndrome hypothesis, confirming the association between PDMCI and fronto-striatal dysfunction. An MRI study has looked at the structural alterations of the caudate nuclei in PD patients without dementia compared to healthy controls, and reported an association between cognitive decline and caudate atrophy[65]. Similar findings were reported in another MRI study by Zhang et al where they observed significant reduction in the volume of the left caudate nucleus and a trend toward atrophy in the right one in PD patients without dementia compared to controls[66]. On the other hand, PDD patients had significant amygdala and hippocampal atrophy compared to non-demented PD and controls, and the atrophy of these structures significantly correlated with both MMSE and memory test[67]. Also, several MRI studies have reported reduced gray matter volume bilaterally in the temporal[68] occipital and frontal lobes in PDD patients compared to controls, while PD patients without dementia showed reduced grey matter volume in the frontal lobe only compared with controls[69]. Thus, PD involves gray matter loss in the frontal lobe with occipital lobe atrophy being specific for PD patients with dementia.

Also, [18F]-fluorodeoxyglucose positron emission tomography (FDG PET) studies have explored these differences between PDD and PDMCI. An FDG PET study showed significant reduced uptake in the caudate nucleus in cognitively impaired

PD patients that was associated with performance in the frontal lobe-sensitive neuropsychological tests but not with neuropsychological tests reflecting temporal lobe function[70]. However, PD cognition-related metabolic pattern (PDCP) expression, which is characterized by increased pallidal, thalamic, and motor cortical metabolic activity associated with reduced lateral premotor and parieto-occipital cortical activities, was significantly greater in PDD relative to non-demented PD subjects[71].

Functional MR imaging studies has also explored the pattern of cognitive impairment in PD. A study by Amboni et al has showed decrease functional connectivity of bilateral prefrontal cortex in PDMCI but not in PD non-MCI. This decrease in connectivity was correlated with cognitive parameters, which might suggest that altered frontal network could be specific for MCI in PD patients[72]. Another fMRI study has demonstrated underactivity in the caudate nucleus and the frontal cortex during working-memory task performance in PD patients with executive dysfunction, compared to both healthy controls and cognitively normal PD subjects, with a significant correlation between the caudate signal intensity and task performance[73]. On the other hand, several studies on PDD have showed decrease posterior cingulate functional connectivity of the medial temporal lobe in PD patients with dementia compared to PD patients with MCI and healthy controls[74,75]

Taken all together, these studies have reported results that support the hypothesis of the dual syndrome in PD patients, separating the pathogenesis of cognitive impairment in PD into fronto-striatal related dysfunction, including the prefrontal cortex and the caudate nucleus, in non-demented PD patients. And posterior cortical and temporal lobe dysfunction in PDD.

3. Hypothesis

The dual syndrome hypothesis suggests that there are two distinct pathologies that are involved with cognitive deficits in PD, i.e., the prefront-caudate abnormality that leads to executive dysfunction and the posterior cortical-temporal abnormality that leads to dementia. Thus, we hypothesized that cognitive performance in PD patients without dementia is separately correlated with the functional connectivity of the caudate nucleus and with the Alzheimer's disease –like cerebral blood flow pattern.

4. Methods

4.1. Study participants

Fifteen PD patients (11 males, 4 females; 7 PDNC (cognitively normal PD; MoCA $\geq$ 26), 8 PDLC (low cognition PD; MoCA < 26) mean age 66.7 ± 7 years, disease duration 8.6 ± 4 years) and **ten age-matched healthy controls** (2 males, 8 females; mean age 62.8 ± 6 years) were included in this study. All subjects were native English speakers. Patients were recruited from the Movement Disorder

Clinic and healthy controls were recruited via advertisement in Winnipeg, Manitoba, Canada. The diagnosis of an idiopathic PD was confirmed by a movement disorder specialist. Patients were screened for MCI by a neuropsychologist. Patient exclusion criteria included diagnoses of anxiety, major depression, neurological disorders other than PD, or any contraindications to MRI. Healthy controls were verbally screened to make sure none had a neurological, psychological, or uncontrolled medical disorder, drug/alcohol abuse, history of severe head injury, or any contraindication to MRI. Control exclusion criteria included impaired cognition (defined as MoCA[76] < 26) or mood disturbance (defined as Beck Depression Inventory – II; BDI-II [77]> 10). The study was approved by the Biomedical Research Ethics Board of University of Manitoba. All participants have provided a written informed consent prior to participating.
PD patients were divided into PDLC (MoCA < 26) and PDNC (normal cognition PD; MoCA ≥ 26). The disease status of patients was assessed with the Movement Disorder Society-Unified Parkinson's Rating Scale (MDS-UPDRS)[78] and they were examined while on their clinically determined antiparkinsonian medications.

4.2. **MRI data acquisition**

All subjects underwent MRI using a 3T Siemens/IMRIS MR System equipped with a 12 channel head coil located at the Kleysen Institute for Advanced Medicine

at the Bannatyne campus of the University of Manitoba. A high resolution T1-weighted image was acquired for anatomical localization using a 3D MPRAGE pulse sequence. Resting state functional MRI scanning parameters are as follows: Repetition Time [TR] = 2000ms; Eco Time [TE] = 28 ms; Flip Angle = 77◦; Slice Thickness = 4.0 mm; Field of View [FOV] = 220mm; voxel size = 3.4 X 3.4 X 4.0 mm; scan duration = 11 min. During scanning, subjects were instructed to keep their eyes open and let their mind wander, but to not fall asleep. The cerebral blood flow acquisition utilized the pseudo-continuous ASL (pCASL) pulse sequence with the following acquisition parameters: Inversion time [TI] = 900 ms; TR = 2300ms; TE = 3.02 ms; Flip Angle = 9◦; Slice Thickness = 1.0 mm; 240 slices; FOV = 256 mm; voxel size = 1.0 X 1.0 X 1.0 mm; scan duration = 5 min.

4.3. **Functional connectivity analysis**

Standard preprocessing has been applied to fMRI data using CONN (http://nitrc.org/projects/conn) running on SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). The resting state data were co-registered to participants' structural T1-MRI scans, spatially normalized to template MRI (MNI space – Montreal Neurological Institute) and the caudate nucleus was visually inspected to make sure it is acutely delineated, then smoothed (FWHM = 8mm × 8mm × 8mm). Individuals' T1 images were segmented and a

grey matter probability map was constructed for masking (inclusive) the 118 different regions of interest (ROIs) defined by Automated Anatomical Labeling (AAL)[79], which additionally include left and right pons[80]. For key subcortical ROIs (i.e., caudate, putamen, pallidum, thalamus, and pons), a cerebrospinal fluid (CSF) map was used for masking (exclusive). For denoising, linear regression was performed with confounding variables of white matter, CSF, realignment, scrubbing, and global signal. Band-pass filter was then applied (0.008-0.09 Hz) and linear detrending performed[81].

The region-to-region connectivity matrix (z-matrix) was constructed using individually masked AAL ROIs. The z-matrix was sorted, and adjacency matrices were defined with varying cost (1-50%), e.g., at 25% cost threshold, the top 25% of the z-values were set to 1 and the rest were set to 0 excluding the diagonal elements; therefore, the graph was undirected and unweighted. Both positive and negative connectivity have been considered[82]. Graph theory metrics including characteristic path length, clustering coefficient, smallworldness, global and mean local efficiency were compared between groups[62,83]. At a regional level (i.e., left and right caudate nucleus), Betweenness Centrality (BC) was estimated. BC identifies nodes crucial for information flow in a brain network; in other words, brain network hubs tend to have high BC[84]. For graph theory analysis, the Brain

Connectivity Toolbox[85] and in-house programs running on MATLAB 8.3.0 (Mathworks, Inc.) were utilized.

4.4. **AD-like CBF pattern analysis**

The cerebral blood flow (CBF) maps derived from pCASL data as previously described[86] using ASL Perfusion MRI data processing toolbox (https://cfn.upenn.edu/~zewang/ASLtbx.php). The resulting CBF images were co-registered to the corresponding T1-weighted image, spatial normalized by wrapping to the MNI standard space, then smoothed using 8mm Gaussian filter. Preprocessing was done using SPM12 with the default parameters. Then we used a classification method to identify PD patients with AD-like CBF pattern expression as previously described[8]. In brief, GLM was used to identify a spatial metabolic pattern that contrasts 94 AD patients vs. 111 age-matched healthy control subjects after proportional scaling to the averaged whole-brain FDG-PET signal. The 3D images were "vectorized" after whole-brain inclusive masking and the dot-product between the GLM-pattern and each individual FDG-PET image represents the scaled similarity between the two. Thus, if one has high score, his/her brain metabolic pattern looks more like AD patients. These subject scores are z-scored to the mean and standard deviation of 111 control subjects. Katako et al. (2018)[8]

showed that the GLM-based AD classification is also sensitive to PD-MCI, and that perfusion imaging may be also useful and potentially replacing FDG-PET.

4.5. **Statistical analysis**

Statistical analysis was performed by SPSS (*IBM Corp., Armonk, NY*). Shapiro-Wilk test was used to determine the normal distribution of each variable. For normally distributed variables (age, sex, disease duration, UPDRS-III, characteristic path length, clustering coefficient, and mean-local efficiency), one-way ANOVA or student t-test were used to assess the group differences, followed by post-hoc Bonferroni test if applicable. For the variables that are not normally distributed (BC, GLM, BDI-II, LEDD, global efficiency, and smallworldness), Kruskal-Wallis and Mann-Whitney tests were used to determine the group differences. Spearman's correlation was used to examine the relation between the imaging-based variables (BC and GLM) and MoCA in PD patients. Results were considered significant at a threshold of $p < 0.05$.

5. **Results**

5.1. **Demographic data**

The relevant demographics and clinical variables of each group are presented in Table 1. No significant difference in age between the groups. As expected, PDLC had significantly lower MoCA scores compared to both PDNC and controls

(p<0.001, Mann-Whitney U). PDNC and healthy controls were not significantly different in MoCA (p=0.813, Mann-Whitney U). Sex was not equally distributed between the groups (more female participants were in the healthy controls) (χ^2 = 6.83, p= 0.026). Also, there was a significant difference across the groups in BDI-II (p = 0.008, Kruskal-Wallis test). PDLC had significantly higher BDI-II than controls (p = 0.002, Mann-Whitney U) while not significantly different from PDCN (p=0.072, Mann-Whitney U). The PDNC and healthy control's BDI-II was not significantly different from each other (p=0.230, Mann-Whitney U). There was no significant difference between the PD groups (PDNC vs. PDLC) in age, sex, disease duration, UPDRS-III motor subscale or LEDD (p>0.300).

5.2. **Global network analysis**

Unlike prior studies[57-60], there was no significant group differences in any of the graph metrics when analyzed as a whole-brain (characteristic path length, clustering coefficient, mean-local and global efficiency, and smallworldness) (p > 0.100; Table 2).

5.3. **The caudate's functional connectivity correlates with MoCA scores in PD patients but not in healthy controls.**

To examine the role of the caudate nucleus as an information hub, and the effect of its dysfunction in PD cognitive deficits, we measured correlation between BC of the caudate and MoCA scores. We found a strong positive correlation between the

BC of the right caudate nucleus and MoCA scores in PD (rho = 0.63, p = 0.011) but not in healthy controls (rho = -0.19, p = 0.59; Figure 5A). Interestingly, PDNC's BC of the right caudate was significantly different from both PDLC and normal controls (p<0.02, Mann-Whitney), while PDLC and normal subjects were not significantly different from each other (p=0.965, Mann-Whitney) (Figure 6). Neither the BC of the caudate nor the MoCA scores were correlated with age, BDI-II scores, disease duration, medications, or UPDRS-III ($p>0.200$). No significant difference between sexes was observed for MoCA and the caudate BC ($p>0.800$). Interestingly, left caudate BC was not correlated with MoCA scores in either the PD group (p>0.900) or healthy controls (p>0.500).

5.4. **AD-like CBF pattern expression and caudate BC**

As expected, GLM-based AD-like CBF pattern score was correlated with MoCA scores in healthy controls (rho = -0.669, p = 0.034), suggesting the feasibility of using FDG-PET-based AD-like pattern quantification in pCASL-based perfusion imaging. However, the correlation was not observed in PD patients (rho = -0.339, p=0.216; Figure 5B). No group differences (PDLC vs. PDNC vs. healthy controls) was observed either (p=0.444, Kruskal-Wallis). Interestingly however, there was a negative correlation between the AD-like CBF pattern scores and the right caudate's BC in PD patients (rho = -0.518, p =0.048) and a trend-level of positive correlation was observed in healthy controls (rho = 0.576, p =0.082; Figure 5C).

This score was not correlated with any other variables; age, sex, disease duration, BD-II, UPDRS-III or medications in any of the groups.

6. Discussion

We found that the functional connectivity of the right caudate positively correlates with MoCA scores in PD, which support the current literature that caudate is involved with PD cognitive deficits[1,27,38]. According to the dual syndrome hypothesis[27], the underlying dysfunction of cognitive impairment in non-demented PD is in the fronto-striatal circuit involving the caudate nucleus and prefrontal cortex. Our patients' cognitive status is mildly impaired (i.e., PDLC), and the correlation that we have found between the functional connectivity of the caudate and MoCA scores further support this hypothesis and the current literature. Furthermore, this association between cognitive performance and the connectivity of the caudate was only seen in the right caudate nucleus but not the left. Laterality of the caudate nucleus in PD patients have been reported in many studies using different imaging modalities. Using PET imaging, an association between the right caudate and cognitive performance have been previously reported[87]; the authors found that decreased dopaminergic function of the right caudate was related to slow processing time in the Stroop test in patients at an early stage of PD. Hypometabolism was more prominent in the right caudate nucleus in the PDD-related spatial metabolic pattern[88]. This may suggest that the right caudate plays

more crucial role in maintaining cognitive functions, and its deterioration could lead to more cognitive impairment.

More detailed group analysis revealed that PDNC had higher right caudate BC than both PDLC and controls, and a similar MoCA scores to the controls. We expect this increase of the connectivity to be a successful compensatory mechanism that helped in maintaining normal MoCA performance in PDNC compared to PDLC who showed lower MoCA scores associated with low connectivity in the right caudate. The same concept of compensation was reported in another study where they found that hubs regions could change in diseases as a compensatory response; the authors noticed an increase in frontal hubs in PDNC compared to both healthy controls and PDMCI and they suggested that this change in brain connectivity to be the cause of improved cognitive functions in PDNC subjects[89]. Likewise, we also predict that higher connectivity in the right caudate has led to improve cognitive performance in our PD patients.

According to the dual syndrome hypothesis, another important axis of PD cognitive deficit is the posterior cortical and temporal abnormality, which is traditionally thought to be relevant to AD-related pathology[7]. FDG-PET is the most frequently used imaging method that complement diagnosis of AD and is often used to quantitate disease progression[90] and treatment responses[91]. Katako et al.[8] recently developed and validated automated quantification method that estimates

how much an individual FDG-PET scan "looks like" a model AD patient scan. And, they further suggested that their method was also sensitive to PDD as well as PDMCI (when used GLM method). The feasibility of using perfusion imaging instead of FDG-PET was also explored.

In the current study, first, we demonstrated that GLM-based AD-like CBF pattern score[8] quantitated using pCASL MRI was inversely correlated with MoCA in normal healthy individuals, suggesting its validity and sensitivity of the proposed method. MoCA and AD-like pattern score was not correlated in PD group. One explanation is that cognitive impairment in our patients (who were not demented) was primarily driven by the caudate abnormality, thus masking the influence of AD-like pathology. Interestingly however, the functional connectivity of the right caudate inversely correlated with the AD-like pattern scores in PD patients only, which means that the higher the connectivity of the caudate the lower the AD-like pattern score and less probability of having AD-like pathology. This relationship could be explained in two ways; one hypothesis is that patients with successful compensation by the caudate (high caudate connectivity) were able to suppress the AD-like pattern expression, which collectively influenced to unimpaired cognitive performance in PDNC. Or it could be also interpreted that the higher AD-like pattern expression interferes with the occurrence of successful compensation mechanism (which is the increased caudate connectivity).

Interestingly, positive trend of correlation was observed in healthy control subjects between BC of the right caudate and AD-like pattern expression without reaching statistical significance. More studies are warranted to explore this relationship.

6.1. **Limitations**

Unlike other previous studies, we did not find any significant differences in the global graph theory metrices between the groups. Increase clustering coeffieients[92], smallworldness[93], and characteristic path length with reduced global efficiency[89] in PDMCI compared to PDND and healthy controls have been previously reported. Others have reported maintained global integration in PD compared to healthy controls[94,80]. However, most of these studies were done on drug naïve PD patients. Our patients in this study were examined while on their prescribed medications. The impact of anti-PD medication on perfusion has been previously documented[95]. Studies suggests that chronic levodopa treatment may induce angiogenesis and increase vascular sensitivity in the putamen[96]. It is less evident if the caudate is also involved in this hyper-vascularity phenomena, which may have influenced the AD-like pattern score estimation using pCASL MRI.

Other limitations for this study was the small sample size in each group. Also, there was a significant group differences in sex and BDI-II scores. But none of these variables correlated with the functional connectivity of the caudate nucleus or MoCA scores. Finally, the lack of longitudinal follow up data to see if those non-

demented PD patients who showed higher expression of the AD-like metabolic/perfusion pattern will convert to dementia in the future or not which might help in validating the use of this new method as a prognostic tool in prediction the conversion of PDMCI to dementia.

7. Future directions

In this study, we have found that the functional connectivity of the right caudate nucleus is related to cognitive performance in PD patients with low cognitive performance measured by MoCA test. We have also found that patients who were able to maintain good performance had higher connectivity than both PDLC and the age-matched healthy controls. We suggested this increase in the connectivity to be a successful compensatory mechanism that helped in maintaining normal performance. Based on these findings, we propose that these PD patients with low functional connectivity in the right caudate might benefit from brain stimulation methods. By increasing the functional connectivity of the right caudate nucleus in those patients using an external stimulation such as the transcranial direct current stimulation (tDCS), cognitive functions might improve. This is what we are seeking in our future studies, we will explore the effect of tDCS on cognitive functions and the functional connectivity of the caudate nucleus in PD patients with MCI as well as in healthy young and age matched controls. We also plan to run another study on PD patients with dementia, to investigate the GLM-based

AD-like CBF pattern expression on pCASL MRI in that population. We expect that in PDD, GLM-based AD-like CBF pattern expression will be more relevant to cognitive performance and can predict MoCA scores better than the BC of the right caudate that we have found to be more suitable for PD patients with MCI.

8. Conclusion:

The dual syndrome hypothesis suggests that there are two distinct pathologies that affects PD cognition – PDMCI vs. PDD. To our knowledge, this is the first study that directly investigated the relationship between those two spectrums quantitated using resting-state functional connectivity and cerebral perfusion imaging. The correlation between caudate connectivity and AD-like perfusion scores in PD patients suggests that those two pathologies may not be distinct but interacting with each other, potentially involving a compensatory mechanism.

	Healthy control subjects (n = 10)	PD patients with normal cognition (PDNC; n = 7)	PD patients with low cognition (PDLC; n = 8)
Age (years)	62.8 ± 5.9	65.4 ± 7	67.8 ± 7
Male/female[$]	2M/8F	5M/2F	6M/2F
MoCA scores[**]	28 ± 1	28.14 ± 1.2	22.7 ± 1.1[***]
BDI scores[*]	3 ± 3.06	5 ± 3	10.7 ± 7.3
Disease duration (years)		9.4 ± 2.6	7.7 ± 4.7
MDS-UPDRS-III		17 ± 7.4	21.9 ± 10
LEDD total (mg/day)		595 ± 772	640 ± 466

TABLE 1: DEMOGRAPHIC AND CLINICAL VARIABLES

MoCA: Montreal Cognitive Assessment test
BDI-I: Beck Depression Inventory test
MDS-UPDRS-III: Movement disorder society - Unified Parkinson's disease Rating Scale – III
LEDD: levodopa equivalent daily dose
Values are listed as mean ± standard deviation
[$]$p<0.05$ by chi-square test
[*]$p<0.05$, [**]$p<0.001$ by Kruskal-Wallis Test
[***]$p<0.001$ by Mann-Whitney U test between PDLC and PDNC.

Global network metrics	Healthy control subjects (n = 10)	PD patients with normal cognition (PDNC; n = 7)	PD patients with low cognition (PDLC; n = 8)
Characteristic path length	*2* ± 0.04	*1.9* ± 0.07	*1.96* ± 0.03
Clustering coefficient	*0.46* ± 0.04	*0.44* ±0.06	*0.43* ± 0.02
Global efficiency	*0.55* ± 0.01	*0.5* ± 0.01	*0.56* ± 0.006
Mean local efficiency	*0.68* ± 0.02	*0.67* ±0.03	*0.66* ± 0.01
Smallworldness	*1.1* ± 0.83	*1.43* ± 0.66	*1.61* ± 0.6

TABLE 2: GLOBAL NETWORK ANALYSIS

Values are listed as mean ± standard deviation

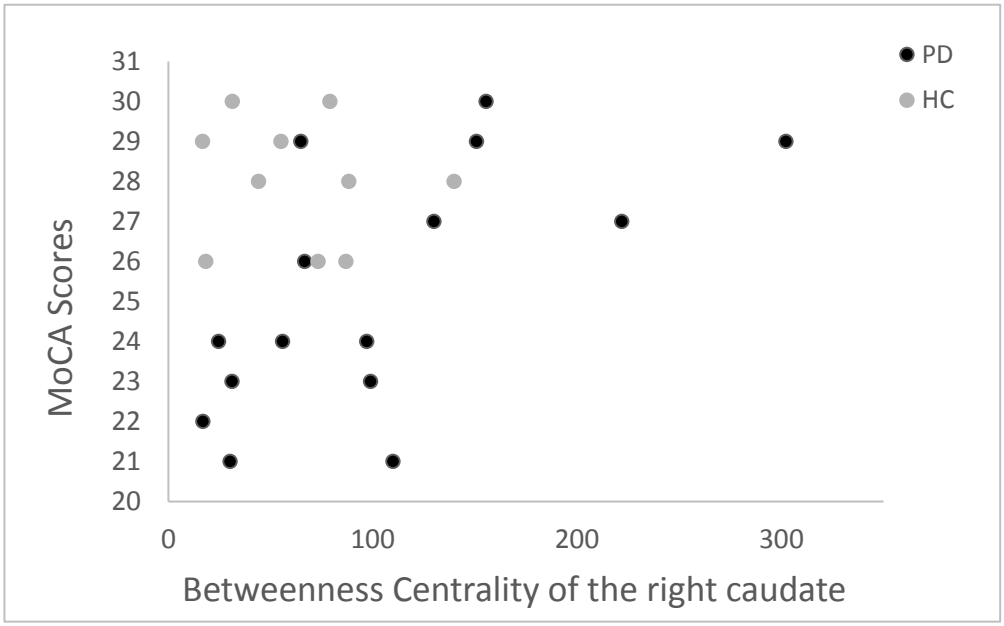

Figure 5: Spearman's correlation between the functional connectivity of the right caudate nucleus and MoCA scores: a strong positive correlation was found in the PD group only (rho = 0.633, p = 0.011) but not with the healthy controls (rho = -0.19, p = 0.59).

MoCA: Montreal cognitive assessment test. PD: Parkinson's disease group. HC: Healthy controls

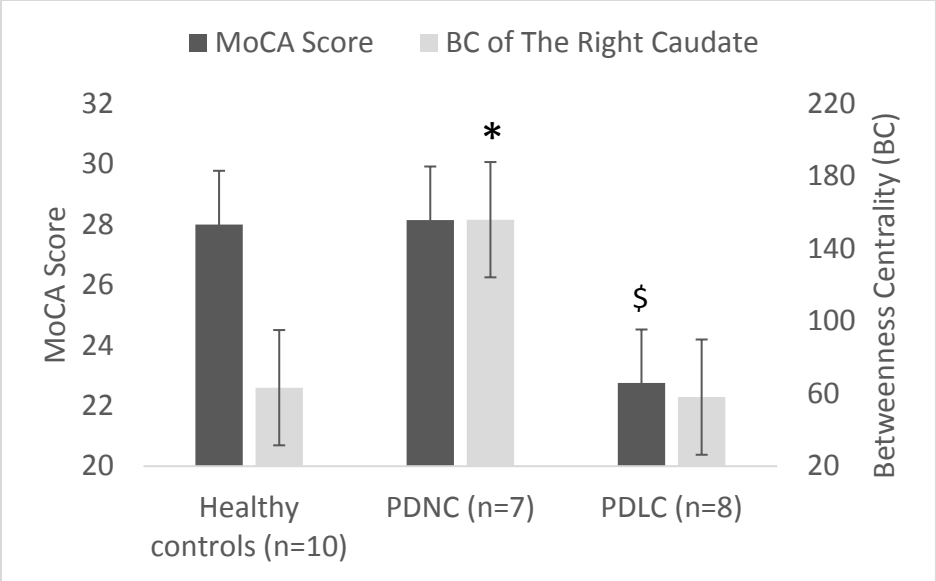

Figure 6: The cognitive performance (MoCA) and caudate connectivity. kruskal-Wallis test showed significant group effects in MoCA score ($H(2)=15.9$, $p < 0.001$) and right caudate betweenness centrality (BC) ($H(2)=7.72$, $p = 0.02$). As expected, PDLC patients' MoCA scores were lower than both groups ($p<0.001$, Mann-Whitney test), while cognitively healthy PD patients show similar level of MoCA score to the healthy controls ($p=.803$, Mann-Whitney test). Interestingly, the right caudate betweenness centrality of these patients (PDNC) were higher compared to both healthy controls and PDLC ($p<0.01$, Mann-Whitney test).

*Indicates significant difference between groups ($p = 0.02$) $ Indicates significant difference between groups ($p < 0.001$). PDLC: PD patients with Low Cognitive performance measured by MoCA test. PDNC: PD patients with normal cognitive performance measured by MoCA. MoCA: Montreal cognitive assessment test. BC: Betweenness centrality. Results were considered significant at a threshold of $p < 0.05$

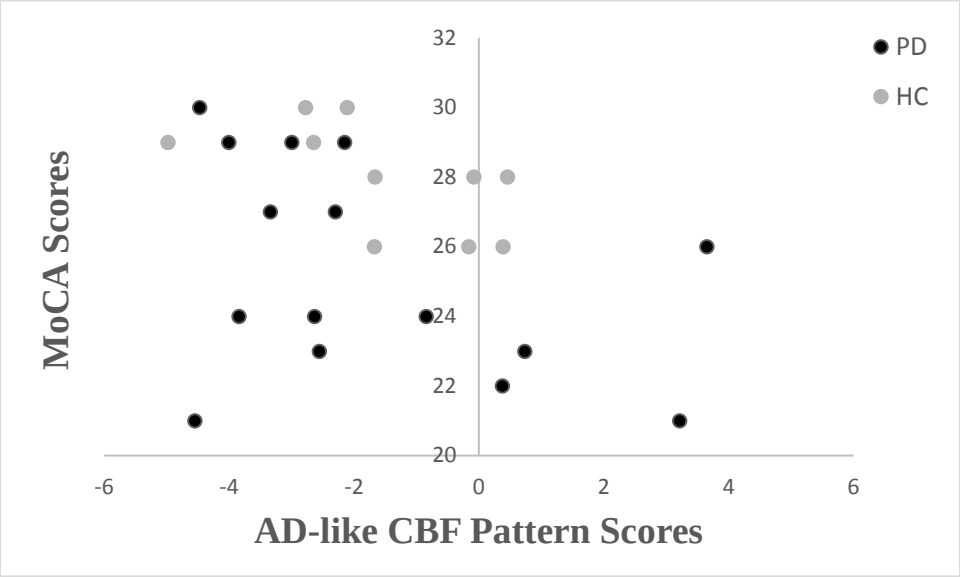

Figure 7A: Spearman's correlation between MoCA scores and AD-like CBF pattern score. Negative correlation between the AD-like CBF score and MoCA scores in healthy controls (rho = -0.669 p = 0.034) but not in PD group (p>0.2). MoCA: Montreal cognitive assessment test. AD: Alzheimer's disease. CBF: cerebral blood flow. PD: Parkinson's disease group. HC: Healthy controls

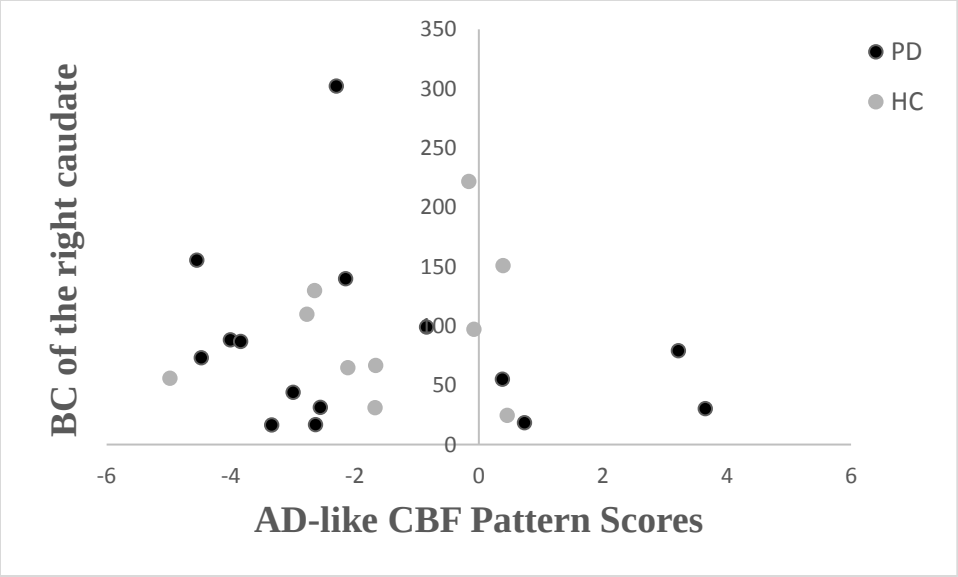

Figure 7B: Spearman's correlation between the BC of the right caudate nucleus and AD-like CBF pattern scores. The BC of the right caudate is inversely correlated with the AD-like CBF pattern scores in PD patients (rho = -0.518, p =0.048) but not in healthy controls (rho = 0.576, p= 0.082). MoCA: Montreal cognitive assessment test. AD: Alzheimer's disease. CBF: cerebral blood flow.PD: Parkinson's disease group. HC: Healthy controls

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