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NEUROPSYCHOLOGICAL CORRELATES OF STRIATAL DOPAMINERGIC DYSFUNCTION IN PARKINSON'S DISEASE

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NEUROPSYCHOLOGICAL CORRELATES OF STRIATAL DOPAMINERGIC DYSFUNCTION IN PARKINSON'S DISEASE

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Arts and Sciences
at the University of Kentucky

By

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2019

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ABSTRACT OF DISSERTATION

NEUROPSYCHOLOGICAL CORRELATES OF STRIATAL DOPAMINERGIC DYSFUNCTION IN PARKINSON'S DISEASE

Parkinson's disease (PD) is a common neurodegenerative disorder associated with dysfunction of the basal ganglia, which contributes to a range of motor, cognitive, and affective symptoms. Striatal dopaminergic deficits are one of the core pathological mechanisms thought to contribute to the extra-motor (i.e., cognitive and affective) symptoms in early PD. The present study investigated the relationship between striatal dopaminergic integrity and cognition in 21 patients with PD and 21 age and education matched controls. Each individual underwent dopamine transporter (DaT) imaging with single photon emission computed tomography (SPECT) (i.e., DaTscan) and standardized neuropsychological testing. Strong positive associations were found between DaT availability in the striatum and verbal memory (r = .52-.61) and problem solving/set-shifting (r = .55) in patients with PD. Additional moderate to strong positive associations (r = .49-.56) between DaT concentrations and visuospatial functions in patients with PD were found. However, similar significant associations between DaT and cognition were observed in age and education matched controls. Clinically, it is important for health care professionals to consider the role of both striatal and extra-striatal mechanisms as they relate to cognition in PD. Future studies examining the full range of pathological mechanisms that contribute to cognitive dysfunction in PD over time are warranted in order to inform more effective and targeted interventions.

KEYWORDS: Parkinson's Disease, Dopamine, DaT, SPECT, Executive Functioning

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08/16/2019

Date

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INTRODUCTION

1.1 Parkinson's Disease

Parkinson's disease (PD) is common neurodegenerative disorder that affects the central nervous system. Approximately one million people are affected in the United States alone, with about 66,000 new diagnoses made each year (Kowal, Dall, Charkabati, Storm, & Jain, 2013). PD is characterized clinically by parkinsonism (e.g., tremor, rigidity, akinesia, and postural instability) (Cummings et al., 2011; McPherson & Cummings, 2009). One of the main neuropathological hallmarks of PD is dopaminergic neuronal loss in the substantia nigra pars compacta (SNc) and accumulation of alpha-synuclein protein aggregates (Lewy bodies) within neurons (Gunzler, Schoenberg, Riley, Walter, & Maciuna, 2011; Jankovic, 2008). Alpha-synuclein targets the autonomic nervous system and the brainstem in PD, resulting in loss of dopaminergic neurons in the SNc and other brainstem nuclei. Protein deposition then spreads to limbic structures (e.g., the amygdala), the medial temporal lobe, and eventually the neocortex as the disease progresses (Braak, Ghebremedhin, Rüb, Bratzke, & Tredici, 2004). Levodopa, the precursor for dopamine (DA), has been successful in alleviating the motor symptoms of PD, however, levodopa's efficacy may decrease over time, with some patients requiring alternative forms of treatment such as DA agonists or deep brain stimulation (Gunzler, Schoenberg, Riley, Walter, & Maciuna, 2011).

1.2 Cognitive Impairment in PD

Much attention is often given to the motor symptoms of PD, however the wide range of non-motor symptoms that accompany the disease can be just as debilitating and are associated with reduced quality of life (Chaudhuri & Schapira, 2009). Cognitive

impairment occurs in 20-60% of patients with PD (Getz & Levin, 2017; Gunzler, Schoenberg, Riley, Walter, & Maciuna, 2011). The most frequently associated cognitive impairment in PD is executive dysfunction, including problems with organization, set-shifting, and inhibition (Kudlicka, Clare, & Hindle, 2011; Rodriquez-Oraz et al., 2009). Executive dysfunction is one of the earliest cognitive impairments seen in PD and is thought to be caused by reduced dopaminergic projections from the striatum to the frontal cortex (Getz & Levin, 2017; Jankovic, 2008; Kudlicka, Clare, & Hindle, 2011). Other cognitive impairments seen in PD include problems with attention, working memory, speed of processing, language, and visuospatial abilities (Adams, 2009; Getz & Levin, 2017; Gunzler, Schoenberg, Riley, Walter, & Maciuna, 2011; Hirano, Shinotoh, & Eidelberg, 2012).

In recent years, research has demonstrated a need to classify patients with PD who have cognitive impairments, but do not have the functional impairments required for a diagnosis of dementia. Approximately 25% of patients with PD have mild cognitive impairment (MCI) (Weintraub & Mamikonyan, 2019). Various criteria for PD-MCI have been proposed in the literature making it difficult to compare studies. Recently, the movement disorders society (MDS) commissioned a task-force to define suggested criteria to be used for PD-MCI (Litvan et al., 2012). PD-MCI is characterized by an insidious decline in cognitive abilities caused primarily by the underlying disease process. The cognitive decline may be reported by either the patient or an informant, or observed by the clinician. These subjective cognitive concerns must be accompanied by objective evidence of cognitive deficits on neuropsychological testing. Finally, the cognitive deficits in PD-MCI are not sufficient enough to interfere with functional

independence (Litvan et al., 2012). The MDS criteria includes guidelines for level 1 and level II diagnostic categories. The Level 1 category allows for PD-MCI to be diagnosed based on an abbreviated cognitive assessment (e.g., a scale measuring global cognition validated for use in PD or a limited battery of neuropsychological tests) as comprehensive testing may not always be practical or available; however this method provides less diagnostic certainty. When using a limited neuropsychological battery, Level I criteria requires impairment in at least two tests. Level II criteria requires comprehensive neuropsychological testing that includes at least two tests in the domains of attention/working memory, executive, language, memory, and visuospatial functions. Impairment must be present on at least two tests within a single domain or across different cognitive domains. Impairment may be defined as 1-2 standard deviations (SD) below normative data, a significant decline in serial testing, or a significant decline from estimated premorbid levels. Level II criteria also allow for subtype classifications (i.e., single or multiple domain) and require specification of the affected domains (i.e., memory, visuospatial) (Litvan et al., 2012). MCI has prognostic value in predicting conversion to dementia (Litvan et al., 2012; Williams-Gray et al., 2013), which occurs in approximately 80% of patients with PD (Aarsland, Brown, Larsen, & Ballard, 2005; Litvan et al., 2012; Weintraub & Mamikonyan, 2019).

1.3 Neuropsychiatric Disorders in PD

The most common psychiatric feature in PD is depression, with clinically significant depressive symptoms occurring in approximately 30% of patients with PD (Reijnders, Ehrt, Weber, Aarsland & Leentjens, 2008). Anxiety, apathy, and impulse control disorders are common as well (Aarsland, Marsh, & Schrag, 2009). The

pathophysiological bases of both cognitive and affective symptoms are complex and likely involve dopaminergic, serotonergic, and noradrenergic systems (Aarsland, Marsh, & Schrag, 2009; Halliday et al., 2014). Furthermore, these affective symptoms may impair cognition and adversely affect neuropsychological performance (Adams, 2009; Getz & Levin, 2017; Litvan et al., 2012). In addition, psychiatric symptoms can predate the motor symptoms of the disease by several years (Aarsland, Marsh, & Schrag, 2009). Finally, autonomic nervous system dysfunction is also prevalent in PD and can manifest as difficulty swallowing, constipation, orthostatic hypotension, urinary leakage, or sexual dysfunction (Gunzler, Schoenberg, Riley, Walter, & Maciuna, 2011; Jankovic, 2008).

1.4 The Basal Ganglia

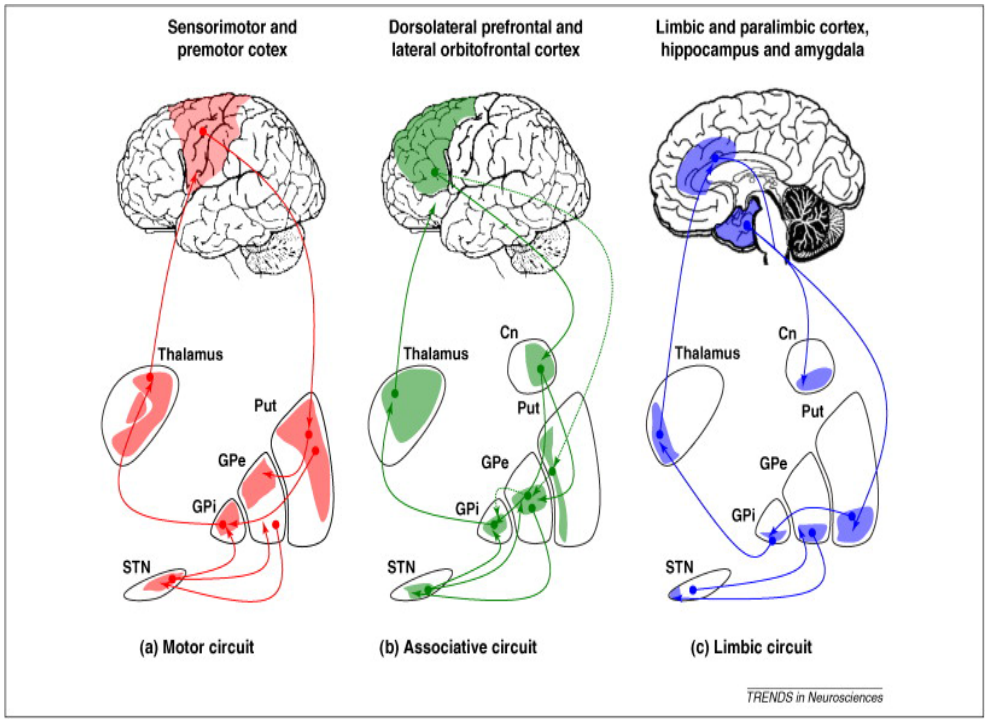
The neuropathology of PD is associated with dysfunction of the basal ganglia. The basal ganglia include the globus pallidi, caudate nuclei, putamina, substantia nigras, and the subthalamic nuclei (see Figure 1.1). The nuclei of the basal ganglia are known to initiate and control motor movement and are specifically important for the fine-tuning of motor movement. When these areas are damaged, motor dysfunction such as tremor, rigidity, and dyskinesias can emerge (Alexander, DeLong, & Strick, 1986; Gunzler et al., 2011; Halliday et al., 2014; Jankovic, 2008).

The basal ganglia are heavily connected to the frontal lobes and communication between the cortex and the basal ganglia is facilitated by multiple (closed) parallel cortico-striato-thalamo-cortical (CSTC) loops (see Figure 2). Each circuit originates in specific regions of the cerebral cortex (e.g., motor, oculomotor, dorsolateral, orbitofrontal, and anterior cingulate), traverse specific regions of the basal ganglia (e.g., striatum, pallidum, and substantia nigra) and thalamus, and project back to one of the

cortical areas, thereby completing the closed loop (Alexander, DeLong, & Strick, 1986). These loops are divided into two motor (i.e., motor and oculomotor) and three cognitive/behavioral (i.e., dorsolateral, orbitofrontal, and anterior cingulate) domains (Alexander, DeLong, & Strick, 1986; Obeso et al., 2014). Although each CSTC circuit constitutes a closed loop, open loop elements are incorporated into the connectivity as well, including afferent and efferent projections to and from other cortical areas (e.g., temporal and parietal lobes) and thalamic and amygdalar nuclei (Bonelli & Cummings, 2007).

Figure 1.1 Cortico-striato-thalamo-cortical loops.

Diagram of the motor, associative (cognitive) and limbic cortico-striatal circuits. The loops connect the cortex to the basal ganglia. Put = putamen; GPe = globus pallidus externa; GPi = globus pallidus interna; STN = subthalamic nucleus; Cn = Caudate nucleus. (Lapidus, Stern, Berlin, & Goodman, 2014).



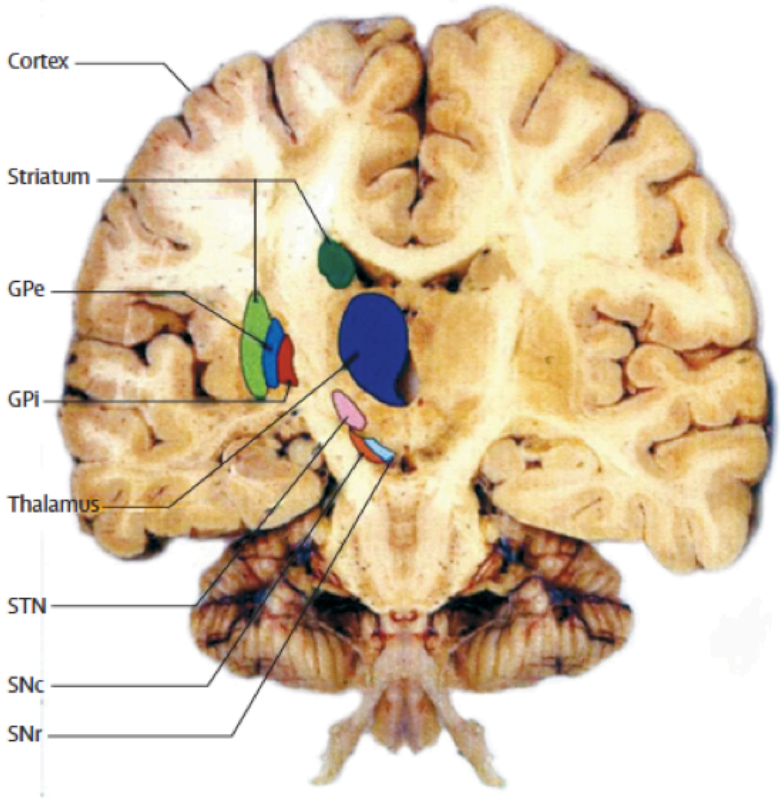
Each CSTC loop can be further divided into two pathways: the direct pathway which increases movement and the indirect pathway which inhibits movement. In the direct pathway, the motor cortex and substantia nigra pars compacta (SNc) excite the striatum via the D1 dopamine receptor. When the striatum is excited, it sends inhibitory signals (GABA) to the globus pallidus interna (GPi) and the substantia nigra pars reticulata (SNr). Once the GPi and SNr are inhibited, the thalamus is free to send excitatory signals (glutamate) to the motor cortex, thereby increasing movement. In the indirect pathway, the motor cortex excites the striatum while the SNc inhibits the striatum via the D2 dopamine receptor. This in turn inhibits the globus pallidus externa (GPe). Once the GPe is inhibited, there is less inhibition of the subthalamic nucleus (STN), which leads to excitation of the GPi. The GPi then sends inhibitory signals to the thalamus, leading to less excitation of the motor cortex and therefore less movement. The direct and indirect pathways create balance between competing excitatory and inhibitory impulses; imbalance between these pathways results in dysfunction (Gunzler, Schoenberg, Riley, Walter, & Maciuna, 2011). Recent research has demonstrated that several cortical areas (e.g., the motor area, premotor cortex, anterior cingulate cortex, dorsolateral prefrontal cortex, etc.) have excitatory projections directly to the STN, creating an additional route beyond the direct and indirect pathways. These pathways are collectively known as the hyperdirect pathway and serve as the quickest route for access to output pathways (Jahanshahi, Obeso, Rothwell, & Obeso, 2015)

1.5 Dopamine Depletion and Dysfunction of Frontostriatal Loops

Although the basal ganglia loops were originally studied within the motor system, we now know the important role that the basal ganglia play in regulating cognition. The

primary CSTC pathway of interest for this study is the pathway that connects the prefrontal cortex and the striatum. The dorsolateral prefrontal cortex (DLPFC) loop originates in the prefrontal cortex (Brodmann's areas 9,10, and 46) and projects to the dorsolateral head of the caudate nucleus (see Figure 1.2). The caudate then in turn projects the GPi/SNr via the direct pathway. The indirect pathway sends fibers to the GPe which projects to the STN and then terminates in the GPi/SNr. Output from the basal ganglia is then projected to the thalamus, which in turn projects back to the dorsolateral prefrontal cortex. Disruptions in the dopaminergic projections along this pathway (i.e., loss of dopaminergic neurons in the SNc which projects to the striatum) can lead to problems with EF (e.g., organization, mental flexibility, and problem solving) (Getz & Levin, 2017; Jankovic, 2008; Poletti & Bonucelli, 2013).

Figure 1.2. Coronal view of the brain showing the main basal ganglia nuclei and related structures.
Striatum = caudate nucleus and putamen; GPe = globus pallidus externa; GPi = globus pallidus interna; STN = subthalamic nucleus; SNc = substantia nigra pars compacta; SNr = substantia nigra reticulate (Obeso, Rodriguez-Oraz, Stamelou, Bhatia, & Burn, 2014)



Because of the spatiotemporal progression of the dopamine depletion, affecting the dorsal striatum first, tasks associated with this region (e.g. set shifting and planning) may improve with dopamine replacement therapy. In contrast, functions such as reversal and implicit learning which are associated with the ventral striatum (i.e., ventral caudate, putamen, and nucleus accumbens) may worsen due to "overdosing" these less dopamine depleted brain regions (Cools, 2006; Getz & Levin, 2017; Poletti & Bonucelli, 2013). Thus, the relationship between dopamine and performance follows an inverted U-shaped function, such that both too little and too much dopamine can impair performance depending on the type of task and the brain region recruited. Furthermore, different individuals may have different baseline levels of dopamine and may demonstrate differential sensitivity to the positive and negative effects of dopamine (Cools, 2006; Cools & D'Esposito, 2011). This individual variation may reflect an individual's position on the hypothetical inverted U-shaped curve (Cools, 2006).

Dopamine also plays a role in regulating affect. Dopaminergic disruptions in the anterior cingulate pathway can lead to problems with motivation and apathy (Leisman, Melillo, & Carrick, 2013). Apathy occurs in approximately 40% of patients with PD and can occur independently of depression, although overlap is common (Weintraub & Mamikonyan, 2019). Dysfunction of the orbitofrontal circuit and lower striatal dopamine transporter (DaT) levels can result in behavioral disinhibition in the form of impulse control disorders (ICDs). Impulse control disorders (ICDs) are common neuropsychiatric disorders in PD with a prevalence of 14-43% (Smith, Xie, & Weintraub, 2014). ICDs can develop following the initiation of dopamine replacement therapy (DRT), particularly with the use of D2- receptor selective dopamine agonists (Smith, Xie,

& Weintraub, 2014; Vriend et al., 2014; Voon et al., 2014). The primary ICDs in PD are compulsive gambling, eating, buying, and sexual behavior; these behaviors are performed repetitively, excessively, and compulsively and can interfere with daily functioning (Weintraub, David, Evans, Grant & Stacy, 2015). Therefore, the basal ganglia has influence on a broad range of behavior, contributing to the heterogeneous nature of symptom presentation in PD.

1.6 Dopamine Transporter Imaging

The diagnosis of PD formerly relied solely on the clinical exam; however, establishing the cause of PD can be challenging, especially in the early stages of the disease (Ravina et al., 2012). Pathological studies have documented that approximately 20-25% of clinically diagnosed cases of idiopathic PD are found to have alternative diseases at autopsy, with most misdiagnosed cases having Progressive Supranuclear Palsy (PSP), Multiple Systems Atrophy (MSA), Alzheimer's Disease (AD), or vascular parkinsonism (Adler et al., 2014; Hughes, Daniel, Kilford, & Lee, 1992). Early and accurate diagnoses in patients with PD and other parkinsonism syndromes is important to avoid unnecessary treatments associated with financial costs and side effects.

Dopaminergic dysfunction can be visualized using a molecular imaging technique called the DaTscan, which measures the amount of DaT available in the striatum. DaTs are presynaptic proteins located on the membrane of dopaminergic neuron terminals. During excitation, their function is to transport dopamine out of the synaptic cleft and back into the presynaptic nerve endings for either storage or degradation (Benamer et al., 2002; Djang et al., 2012). The DaTscan uses a dopamine transporter radioligand (i.e., 123-I-Ioflupane) along with single photon emission computed tomography (SPECT) to

visualize the distribution of dopamine within the striatum. 123-I-Ioflupane (DaTscan) is a cocaine analogue substance that is injected intravenously, with imaging enabled 3-6 hours after administration. 123-I-Ioflupane binds to the dopamine transporter and the reduction of which correlates with loss of dopamine (Cummings et al., 2011).

The DaTscan was approved by the European Medicine Agency in 2000 and by the Food and Drug Administration in the United States in 2011 for the clinical use of in vivo diagnostic imaging of suspected parkinsonian syndromes (Bajaj, Hauser, & Grachev, 2013). The DaTscan can be used in patients with clinically uncertain parkinsonism in order to help differentiate degenerative parkinsonian syndromes (e.g., PD, MSA, PSP, and Corticobasal Degeneration) from disorders that are not associated with a striatal dopaminergic deficit (e.g., essential tremor and drug induced, vascular, or psychogenic parkinsonism) (Bajaj, Hauser, & Grachev, 2013; Cummings et al., 2011; Djang et al., 2012).

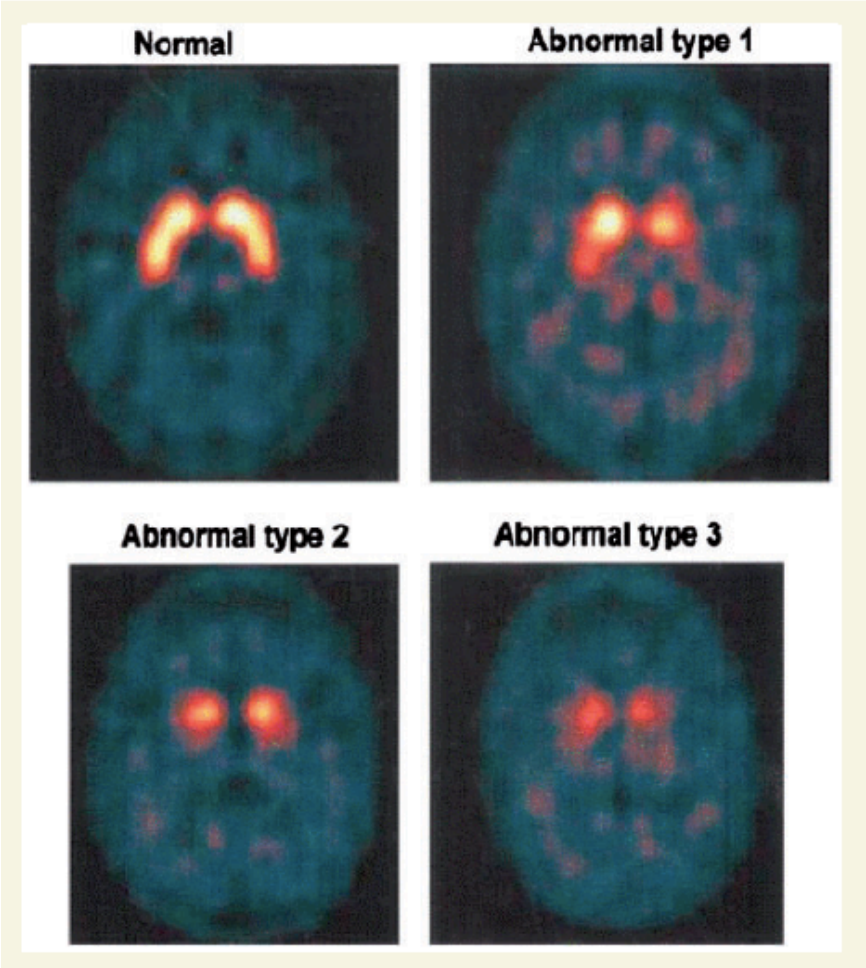
The DaTscan has demonstrated excellent sensitivity and specificity (Bajaj, Birchall, & Jones, 2012; Suwijn et al., 2015). A study of 743 DaTscan cases performed at the United Kingdom National Centre of Excellence for PD over a 9-year period found a sensitivity of 99.4% and specificity of 98.6% when compared to clinical diagnosis (Bajaj, Birchall, & Jones, 2012). A recent systematic review of eight DaT SPECT studies using several different radiotracers found that the sensitivity and specificity of DaT SPECT to detect nigrostriatal cell loss was 98% (Suwijn et al., 2015). Certain medications (e.g., anticholinergics, bupropion, radafaxine, and mazindol) and drugs of abuse (e.g., amphetamines, and modafinil) are contraindicated with the scan as they bind to the DaT with high affinity, potentially interfering with the DaTscan. Antiparkinsonian

drugs including levodopa, dopamine agonists, monoamine oxidase-B inhibitors, and catchol-O-methyl transferase inhibitors do not interfere with the DaTscan and do not need to be withdrawn prior to scanning (Booij & Kemp, 2008).

1.6.1 Visual Interpretation and Quantitative Analysis

DaTscan results can be classified as normal or abnormal through visual interpretation of the striatum, specifically by looking at the shape and symmetry of the striata and degree of reduction (Park, 2012). A normal DaTscan (such as those typically seen in patients with essential tremor) looks like two symmetric crescent-shaped areas of radioligand uptake in the striatum in both hemispheres. An abnormal DaTscan shows asymmetric or bilateral symmetric decrease in the size or color intensity of the radioligand in the striatum (Park, 2012; Waln et al., 2015) (see Figure 1.3). The side with relatively lower uptake generally matches contralaterally to the clinically more affected side (Djang et al., 2012; Park, 2012). Several studies have yielded excellent results with visual interpretation only (Benamer et al 2000; Catafau & Tolosa 2004; Tissingh et al., 1998, Marshall et al 2009). Imaging results can also be analyzed using semiquantification methods, during which binding ratios are calculated by comparing activity in the striatum with activity in an area of low DaT concentration, usually the occipital lobe (Park 2012; Djang et al 2012). Semiquantification can be done manually or by using automated software (Djang et al., 2012)

Figure 1.3. Normal and abnormal DaTscans. (Cummings et al., 2011)



1.7 Review of Prior Dopamine Neuroimaging Studies

Dopamine transporter availability in the brain can be investigated using different radioligands (e.g., 123-I-FP-CIT, 18F-FP-CIT, 99mTc-TRODAT, etc.) with SPECT or positron emission tomography (PET) imaging. SPECT scans are much more available and widely used compared to PET scans, however SPECT scans have lower image resolution (Cummings et al., 2011; Djang et al., 2012). Studies investigating the relationship between DaT availability and cognition have most prominently been characterized by significant associations between dopamine and EF (Chung et al., 2018; Cropley, Fujita, Innis & Nathan, 2008; Duchesne, Soucy, Masson, Chouinard & Bedard, 2002; Muller, Wachter, Barthel, Reuter, & von Cramon, 2000; Nobili et al., 2009; Pellechia et al., 2015; Pollito et al., 2012; Rinne et al., 2000; Siepel et al., 2014). A study by Duchesne and colleagues found reduced DaT binding in the left striatum was associated with deficits in a simultaneous processing task in 10 patients with PD; however, this relationship disappeared when patients were tested on their dopaminergic medication (Duchesne, Soucy, Masson, Chouinard & Bedard, 2002). A similar observation was found in a study of 20 PD patients in which DaT availability in both the caudate and putamen were significantly associated with set-shifting, cognitive flexibility, and working memory (Muller, Wachter, Barthel, Reuter, & von Cramon, 2000). However, all of the associations disappeared after patients in the early stages of the disease (i.e., Hoehn and Yahr stage < 2) were excluded, suggesting that disease severity could have affected their results (Muller, Wachter, Barthel, Reuter, & von Cramon, 2000). Another study investigated striatal dopamine in 26 patients with PD using fluorodopa (i.e., FDOPA) PET scans. FDOPA is another measure of presynaptic

dopamine commonly used with PET scans, however, it is also sensitive to noradrenergic and serotonergic neurons, thus it does not solely reflect the activity of dopamine (Cropley et al., 2008; Rinne et al., 2000). This study found that reduced FDOPA uptake in the caudate correlated with impaired working memory, attention, and verbal fluency; however, this study also consisted of six patients with dementia, which likely confounded the results (Rinne et al., 2000).

Pollito and colleagues (2012) examined both DaT binding and brain glucose metabolism using 18F-fluorodeoxyglucose (FDG) PET in 18 drug-naïve patients with PD. The researchers found that impaired letter fluency was significantly associated with reduced DaT in the caudate nucleus; furthermore, lower brain glucose metabolism in the DLPFC, orbitofrontal cortex, and the anterior cingulate cortex was associated with worse performance on letter fluency. Nobili and colleagues (2010) compared 30 *de novo* PD patients and 15 patients with essential tremor (ET) and found that DaT availability in the caudate was positively associated with EF. Conversely, there were no significant correlations between DaT and cognition in the ET control group (Nobili et al., 2010). One study found an association between FDOPA in the putamen and the number of categories achieved on the WCST (Cropley, Fujita, Innis & Nathan, 2008). In contrast to the above studies, other studies have failed to find significant associations between DaT availability in the striatum and EF (Jokinen et al., 2010; Kubler, Schroll, Buchert &Kuhn, 2017).

A few studies have compared DaT imaging in PD patients with versus without MCI. A study comparing 19 patients with PD and 15 with PD-MCI found lower caudate and putamen DaT availability was associated with lower scores on the Frontal

Assessment Battery (FAB), lower DaT in the caudate was related to lower scores on Trailmaking B minus Trailmaking A (i.e., Trails B minus A), and lower DaT availability in the caudate and putamen were associated with lower scores on the Rey-Osterrieth Copy Figure test (ROCF) in patients with PD-MCI (Pellechia et al., 2015). There were no significant correlations found between neuropsychological scores and DaT imaging in PD patients without MCI (Pellechia et al., 2015). Chung et al. (2018) found DaT availability in the caudate nucleus was positively associated with attention/working memory, EF, and visuospatial function in a large sample of drug naïve PD patients with and without MCI. Additional associations were found between attention/working memory, EF, language and visuospatial function and DaT binding in the ventral striatum. Finally, a recent, large (N =339), multicenter study using patients from the Parkinson's Progression Markers Initiative (PPMI) found small but significant associations between DaT availability and verbal memory and attention/executive functioning; however, after adjusting for age none of the relationships were significant. Additionally, DaT binding mediated the EF deficit in PD, and age moderated this effect such that the mediation effect was stronger for younger patients than in older. The authors suggested that this finding indicated that cognition in the older adults of their sample was likely influenced by other neurotransmitters or structural changes (Siepel et al., 2014).

There is less data examining the extent that DaT availability contributes to cognitive domains outside of EF. A study by Jokinen et al. (2010) found that caudate FDOPA uptake correlated with verbal and visual memory performance in 19 patients with PD. This study also found that the PD patients had more atrophy in the hippocampus and prefrontal cortex compared to controls through volumetric

neuroimaging analysis, which may have partially explained their memory findings. Muller and colleagues (2000) also found significant associations between DaT availability in the striatum and verbal memory. A few studies have also found significant associations between DaT availability in the striatum and performance on the Rey-Osterrieth Copy Figure test (Chung et al, 2018, Pellechia et al., 2015), however the motor component of this measure may have confounded these results.

In sum, the literature thus far has found significant relationships between the striatal DaT availabilty and EF, although some studies have not (Jokinen et al., 2010; Kubler, Schroll, Buchert & Kuhn, 2017). Fewer studies have found relationships between DaT availability and verbal (Jokinen et al., 2010; Muller et al., 2000) and visual memory (Jokinen et al., 2010) as well as visuospatial functioning (Chung et al, 2018, Pellechia et al., 2015). Some studies found cognition correlated with DaT availability solely in the caudate (Pollito et al., 2012; Nobili et al., 2010, Pellechia et al., 2015; Rinne et al., 2000), while DaT availability in both the caudate and putamen correlated with cognition in other studies (Chung et al., 2018; Duchesne, Soucy, Masson, Chouinard & Bedard, 2002; Muller et al., 2000; Siepel et al 2014).

1.7.1 Limitations of Prior Studies

There are several methodological issues that should be considered when interpreting the results of prior studies. First, most of the previous studies included small and heterogeneous samples, including patients at different stages of the disease and patients both on and off dopaminergic medication. Furthermore, the neurocognitive batteries utilized in the majority of these studies have been fairly limited and could potentially underestimate the relationship between DaT and cognition, particularly in

domains outside of EF. Although dopamine systems are mainly involved in prefrontal executive functions, other cognitive domains have to be investigated from this perspective. Additionally, various EF measures assess different aspects of the executive functioning process, and thus may be differentially relatedly to dopaminergic activity. Utilization of a broader neurocognitive battery, including additional EF tests, is warranted to fully test these relationships. Finally, differences in the spatial and temporal resolution of PET vs. SPECT scanners, the use of different radioligands, and variability in the striatal subregions analyzed likely also contribute to the inconsistencies across studies.

1.8 Purpose of the Present Study

As described above, studies have looked at the relationship between DaT striatal availability and cognition, however sample sizes have been small and heterogeneous along with fairly limited neurocognitive batteries. The present study utilized a comprehensive neuropsychological battery assessing multiple domains (e.g., verbal and visual memory, language, EF, processing speed, and visuospatial). Furthermore, given the known role of dopaminergic dysfunction on EF abilities, more tests measuring EF were included in the present study compared to prior studies. The present study retrospectively examined the relationship between striatal DaT availability using SPECT and cognitive data within a consecutive series of PD patients. Using these data, we can understand the relationship more specifically between measurable dopamine availability in the brain and changes in reasoning, memory, decision-making, and affect. Some of these relationships will teach us about the direct effects of Parkinson-induced changes in brain structure and function that can be used for other critical areas, such as new

treatment targeting. Based on the previous literature the following hypotheses were tested:

1. Study Aim 1: Investigate the pattern of cognitive impairment in patients with PD compared to age and education matched controls.
    a. Hypothesis 1: Given, the role of striatal dopaminergic deficits in cognition, we predicted that the PD group would demonstrate worse scores on measures of attention, executive functioning, learning, and memory when compared to age and education matched controls.
        i. Power analysis: Based on a power analysis, a sample size of 21 PD patients and 21 controls provided an achieved power of 0.72 to detect a large effect ($d = 0.8$).
2. Study Aim 2: Examine the relationship between cognition and striatal DaT availability in patients with PD at different striatal regions of interest (e.g., left and right striatum, left and right caudate nucleus, and left and right putamen)
    a. Hypothesis 2: We expected DaT availability in the striatum to correlate with measures of executive functioning, learning, and memory. Furthermore, we expected moderate to strong positive correlations between executive functioning measures and DaT availability in the caudate nucleus, specifically.

i. Power analysis: Based on a power analysis, the sample size of 21 PD patients provided an achieved power of 0.71 to detect a large effect (r = .50).

METHOD

2.1 Participants

The present study was a retrospective chart review. The data was obtained from a movement disorders clinical database at the Norton Neuroscience Institute Nuclear Medicine Department in Louisville, Kentucky. All subjects in the PD group received a diagnosis of idiopathic PD by a movement disorders neurologist. The patients without dopaminergic deficit on DaTscan were chosen for the comparison group in order to highlight the differences in cognition directly resulting from differences in DaT availability in the basal ganglia. Twelve of the control participants had a diagnosis of ET, a non-neurodegenerative disorder typically associated with a normal DaTscan. Exclusion criteria for both groups included dementia, history of major stroke(s), structural lesions, chronic use of antipsychotics or neuroleptics, and major psychiatric disorders. We did not exclude for depression or anxiety in the PD group because PD patients commonly report such symptoms.

2.2 Procedure

2.2.1 DaTscan

All subjects received an intravenous injection of 3-5 millicurie (mCi) of 123-I-Ioflupane after oral administration of a thyroid-blocking agent (Lugols Solution) one hour prior to the scan. Patients were instructed to stop taking drugs that may alter the

tracer binding (e.g., amphetamines, methylphenidate, ephedrine, phentermine, bupropion, fentanyl, and some anesthetics) for at least 5 half lives. SPECT imaging was conducted 3-6 hours post-injection of the radiotracer. Imaging lasted approximately 30-40 minutes. A gamma camera fitted with high-resolution collimators and set to a photo peak of 159 keV with a $\pm$ 10% energy window was utilized for SPECT imaging. Images were acquired using a 128 x 128 image matrix (pixel size between 3.5 and 4.5 millimeters) and reconstructed using a Butterworth filter. Images were corrected for attenuation using Chang's algorithm. Expert readers in the nuclear medicine department at Norton Neuroscience Institute performed visual interpretation of the DaTscan. Scans were read clinically as either showing evidence of DaT deficit (i.e.. abnormal) or not showing evidence of dopamine transporter deficit (i.e., normal).

Basal ganglia regions of interest (ROIs) were generated using the MIM Neuroimaging software. This software uses an anatomic atlas (i.e., MIM DaTscan atlas) that was created by defining volumes of interest on 10 high resolution T1 weighted MRI scans. Each of the MRI scans were then registered to a template space using their co-registered SPECT scans. Manual realignments were made when necessary to adjust the generated ROI to the boundaries of the respective DaTscan. Anatomic interrater reliability across two raters was excellent ICC = 0.98, 95% CI [0.96-0.99]. Mean DaT counts for each striatal subregion in both hemispheres were generated by the MIM Neuro software and used for analyses.

2.2.2 Neuropsychological Assessment

Raw test scores were standardized into z-scores based on demographically published norms. To reduce the number of analyses, individual test z-scores were then

averaged into z-score composites determined a priori. The composite groupings were based on the cognitive domains discussed within the clinical neuropsychological literature (Lezak, Howieson, Bigler, & Tranel, 2012). Due to the large number of EF tests which tapped different aspects of EF, the EF composite was split into subdomains rather than utilizing a unitary EF composite. Executive functions are separable and different executive functions contribute differently to various complex executive tasks (Lezak, Howieson, Bigler, & Tranel, 2012). EF measures were subject to a factor analysis by principal components using an orthogonal (Varimax) rotation. Factor analysis confirmed a 5-factor structure accounting for 93.25% of the total variance in EF. The first factor (problem solving/set-shifting) accounted for 25.84% of the variance. The second factor (inhibition) accounted for 21.30% of the variance. Verbal fluency accounted for 17.18% of the variance. The final two factors, mental flexibility and abstract reasoning, accounted for 15.85 and 13.08% of the variance, respectively.

The verbal memory domain consisted of the Hopkins Verbal Learning Test-Revised (Trials 1-3 and delayed recall) and the immediate and delayed recall scores from the Neuropsychological Assessment Battery (NAB) List Learning test. Visual memory was assessed using the NAB Shape Learning test (immediate and delayed recall). Language measures included the Boston Naming Test (BNT) and NAB Naming. Visuospatial functioning was assessed using the Benton Judgment of Line Orientation (JLO) test. Processing speed was measured using Oral Trails A. EF was divided into 5 subdomains: mental flexibility (Oral Trails B), inhibition (Delis-Kaplan Executive Functioning System Color Word Interference Test (D-KEFS) Conditions 3 and 4), verbal fluency (Controlled Oral Word Association Test (COWAT) and Animals), abstract

reasoning (Wechsler Adult Intelligence Test- Fourth Edition (WAIS-IV) Similarities subtest), and problem solving/set-shifting (Wisconsin Card Sorting Test (WCST) total errors and perseverative errors). Affective measures included the Apathy Evaluation Scale (AES) and the Barratt Impulsiveness Scale (BIS).

2.3 Measures

2.3.1 Descriptive Measures

2.3.1.1 Demographic and Clinical Measures

Demographic information was extracted from each patient's medical record (e.g., age, education, estimated premorbid IQ, gender, and ethnicity). Additionally, clinical measures of disease duration, levodopa equivalent daily dosage (LEDD), non-dopaminergic medications, and modified Hoehn and Yahr (HY) stage were also collected for each individual. The modified HY scale is a measure of disease severity in PD and ranges from 1-5, with higher stages correlating with neuroimaging studies of dopaminergic loss (Goetz et al., 2004).

2.3.2 Neuropsychological Measures

2.3.2.1 Hopkins Verbal Learning Test-Revised

The HVLT-R (HVLT-R; Brandt & Benedict, 2001) is a task of verbal learning and memory. The task consists of a 12-item word list presented 3 times in the same order, with a test of recall after each trial. The measure also includes a test of delayed recall and recognition. The test has shown evidence of convergent validity with other measures of verbal memory, such as the CVLT-II. The measure is sensitive to cognitive deficits associated with a variety of neurological conditions (e.g., dementia, traumatic brain

injury, mood disorders, and substance abuse). (Lezak, Howeison, Bigler, & Tranel, 2012; Strauss, Shermann & Spreen, 2006).

2.3.2.2 NAB List Learning

The NAB List Learning **(**Stern & White, 2003) subtest assesses verbal learning and memory. The measure consists of a 12-item word list presented across three trials, followed by an interference list, short and long delayed free recall, and forced-choice recognition (Strauss, Shermann & Spreen, 2006). NAB List Learning recall scores have demonstrated moderate validity levels with the CVLT-II recall (i.e., r = .43 for immediate recall and r = .59 for short delay recall) (Lezak, Howeison, Bigler, & Tranel, 2012).

2.3.2.3 NAB Shape Learning

The NAB Shape Learning **(**Stern & White, 2003) subtest is a measure of visual learning and memory. The task consists of three learning trials of nine target nonsense shapes. Each learning trial is followed by a multiple choice recognition test in which each correct target is paired with three foils. The subtest also consists of a delayed recall and forced-choice recognition trial (Lezak, Howeison, Bigler, & Tranel, 2012; Strauss, Shermann & Spreen, 2006). This task does not require a motor response, thus it is an ideal assessment of visual memory in populations who may have compromised motor abilities.

2.3.2.4 Boston Naming Test

The BNT (Kaplan, Goldglass & Weintraub, 1978) is a measure of visual confrontation naming ability. The test consists of 60 line drawings of objects with increasing range of difficulty. Semantic and phonemic cues are provided if necessary and are useful in differentiating between problems with storage of information vs. problems with retrieval (Lezak, Howeison, Bigler, & Tranel, 2012; Strauss, Shermann & Spreen, 2006). This measure elicits naming impairments in a variety of neurological conditions. (Strauss, Shermann & Spreen, 2006).

2.3.2.5 NAB Naming

The NAB *(*Stern & White, 2003) naming subtest requires the examinee to name pictured items. Semantic and phonemic cues are provided if necessary. (Strauss, Shermann & Spreen, 2006). Forms 1 and 2 of NAB Naming are moderately correlated (r = .45 and r = .50, respectively) with the BNT (Yochim, Kane, & Mueller, 2009).

2.3.2.6 Benton Judgment of Line Orientation

The JLO (Benton, Hannay, & Varney, 1975) measures the ability to estimate angular relationships between line segments and is a measure of spatial perception and orientation (Lezak, Howeison, Bigler, & Tranel, 2012; Strauss, Shermann & Spreen, 2006). This test consists of 30 pairs of angled lines to be matched to display cards. JLO impairment has been reported in a variety of conditions known to affect visuospatial ability including left-visual neglect, Parkinson's Disease, and dementia. This measure has high internal consistency (.90) and demonstrated validity. In addition, this measure does not require

motor skills and demands little to no verbal mediation. (Strauss, Shermann & Spreen, 2006).

2.3.2.7 Oral Trailmaking A and B

Oral TMT (Ricker & Axelrod, 1994) is an alternative version of the Trailmaking Test A & B and is often used with populations with motor deficits or visual impairment. The test is divided into two parts, A and B. In part A, the examinee is asked to count from 1 to 25 as quickly as possible. Part B asks the examinee to alternate between numbers and letters aloud up to 13. Scores are obtained for time and errors. The correlations between the oral and written versions are moderately strong (r= -.68 for part A; r =-.72 for part B) (Ricker & Axelrod, 1994).

2.3.2.8 D-KEFS System Color-Word Interference Test

The D-KEFS (Delis, Kaplan, & Kramer, 2001) Color-Word Interference Test is a variant of the Stroop procedure and measures inhibition of a prepotent response and mental flexibility (Strauss, Shermann & Spreen, 2006). The present study utilized Conditions 3 and 4. Condition 3 requires the examinee to name the color of the ink in which the words are printed. Condition 4 requires the examinee to switch back and forth between naming the dissonant ink colors and reading conflicting words (Strauss, Shermann & Spreen, 2006). Internal consistency for Conditions 3 and 4 are adequate. Several studies have documented that performance on the D-KEFS is affected by frontal lobe lesions and subcortical disease (Lezak, Howeison, Bigler, & Tranel, 2012).

2.3.2.9 Controlled Oral Word Association Test

The COWAT (Reitan & Wolfson, 1985) is a test of phonemic fluency and is part of the Expanded Halstead-Reitan Neuropsychological Battery. The COWAT requires the examinee to say as many words as the individual can think of that begin with a specified letter in one minute. The present study used the standard version with the letters F, A, and S. Reduced capacity to generate words on the COWAT is a sensitive indicator or brain dysfunction (Lezak, Howeison, Bigler, & Tranel, 2012). FAS has demonstrated high test-retest reliability and correlates highly with other letter sets (e.g., CFL and PRW) (Strauss, Shermann & Spreen, 2006).

2.3.2.10 Animals

The "Animals" (Reitan & Wolfson, 1985) category is the most common category used to test semantic fluency. The test requires the examinee to orally produce as many animals as possible within one minute. "Animals" is sensitive to impaired verbal fluency in PD (Henry & Crawford, 2004). There is evidence that semantic fluency tests are more useful than other neuropsychological tests in the detection of dementia and discrepancies between phonemic and category fluency may be useful in distinguishing cortical and subcortical dementias (Lezak, Howeison, Bigler, & Tranel, 2012).

2.3.2.11 Wechsler Adult Intelligence Scale-Fourth Edition Similarities Subtest

(WAIS-IV Similarities) Similarities is a test of verbal concept formation and requires the examinee to state how two concepts are alike. Relatively depressed Similarities scores

tend to be associated with left temporal and frontal involvement. (Lezak, Howeison, Bigler, & Tranel, 2012).

2.3.2.12 Wisconsin Card Sorting Test

The WCST (Berg, 1948; Grant & Berg, 1948) measures the ability to form abstract concepts, to shift and maintain set, and to utilize feedback. The WCST is one of the most commonly used measures to assess executive functions and provides information regarding problem-solving behavior. The test consists of two decks of 64 response cards, which have designs similar to four stimulus cards. The participant is asked to match each of the response cards to one of the four stimulus cards and is given feedback on whether he or she is right or wrong each time. Several component scores provide information regarding the examinee's strategy and problem-solving behavior while completing the test (e.g., the number of categories achieved, total errors, perseverative errors, and perseverative responses). Perseverative errors occur either when the examinee continues to sort to a previously successful principle or when the participant continues to sort on the basis of an initial error. The perseverative error score may be useful in documenting problems in forming concepts, benefitting from correction, and conceptual flexibility. A correct response may also be counted as a perseverative response if it matches a previously correct category (Strauss, Shermann & Spreen, 2006).

2.3.2.13 Barratt Impulsiveness Scale

The BIS (Barratt, 1959) is a 30-item self report measure of impulsivity. The responses load on three 2nd order factors (i.e., Attentional, Motor, and Nonplanning Impulsiveness).

Attentional impulsiveness is defined as an inability to focus attention or concentrate, motor impulsiveness involves acting without thinking, and non-planning impulsiveness refers to a lack of forethought (Stanford et al., 2009).

2.3.2.14 Apathy Evaluation Scale

The AES (Marin, Biedrzycki,& Firinciogullari, 1991) is a measure of apathy and assesses the behavioral, cognitive, and emotional components associated with goal-directed behavior. A score greater than or equal to 14 indicates the presence of apathy. There are three versions (e.g., self, informant, and clinical). The present study used the self-report version of the AES (Marin, Biedrzycki,& Firinciogullari, 1991).

2.4 Data Analysis

Alpha was set at $p < .05$ for all inferential tests. Chi-square tests were used to determine demographic equivalence between the groups. The Mann-Whitney U test was used in the case of non-normally distributed variables. Independent samples *t*-tests were used to examine mean-level differences in striatal DaT availability between the PD and control group. The association between neurocognitive measures and DaT availability for each ROI was calculated using the Pearson's product-moment correlation coefficient matrix. Pearson's correlations were also used to test the association between mean DaT availability and affect. Partial correlations were utilized when appropriate.

3 RESULTS

3.1 Outliers and Normality

Descriptive statistics revealed that most continuous variables were normally distributed. Examination of skewness and kurtosis statistics, scatterplots, and boxplots revealed no problematic outliers or significant skewness or kurtosis for most variables. However, there were two neurocognitive variables that exhibited some skewness and kurtosis (Oral Trails A and Oral Trails B). To correct for this, three outliers for the Oral Trails A variable and two outliers for the Oral Trails B variable were identified using the criteria of > 3 SD from the mean and were not included in the analyses. Additionally, the distribution of HY stages was negatively skewed (Skewness statistic = -1.216, *SE* = .501), thus non-parametric analyses were utilized for this variable.

3.2 Demographic Characteristics

As previously noted, participants were identified from archival clinical database at Norton Neuroscience Institute. There were 73 available cases with both a DaTscan and neuropsychological testing data, including 34 patients with an abnormal DaTscan and 43 controls with a normal DaTscan. Of the 34 participants with an abnormal DaTscan, patients were excluded for the following reasons: dementia (*n* = 11), incomplete neuropsychological test data (*n* =1) and poor effort on neuropsychological testing (*n* =1). Of the 43 participants with a normal DaTscan and neuropsychological test data, 22 participants were excluded for the following reasons: dementia (*n* = 8), neurologic disorder (*n* = 4), major psychiatric disorder (n = 6), structural lesion (*n* =1), chronic antipsychotic use (*n* =2), and incomplete neuropsychological test data (*n* =1). This

resulted in a final sample size of 42 participants, including 21 participants with PD and 21 age and education matched controls.

Demographic characteristics and clinical information of the sample are presented in Table 3.1. PD and control participants did not differ significantly on age, education, race, and gender variables. The overall sample was 90.5% Caucasian and 57.1% percent male. Additionally, 90.5% of the sample was right handed. The PD group had a mean age of onset of 61.45 years (*SD* = 11.83) and mean disease duration of 4.80 years (*SD* = 5.08). HY stage of the PD group ranged from 1-2.5, with a mean of 1.95 (*SD* =0.44). Three PD patients were at HY stage 1 of the disease, 14 were at stage 2, and four at stage 2.5. Fifteen of the 21 PD patients were taking dopaminergic medication at the time of the DaTscan and 19 at the time of the neuropsychological evaluation. The mean LEDD at the time of the DaTscan (*M* = 978.71; *SD* = 646.606) was statistically significantly higher than the mean LEDD during the neuropsychological evaluation (*M*= 432.38; *SD* = 408.374) (*t* = 6.94. *p* = .000).

Table 3.1. Descriptive Statistics by Group

		PD	*C*		
		n = 21	*n = 21*	*t or* X^2	*p*
Age DaTscan	M (SD)	66.67 (11.16)	68.43 (8.85)	-0.57	0.58
Age NP	M (SD)	67.14 (10.49)	68.29 (8.67)	-0.39	0.70
Education	M (SD)	13.71 (2.37)	14.48 (3.09)	-0.90	0.38
Gender	% Male	62.0%	52.0%	0.39	0.53
Race	% Caucasian	91%	91%	1.33	0.51
Age Sx Onset	M (SD)	61.45 (11.83)			
Disease Duration	M (SD)	4.80 (5.08)			
Hoehn and Yahr	M (SD)	1.95 (0.44)			
LEDD DaTscan	M (SD)	432.38 (408.374)			
LEDD NP	M (SD)	978.71 (646.06)			

Note: *PD*, Parkinson's Disease patient group; *C,* Controls; *M,* Mean; *SD* , Standard Deviation**;** NP, Neuropsychology; Sx, Symptom; LEDD, Levodopa Equivalency Daily Dosage

3.3 Group Differences in DaT Imaging

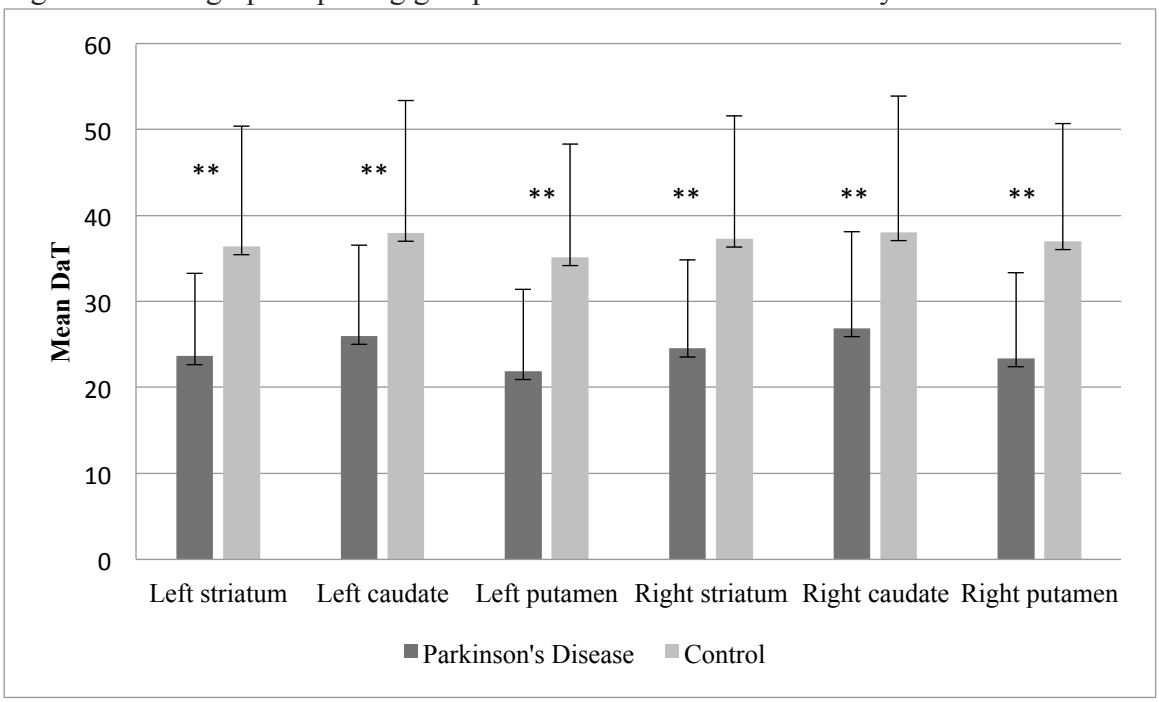
Table 3.2 presents mean group differences for DaT availability in each striatal ROI by group. The left striatum value is a composite of the left caudate nucleus putamen, and the right striatum is a composite of the right caudate nucleus and putamen. Significant group differences at $p < 0.01$ level were found in each of the striatal ROIs analyzed: left striatum (t= -3.45, p = 0.001), left caudate (t= -2.96, p = 0.005), left putamen (t = -3.75, p = 0.001), right striatum (t = -3.33, p = 0.001), right caudate (t = -2.64, p = 0.012), and right putamen (t = -3.69, p = 0.001). In all instances the PD group had significantly lower mean counts of DaT availability in each striatal ROI. Additionally, Table 3.2 shows that group differences in mean counts of DaT at each ROI demonstrated large effect sizes (d= 0.81-1.14). A graphical depiction of the mean group differences on DaT availability are presented in Figure 3.1. Paired sample t tests were used to examine laterality differences in mean DaT availability within each group. There were no significant differences between DaT availability in the left and right striatum (t =-1.96, p = .06), left and right caudate (t =-1.55, p = 0.14), or left and right putamen (t =-2.21, p = 0.04) in the PD group. In the control group the left putamen had significantly lower mean DaT availability than right putamen (t =-3.26, p = 0.004), despite being clinically read as normal. There were no significant differences between left and right striatum (t = -1.74, p = 0.10) and left and right caudate (t = -.013, p =0.99).

Table 3.2. Group differences in DaT availability

		PD *n = 21*	*C* *n = 21*	*p*	*d*
Left striatum	M (SD)	23.65 (9.62)	36.41 (13.99)	0.001	1.06**
Left caudate	M (SD)	26.01 (10.55)	38 (15.37)	0.005	0.91**
Left putamen	M (SD)	21.89 (9.50)	35.15 (13.19)	0.001	1.15**
Right striatum	M (SD)	24.54 (10.32)	37.33(14.28)	0.001	1.03**
Right caudate	M (SD)	26.89 (11.26)	38.08 (15.83)	0.012	0.81**
Right putamen	M (SD)	23.41 (9.96)	37.01 (13.68)	0.001	1.14**

Note: *PD,* Parkinson's Disease; *C,* Control; *M,* Mean; SD, Standard Deviation
** $p < .01$

Figure 3.1. Bar graph depicting group differences on DaT availability



Note: DaT, Dopamine Transporter

3.4 Group Differences on Cognitive Composites

Hypothesis 1 aimed to examine group differences on neurocognitive measures between the PD group and controls. There were no statistically significant group differences on any of the cognitive composites (Table 3.3). Both PD and control participants mean z-scores were within the normal range, not exceeding 1.5 SD. The mean scores of only two domains across both groups (i.e., verbal memory and processing speed) were greater than 1 SD; however as stated previously, group performances were statistically comparable on these domains. Therefore, Hypothesis 1 was not supported in that the PD group did not perform statistically worse on measures of executive functioning, learning, and memory compared to controls.

Table 3.3 Group differences on cognitive composites

		PD *n = 21*	*C* *n = 21*	*p*	*d*
	M	0.39	0.13	0.34	0.31
Language (z-score)					
	(SD)	(0.70)	(1.01)		
Verbal Memory (z-score)	M	-1.25	-1.02	0.51	0.21
	(SD)	(1.15)	(1.04)		
Visual Memory (z-score)	M	-0.12	-0.32	0.47	0.22
	(SD)	(1.01)	(1.13)		
Visuospatial (z-score)	M	0.01	-0.01	0.96	0.02
	(SD)	(1.13)	(1.11)		
Processing Speed (z-score)	M	-1.10	-1.37	0.41	0.36
	(SD)	(0.67)	(1.00)		
Mental Flexibility (z-score)	M	0.10	-0.54	0.66	0.16
	(SD)	(0.77)	(1.04)		
Inhibition (z-score)	M	-0.42	-0.87	0.35	0.34
	(SD)	(1.30)	(1.36)		
Verbal Fluency (z-score)	M	-0.69	-0.76	0.86	0.06
	(SD)	(1.18)	(0.98)		
Abstract Reasoning (z-score)	M	-0.54	-0.51	0.99	0.004
	(SD)	(0.74)	(0.64)		
Problem Solving/Set-Shifting (z-score)	M	-0.52	-0.68	0.67	0.17
	(SD)	(0.95)	(0.88)		

Note: *M,* Mean; SD, Standard Deviation; PD, Parkinson's Disease; C, Controls; EF, Executive Functioning

3.5 DaT and Cognitive Composites: PD Group

Hypothesis 2 predicted that DaT availability in the striatum would be significantly related to performance on measures of executive functioning, learning, and memory. It was further predicted that the association between DaT and executive functioning would be strongest in the caudate nucleus. Table 3.4 provides Pearson's correlations between mean DaT availability and cognitive composites for the PD group only. Regarding executive functioning, there was a strong positive relationship (r =. 55, p = .03), between DaT availability in the left caudate and the problem solving/set-shifting composite, such that increased DaT availability was associated with better problem solving/set-shifting abilities (see Figure 3.2). Strong relationships (r = .52-.61) were found between DaT availability and verbal memory in all striatal ROIs (e.g. left striatum, left caudate, left putamen, right striatum, right caudate, and right putamen), such that increased DaT availability was associated with stronger verbal memory performance for PD patients. The strongest association was between DaT availability in the right caudate and verbal memory and is presented in Figure 3.3. Finally, there were modest to strong positive correlations (r = .49-.56) between DaT availability in all ROIs and visuospatial functioning, such that higher DaT availability was significantly related to better performance on the JLO.

Table 3.4 Pearson's correlations between DaT availability and cognitive composites in PD

	LS	LC	LP	RS	RC	RP
Verbal Memory	.548*	.543*	.518*	.594**	.611**	.578**
Visual Memory	.234	.283	.176	.248	.250	.243
Language	.167	.091	.221	.122	.145	.108
Visuospatial	.551*	.511*	.541*	.521*	.562*	.492*
Processing Speed	-.135	-.019	-.222	-.160	-.059	-.214
Mental Flexibility	-.157	-.057	-.226	-.173	-.127	-.196
Inhibition	.336	.358	.289	.344	.404	.306
Verbal Fluency	.011	.156	-.113	-.036	.067	-.091
Abstract Reasoning	.248	.260	.220	.186	.209	.170
Problem Solving/Set Shifting	.490	.549*	.390	.512	.510	.506

Note: LS=Left Striatum; LC= Left Caudate; LP= Left Putamen; RS=Right Striatum; RC= Right Caudate; RP= Right Putamen

* $p < .05$, ** $p < .01$

Figure 3.2. Scatterplot showing the correlation between problem solving/set-shifting and DaT availability in the left caudate region of interest

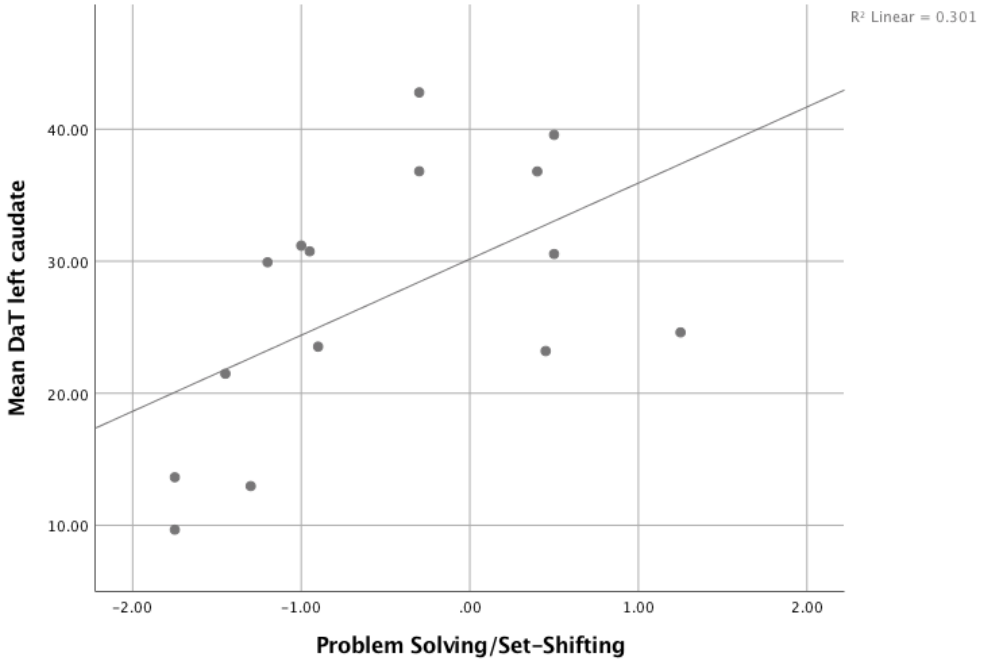
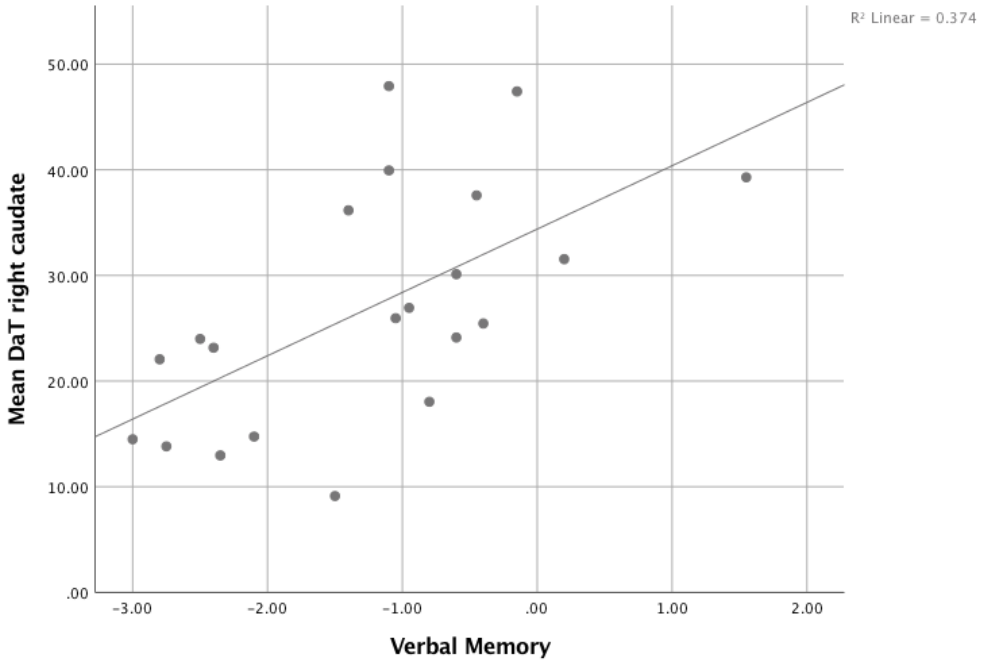


Figure 3.3 Scatterplot showing the correlation between verbal memory and DaT availability in the right caudate region of interest



Correlations between potential confounding variables (e.g. depression, LEDD, disease duration, and HY stage) were examined to determine whether there was a need to control for these variables. HY stage was significantly positively associated with DaT availability in all ROIs (r_s= .45-.55) . Given the significant relationships between HY stage and DaT availability, partial correlations were utilized to examine the relationship of DaT and cognition while controlling for Hoehn and Yahr stage. Table 3.5 provides the partial correlations for relationships between DaT availability and verbal learning/memory, problem solving/set shifting, and visuospatial domains when controlling for HY stage within the PD group only. Partial correlations between DaT availability and verbal memory and DaT availability and visuospatial skills were generally in the medium to large range (Table 3.5). The correlation between DaT availability and problem solving/set shifting was no longer significant after controlling for HY stage. There was no need to statistically control for other suspected confounding variables (e.g. depression, LEDD, and disease duration) due to the lack of significant relationships.

Table 3.5 Partial correlations between DaT availability and cognitive composites in PD controlling for Hoehn and Yahr stage

	LS	LC	LP	RS	RC	RP
Verbal Memory	.479*	.373	.461*	.528*	.534*	.454*
Visuospatial	.518*	.512*	.471*	.529*	.565*	.422
Problem Solving/Set Shifting	.470	.467	.521	.493	.527	.493

Note: LS=Left Striatum; LC= Left Caudate; LP= Left Putamen; RS=Right Striatum; RC= Right Caudate; RP= Right Putamen

* $p < .05$, ** $p < .01$

Hypothesis 2 was partially supported such that increased DaT availability was significantly associated with better performance on measures of verbal memory and problem solving/set shifting as predicted. The positive association between DaT availability and problem solving/set shifting was significant within the caudate nucleus specifically, consistent with our hypothesis. Additionally, the significant associations between DaT availability and both verbal memory and visuospatial functioning were strongest in the caudate nucleus. Contrary to our hypothesis, there were not any significant relationships between DaT availability and visual memory or other aspects of EF (e.g., mental flexibility, inhibition/switching, verbal fluency, and abstract reasoning) within the PD group.

3.6 DaT and Cognitive Composites: Control Group

Similar to the PD group, large positive relationships (r = .54-.59) were found between the verbal memory composite and several ROIs (e.g. left striatum, left caudate, left putamen, and right striatum) (Table 3.6). Additionally, DaT availability in the control group was significantly related to some aspects of EF. Strong positive relationships (r= .68-.72) were found between DaT availability in all striatal ROIs and the inhibition composite, such that higher levels of DaT availability were associated with better ability to inhibit a prepotent response. Increased DaT in the left caudate and right putamen were significantly associated with better problem solving/set shifting (r = .61 and .60, respectively). In sum, in age and education matched controls there were strong positive correlations found between DaT availability and verbal memory and subdomains of EF.

Table 3.6 Pearson's correlations between DaT availability and cognitive composites in Controls

	LS	LC	LP	RS	RC	RP
Verbal Memory	.573**	.543*	.589**	.585**	.580	-.329
Visual	.185	.232	.133	.131	.194	.096
Language	.366	.414	.295	.386	.448	.346
Visuospatial	.256	.250	.258	.272	.226	.295
Processing	.401	.407	.391	.426	.422	.425
Mental	.396	.371	.412	.390	.340	.415
Inhibition	.702**	.681*	.711**	.708**	.687**	.715**
Verbal	.325	.314	.332	.324	.343	.318
Abstract Reasoning	.285	.249	.313	.279	.218	.312
Problem Solving/Set Shifting	.590	.606*	.568	.602	.593	.604*

Note: LS=Left Striatum; LC= Left Caudate; LP= Left Putamen; RS=Right Striatum; RC= Right Caudate; RP= Right Putamen

* $p < .05$, ** $p < .01$

3.7 Exploratory analyses: Correlations between DaT and Affect

Additional exploratory analyses were conducted to examine the relationship between DaT availability and symptoms of apathy and impulsivity. Table 3.7 presents group differences on the AES and BIS. There were no statistically significant group differences on self-reported symptoms of apathy and impulsivity between the PD group and controls. Table 3.8 presents Pearson's correlations between DaT availability and affective measures. In the PD group, there was a strong negative correlation (r =-.62, p = .01) between DaT in the left putamen and motor impulsiveness on the BIS, such that decreased DaT was associated with greater motor impulsiveness (see Figure 3.4). Further, a strong negative correlation was found between mean DaT availability in the left striatum (r = -.56, p = .03) and motor impulsiveness (see Figure 3.5). Given the significant relationships between and HY stage and DaT, partial correlations were utilized to examine the relationship between DaT and motor impulsiveness while controlling for HY stage. When controlling for HY stage, partial correlations remained significant for relationships between DaT and both the left putamen (r = -.56, p = .04) and left striatum (r = -.54, p = .04). There were no significant associations between DaT availability and symptoms of affect within the PD group. Finally, neither apathy nor impulsivity was significantly associated with DaT availability in the control group.

Table 3.7 Group differences on affective measures

		PD *n* = *14*	*C* *n* = *11*	*p*	*d*
AES	M	11.27	15.00	0.21	0.51
	(SD)	(6.92)	(7.79)		
BIS Total (z-score)	M	-0.31	-0.01	0.51	0.27
	(SD)	(1.27)	(0.97)		
BIS Att Imp (z-score)	M	-0.36	-0.81	0.52	0.43
	(SD)	(1.17)	(0.90)		
BIS Motor Imp (z-score)	M	-0.24	-0.69	0.26	0.46
	(SD)	(1.11)	(0.81)		
BIS Nonp Imp (z-score)	M	-0.12	0.45	0.23	0.28
	(SD)	(1.18)	(1.18)		

Note: *M,* Mean; SD, Standard Deviation; *PD*, Parkinson's Disease; *C,* Controls; AES, Apathy Evaluation Scale; BIS Total, Barratt Impulsiveness Total Score; BIS Att Imp

Table 3.8 Pearson's correlations between DaT uptake and affective measures in PD

	LS	LC	LP	RS	RC	RP
AES	-.036	.019	-.099	-.052	-.075	-.037
BIS Total	-.267	-.309	-.424	-.305	-.339	-.282
BIS Att Imp	-.101	-.159	-.221	-.151	-.216	-.113
BIS Motor Imp	-.555	-.483	-.622*	-.480	-.483	-.473
BIS Non Planning Imp	-.262	-.209	-.319	-.218	-.232	-.208

Note: LS=Left Striatum; LC= Left Caudate; LP= Left Putamen; RS=Right Striatum; RC= Right Caudate; RP= Right Putamen; AES, Apathy Evaluation Scale; BIS Total, Barratt Impulsiveness Total Score; BIS Att Imp

* $p < .05$, ** $p < .01$

Figure 3.4 Scatterplot showing the correlation between motor impulsiveness and DaTscan availability in the left putamen region of interest

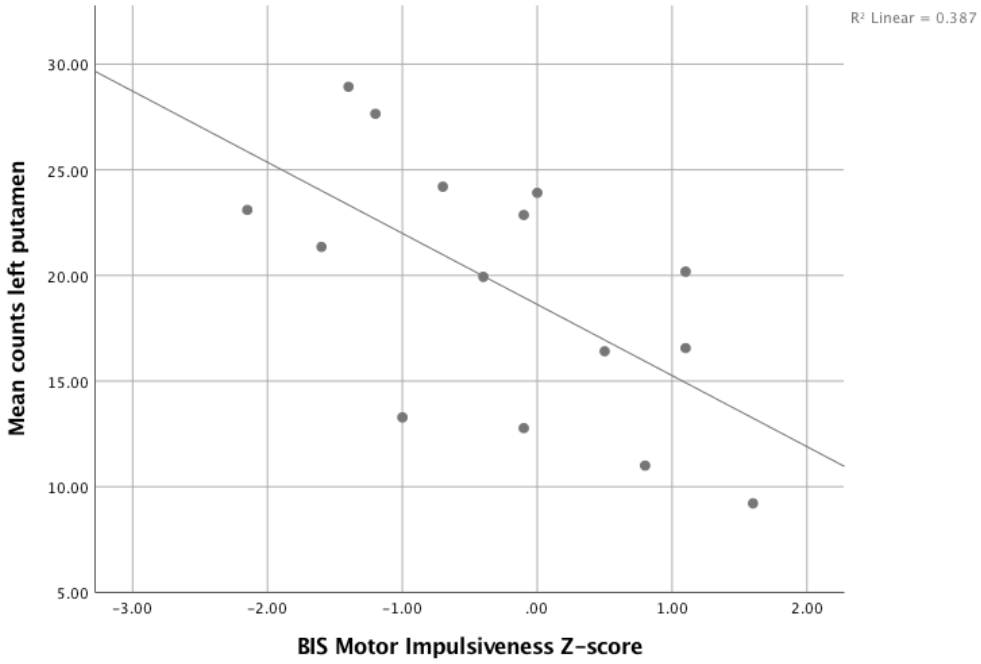
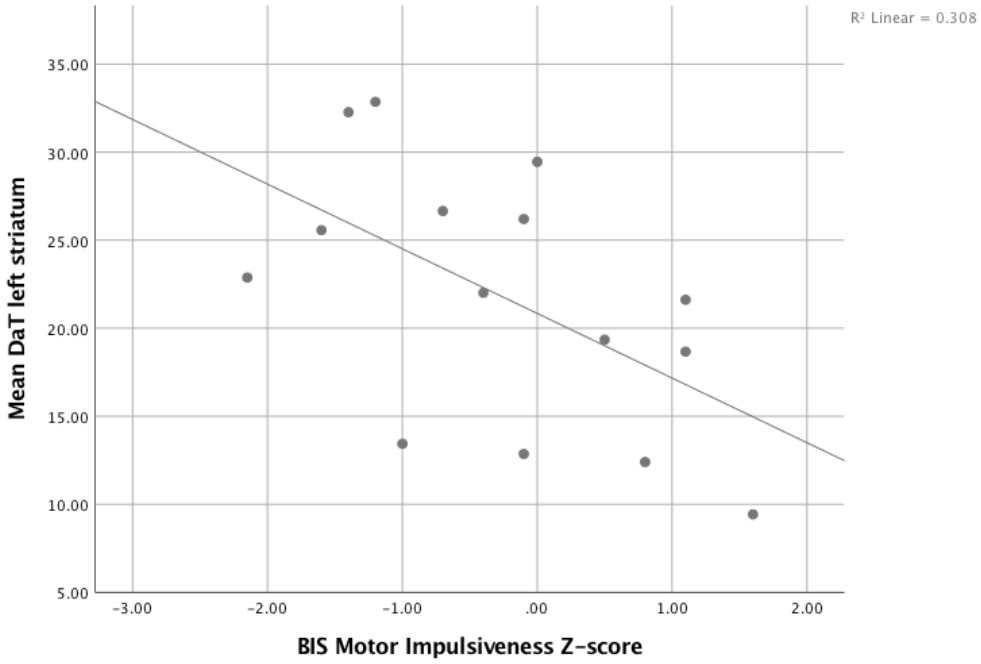


Figure 3.5. Scatterplot showing the correlation between motor impulsiveness and DaTscan availability in the left striatum region of interest



DISCUSSION

4.1 Overview of the Findings

Although PD is defined classically by motor symptoms, non-motor deficits (e.g., cognitive, affective, and autonomic abnormalities) form an important part of the disease. Greater understanding about the neuropathology underlying the cognitive and emotional sequelae of PD is of the utmost importance in order to potentially enhance treatment planning. The current study aimed to elucidate the relationship between striatal dopamine and cognitive functioning in patients with PD using neuroimaging, neuropsychological, and psychological methods. Additional exploratory analyses examined the relationship between dopamine and affect (i.e., apathy and impulsivity). An innovative aspect of this project was the exploration of these relationships using a comprehensive neuropsychological battery that covered multiple cognitive domains, as well as assessing the regional effects of DaT availability on cognition in PD.

4.2 Cognition in PD versus Controls

Although the PD group did demonstrate significant reductions of DaT in all striatal ROIs compared to controls, this did not translate into reduced neurocognitive deficits in the PD group as predicted. Contrary to our hypothesis, the PD group did not demonstrate statistically worse performance on cognitive tasks that are associated with frontostriatal dysfunction (e.g., attention, learning, and EF). This is inconsistent with prior studies that have found deficits on these tasks secondary to loss of dopamine in the striatum, which has direct connections to the frontal cortex (Kehagia, Barker, & Robbins, 2010; Kudlicka, Clare, & Hindle, 2011; Williams-Gray et al., 2013). One possible explanation for this finding is that the majority of the PD patients in our sample were on

dopaminergic medication. Administration of dopaminergic medication may replete dopamine deficient circuits, thus in the early stages of the disease, may have a beneficial effect on cognitive functions associated with the cortico-striato-thalamo-cortical loop (e.g., EF) (Cools, 2006; Cools & D'Esposito, 2011; Poletti & Bonnucelli, 2013). Therefore, it is presumed that the normalizing effects of dopaminergic medications may have contributed to the overall lack of cognitive impairment findings within the PD sample. Additional studies assessing PD patients off of their medication or drug naive patients are warranted. Furthermore, the PD patients were in the early stages of the disease (i.e., disease duration *M*= 4.8 years), which could have contributed to the lack of neuropsychological deficits found in this sample. Our findings of no statistical differences in cognition between PD and controls did converge with one study (Cropley et al., 2008), however this study only utilized two neuropsychological measures to assess cognition in their groups. Additionally, a recent study of PD patients without dementia (*n* =143) found that significant caudate nucleus dopaminergic denervation was frequent in those with minimal to no cognitive changes (51.1%) (Bohnen et al., 2015), therefore illustrating that biochemical and structural change does not always result in cognitive deficits or clinical symptoms.

4.3 Relationships between Dopamine and Cognition: PD

The present study demonstrated that DaT imaging correlates with certain measures of cognitive functioning within a sample of PD patients. A strong positive association was found between DaT availability in the left caudate and problem solving/set-shifting. This finding is in agreement with other studies that have demonstrated significant associations between DaT availability in the caudate and set-

shifting (Monchi et al., 2001; Rogers et al., 2000), as well as various other aspects of EF in patients with PD (Chung et al., 2018; Muller, 2000; Nobili, 2010; Pollito, 2012; Pellechia et al., 2015; Rinne, 2000; Siepel et al., 2014). Set-shifting is defined as the ability to change our attention from one response set to another according to the changing goals of a task (Provost, Hanganu, & Monchi, 2015). Secondly, there were significant strong relationships between DaT in all striatal areas and verbal memory, such that greater DaT availability was associated with better verbal memory. This result is consistent with findings from other studies that have found a significant relationship between DaT availability in the caudate nucleus and verbal memory (Siepel et al., 2014) and significant associations between FDOPA uptake in the caudate and both verbal and visual memory (Jokinen et al., 2010). Memory deficits in PD patients without dementia often stem from inefficient learning and organization due to frontostriatal dysfunction (Adams, 2009; Getz & Levin, 2017). Patients with PD have also demonstrated difficulty with free recall on memory tasks, but benefit from cues, suggesting that the memory problems in PD are sometimes related to impaired executive functioning required for memory retrieval (Getz & Levin, 2017). Thus, the memory findings in our sample may be representing a dysexecutive process rather than a pure memory deficit, however due to the use of a composite scores we could not examine retention scores explicitly.

Finally, our study found that DaT availability in the striatum was significantly positively related to visuospatial functioning. This finding is consistent with a recent study by Chung and colleagues (2018) who found that DaT availability in the caudate was positively associated with visuospatial functioning in a large sample of PD patients without dementia (n = 311). A similar finding was found in a sample of PD patients

with MCI, in which reduced DaT availability in the caudate and putamen were associated with lower scores on a visuospatial construction task (Pellechia et al., 2015). Of note, both studies used the Rey Complex Figure Copy to assess visuospatial functioning; thus, the motor component involved in the task could have confounded their results. In contrast, another large multicenter study consisting of patients from the PPMI, a cohort of *de novo* PD patients, failed to find significant relationships between DaT binding and the JOLO (Siepel et al., 2014). As observed with memory deficits, visuospatial deficits in early PD may reflect executive deficits related to frontostriatal dysfunction, rather than a pure visuospatial difficulty (Adams, 2009; Getz & Levin, 2017). Pure visuospatial deficits may represent more posterior cortical dysfunction and can predict dementia (Getz & Levin, 2017; Kehagia, Barker, & Robbins, 2010; Williams-Gray et al., 2013).

4.4 Relationships between Dopamine and Cognition: Controls

Similar relationships were found between DaT availability and cognition in age and education matched controls. Specifically, there were significant positive relationships between DaT availability in the striatum and performance on measures of verbal memory, inhibition, and problem solving/set-shifting. There are several potential explanations for the amount of significant correlations in the control group. First, 12 subjects in the control group had a diagnosis of ET. ET is a non-neurodegenerative disorder and is the most common cause of tremor. ET results in an action or postural tremor as opposed to the resting tremor associated with parkinsonism (Gunzler, Schoenberg, Riley, Walter,& Maciuna; 2011). Although ET is typically associated with a normal DaTscan, some studies have reported mild striatal dopaminergic deficit in patients with ET compared to healthy controls, particularly in the caudate nucleus (Isais et al.,

2010; Gerasimou et al., 2012; Waln et al., 2015). Furthermore, some studies have reported neuropsychological deficits in patients with ET, particularly in the domains of attention, working memory, and EF (Gasparini et al., 2001; Lombardi et al., 2001; Troster et al., 2002), which can occur as a result of the cerebello-thalamo-cortical circuit dysfunction that occurs with ET (Troster et al., 2002).

Additionally, there are other confounding variables that are inevitable when assessing cognition within an older adult sample. The presence of cognitive impairment increases with age, with EF abilities being among the first to decline (Aine et al., 2014; Zelazo, Craik, & Booth, 2004). Furthermore, age-related changes in dopamine have also been reported, albeit at a slower rate than patients with PD (Kassinen & Rinne, 2002; Volkow et al., 1998) Specifically, the availability of D1-like (i.e., D1 and D5) dopamine receptors in the striatum decrease at a rate ~7% per decade and D2-like (i.e., D2 ,D3, and D4) receptors decrease between 5-10 % per decade in striatal availability (Kassinen & Rinne, 2002). Of note, the DaTscans of all control participants in this study were interpreted as having normal striatal uptake.

White matter hyperintensities (WMH) are a common finding in the brains of older individuals, and are associated with vascular risk factors (e.g. hypertension, diabetes mellitus, and cerebral amyloid angiopathy). These vascular risk factors have been independently associated with cognitive decline of a frontal-subcortical nature initially, affecting executive functioning and processing speed in particular (Adams, 2009; Aine et al., 2014). Thus, the increased incidence of vascular risk factors that come with old age may cause otherwise "normal" controls to look neuropsychologically similar to other subcortical illnesses, such as PD. Due to limited sample sizes, we did not exclude

patients with vascular risk factors, with the exception of major strokes and structural lesions. As such, over half (n =14) of the participants in the control group had evidence of cardiovascular disease according to medical record review (i.e., hypertension, hyperlipidemia, and diabetes mellitus type 2), which may have confounded the results. By including a control group consisting of patients with ET and older adults we are aware of the suboptimal "healthy" control group. However, there are ethical considerations when studying radioactive compounds in healthy subjects; as such, control participants in neuroimaging studies are often bound by certain constraints.

Finally, low and/or abnormal neuropsychological test scores are common in normative samples, with the frequency increasing with the more tests included in the battery. Additional explanations for subtest scatter within a normative sample may also include measurement error, longstanding weaknesses in certain domains of cognitive functioning, and other situational factors (e.g., fluctuations in attention, motivation, or effort, and fatigue) (Binder, Iverson, & Brooks, 2009)

4.5 Relationships between DaT and Affect

The present study found strong inverse associations between DaT availability in the left striatum and putamen and motor impulsiveness, such that lower DaT levels were associated with greater motor impulsiveness. Impulsivity is a heterogeneous construct and can be broadly divided into decisional (e.g., reduced sensitivity to adverse outcomes during learning and risk taking) and motor forms (e.g., impaired inhibition of a prepotent response) (Voon et al., 2017). DaT imaging studies have consistently reported reduced striatal DaT availability in patients with PD with ICD symptoms compared to those without ICD symptoms (Smith, Xie, & Weintraub, 2016;Voon et al., 2010; Vriend et al.,

2014). Small preliminary studies that have found associations between reduced striatal DaT availability and increased ICD symptoms in both prevalent (Voon et al., 2014) and incident (Vriend et al., 2014) ICD samples. A large study using data from the PPMI database followed patients longitudinally to investigate neurobiological risk factors for ICD symptoms. The sample included patients both on and off DRT. In patients on DRT, a greater decrease in right caudate and mean striatal DaT over the first year was significantly associated with an increased risk of incident ICD symptoms. In addition, lower right putamen DaT availability at a given post-baseline visit was associated with incident ICD symptoms at that visit in the DRT subgroup (Smith, Xie, & Weintraub, 2016).

This relationship between reduced DaT availability and ICD symptoms is not entirely clear and several hypotheses have been suggested. One hypothesis is a more pronounced dopaminergic denervation in patients with PD with ICD symptoms. The DaT is the primary mechanism by which dopamine is removed from the synapse to terminate its action. The low DaT concentrations in patients with PD with ICD symptoms could result in increased synaptic accumulation and therefore longer duration of action for dopamine (Vriend et al., 2014). Additionally, having a genetic risk factor for lower DaT availability or premorbid personality traits predisposing an individual to ICD symptoms have also been proposed as possible explanations (Voon et al., 2017; Vriend et al., 2014).

Executive functioning deficits have also been associated with ICD symptoms, including impulsive decision making and impaired set-shifting (Voon et al., 2010). Dopaminergic medications can have influence cognitive processes by enhancing learning

from positive feedback, but impairing learning from negative feedback thereby increasing impulsive behaviors. ICD behaviors in PD tend to be under recognized, in part due to the fact that screening is not common and patients may not report symptoms associated with ICDs secondary to embarrassment or lack of awareness. DaT imaging may be a useful tool in identifying predictive factors that may guide treatment decisions regarding DRT use. Future studies should also examine the differential role of dopamine agonists versus other DRT, as well as the relationship between DaT availability in the four major ICDs independently (e.g., compulsive gambling, eating, buying, and sexual behavior).

4.6 Limitations

While the study provided an important contribution to the literature on the role of striatal dopamine on cognitive and emotional functioning in patients with PD, limitations must be acknowledged. First, the patient and control samples were both small and varied, as is typical for SPECT imaging studies due to the use of radioactive compounds. The study was also limited by low power which may have reduced the possibility of finding significant correlations between biological and cognitive variables. Conversely, the significant findings in small samples also raise the possibility of overestimation; therefore, the *p*-values in this small sample should be interpreted with caution. A related methodological concern is Type 1 error (i.e., rejecting the null hypothesis when the null is true, a false positive) due to multiple comparisons. The current study did not involve a correction (e.g. Bonferroni) for Type I error due to the exploratory nature of the analyses. Further, given the limited sample size, the caution in relying on *p*-values in small samples, and the risk of neglecting Type 2 error, preservation of power was a priority.

Additionally, the present study utilized a cross-sectional design, thus significant correlations suggest an association between variables but do not imply causation.

Most PD patients in this sample were on dopaminergic medication at the time of their neuropsychological evaluation, which could have influenced the cognitive results by potentially ameliorating deficits. Furthermore it is important to consider our findings in the context of the broader scope of neuropathological mechanisms that contribute to cognitive dysfunction in PD, beyond those of the striatal dopaminergic system. Cortical and striatal beta-amyloid deposition, alpha-synuclein, genetic variation in the microtubule-associated tau (MAPT) H1 haploptype, and the involvement of other neurotransmitter systems (e.g., noradrenergic, cholinergic, serotonergic) have demonstrated a role in the cognitive deficits seen in PD, particularly in the later stages of the disease (Cools, 2006; Halliday, Leverenz, Schneider & Adler, 2016; Kehagia, Barker, & Robbins, 2010; Shah et al., 2016). For the purpose of this study, the neurochemical focus was restricted to imaging the nigrostriatal dopamine system, thus our study could not account for these other factors known to contribute to cognitive functioning in PD, which we acknowledge as a limitation. Future studies should examine the potential interactions of these multiple pathological mechanisms in large samples to fully capture the variety of neural underpinnings associated with cognitive functioning in PD. Additional longitudinal studies that follow patients from the early un-medicated stages to dementia are also warranted.

4.7 Conclusions

In sum, if cross-validated, the results of the present study suggest that striatal dopamine is associated with performance in executive, verbal memory, and visuospatial

functions in patients with PD. However, the literature suggests that the correlates of these deficits to DaT availability likely depend on the neuropsychological tasks utilized and the severity of the disease in the sample (e.g., early vs. advanced disease). As the disease progresses and with advancing age, the risk of other biological systems and co-occurring pathology (e.g., senile plaques and neurofibrillary tangles, microvascular disease, and cerebral amyloid angiopathy) increases. Clinically, it is important for health care professionals to be aware and consider the multiple neurobiological bases of cognitive impairment in PD. In particular, investigations of how deficits early in the disease relate to later developments (e.g., dementia) will continue to be increasingly important in order to inform disease-modifying therapies.

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VITA

BRITTANY DANIELLE WALLS, M.S.

2016	**M.S., Clinical Psychology** University of Kentucky, Lexington, KY *Thesis Title:* Utility of the CAARS Validity Scales in Identifying Feigned ADHD, Random Responding, and Genuine ADHD in a College Sample *Chair/Advisor:* David T.R. Berry, Ph.D Defended: July 2016
2012	**B.S., Psychology (Minor in Cultural Anthropology)** Duke University Durham, NC

HONORS AND AWARDS

2018-2019	Cressman Parkinson's Center Research Fellow, Norton Neuroscience Institute
2018	Pre-doctoral Research Award, University of Kentucky
2017	International Society of Neurogastronomy Travel Award, University of Kentucky
2014, 2017, 2019	Graduate Student Travel Award, University of Kentucky
2014, 2017, 2019	Department of Psychology Student Travel Award, University of Kentucky
2014-present	Southern Regional Educational Board (SREB) Doctoral Scholar
2014-2017	Lyman T. Johnson Fellow, University of Kentucky
2014-2015	Psychology Graduate Student Fellowship, University of Kentucky

LEADERSHIP POSITIONS

2015-2018	Association of Neuropsychology Students in Training: Interest Group Representative
2015-2018	Bluegrass Area Neuropsychology Group: Student President

PEER-REVIEWED JOURNAL ARTICLES

Wallace, E.R., Garcia-Willingham, N.E., **Walls, B.D.**, Bosch, C.M., Balthrop, K.C., & Berry, D.T.R. (in press). Attention-Deficit/Hyperactivity Disorder Malingering Detection in College Students: A Meta-Analysis of Performance and Symptom Validity Tests. *Psychological Assessment.*

Koehl, L.M., **Walls, B.D**., Brothers, S.L. Morris, S.N., Glueck, A.C., Schmitt, F.A., Berry, D.T.R., & Han, D.Y. (2018). Convergent and discriminant validity of the Immediate Post-Concussion Assessment and Cognitive Testing Battery (ImPACT) in young athletes. *Applied Neuropsychology: Child.*

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Berry, D.T.R., **Walls, B.D.**, Bouquet, C.M. & Wallace, E. (2016). Malingered neurocognitive deficits in Mild Traumatic Brain Injury. In. D.Y Han (Ed.) *Acquired brain injury: clinical essentials for neurotrauma and rehabilitation professionals*. New York: Springer Publishing Company.

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MANUSCRIPTS UNDER REVISION

Dunham, K.J., **Walls, B.D**., Anderson-Mooney A.J., Schmitt, F.A. (under revision). Predicting WAIS-IV Full Scale IQ in a General Neurological Clinic Referral Sample. *Neuropsychological Rehabilitation.*

Wallace, E.R., Balthrop, K.C., Brothers, S.L., Borger, T.N., Garcia-Willingham, N.E., **Walls, B.D.**, & Berry, D.T.R. Conners' Adult ADHD Rating Scale Infrequency Index validation and pilot comparison of administration formats. *Journal of Psychoeducational Assessment.*