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## Dopaminergic Medication Decreases Motor Impulsivity on the Go/No-go Task in Parkinson's Disease

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Graduate Program in Psychology  
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## Abstract

Parkinson's disease (PD) is characterized by resting tremor, rigidity, and bradykinesia. Dopaminergic medications treat motor symptoms, but have complex effects on cognition, including impulse control. Impulsivity is multifaceted in nature. Motor impulsivity involves inability to withhold prepotent, automatic responses whereas cognitive impulsivity refers to increased risk-taking and reward-seeking. We anticipated that dopaminergic therapy would decrease motor impulsivity. We employed the Go/No-go paradigm to assess motor impulsivity. PD patients were tested on and off their dopaminergic medication. PD patients on medication had a significantly higher proportion of Go Timeouts (i.e., Go responses not completed by the 750 millisecond deadline) compared to off medication ( $p=0.01$ ). We interpret that dopaminergic therapy induces more conservative responding (i.e., decreased motor impulsivity) in PD patients. This contrasts with the widely-recognized notion of dopaminergic therapy increasing cognitive impulsivity and risk of impulse control disorders. Understanding the nuanced effects of dopaminergic treatment in PD will inform clinical decisions.

## Keywords

Parkinson's disease, Dopaminergic therapy, Go/No-go task, motor impulsivity, striatum

## Co-Authorship Statement

Data collection was completed with the assistance of Brian Lauzon. Wannipat Buated, Mikayla Lynds, and Emma MacDonald also assisted with data entry. Ken Seergobin and Dr. Penny MacDonald provided assistance with data processing and analysis. I prepared the referenced manuscript with editing by Dr. Penny MacDonald and input from Brian Lauzon.

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## List of Abbreviations

ANART	-	American National Adult Reading Test
ANOVA	-	Analysis of variance
BAI	-	Beck Anxiety Inventory
BART	-	Balloon Analogue Risk Task
BDI	-	Beck Depression Inventory
BIS	-	Barratt Impulsiveness Scale
BP	-	Blood pressure
COWAT	-	Controlled Oral Word Association Test
DAT	-	Dopamine transporter
DS	-	Dorsal striatum
HR	-	Heart rate
ICD	-	Impulse control disorder
L-dopa	-	L-3,4-dihydroxyphenylalanine
LED	-	Levodopa Equivalent Dose
MoCA	-	Montreal Cognitive Assessment
MRI	-	Magnetic resonance imaging
MSN	-	Medium spiny neuron
NAcc	-	Nucleus accumbens
NFOG	-	New Freezing of Gait Questionnaire

PD	-	Parkinson's disease
QUIP-RS	-	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease – Rating Scale
RT	-	Reaction time
SAS	-	Starkstein Apathy Scale
SN	-	Substantia nigra
SNC	-	Substantia nigra pars compacta
SSD	-	Stop Signal Delay
SSRT	-	Stop Signal Reaction Time
SSS	-	Sensation Seeking Scale
UPDRS	-	Unified PD Rating Scale - Motor Subscale
VAS	-	Bond-Lader Visual Analogue Scale
VS	-	Ventral striatum
VTA	-	Ventral tegmental area

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## Chapter 1 : Introduction

A version of subsections 1.4.2 and 1.5 of this chapter has been published (Yang, Lauzon, Seergobin, & MacDonald, 2018).

### 1.1 Parkinson's disease

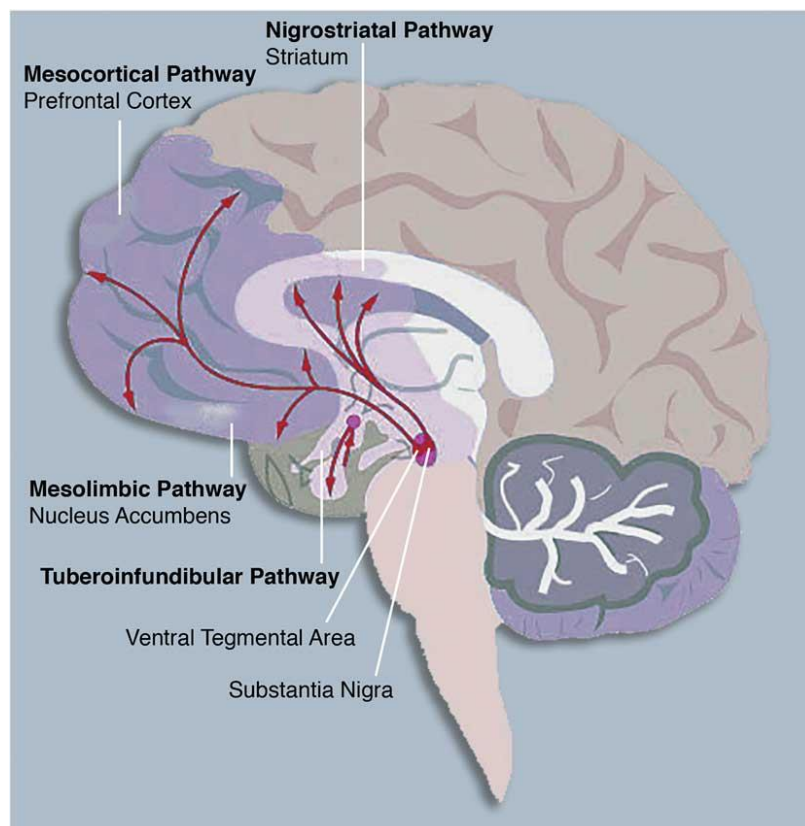
#### 1.1.1 Symptomatology

Parkinson's disease (PD) is a progressive and incurable neurodegenerative disorder. Risk of PD increases with age; prevalence of the disease worldwide is 428 per 100 000 individuals aged 60-69, 1087 per 100 000 individuals aged 70-79, and 1903 per 100 000 individuals aged 80+ (Pringsheim, Jette, Frolkis, & Steeves, 2014). It is the neurodegenerative disorder with the second highest prevalence, behind only Alzheimer's disease (de Lau & Breteler, 2006). Symptoms of PD typically arise in older age, with average PD age-of-onset of 65 years old, with a smaller number of early-onset PD patients (Connolly & Lang, 2014). The disease primarily affects motor functioning, with the cardinal symptoms of PD being resting tremor, rigidity, and bradykinesia (Jankovic, 2008). Resting tremor refers to a tremor in various areas of the body, commonly the limbs, that occurs at rest but dissipates or even disappears with the assumption of posture or with deliberate movement (Jankovic, 2008). Patients with PD often experience a phenomenon called cogwheel rigidity in the upper limbs (Jankovic, 2008). When the forearm is passively extended at the elbow, intermittent resistance can be felt that resembles ratcheting, or 'cogwheeling'. Bradykinesia is the presence of slowed movements (Jankovic, 2008). A unique feature of PD symptomatology is unilateral onset of motor symptoms and asymmetry of motor impairments that persist throughout the disease course (Dickson, 2012). The asymmetry of symptoms is not observed in multiple systems atrophy and progressive supranuclear palsy that are diseases under the parkinsonism umbrella, helping with diagnosis, though corticobasal ganglionic degeneration and Lewy body dementia can present asymmetrically (Dickson, 2012). In addition to motor symptoms, PD diagnosis is commonly associated with subtle cognitive dysfunction that might not necessarily reduce daily function (Aarsland, Brønnick, & Fladby, 2011; Litvan et al., 2012). As PD progresses, motor function becomes

increasingly impaired and the risk of developing motor complications such as dyskinesias increases (Coelho & Ferreira, 2012; Kalia & Lang, 2015). In late stage PD, patients also experience disruptions in cognition, gait/balance, and autonomic function (Coelho & Ferreira, 2012; Kalia & Lang, 2015). Unfortunately, there is no cure for Parkinson's disease at present.

### 1.1.2 Dopaminergic system

The principal neurotransmitter system impacted by PD is the dopaminergic system. The main dopamine-producing neurons are found in the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA), both located in the midbrain. The striatum receives significant investment of dopaminergic projections and is the input region of the basal ganglia, a collection of sub-cortical nuclei (Meyer & Quenzer, 2013). The striatum is commonly conceptually divided into dorsal and ventral components (i.e., DS and VS, respectively) based on differences in function, dopaminergic inputs, and glutamatergic projections from cortex (Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004). DS is comprised of the bulk of the caudate nuclei and putamen, whereas VS includes the nucleus accumbens (NAcc) and the most ventral aspects of the caudate and putamen (Voorn et al., 2004). The striatum is also divided histochemically into striosomes, which are labyrinth-like structures containing 10-15% of striatal volume, and the matrix, which comprises the remaining majority of striatal volume (Brimblecombe & Cragg, 2017). The dopaminergic system consists of three primary pathways (see **Figure 1**): the nigrostriatal, mesolimbic, and mesocortical pathways (Meyer & Quenzer, 2013). The nigrostriatal pathway originates in the SNc and projects to the DS (Meyer & Quenzer, 2013). The mesolimbic and mesocortical pathways originate in the VTA and innervate a) the VS, hippocampus, and mediotemporal regions, versus b) the prefrontal cortex, respectively (Meyer & Quenzer, 2013).

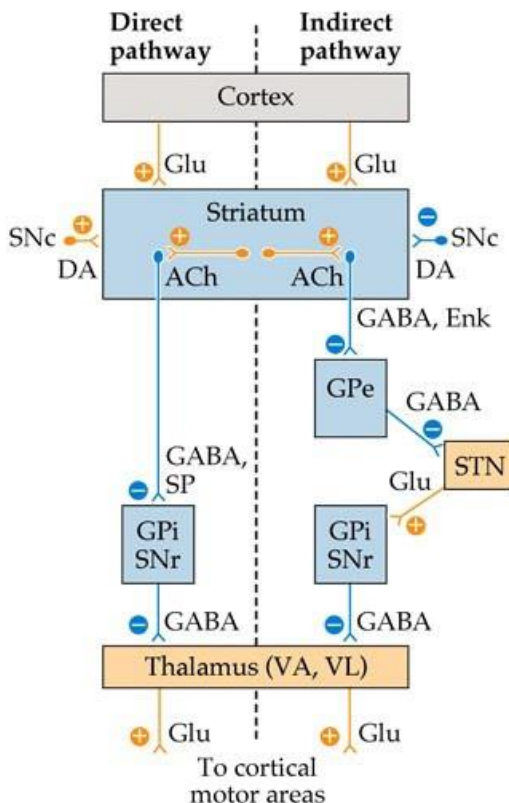


**Figure 1. Major dopaminergic brain regions and dopamine pathways in the brain.**

Ernst, M. & Luciana, M. (2015). Neuroimaging of the dopamine/reward system in adolescent drug use. *CNS Spectrums*, 20(4), 427-441. Reproduced with permission. © Cambridge University Press 2015.

Dopamine secreted by the SNc and VTA bind to and activate dopamine receptors located on medium spiny neurons (MSNs) throughout the striosomes and matrix of the striatum (Bolam, Hanley, Booth, & Bevan, 2000). Dopamine receptors, which are G-protein coupled receptors, are loosely divided into D1-like and D2-like receptors. D1-like receptors (i.e., D1, D5) couple to  $G_s$  stimulatory G proteins to induce downstream activation, whereas D2-like receptors (i.e., D2, D3, D4) cause inhibition by coupling to  $G_i$  inhibitory G proteins (Jaber, Robinson, Missale, & Caron, 1996). D1-like receptors are largely found within striosome structures and D2-like receptors are richly expressed in the striatal matrix (Brimblecombe & Cragg, 2017). The two types of dopamine receptors contribute to the direct and indirect pathways of the basal ganglia (see **Figure 2**). Engagement of the direct pathway results in overall increased activation of the cortical region to which the striatal segment projects (Purves et al., 2001). The indirect pathway

dampens the activation of the direct pathway through inhibitory connections to the external segment of the globus pallidus and subthalamic nucleus (Purves et al., 2001). As such, engagement of the indirect pathway leads to decreased thalamic and cortical activation (Purves et al., 2001). Collectively, these two pathways constitute a fine-tuned and highly-precise system for coordinating complex cortical networks that underlies functions such as motor movements.



**Figure 2. Direct and indirect pathways of the basal ganglia.**

Leisman, G., Melillo, R., & Carrick, F. R. (2012). Clinical motor and cognitive neurobehavioral relationships in the basal ganglia. In C. Bauer (Ed.), *Basal ganglia - An integrative view* (pp. 1-30). London, UK: IntechOpen Limited. Reproduced with permission. © 2012 Leisman et al., licensee InTech.

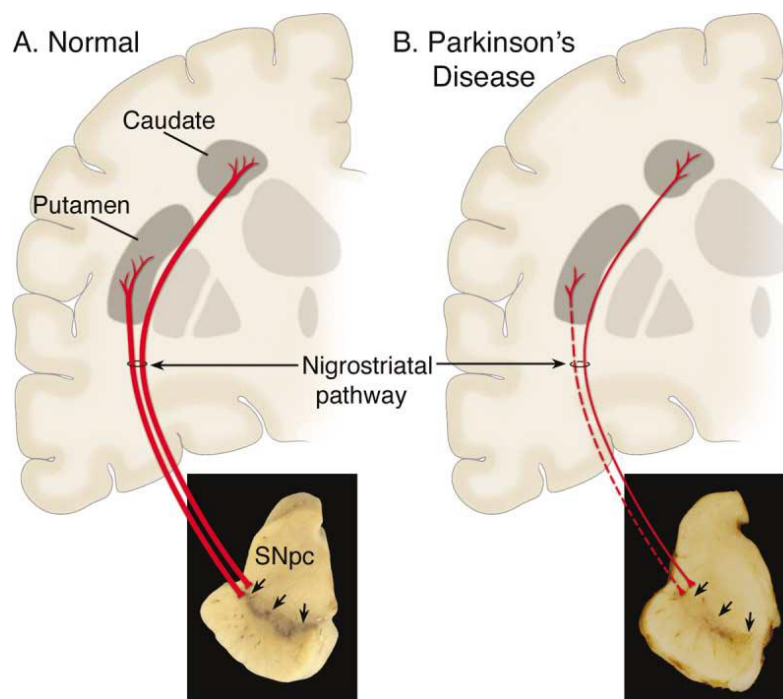
DA synaptic signaling is regulated by the activity of dopamine transporter (DAT), which engages in the reuptake of dopamine back into the presynaptic nerve terminal or into surrounding glia (Purves et al., 2001). DAT is a sodium-dependent transporter and can be located on presynaptic MSNs throughout the striatum (Chen & Reith, 2000; van Dyck et al., 2002). After reuptake, dopamine is metabolized by catechol O-methyltransferase

(COMT), which is a cytoplasmic enzyme, and monoamine oxidase (MAO), which is located on the outer mitochondrial membrane (Purves et al., 2001). These dopamine-degrading enzymes can be found in striatal neurons as well as associated glial cells (Purves et al., 2001).

### 1.1.3 PD neuropathology

The central neuropathology in PD is the degradation of the SNc, a dopamine-producing subregion of the SN (Dauer & Przedborski, 2003). This neurodegeneration results in disruption to the nigrostriatal pathway and dopamine deficiency in the DS (Meyer & Quenzer, 2013), giving rise to the hallmark motor symptoms of PD (Dickson et al., 2009). In normal brains, slices of the midbrain show a visible dark band along the SNc (see **Figure 3A**). This is attributed to neuromelanin pigmentation found in dopaminergic neurons of the SNc (Dauer & Przedborski, 2003). The nigrostriatal pathway is intact and appropriately supplies the caudate and putamen with dopamine. However, the pigmentation along the SNc ridge in midbrain slices of PD patients is greatly reduced because of the loss of dopaminergic neurons and the associated production of neuromelanin (see **Figure 3B**). The degeneration of SNc neurons is extensive; by the time PD patients exhibit clinical symptoms, approximately 60% of neurons in the SNc have already been lost and dopamine supply to the putamen is reduced by approximately 80% (Dauer & Przedborski, 2003). Neurodegeneration can also be detected in other brain regions in PD, including the locus ceruleus, amygdala, and hypothalamus (Dickson, 2012).





**Figure 3. Neuropathology of PD.**

A) Schematic of a normal brain. The SNc is clearly visible as a darker pigmented line in the midbrain due to neuromelanin produced in dopaminergic neurons. The nigrostriatal pathway is intact and supplies dopamine to the caudate and putamen. B) Schematic of a PD brain. Decreased neuromelanin pigmentation in SNc is observed due to the marked loss of dopaminergic neurons. The nigrostriatal pathway degenerates.

Dauer, W. & Przedborski, S. (2003). Parkinson's disease: Mechanisms and models. *Neuron*, 39(6), 889-909. Reproduced with permission. © 2003 by Cell Press.

Another characteristic pathology of PD is the formation of  $\alpha$ -synuclein protein aggregates called Lewy bodies (Schulz-Schaeffer, 2010; Wakabayashi et al., 2013). Research has suggested that Lewy bodies interfere with dopamine release from pre-synaptic neurons of the SN (Schulz-Schaeffer, 2010; Wakabayashi et al., 2013). Lewy pathology is hypothesized to progress along a predictable temporal and spatial pattern, giving rise to the Braak staging system for the clinical course of PD (Braak et al., 2003). Studies in PD and dementia patients have also linked Lewy body pathology to mild cognitive impairment and dementia (Irwin et al., 2012; Kempster, O'Sullivan, Holton, Revesz, & Lees, 2010; Selikhova et al., 2009).

Aside from a small percentage of cases for which the risk of developing PD is genetically inherited, the vast majority of PD is of idiopathic origin (Dauer & Przedborski, 2003). Research has suggested the influence of PD-related genes, environmental neurotoxins, and endogenous toxins generated by altered metabolism as potential factors contributing to the onset of PD neurodegeneration (Dauer & Przedborski, 2003). However, no single explanatory model exists for the etiology of PD. The characteristic motor symptoms of PD are largely attributed to the loss of dopaminergic innervation to the DS as a result of neurodegeneration of the SNc (Jankovic, 2008). However, the integrity of the VTA is largely intact until late stages of disease progression (Kish, Shannak, & Hornykiewicz, 1988; Rakshi et al., 1999). As a result, VTA dopamine production and downstream VS functioning is relatively spared in PD (Kish et al., 1988; Rakshi et al., 1999).

## 1.2 Dopaminergic medications

### 1.2.1 L-dopa

Although no therapies to stop or slow down PD disease progression exist, pharmacological treatments can alleviate motor symptoms. The most commonly used dopaminergic medication is L-3,4-dihydroxyphenylalanine (L-dopa or levodopa; Connolly & Lang, 2014). L-dopa is taken orally and acts as a precursor for dopamine production (Lang & Lees, 2002). Because L-dopa is subject to degradation in the bloodstream, it is almost always co-administered with carbidopa, a dopamine decarboxylase inhibitor that prevents premature degradation. Once L-dopa crosses the blood-brain barrier, it is metabolized into dopamine by the enzyme aromatic amino acid decarboxylase (Meyer & Quenzer, 2013). As such, treating with L-dopa acts as an exogenous source of dopamine for PD patients, who are unable to produce the required concentrations from the SNc.

Although L-dopa is initially effective at improving motor functioning, approximately 50% of PD patients on L-dopa therapy begin to experience motor fluctuations within 4-6 years (Ahlskog & Muenter, 2001). Dyskinesia, which can be described as involuntary non-rhythmic motions, is one such motor disruption (Connolly & Lang, 2014). Because dyskinesia results in unintended jerky or swaying movements, PD patients can experience

substantial social embarrassment and stigma (Connolly & Lang, 2014). The onset of dyskinesia is strongly correlated with the peak in L-dopa concentration (Obeso, Olanow, & Nutt, 2000). Unfortunately, because PD patients often take larger and more closely-spaced doses of L-dopa as the disease progresses, the risk of dyskinesia increases (Obeso et al., 2000). Late PD patients also commonly experience on-off fluctuations, which involve a rapid loss of motor functioning as the L-dopa wears off (Blandini & Armentero, 2014). The presence of these motor disturbances has been found to correlate with the duration and dose of L-dopa therapy (Ahlskog & Muentzer, 2001). As such, it is preferable to avoid the initiation of L-dopa treatment if possible, within the limits of patient comfort and quality of life (Ahlskog & Muentzer, 2001).

### 1.2.2 Dopamine agonists

DA agonists, another common class of dopaminergic treatment, bind directly to dopamine receptors and upregulate post-synaptic receptor activity (Blandini & Armentero, 2014). Dopamine agonists can be divided into the first generation ergot-based agonists (e.g., bromocriptine, cabergoline, pergolide), and newer non-ergot agonists (e.g., pramipexole and ropinirole; Borovac, 2016). Both classes of dopamine agonists target D2 receptors. However, one of the issues with ergot-based agonists is that they do not bind to D2 receptors with high affinity (Borovac, 2016). Ergotine agonists can bind with D1 receptors, as well as serotonergic and adrenergic receptors, causing a range of adverse side effects (Borovac, 2016). In particular, ergot-based dopamine agonists have been associated with an increased risk of cardiac and valvular fibrosis (Blandini & Armentero, 2014). The newer non-ergot agonists have higher affinity with D2 receptors and elicit fewer adverse side effects (Borovac, 2016). For these reasons, non-ergot dopamine agonists such as pramipexole and ropinirole are much more commonly prescribed for the treatment of PD (Connolly & Lang, 2014). When dopamine agonists were first introduced for the treatment of PD, they were incorporated into medication regimens as an adjunct therapy for L-dopa (Fischer, 1995). With the addition of dopamine agonists, PD patients required 20-30% less L-dopa, decreasing the risk and severity of L-dopa-related motor complications (Brooks, 2000). Dopamine agonists are now commonly used

as a monotherapy, especially for early-onset PD patients, for whom it is advisable to delay the initiation of L-dopa treatment (Brooks, 2000).

However, dopamine agonists in particular have been linked to the development of impulse control disorders (ICDs; see Section 1.4 for more details). Further, age has been found to be negatively correlated with ICD risk (Voon et al., 2007; Weintraub et al., 2010). Voon and colleagues (2007) found that PD patients with history of pathological gambling were significantly younger than a control group of non-ICD PD patients. In a large-scale study of 3090 PD patients, younger age was also identified as a risk factor for developing an ICD, along with the use of dopamine agonist medication (Weintraub et al., 2010). As such, it is crucial to assess pre-existing risk of ICD before incorporating a dopamine agonist into a patient's medication regimen. Each medication is associated with unique advantages and disadvantages; the development of a medication regimen that is best suited for each individual PD patient is often a delicate balancing act between different therapies.

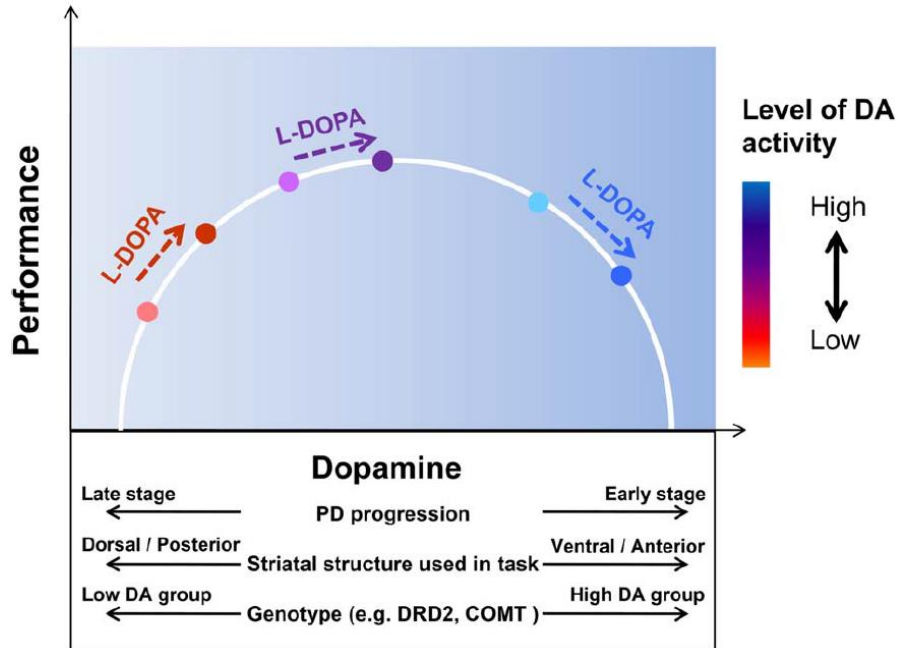
### 1.3 Dopamine overdose hypothesis

L-dopa and dopamine agonists as described above are prescribed by physicians to remedy the motor symptoms of PD. However, because of the asymmetrical nature of SNc and VTA degradation, treatment with dopaminergic therapies affect DS- and VS-mediated functions differently (Vaillancourt, Schonfeld, Kwak, Bohnen, & Seidler, 2013). Although dopaminergic treatment has clear benefits for motor ability, its impact on cognitive functioning is more complex. Dopaminergic therapy has been shown to improve some cognitive functions but impair others (MacDonald & Monchi, 2011). The dopamine overdose hypothesis has been proposed to explain this phenomenon (Vaillancourt et al., 2013).

The dopamine overdose hypothesis originates from research in the late 1980s showing that the treatment of L-dopa in PD patients can benefit or worsen aspects of frontal cognitive function (Gotham, Brown, & Marsden, 1986, 1988). Since then, the hypothesis has gained support from behavioural, neuroimaging, and animal research (MacDonald & Monchi, 2011). The dopamine overdose hypothesis posits that as dopaminergic

treatments remediate dopamine insufficiency in the DS, an unintentional overdosing of the VS occurs and other brain regions receiving dopamine from the VTA, which maintains relatively normal dopamine levels in PD (Vaillancourt et al., 2013). Functioning of dopaminergic structures has been modelled in the shape of an inverse-U curve (see **Figure 4**). Because the DS is dopamine-deficient in PD, it falls left of peak performance on the inverse-U curve (Vaillancourt et al., 2013). Functions mediated by VS as well as by prefrontal and limbic cortex are already at peak on the curve because of intact VTA dopamine production (Kish et al., 1988; Rakshi et al., 1999). Dopaminergic medication brings DS functioning to a maximal level, but also pushes VS functioning past the peak to a lower level of function (Vaillancourt et al., 2013). This phenomenon can be influenced by disease duration, medication dosage, and genetic factors (Cools, 2006).

In accordance with the dopamine overdose hypothesis, cognitive functions that have been shown to be DS-mediated through neuroimaging and lesion studies largely improve with dopaminergic medication. These include selective attention, memory retrieval, decision making, task switching, and particularly inhibiting prepotent or habitual responding (MacDonald & Monchi, 2011). Conversely, functions that are suggested by neuroimaging to be VS-mediated typically show a worsening of performance with the addition of dopaminergic treatment. Implicit and explicit learning, reversal learning, orienting to stimuli, and cognitive impulsivity all show this expected pattern (MacDonald & Monchi, 2011). Behavioural studies commonly use these established patterns of behaviour to theorize the neurological basis of the cognitive function of interest (i.e., DS-versus VTA-innervated brain region-mediated; MacDonald & Monchi, 2011).



**Figure 4. The dopamine overdose hypothesis.**

If baseline dopamine level is low (shown in red), L-dopa will improve performance. However, if baseline dopamine level is high (shown in blue), L-dopa will worsen performance by pushing performance past the maximal level. Vaillancourt, D. E., Schonfeld, D., Kwak, Y., Bohnen, N. I., & Seidler, R. (2013).

Dopamine overdose hypothesis: Evidence and clinical implications. *Movement Disorders*, 28(14), 1920-1929. Reproduced with permission. © 2017 John Wiley & Sons, Inc.

### 1.3.1 Mechanisms

The mechanisms for the dopamine overdose hypothesis are rooted in the unique neurobiological properties of the DS and VS. The DS contains MSNs with more and denser dendritic projections that allow for rapid maximal response to dopamine (Wickens, Budd, Hyland, & Arbuthnott, 2007; Zhang et al., 2009). The DS is also rich in DAT, allowing for rapid synaptic clearance, resulting in dopamine activation patterns in this region that summate and rapidly decay (MacDonald & Monchi, 2011). When dopaminergic therapies are administered in PD, this maximal rapid receptor stimulation is remediated in the dopamine-deficient DS (MacDonald & Monchi, 2011). Because of the characteristics of DS dopamine signaling, the DS has been theorized to summate inputs from many sources and mediate binary responding (i.e., engage or suppress) between

alternative choices (MacDonald & Monchi, 2011). As such, the DS has been linked to decision-making and selection between stimuli (MacDonald & Monchi, 2011).

Compared to DS neuroanatomy, the VS is comprised of smaller MSNs with fewer and sparser dendritic projections (Wickens et al., 2007). Lower DAT concentration can also be found throughout the VS, leading to prolonged synaptic presence of dopamine (Wickens et al., 2007). These properties contribute to dopamine signaling patterns in the VS that are slower, graded and variable in intensity, and longer lasting (Zhang et al., 2009). These properties allow the VS to be a suitable mediator of generating associations between stimuli and rewards across time, as well processing response outcomes in probabilistic events (MacDonald & Monchi, 2011). Indeed, the presence of reciprocal connections between VS and memory- and association-related regions of the brain such as the anterior cingulate cortex, orbitofrontal cortex, and hippocampus, support the interpretation of VS involvement in learning and memory (MacDonald & Monchi, 2011). Whereas dopaminergic treatment enhances rapid absolute dopamine signaling in the DS, excess dopamine concentration disrupts delicate phasic dopaminergic signaling patterns in the VS, leading to impairments in VS-mediated cognitive functions such as associative learning (MacDonald & Monchi, 2011).

## 1.4 Impulsivity

The influence of dopamine on impulse control has been a point of scientific interest since the idea of dopamine's role in cognition was recognized. One of the earliest accounts of impaired impulse control in PD originated from a group of German researchers who presented two case studies of PD patients being treated with dopaminergic therapies who experienced strong sexual urges and engaged in sexual delinquency (Berger, Mehrhoff, Beier, & Meinck, 2003). Driver-Dunckley, Samanta, and Stacy (2003) then described nine PD patients who developed pathological gambling after beginning dopamine agonist treatment. The following year, Avanzi, Uber, and Bonfà (2004) published a paper discussing two cases of pathological gambling in PD patients who were taking dopaminergic replacement therapy. These papers paved the way for the popularization of PD-impulse control research in subsequent years (Dodd et al., 2005; Silver, 2005; Stocchi, 2005; Weintraub et al., 2006).

In the present-day literature, it is commonly known that dopaminergic treatment, in particular dopamine agonists, increase risk of developing ICDs. Weintraub and colleagues (2010) in a large-scale study of 3090 PD patients found that as many as 13.6% of PD patients experienced one or more ICD behavioural symptoms. These problem behaviours include pathological gambling, hypersexuality and sex addiction, compulsive buying, and binge eating disorder (Weintraub et al., 2010). ICDs often present with similar characteristics as drug addiction, such as tolerance effects and/or withdrawal symptoms (Leeman & Potenza, 2012). Neuroimaging studies in PD patients with and without ICD(s) have found increased dopamine release to the VS in PD subjects with concurrent ICD compared to PD patients without ICD (O'Sullivan et al., 2011; Steeves et al., 2009; Wu et al., 2015), demonstrating a clear link between the presence of ICDs and dysfunctional mesolimbic activation.

DA agonists were identified as a significant ICD risk factor, having been associated with almost three-fold increased odds of developing one or more ICDs, compared to PD patients not treated with dopamine agonists (Weintraub et al., 2010). However, L-dopa use can also precipitate ICDs, and in fact PD patients with ICDs tend to require higher L-dopa dosage (Voon, Sohr, et al., 2010). It is standard practice for neurologists to warn PD patients of the risk of developing ICDs and to be vigilant for new ICD behaviours when starting dopaminergic treatment and especially dopamine agonist therapy (Connolly & Lang, 2014). This is particularly critical for PD patients who already have underlying obsessive-compulsive tendencies, addictive personalities, or history of addiction (Weiss & Marsh, 2012). For these individuals, dopamine agonist treatment might be advised against altogether, despite potential motor benefits. ICDs can have serious ramifications for quality of life. Anecdotal accounts have been described of PD patients who have gambled their life savings away and lost their home in the process, engaged in sexually deviant behaviours and ruined their marriage, or developed obesity due to continued binge-eating. These dangerous real-life ramifications highlight the importance of maintaining appropriate impulse control abilities for everyday function.



### 1.4.1 Multifaceted nature of impulsivity

Although it is tempting to view impulsivity as a single concept for the sake of simplicity, impulsivity has been increasingly understood as a multifaceted construct (Antonelli, Ray, & Strafella, 2011). Nombela, Rittman, Robbins, and Rowe (2014) used a factor analysis approach to compare different behavioural measures under the umbrella of “impulsivity”. They identified four main impulsivity factors: 1) response conflict, interference effects, and self-reported impulsivity; 2) motor inhibitory control; 3) time estimation and delay aversion; and 4) temporal discounting and reflection impulsivity (Nombela et al., 2014). Another research group has suggested a simpler model of motivational/cognitive impulsivity and performance/motor impulsivity (Antonelli et al., 2011). Cognitive impulsivity corresponds with behaviours including risky decision-making, increased propensity towards reward-seeking, and impoverished feedback-learning (Antonelli et al., 2011). Cognitive impulsivity is purportedly the underlying factor for the development of ICDs (Claassen et al., 2011). On the other hand, motor impulsivity refers to the inability to withhold automatic and pre-potent responses and impaired ability to cancel responses that have already been planned or initiated (Antonelli et al., 2011). Motor impulsivity can also impact quality of life, as it has been linked with greater risk of falls (Wylie et al., 2012). Collectively, cognitive and motor impulsivity comprise aspects of cognition that are of clinical relevance in PD.

#### 1.4.1.1 Cognitive impulsivity

Because of the link between cognitive impulsivity and ICDs, cognitive impulsivity in PD has been a point of clinical interest for researchers. Antonelli and colleagues (2011) describe cognitive impulsivity as a complex psychological domain comprised of altered decision-making, elevated risk-taking under stable or unknown probabilistic contingencies, poor ability to delay rewards in lieu of smaller immediate rewards, and impaired reward and reversal learning. Using tasks aimed at assessing cognitive impulsivity such as the Iowa Gambling Task, Cambridge Gambling Task, and Risk Task, imaging studies have implicated mesolimbic and mesocortical structures including the VTA, NAcc, amygdala, and inferior, orbital, and dorsolateral prefrontal cortices (Hsu, Bhatt, Adolphs, Tranel, & Camerer, 2005; Rogers et al., 1999; Verdejo-García &

Bechara, 2009). The same regions have been implicated in PD patients with concurrent pathological gambling (van Eimeren et al., 2010).

Another popular behavioural paradigm for assessing cognitive impulsivity is the Balloon Analogue Risk Task (BART; Lejuez et al., 2002). This task, which is typically administered in the form of a computer program, consists of a series of balloons that the participant is presented with. For each trial, the participant can choose to pump the balloon larger with air by making a keypress response. With each pump, an amount of money is accrued for the balloon. Once the participant is satisfied, he/she can press a key to collect the accrued money into a permanent bank and move onto the next trial. However, if the balloon is over-pumped, the balloon pops and all money is lost for that trial. Typically, each balloon has a randomly-determined pop point as to avoid systematic learned responses. This task is a measure of risk-taking (i.e., how far participants are willing to pump up each balloon before collecting at the risk of the balloon popping). The BART has shown sound construct validity; it correlates with other measures of sensation seeking, impulsivity, and self-reported history of addiction (Lejuez et al., 2002). Functional magnetic resonance imaging (MRI) has supported the involvement of the mesolimbic and mesocortical pathways in BART performance, with participants showing increased neural activation in the VTA, striatum including the NAcc, insular cortex, anterior cingulate cortex, and dorsolateral prefrontal cortex during the task (Rao, Korczykowski, Pluta, Hoang, & Detre, 2008).

The BART has been implemented in the PD population to examine differences between PD patients and healthy controls (Simioni, Dagher, & Fellows, 2012), and between PD patients with and without ICDs while also comparing medication status (Claassen et al., 2011). Simioni and colleagues (2012) tested PD patients and age-matched healthy adults using the BART. They found that as the trials progressed, PD patients made significantly riskier choices compared to controls. This finding parallels the observation of higher prevalence of ICDs in PD patients compared to the general population (Ceravolo, Frosini, Rossi, & Bonuccelli, 2010). The effect described by Simioni and colleagues (2012) persisted at a 1.5-3 year follow-up study. Claassen and colleagues (2011) were interested in whether PD patients with ICDs and without ICDs differed on BART performance on

and off dopamine agonist medication. They found that on medication, the PD group with ICD showed greater risk-taking (i.e., cognitive impulsivity) but this was not found for the PD group. Further, dopamine agonists increased risk-taking in participants who were taking higher doses compared to those taking lower dopamine doses. Taken together, these findings suggest that the effect of dopamine agonists on cognitive impulsivity might be dose-dependent and interact with other vulnerabilities of the dopaminergic system that promote ICD behaviours.

#### 1.4.1.2 Motor impulsivity

Motor impulsivity refers to the inability to withhold pre-potent and automatic responses (Antonelli et al., 2011). A number of behavioural paradigms have been developed to investigate response inhibition and motor impulsivity. One such paradigm is the Stop Signal Task (SST; Logan, Van Zandt, Verbruggen, & Wagenmakers, 2014; Verbruggen & Logan, 2008). The Stop Signal paradigm requires participants to respond as quickly as possible to some stimulus/stimuli (Go trials). However, if they hear an auditory tone (the Stop Signal), participants are asked to withhold the response (Stop trials). The Stop Signal appears after a variable Stop Signal Delay (SSD) that is typically dynamically adapted until participants are able to inhibit their responses with a 50% success rate. The latency between the SSD and the mean reaction time on Go trials, or Stop Signal Reaction Time (SSRT), is an estimate of the stop process that is activated by presentation of the Stop Signal. A longer SSRT is interpreted as worse inhibitory ability whereas shorter SSRT reflects better inhibition.

Studies that have used the SST to assess motor impulsivity in PD generally find that PD patients show worse motor inhibition compared to older adult controls (Obeso, Wilkinson, Casabona, et al., 2011; Obeso, Wilkinson, & Jahanshahi, 2011; but see Vriend et al., 2015). Research groups who examine the effect of dopaminergic medication on SST performance in PD patients have not observed medication effects (Claassen et al., 2015; Obeso, Wilkinson, & Jahanshahi, 2011). However, an imaging study by Ray Li, Yan, Sinha, and Lee (2008) revealed that activity in the caudate correlated with shorter SSRTs (i.e., better inhibitory control). This suggests an influence of the dopaminergic system on motor inhibition performance on the SSRT. Claassen and

colleagues (2015) compared PD patients with concurrent ICD and PD patients without ICD on the SST. They found that the PD group with ICD had motor impulse control abilities that were just as proficient as the non-ICD group, despite overwhelming evidence that PD patients with ICDs have greater cognitive impulsivity (Claassen et al., 2011; O'Sullivan et al., 2011; Simioni et al., 2012; Steeves et al., 2009; Wu et al., 2015). This finding reinforces the important distinction between motor and cognitive impulsivity.

Another simple behavioural paradigm that assesses motor impulsivity is the Go/No-go task (Yang, Glizer, Vo, Seergobin, & MacDonald, 2016). The participant is presented with a random series of Go and No-go stimuli. For the Go stimulus (e.g., 'X'), the participant is required to make a keypress response (e.g., press the spacebar). Conversely, the participant is instructed to withhold any keypress responses for the No-go stimulus (e.g., 'K'). Participants are asked to make their responses as quickly and accurately as possible. Importantly, the Go stimulus is presented at a much higher probability than the No-go stimulus (e.g., 75% Go, 25% No-go), establishing 'Go' as the pre-potent automatic response. As such, the number of No-go errors, which refers to trials for which the participant was unable to suppress the Go response and erroneously responded to the No-go stimulus, acts as a measure of motor impulsivity. Along a parallel line of reasoning, the number of Go timeouts, which refers to the trials for which the participant failed to make a Go response in time, corresponds to more conservative responding, or less motor impulsivity. In summary, greater motor impulsivity can be observed as increased No-go errors and/or decreased Go timeouts. Conversely, less motor impulsivity corresponds with fewer No-go errors and/or more Go timeouts. Although the Go/No-go paradigm is a rather simple task, it constitutes a good measure of motor impulsivity and is easy for participants to comprehend. This is especially important when testing an elderly clinical population.

In a study using the Go/No-go task in young healthy adults, Yang and colleagues (2016) found that administration of pramipexole, a dopamine agonist, increased Go timeouts. However, they did not observe the parallel observation of decreased No-go errors. The researchers attributed this to the fewer number of No-go trials (i.e., 25% of trials) and

thus less power in statistical analyses. Nonetheless, the presence of increased Go Timeouts suggests that dopaminergic treatment results in more considered responding (i.e., decreases motor impulsivity). Importantly, reaction times (RTs) were not different between medication states, suggesting that the conservative responding was not due to general slowing, sleepiness, or impaired motor ability. In the current study, we wanted to extend the same task to a clinical PD sample and examine the effect of dopaminergic medication.

#### 1.4.2 Previous Go/No-go studies in PD

The Go/No-go paradigm has been employed to investigate motor impulsivity and response inhibition in PD. Most studies focused on differences between various subgroups of PD (Cohen et al., 2014; Marzinzik et al., 2015; O’Callaghan, Naismith, Hodges, Lewis, & Hornberger, 2013; Pessiglione et al., 2005; Peterson et al., 2015). Other studies compared PD performance to that of healthy, age-matched controls (Cooper, Sagar, Tidswell, & Jordan, 1994; Dujardin et al., 2013; Franz & Miller, 2002; Nakashima, Shimoyama, & Takahashi, 1993). However, few studies have sought to understand the effect of dopaminergic therapy on motor impulsivity in PD, contrasting performance in the on and off dopaminergic states (Antonelli et al., 2014; Farid et al., 2009; Herz et al., 2014). To this point, studies using the Go/No-go task to investigate motor impulsivity in PD have generally failed to reveal significant group or on-off differences (Antonelli et al., 2014; Farid et al., 2009; Herz et al., 2014), though most included low numbers of participants and potentially were underpowered to detect differences. Further, the Go/No-go procedures in these studies often featured task parameters that failed to clearly establish a pre-potent Go response either by having low proportions of Go trials or multiple Go and No-go stimuli (Antonelli et al., 2014; Herz et al., 2014). Consequently, to our knowledge, this represents the first study to implement a straightforward Go/No-go paradigm in which clear Go responses were biased, and in which the impact of dopaminergic therapy on PD patients was tested.

Geffe and colleagues (2016) used a variant of the Go/No-go task to assess implicit learning in de novo untreated PD patients on versus off a single dose of L-dopa. In the conditioning phase, a series of stimuli were presented such that one non-target prime

stimulus acted as a reliable cue for presentation of the target stimulus in the subsequent trial. During the conditioning phase, participants learned to anticipate that the target stimulus would follow a particular non-target prime stimulus. Each conditioning phase was followed by a deconditioning phase, during which non-target stimuli and the target stimulus were presented randomly. PD patients off medication and healthy controls were found to make more errors in the No-go condition of the deconditioning phase. This was interpreted as evidence that associations between the prime stimulus and the target stimulus had been learned in the conditioning phase. This learning enhanced the anticipation that the target stimulus would follow, leading to more No-go responses. When PD patients were on medication, they evidenced fewer No-go errors in the deconditioning phase. The authors interpreted this as evidence that association learning between prime stimuli and target stimuli had been less well-learned by patients treated with dopaminergic therapy. This finding is consistent with previous research showing that dopaminergic therapy impairs learning (Cools, Barker, Sahakian, & Robbins, 2001; Cools, Lewis, Clark, Barker, & Robbins, 2007; Gallant, Vo, Seergobin, & MacDonald, 2016; MacDonald et al., 2011; MacDonald & Monchi, 2011; Swainson et al., 2000; Vaillancourt et al., 2013; Vo et al., 2014; Vo, Seergobin, & MacDonald, 2017). However, the fact that PD patients performed fewer No-go responses on dopaminergic therapy in the deconditioning phase could also be reflective of enhanced motor control. Due to the design, either interpretation is possible. Geffe and colleagues (2016) used their variant of the Go/No-go task to investigate implicit learning whereas the current study is focused on motor impulsivity and inhibition. Our version of the Go/No-go task is designed to establish a strong pre-potent Go response and accordingly acts as a measure of motor inhibition.

## 1.5 Current study

Our goal in this study was to elucidate the effect of dopaminergic therapy on motor impulsivity in PD. Toward this end, we tested PD patients on and off dopaminergic medication with the Go/No-go paradigm. PD patients took their usual dopaminergic therapy as prescribed by their treating neurologist in the ON Session. For the OFF Session, PD patients refrained from their dopaminergic therapy for 12 to 20 hours as

detailed in the Methods section. To our knowledge, this represents the first study to implement a straightforward Go/No-go paradigm that clearly established the Go response as the pre-potent response, in which the impact of dopaminergic therapy in PD patients was directly tested with an on-off design.

Based on this previous research, here, we hypothesized that PD patients would evidence more impulsive responding in the off state. We expected that dopaminergic therapy would remedy motor impulsivity, resulting in more considered and cautious responding. Again, impulsive responding was expected to be indexed by a) lower Go Timeout rate and/or b) higher No-go Error rate. In contrast, more cautious and considered responding would be expressed a) higher Go Timeout rate and/or b) lower No-go Error rate, as described above.

## Chapter 2 : Methods

A version of this chapter has been published (Yang et al., 2018).

### 2.1 Participants

Twenty-seven PD patients (16 males, mean age  $67.81 \pm 8.64$  years) were recruited from the University of Western Ontario and Health Sciences North Hospital in Sudbury, Ontario. Participants were pre-screened for inclusion and exclusion criteria. All PD patients had been previously clinically diagnosed with PD by a licensed neurologist and met the UK Brain Bank criteria for a diagnosis of PD (Hughes, Daniel, Kilford, & Lees, 1992). Participants were excluded for the following reasons: neurological disorders other than PD (e.g., stroke, seizures, dementia, mild cognitive impairment), psychiatric disorders other than mild-to-moderate depression [i.e.,  $29/63 >$  on Beck Depression Inventory (BDI; (Aaron T Beck, Steer, & Brown, 1996))] or anxiety [i.e.,  $36/63 >$  on Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988)], or history of alcoholism or drug abuse. Further, PD patients were excluded if they were not treated with dopaminergic therapy. Two patients were taking entacapone as an adjunct to L-dopa. One patient was taking both entacapone and amantadine as adjunctive therapies. One patient was taking dopamine agonists alone as primary therapy. The remaining patients were taking L-dopa as their primary therapy: either L-dopa alone ( $N = 15$ ), or L-dopa in combination with dopamine agonists ( $N = 8$ ). The data of participants who scored below 24 on the Montreal Cognitive Assessment (MoCA) were excluded from analyses. One PD patient was excluded for this reason. Finally, participants were excluded if their mean RTs or error rates in the Go or No-go conditions fell outside 2.5 standard deviations of the Group mean for that Medication Session (i.e., outliers). Four additional PD patients were excluded for having data that were deemed outliers. Analyses were completed with the data of the remaining 22 PD patients. This study was carried out in accordance with the recommendations of the Health Sciences Research Ethics Boards of the University of Western Ontario with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki (World Medical



Association, 2013). The protocol was approved by the Health Sciences Research Ethics Boards of the University of Western Ontario (see **Appendix A**).

## 2.2 Apparatus

The Go/No-go task was conducted on a desktop computer (LG model 73821B-10) using the Windows 7 Professional operating system and a 22.0" monitor (LG Flatron W2242TQ) running on a resolution of 1600 x 900 pixels. Participants were seated approximately 50 cm away from the screen and used a keyboard (Logitech K120) to record their responses.

## 2.3 Procedures

All participants completed two testing sessions on consecutive days at the University of Western Ontario or Health Sciences North Hospital. For the OFF Session, PD patients were instructed to abstain from taking L-dopa/carbidopa and entacapone for 12-18 hours before the start of the session, and dopamine agonists (e.g., pramipexole, ropinirole, pergolide) as well as amantadine, rasagiline, and selegiline for 16-20 hours before the start of the session. For the ON Session, PD patients were instructed to take all dopaminergic medications for PD as prescribed by their treating neurologist. On-off order was randomly assigned and counterbalanced. After the exclusion of five PD patients as previously described, twelve participants had an on-off medication order and the remaining ten participants had an off-on order. All participants were debriefed about the details of the study once they completed the second session. Participants were compensated for their time and participation.

### 2.3.1 Pre-task assessments

Demographic and clinical data [i.e., age, sex, education, years of education, handedness, PD duration, Levodopa Equivalent Dose (LED)] were collected from all participants. PD duration refers to the number of years since a diagnosis of PD. LED is a calculation of the daily dose of dopaminergic therapy in units of L-dopa equivalents. Calculation of LED (mg) for each PD patient was based on the theoretical L-dopa equivalence (Hiebert, Seergobin, Vo, Ganjavi, & MacDonald, 2014; Wüllner et al., 2010) as follows: L-dopa

dose (mg) x 1 + L-dopa controlled release (mg) x 0.75 + L-dopa x 0.33 if taking entacapone + amantadine (mg) x 0.5 + bromocriptine (mg) x 10 + cabergoline (mg) x 50 + pergolide (mg) x 100 + pramipexole (mg) x 67 + rasagiline (mg) x 100 + ropinirole (mg) x 16.67 + selegiline (mg) x 10.22.

Heart rate (HR), systolic blood pressure (BP), and diastolic BP were measured using an automated blood pressure monitor (Omron model BP785N) at the beginning and end of each testing session. Participants were also given a self-reported visual analogue scale (VAS; see **Appendix B**) at these two time-points to assess subjective alertness (Bond & Lader, 1974).

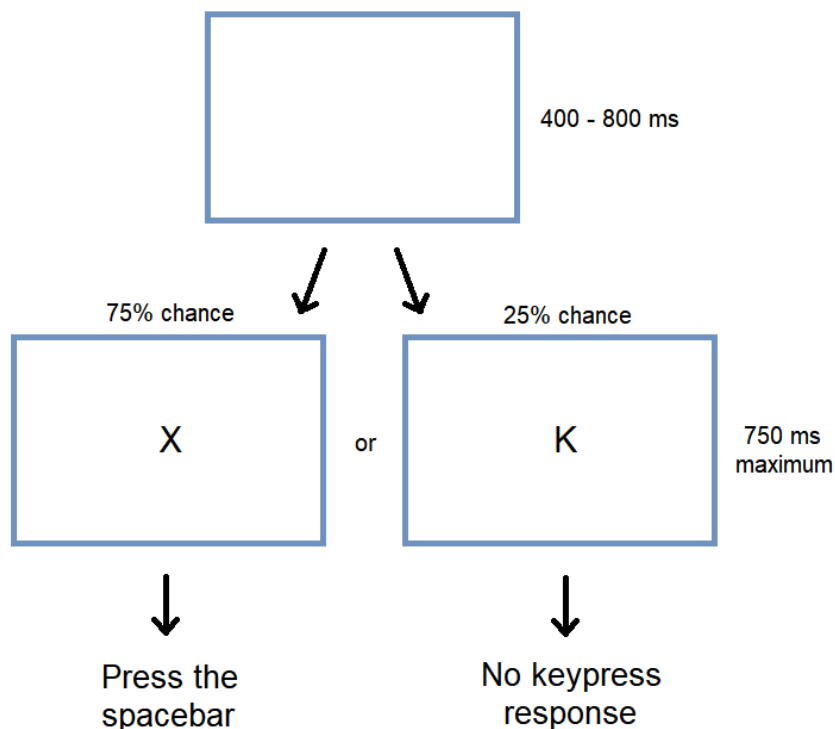
To assess baseline cognitive functioning, PD patients completed general cognitive assessments in the on state. These general cognitive assessments and questionnaires were the American National Adult Reading Test (ANART; see **Appendix C**), MoCA (see **Appendix D**), and Controlled Oral Word Association Test (COWAT; see **Appendix E**). The ANART is a measure of verbal intelligence that has been adapted for use in North America (Grober & Sliwinski, 1991). The MoCA is a validated cognitive screening tool used to detect mild cognitive impairment (Nasreddine et al., 2005). The COWAT is used to assess verbal and category fluency (Ross et al., 2007). Participants also completed the Barratt Impulsiveness Scale (BIS; see **Appendix F**), Sensation Seeking Scale (SSS; see **Appendix G**), Questionnaire for Impulsive-Compulsive Disorders in PD – Rating Scale (QUIP-RS; see **Appendix H**), and New Freezing of Gait (NFOG; see **Appendix I**) questionnaire. The BIS and SSS are validated questionnaires estimating trait impulsiveness (Patton, Stanford, & Barratt, 1995) and sensation-seeking (Zuckerman, Eysenck, & Eysenck, 1978), respectively. The QUIP-RS is a valid and reliable measure of ICD symptom severity (Weintraub et al., 2012). The NFOG is a questionnaire used to assess freezing of gait in PD (Giladi et al., 2000).

Additionally, all participants completed the BDI, BAI, and Starkstein Apathy Scale (SAS; see **Appendix J**) in both sessions. The BDI, BAI, and SAS are commonly used assessments of depression (Beck et al., 1996), anxiety (Beck et al., 1988), and apathy (Starkstein et al., 1992) in PD populations. Motor function was assessed on both testing

days using the Motor Subscale of the Unified PD Rating Scale (UPDRS; Goetz et al., 2008; see **Appendix K**).

### 2.3.2 Go/No-go task

The Go/No-go paradigm is commonly used to assess motor impulsivity. The task consists of Go trials and No-go trials. On Go trials, participants were asked to respond by making a keypress as quickly as possible when the letter 'X', the visual Go signal, was presented. On No-go trials, participants were instructed to withhold keypress responses, when the letter 'K', the visual No-Go signal, was presented. On every trial, either the letter 'X', the Go signal, or the letter 'K', the No-Go signal, appeared in the center of the screen. Participants were instructed to press the spacebar for 'X' and avoid pressing any keys for 'K'. The visual stimuli were presented for a maximum of 750 milliseconds (ms), or until participants responded with a keypress. A blank screen was presented for a random duration between 400 and 800 ms during the inter-trial interval. See **Figure 5** for a schematic of the Go/No-go task. The letter 'X' was presented on 75% of trials, and the letter 'K' was shown in the remaining 25% of trials, in a random order. This ratio of Go to No-go trials was intended to establish the Go keypress as the pre-potent response. Participants were instructed to make responses as quickly and accurately as possible. On each testing day, participants completed a total of 256 trials, organized into 2 blocks of 128 trials each, with 10 second breaks at the midpoint of each block and for a slightly longer break between the two blocks.



**Figure 5. Schematic of the Go/No-go task.**

A blank screen was displayed for a random period between 400 and 800 ms as the inter-trial interval. Either the Go stimulus ('X') or No-go stimulus ('K') was displayed for a maximum of 750 ms or until response.

For the Go stimulus, participants were required to press the spacebar as quickly and accurately as they could. For the No-go stimulus, no response was required. The Go stimulus was presented 75% of the time whereas the No-go stimulus was presented 25% of the time, establishing "Go" as the pre-potent response.

## 2.4 Data analysis

Physiological measures (i.e., HR, Systolic BP, Diastolic BP, and VAS Alertness) were compared using 2 x 2 analyses of variance (ANOVAs), with Medication (on vs. off) and Time (Pre-Task vs. Post-Task) as within-subject variables. Affective measures (i.e., mean BDI, BAI, and SAS scores) were compared between on and off Medication states using paired-samples two-tailed *t*-tests. The dependent measures for the Go/No-go task were a) Go RT, comprising the mean RT for responses that occurred prior to the 750 ms deadline, b) No-go Error RT, consisting of the mean RT for erroneous responses provided in the No-go condition, c) Go Timeout Rate, reflecting the percentage of trials on which participants failed to respond prior to the 750 ms deadline, and d) No-go Error Rate, denoting the percentage of trials on which participants erroneously made a keypress

response in the No-go condition. RTs were calculated as the time in ms between the onset of the visual stimuli and the keypress responses. Data values for Go RTs were trimmed if they fell more than 2.5 standard deviations from the mean Go RTs in each medication state for each participant. The same process was used to trim No-go Error RT values. Lower Go Timeout rates and higher No-go Error rates were indicative of greater motor impulsivity whereas higher Go Timeout rates and lower No-go Error rates indexed less impulsive responding. Go RTs and No-go Error RTs were analyzed using non-parametric two-tailed Wilcoxon Signed Ranks Tests, and Go Timeout Rate and No-go Error Rate were analyzed using paired-sample two-tailed *t*-tests, with Bonferroni correction for multiple comparisons. Analyses were performed using Excel (Version 2016), IBM SPSS Statistics (Version 21), and GraphPad Prism (Version 6). Data were considered significant if  $p < 0.05$ .

## Chapter 3 : Results

A version of this chapter has been published (Yang et al., 2018).

### 3.1 Demographic, baseline screening cognitive, affective, and physiological measures

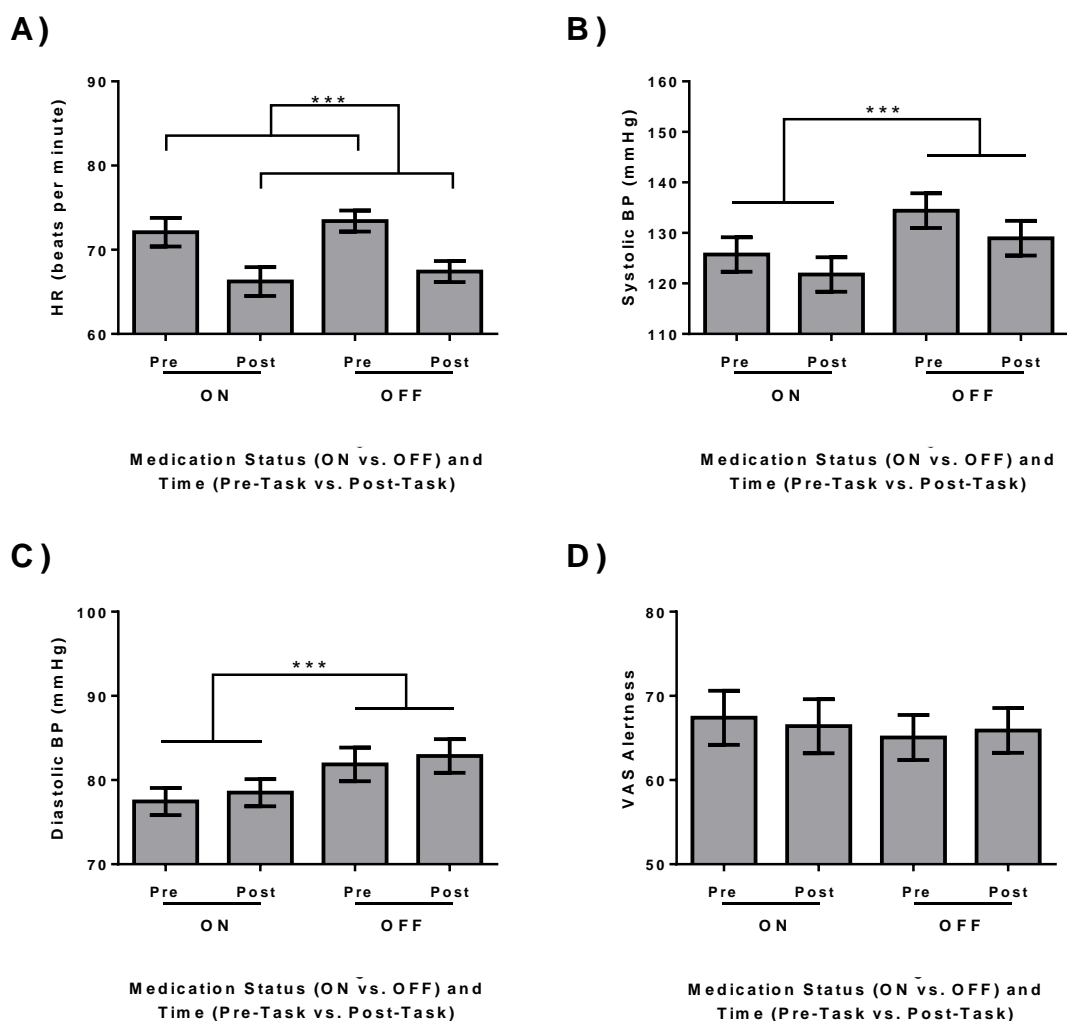
Demographic and cognitive measures are presented for PD patients (see **Table 1**). All PD patients were within 2.5 standard deviations of the group mean for the NFOG, BIS, SSS, QUIP-RS ICD, QUIP-RS Total, MoCA, ANART, COWAT FAS, and COWAT Animal. UPDRS scores were compared between on and off medication states using a paired-samples two-tailed *t*-test. PD patients showed significantly higher UPDRS scores off dopaminergic medication compared to on, which was expected ( $t(21) = 10.139$ ,  $p < 0.001$ ).

Physiological measures, including HR, Systolic BP, Diastolic BP, and VAS Alertness were analyzed using 2 x 2 ANOVAs, with Medication (on vs. off) and Time (Pre-Task vs. Post-Task) as within-subject variables. HR was significantly higher Pre-Task compared to Post-Task (**Figure 6 A**;  $F(1,21) = 24.569$ ,  $MSe = 31.507$ ,  $p \leq 0.001$ ). Additionally, Systolic BP was significantly higher off compared to on (**Figure 6 B**;  $F(1,21) = 15.647$ ,  $MSe = 88.459$ ,  $p = 0.001$ ). Diastolic BP showed a similar significant effect of Medication, with significantly higher Diastolic BP off compared to on dopaminergic therapy for PD patients (**Figure 6 C**;  $F(1,21) = 11.743$ ,  $MSe = 36.046$ ,  $p = 0.003$ ). For VAS Alertness (**Figure 6 D**), no significant differences were found across Medication and Time ( $p > 0.05$ ).

Variable	Value	SD
N	22	-
Age	66.77	9.15
Sex	11 males, 11 females	-
Education	15.18	4.11
Handedness	20 right, 2 left	-
PD duration	5.23	5.71
LED	626.59	276.31
UPDRS - ON	17.43	6.25
- OFF	21.82	6.06
	$t(21) = 10.139$	$p < 0.001$
NFOG	7.86	7.52
BIS	59.23	8.99
SSS	11.59	4.74
QUIP-RS ICD	13.05	8.62
QUIP-RS Total	24.91	14.70
MoCA	27.32	1.73
ANART	122.72	6.46
COWAT FAS	15.71	5.22
COWAT Animal	21.23	6.93

**Table 1. Demographic and cognitive measures.**

Average demographic and cognitive measures for non-excluded PD patients. Values are presented as group means  $\pm$  SD unless otherwise listed. All values are in units of the respective questionnaire or task scale. N: number of participants; Education (years): number of years of secondary and post-secondary education; PD duration (years): number of years since PD diagnosis; LED (mg): Levodopa Equivalent Dose; UPDRS: Motor Subscale Score of the Unified PD Rating Scale/56, listed for on and off medication; NFOG: New Freezing of Gait Questionnaire/28; BIS: Barratt Impulsiveness Scale/120; SSS: Sensation-Seeking Scale/40; QUIP-RS ICD: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease Rating Scale – Impulse-Control Disorders/64; QUIP-RS Total: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease Rating Scale – Total score/112; MoCA: Montreal Cognitive Assessment/30; ANART: American National Adult Reading Test/135.6; COWAT FAS (number of words): Controlled Oral Word Association Test FAS Task; COWAT Animal (number of words): COWAT Animal Task. UPDRS scores were significantly higher off medication ( $p < 0.001$ ).

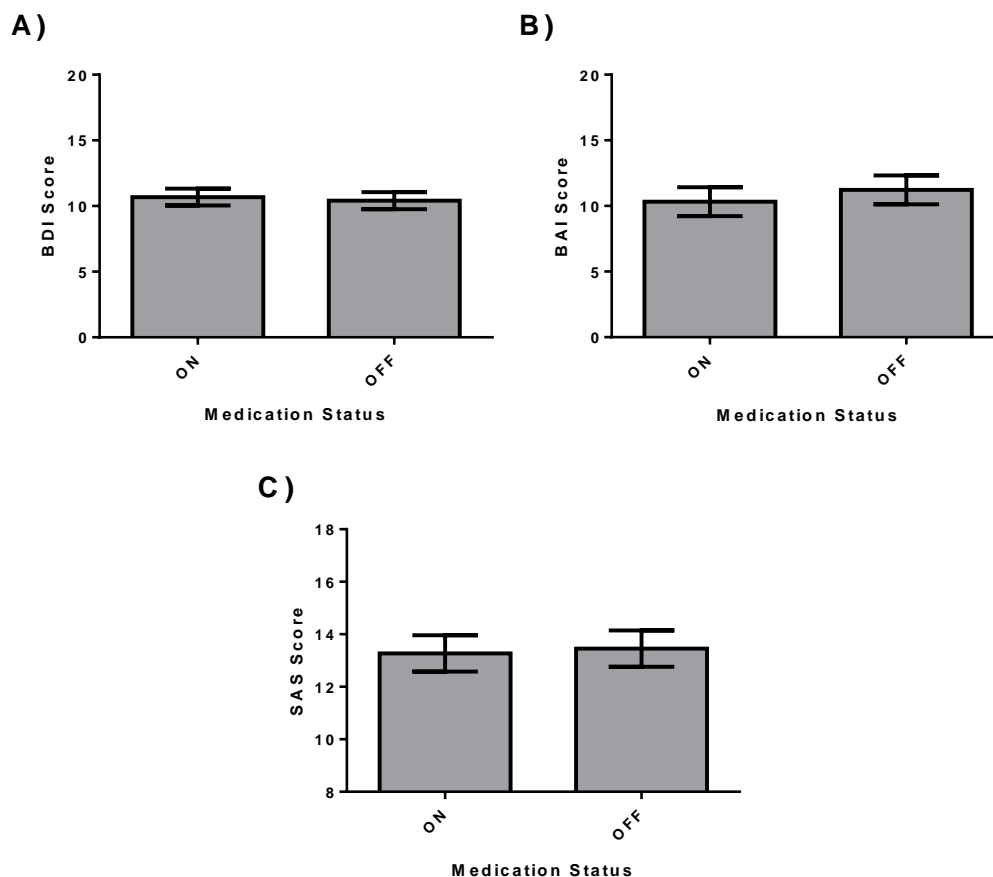


**Figure 6. Physiological measures.**

Physiological measures for PD patients ( $N = 22$ ). Values are presented as group means  $\pm$  95% confidence interval as per Cousineau (2005). Data were analyzed using two-way ANOVAs. **A)** HR (beats per minute) was significantly higher Pre-Task compared to Post-Task ( $*** p \leq 0.001$ ). **B)** Systolic BP (mmHg) was significantly higher for the OFF Session compared to the ON Session ( $***$ ). **C)** PD patients had significantly higher diastolic BP (mmHg) off medication compared to on ( $***$ ). **D)** No differences in VAS Alertness were found across Time and Medication ( $p > 0.05$ ).

Affective measures (BDI, BAI, and SAS) were compared between on and off medication states using paired-samples two-tailed  $t$ -tests (**Figure 7**). For all affective measures, there were no significant differences across Medication states (all  $p > 0.05$ ).





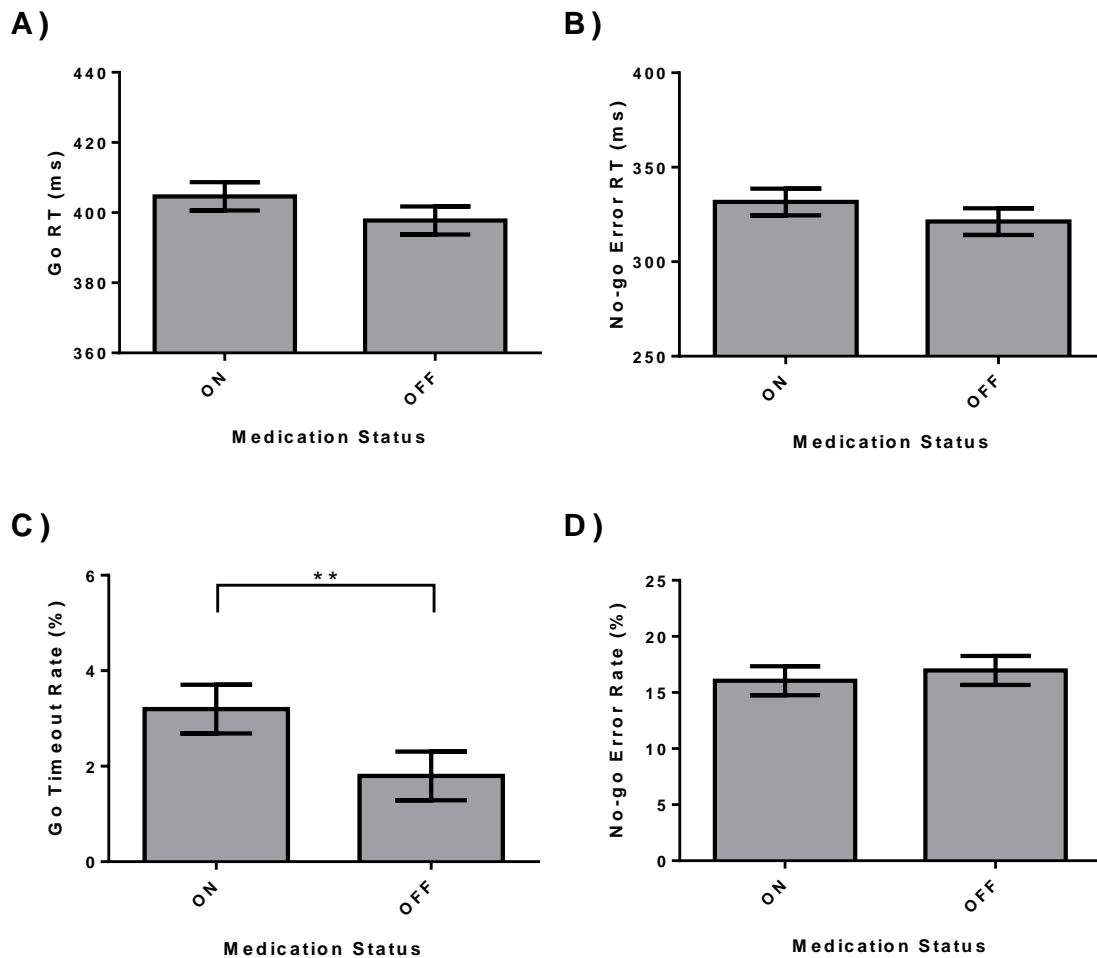
**Figure 7. Affective measures.**

Affective measures for PD patients (N = 22). Values are presented as group means  $\pm$  95% confidence interval for repeated measures as per Cousineau (2005). Affective measures were analyzed using paired-samples two-tailed *t*-tests. **A)** PD patients did not significantly differ on the BDI between on and off medication states ( $p > 0.05$ ). **B)** There was no significant effect of Medication state on the BAI ( $p > 0.05$ ). **C)** SAS score did not show a significant difference between on and off states ( $p > 0.05$ ).

### 3.2 Go No-go task

We investigated the effect of Medication (on vs. off) on the dependent measures of mean Go RT and No-go Error RT using two-tailed Wilcoxon Signed Ranks Tests, and Go Timeout Rate and No-go Error Rate using paired-samples two-tailed *t*-tests in the Go/No-go task using the Bonferroni correction. Mean Go RT was not significantly different for PD patients on and off dopaminergic medication (**Figure 8 A**;  $p > 0.05$ ). No significant difference was found between on and off No-go mean RT (**Figure 8 B**;  $p > 0.05$ ). PD patients on medication had a significantly higher Go Timeout Rate compared to off

dopaminergic therapy (**Figure 8 C**;  $t(21) = 2.851$ ,  $p = 0.010$ ) even after applying the Bonferroni correction (i.e.,  $\alpha = 0.0125$ ). Examining No-go Error Rate, there were no significant effects of Medication (**Figure 8 D**;  $p > 0.05$ ).



**Figure 8. Go/No-go task measures.**

Dependent Go/No-go measures for PD patients ( $N = 22$ ), on and off dopaminergic medication. Values are presented as group means  $\pm$  95% confidence interval for repeated-measures as per Cousineau (2005). Go RTs and No-go Error RTs were analyzed using non-parametric two-tailed Wilcoxon Signed Ranks Tests, and Go Timeout Rate and No-go Error Rate were analyzed using paired-sample two-tailed  $t$ -tests, with the Bonferroni correction for multiple comparisons. **A)** Mean Go RT was not significantly different for PD patients on and off dopaminergic medication ( $p > 0.05$ ). **B)** No-go Error RT did not show a significant effect of Medication ( $p > 0.05$ ). **C)** PD patients had a significantly higher Go Timeout Rate on dopaminergic medication compared to off (\*\*  $p = 0.010$ ). **D)** No significant differences were found between on and off medication for No-go Error Rate.

## Chapter 4 : Discussion

A version of subsections 4.1, 4.2, 4.4, 4.6, and 4.7 of this chapter has been published (Yang et al., 2018).

### 4.1 Summary of results

We found that dopaminergic medication increased the Go Timeout rate in PD patients compared to their performance off medication. In this way, dopaminergic therapy reduced motor impulsivity, inducing a more conservative response pattern for PD patients. We did not see a concomitant decrease in No-go errors for patients on relative to off dopaminergic treatment, however. A lower No-go Error rate in the on state would also signal decreased motor impulsivity in the No-go condition to parallel adoption of a more considered response strategy in the Go condition producing more Go Timeouts. To engender a pre-potent Go response, there were far fewer No-go trials relative to Go trials, however. It is possible that the No-go condition did not have the statistical power to reveal No-go error differences between on and off medication states. Although the effect of dopaminergic medication on No-go errors did not reach significance, more Go Timeouts when on medication corroborates the notion that dopaminergic treatment causes more conservative responding. This is despite the fact that for PD patients, dopaminergic therapy improves motor function and speeds movements overall. In contradistinction to the widely-recognized *enhancement* of cognitive/motivational impulsivity producing ICDs in PD, increased Go Timeouts in the ON Session suggests that dopaminergic medications *reduce* motor impulsivity.

Comparisons of physiological measures showed that PD patients had lower HR post relative to pre Go/No-go Task. This effect of lower HR was fully expected because participants were sitting and inactive for the study period and had acclimatized to the novelty of the setting. PD patients also had increased systolic and diastolic BP off relative to on dopaminergic medication. This was anticipated as L-dopa is known to lower BP (Noack, Schroeder, Heusser, & Lipp, 2014). Participants did not show any differences in subjective alertness, BDI score, BAI score, or SAS score across ON-OFF Sessions,

demonstrating that our Go/No-go findings were not due to changes in alertness or mood between the two medication states.

## 4.2 Effects of dopaminergic therapy on the Go/No-go task

There are few studies in the PD literature that have investigated motor impulsivity using the Go/No-go in PD patients. Fewer still have investigated the effect of dopaminergic therapy on performance though an important and concerning side effect of dopaminergic therapy is disordered impulse control. Herz and colleagues (2014) compared Go/No-go performance between PD patients with ( $N = 13$ ) and without ( $N = 13$ ) dyskinesia, and healthy controls ( $N = 13$ ), with both patient groups being tested on and off dopaminergic medication. Herz and colleagues (2014) used a variant of the Go/No-go task that included multiple Go responses (i.e., pressing either the left or right key) in addition to the No-go response. They did not find a modulation of Go/No-go performance by dopaminergic treatment. The added complexity related to multiple Go responses potentially reduced the pre-potency of Go relative to No-go, resulting in less difficulty withholding responses in the No-go condition. In another study, Farid and colleagues (2009) compared Go/No-go performance of PD patients ( $N = 9$ ) on and off medication relative to healthy controls ( $N = 9$ ) who performed the task only once. They did not find behavioral differences between patients ON versus OFF medication, or relative to performance of healthy older controls on Go/No-go accuracy or RT. However, with only nine participants in each group, the study likely was underpowered statistically to detect true differences if they occurred. Further, medication order was not counterbalanced. PD patients were always assessed in the OFF-ON order. In this way, and because healthy controls only performed the task once, order effects were confounded with medication effects. Antonelli and colleagues (2014) contrasted Go/No-go performance of PD patients ( $N = 7$ ) on and off the dopamine agonist pramipexole. They found that administration of pramipexole increased impulsive choices on a delayed discounting task — their measure of cognitive impulsivity. However, no on-off differences were observed on Go/No-go performance — their measure of motor impulsivity. This study was important in providing evidence that dopaminergic treatment affects distinct forms of impulsivity dissimilarly, supporting the idea that impulsivity is not a unitary concept, but rather is multifaceted. These results must be viewed with

caution, however, considering that due to a sample size of only seven PD patients, this study was likely entirely underpowered. Further, the authors' rendition of the Go/No-go task involved presenting Go signals at 60%, and No-go signals at 40%, limiting the prepotency of the Go response.

In the single occasion to our knowledge when on-off differences have been observed, these effects are not interpreted with respect to the effects of dopaminergic therapy on motor impulsivity or the ability to withhold pre-potent responses. Geffe and colleagues (2016) tested a version of the Go/No-go task in PD patients on and off dopaminergic therapy though they included an implicit learning component to their study which was in fact the focus (Geffe et al., 2016). Geffe and colleagues' variant of the Go/No-go task involved a conditioning phase during which participants were presented with a series of stimuli consisting of one of three non-target cues or a target stimulus, such that one cue consistently predicted subsequent target presentation in the following trial. In the Go block, participants were instructed to make a keypress in response to the target stimulus. In the No-go block, participants were required to make keypress responses to all non-target cues and inhibit the keypress response for target stimuli. In addition, they had a deconditioning phase during which no particular non-target cue predicted the target stimulus. Geffe and colleagues found that for the No-go condition, PD patients off medication and healthy controls showed increased errors in the deconditioning phase, which was interpreted as evidence of implicit learning in the conditioning period. However, this increase in error rate was not observed for PD patients when on medication, which they interpreted as an impairment in implicit learning with the addition of dopaminergic medication. Given that dopaminergic therapy is known to adversely impact association learning, this interpretation is highly plausible. These effects could also be interpreted as evidence that dopaminergic therapy reduces impulsive responding (i.e., lower No-go error rate on relative to off dopaminergic therapy). This latter account was not articulated by the researchers but remains a possible reinterpretation. Overall, due to the many differences between the Go/No-go task used by Geffe and colleagues (i.e., conditioning and deconditioning phases, blocked design of Go and No-go trials, four stimuli of which one is the target stimulus), straightforward inferences regarding the effect of dopaminergic therapy on motor impulse control were

precluded. There were substantial differences in task parameters and research goals between Geffe and colleague's (2016) study and ours. However, their results are not at odds with our findings. Consequently, to our knowledge, this represents the first study to implement a straightforward Go/No-go paradigm in which clear Go responses were biased, and in which the impact of dopaminergic therapy on motor impulsivity in PD patients was unambiguously tested.

### 4.3 Go/No-go performance in PD subgroups

The Go/No-go paradigm has been employed to investigate impulsivity and response inhibition in various subgroups of PD (Cohen et al., 2014; Marzinzik et al., 2015; O'Callaghan et al., 2013; Peterson et al., 2015). In a study investigating inhibition and dementia in PD, O'Callaghan and colleagues (2013) compared Go/No-go performance of PD patients (n = 25), PD with frontotemporal dementia (n = 11), and older controls (n = 15). The PD group with frontotemporal dementia conducted more No-go errors (i.e., more motor impulsivity) than the PD group, which in turn made more No-go errors than controls. Using neuroimaging, the authors provide evidence that frontostriatal atrophy might contribute to motor impulsivity in PD. Cohen and colleagues (2014) conducted a study contrasting PD patients (n = 13), PD patients with freezing of gait (n = 15), and older controls (n = 16). PD patients with freezing of gait were observed making more Go Timeouts (i.e., less motor impulsivity) than PD patients, suggesting differential motor inhibitory abilities depending on freezing of gait status. In another study of motor impulse control and freezing of gait, Peterson and colleagues (2015) contrasted PD patients with (n = 13) and without (n = 12) freezing of gait using a Go/No-go task. Participants were also fitted with inertial sensors to assess gait metrics during normal walking and dual-task walking, for which participants completed a concurrent simple behavioural task. The researchers found that Go/No-go performance was correlated with dual-task interference for only the PD group with freezing of gait, suggesting a link between impaired motor inhibition and freezing of gait in PD. Marzinzik and colleagues (2015) examined PD patients with mild (n = 11) and advanced (n = 11) motor symptoms, PD patients with dementia (n = 11), Alzheimer's patients (n = 11), and healthy older controls (n = 11) on a cued Go/No-go task. PD patients with advanced motor symptoms

and dementia committed more Go Timeouts than controls, but the PD with dementia group also committed more No-go errors than controls. In the PD group with dementia, task performance was low and correlated with disease severity. The authors concluded that deficits in PD dementia develop from dysfunctional inhibitory abilities.

Findings from these studies suggest that different subgroups of PD patients such as those with freezing of gait or dementia might have altered motor impulse control as assessed by the Go/No-go task. The current study did not separate PD patients by freezing of gait status, and the PD participants tested did not have current or history of dementia. Our specific aim in this study was to investigate the effect of dopaminergic medication on motor impulsivity in a sample of non-demented PD patients. Future investigations of motor impulsivity using the Go/No-go task could expand on the differences in motor inhibition between subgroups of PD.

#### 4.4 Other tasks of response inhibition

Consistent with the notion advanced here that dopaminergic treatment in fact *increases* motor impulse control, Hiebert and colleagues (2014) found that PD patients evidenced greater facilitation in the congruent condition of a modified Stroop task when tested off dopaminergic therapy relative to the degree of facilitation observed in healthy age-matched controls. Facilitation was normalized when PD patients were tested on their usual dopaminergic therapy. We surmised that enhanced facilitation in the off state arose due to more impulsive and less considered responding, which was rectified by usual dopaminergic therapy. The current study and those presented above highlight the fact that dopaminergic treatment has varied effects on different aspects of impulsivity. These studies present evidence that dopaminergic therapy *reduces* motor impulsivity in contrast to the more widely-understood effect of *increasing* cognitive/motivational impulsivity producing ICDs in PD patients. This understanding is important for the clinical approach to PD and decisions regarding titration of dopaminergic therapy considering motor as well as cognitive symptoms.

Although SST studies investigating the effect of dopaminergic medication on motor impulsivity have not shown effects of medication on SST performance in PD (Claassen et

al., 2015; Obeso, Wilkinson, & Jahanshahi, 2011), neuroimaging has linked motor impulse control on the SST to caudate activity (Ray Li et al., 2008). Further, the version of the SST used by Obeso, Wilkinson, and Jahanshahi (2011) was a conditional SST involving interleaved ‘critical’ and ‘non-critical’ trials, denoted by direction of the stimulus. For ‘critical’ trials, participants were asked to stop their responses if they heard the auditory Stop Signal. For ‘non-critical’ trials, participants were to ignore the Stop Signal and complete the response. The interleaved nature of the trials introduces the additional factor of conflict resolution, which potentially acted as a confound in their study. Claassen and colleagues (2015) employed a traditional SST paradigm without multiple conditions. They contrasted SST performance of 12 PD patients with ICD(s) on and off dopaminergic medication, 12 PD patients without ICD on and off medication, and 12 matched healthy controls. With 12 participants in each group, it is entirely possible that the study was underpowered to discover potential medication effects. The current study aimed to address the common issue of small sample size in motor inhibition studies in PD by testing a total of 27 PD patients.

Our observations in this study are in accordance with previous research on response inhibition and/or response withholding in PD generally. In a meta-analysis of the effects of dopaminergic medication and PD disease duration on measures of response inhibition, Manza and colleagues (2017) found that for studies of response inhibition with PD participants on dopaminergic medication, response inhibition deficits were significantly correlated with disease duration. The authors examined studies of common measures of response inhibition, including the anti-saccade, Stop Signal, Stroop, and Go/No-go tasks. PD patients were found to have poorer response inhibition compared to matched healthy controls, in agreement with conclusions from another previous meta-analysis (Kudlicka, Clare, & Hindle, 2011). For studies with PD patients at earlier disease stages (i.e., < than 7 years since diagnosis), dopaminergic medication tended to improve the ability to inhibit inappropriate responses, resulting in performance that was worse than but approached the level of healthy controls (Manza et al., 2017). Conversely, studies with PD patients at later disease stages (i.e., > than 7 years since diagnosis) tended to find that dopaminergic medication worsened response inhibition compared to the unmedicated state. The current study investigated PD patients with an average disease duration of approximately five



years (range 1-26 years), comparable to the patient samples in the studies examined by Manza and colleagues (2017) in their meta-analysis of PD patients at earlier disease stages. Our finding that dopaminergic therapy caused PD patients to enact more cautious responding, yielding more Go Timeouts, is entirely in line with the overall observation in the PD literature that dopaminergic therapy improves inhibition of inappropriate motor responses in PD.

## 4.5 Mechanisms of impulsivity

### 4.5.1 Cognitive impulsivity

Several neurophysiological mechanisms have been proposed to explain the link between dopaminergic medication and increased cognitive impulsivity. First, as previously described, dopaminergic treatment is known to impair response learning (Foerde & Shohamy, 2011; MacDonald & Monchi, 2011). Impaired ability to learn from negative consequences or loss could contribute to increased risk-taking (Claassen et al., 2011). The increase in tonic dopamine levels in response to dopaminergic therapy might mitigate the gaps in phasic dopamine activity corresponding to lack of reward or a negative consequence (Cools et al., 2001; Guthrie, Myers, & Gluck, 2009; van Eimeren et al., 2010). Next, dopaminergic treatment has been suggested to increase response to rewarding stimuli (Claassen et al., 2011). Increased tonic dopamine signaling in the VS (especially the NAcc) could amplify the bursts of dopamine activity corresponding to rewards (Cools et al., 2001). This interpretation could also be caused by increased attentional focus on rewarding experiences, or amplified downstream subjective appraisal of rewarding stimuli (Cools et al., 2001; Voon, Reynolds, et al., 2010). Lastly, an alternative account suggests that chronic dopaminergic treatment results in a blunted response to rewards, leading to increased reward-seeking to compensate for the dampened sensation of reward (Riba, Krämer, Heldmann, Richter, & Münte, 2008). Consistent with this explanation, PD patients with ICDs have been shown to have lower DAT density in the VS compared to non-ICD PD patients (Cilia et al., 2010; Cilia & van Eimeren, 2011). Less dopamine synaptic clearance by DAT decreases the dopamine receptor availability for phasic responses to rewarding stimuli (Cilia et al., 2010; Mata, Hau, Papassotiropoulos, & Hertwig, 2012). It is unclear which one of these explanations

best accounts for dopamine-related increased cognitive impulsivity and subsequent ICD development; all three explanations likely contribute to this phenomenon. Additional theoretical framing is required to combine these different interpretations into a single explanatory model.

#### 4.5.2 Motor impulsivity

Neuroimaging has linked motor impulsivity with activation in the DS, especially in the caudate (Ray Li et al., 2008; Zandbelt & Vink, 2010). The mechanism for improved motor impulse control with dopaminergic therapy is likely linked to the neurophysiological properties of the many dense MSNs in the DS (Wickens et al., 2007; Zhang et al., 2009). Dopamine stimulation results in rapid maximal responses in the DS, leading to enhanced signaling of motor impulse control related processes. Because the DS tends to mediate binary response patterns (i.e., engage or suppress), it does not appear to be susceptible to overdosing effects. No studies to date have demonstrated overdosing of the DS; administration of dopaminergic treatment seems to simply increase DS-mediated cognitive functions. This explains the observation of increased motor impulse control with dopaminergic medication in young healthy adults (Yang et al., 2016), who presumably have normal dopamine production at baseline.

The notion of motor impulse control being mediated by DS activity is entirely consistent with our findings in the present study. When PD patients are off medication, the SNc is unable to supply sufficient dopamine to the DS. Lower motor impulse control abilities manifest as greater motor impulsivity on a motor inhibition task such as the Go/No-go task. When the patients remediate dopamine-deficiency in the DS using dopaminergic medication, motor impulse control is improved, leading to more conservative responding (i.e., increased Go Timeouts) on the Go/No-go task.

### 4.6 Effects of dopaminergic therapy on cognition

It is now understood that dopaminergic treatment in PD leads to improvements in some aspects of cognition, but impairments in others (Cools et al., 2001; MacDonald et al., 2011; MacDonald & Monchi, 2011; Rowe et al., 2008). These complex cognitive effects are explained by differences in dopaminergic levels at baseline across different brain

regions in PD. According to this view, dopaminergic therapy is titrated to a dose needed to replenish the dopamine-deficient DS and improve movement symptoms in PD. Dopaminergic therapy distributes in a non-targeted fashion, however, overdosing regions such as the VS and medial prefrontal regions that are at baseline dopamine-replete, innervated by the relatively-spared VTA (Cools, 2006; Cools et al., 2001; Gotham et al., 1986, 1988; Swainson et al., 2000; Vaillancourt et al., 2013). As a result, DS-mediated cognitive functions such as selective attention (Baunez & Robbins, 1999; de Manzano et al., 2013; MacDonald et al., 2011), decision-making (Balleine, Delgado, & Hikosaka, 2007; Hiebert, Vo, et al., 2014; MacDonald et al., 2011), response inhibition (MacDonald & Monchi, 2011; Wylie et al., 2012; Zandbelt & Vink, 2010), and overriding pre-potent and automatic responses to enact more considered and accurate responding (Ali, Green, Kherif, Devlin, & Price, 2009; MacDonald et al., 2014; MacDonald et al., 2011; Robertson, Hiebert, Seergobin, Owen, & MacDonald, 2015) show improvements with the addition of dopaminergic treatment. This is entirely in line with our findings here in the Go/No-go task. In contrast, cognitive functions mediated by brain regions receiving dopamine from VTA such as reward processing and feedback learning (Cools et al., 2001, 2007; Gallant et al., 2016; MacDonald & Monchi, 2011; MacDonald et al., 2013; Swainson et al., 2000; Vaillancourt et al., 2013; Vo et al., 2014; Vo et al., 2017), motivation (Humphries & Prescott, 2010; MacDonald & Monchi, 2011; Simões-Franklin, Hester, Shpaner, Foxe, & Garavan, 2010), and orienting (Anderson et al., 2016; Esslinger et al., 2013; Jensen et al., 2007; MacDonald & Monchi, 2011; Zink, Pagnoni, Martin, Dhamala, & Berns, 2003) are impaired.

Both our findings in the Go/No-go task, clarifying the effect of dopaminergic therapy on motor impulsivity in PD, and the effects of dopaminergic medication on cognitive/motivational impulsivity producing ICDs can be understood through the framework provided above. DS has been implicated in *limiting* motor impulsivity by ensuring more considered and less habitual responding (Cools, Rogers, Barker, & Robbins, 2010; Djamshidian, O'Sullivan, Lees, & Averbeck, 2011; Hood et al., 2007; MacDonald et al., 2011; Ness & Beste, 2013; Robertson et al., 2015). In contrast, VTA-innervated brain regions such as VS and orbitofrontal cortex mediate motivation and reward processing (Balleine et al., 2007; Drijgers et al., 2012; Rowe et al., 2008). In PD,

dopaminergic therapy normalizes DS dopamine deficiency and therefore predictably improves the ability to make deliberate and less impulsive responses as we see here (Balleine et al., 2007; Drijgers et al., 2012; Rowe et al., 2008). Conversely, treatment with dopaminergic agents overdoses VS and other VTA-innervated brain areas, dysregulating motivation and impairing reward processing, leading to ICDs. Our findings and the literature linking ICDs to dopaminergic therapy are easily reconciled, understanding that impulsivity is a multifaceted concept, with its various forms mediated by distinct brain regions that are differentially dopamine-depleted in PD and hence dissimilarly affected by dopaminergic therapy.

## 4.7 Limitations

By not presenting baseline PD performance relative to that of controls, we have not established abnormal control of motor responses (i.e., motor impulsivity) in the PD patients in our study. This was not our aim, though, as detailed above, reviews of this literature confirm that PD patients consistently exhibit deficits in inhibition of pre-potent responses and motor impulsivity (Kudlicka et al., 2011; Manza et al., 2017). Our objective was to explicitly investigate, in back-to-back tests within PD patients, the effect of dopaminergic therapy on motor impulse control using an accepted measure of this process (i.e., Go/No-go; Antonelli et al., 2014; Hamidovic, Kang, & de Wit, 2008; Rubia et al., 2001). Here, in PD patients, we entirely replicated the pattern that we observed in healthy young controls (Yang et al., 2016). Specifically, we previously showed that dopaminergic therapy increases the Go Timeout rate in healthy young controls. We previously interpreted this pattern of results, as we have here, as evidence that dopaminergic therapy increases control over motor responses and decreases the tendency to make more impulsive responses (Yang et al., 2016).

The alternative explanation that dopaminergic therapy simply slowed cognitive processes and/or motor execution rather than specifically promoting a more conservative response pattern is contradicted by other measures in our study, in addition to well-studied, established effects of dopaminergic therapy on behavior in the wider PD literature. Dopaminergic therapy did not affect overall RTs in our PD patients and it significantly speeded motor responses assessed with the UPDRS. Addressing bradykinesia and

increasing the speed and fluency of movements and motor responses is the chief beneficial effect of dopaminergic therapy in PD (Espay et al., 2011; Macerollo et al., 2016). There is little evidence to suggest that dopaminergic therapy generally slows cognitive processes and in fact there is support that it hastens them (Cools et al., 2001; Hanna-Pladdy, Pahwa, & Lyons, 2015; Hood et al., 2007; MacDonald et al., 2011; MacDonald & Monchi, 2011; Righi, Viggiano, Paganini, Ramat, & Marini, 2007; Shook, Franz, Higginson, Wheelock, & Sigvardt, 2005). In contrast, dopaminergic therapy has been shown to increase response inhibition abilities as well as to promote the adoption of a more conservative response criterion, consistent with our explanation for increased Go Timeouts in the on state for PD patients in our study.

It was also not possible for PD patients to be blinded to their medication status during the on-off manipulation in our study. This is because patients had to comply with particular instructions to take or abstain from their usual dopaminergic therapy in a certain manner for on and off session, respectively. Even if these instructions could be concealed, patients are well acquainted with their symptoms both on and off dopaminergic therapy which precluded blinding patients to our medication manipulation. Consequently, we cannot rule out the possibility that expectancy effects contributed to our results. However, as previously noted, dopaminergic medications are known to speed motor functions in PD patients (Espay et al., 2011) and consequently any expectancy effects would have acted contrarily to the results that we obtained. Overall, despite these acknowledged alternative interpretations, we interpret enhanced Go Timeout responses in the on state as evidence that dopaminergic therapy reduces motor impulsivity. This account for our findings is supported by a larger literature as detailed in the sections above.

Our finding of more Go Timeouts with the administration of dopaminergic therapy could alternatively be interpreted as a worsening of ability to orient to stimuli. Lesion and neuroimaging studies have linked orienting to stimuli with the VS (see MacDonald & Monchi, 2011 for a review). A reinterpretation of our results in response to dopaminergic treatment as poorer ability to orient to stimuli, which is presumably a VS-mediated function, is entirely consistent with the patterns described by the dopamine overdose hypothesis (Anderson et al., 2016; Esslinger et al., 2013; Jensen et al., 2007; MacDonald

& Monchi, 2011; Zink et al., 2003). Here, we explain our finding of increased Go Timeouts with the addition of dopaminergic treatment as decreased motor impulsivity because the Go/No-go task has largely been interpreted in the context of response inhibition and motor impulse control (Antonelli et al., 2014; Ballanger et al., 2009; Fillmore, 2003; Liddle, Kiehl, & Smith, 2001; Rubia et al., 2001). However, we are not able to fully rule out the possibility of an effect of dopaminergic treatment on the ability to orient to stimuli.

Another limitation of the current study was that we did not conduct functional neuroimaging despite interpreting our behavioural results with respect to changes in activity in different brain areas. Our conclusions are supported by the wider literature implicating the DS in motor impulse control (Ray Li et al., 2008; Zandbelt & Vink, 2010) as well as imaging studies that show improvements in DS-mediated cognitive functions with the addition of dopaminergic therapy (Ali et al., 2009; MacDonald et al., 2014; MacDonald et al., 2011; Robertson et al., 2015; Zandbelt & Vink, 2010). However, the interpretation of our behavioural results would have been further strengthened with the use of functional neuroimaging to demonstrate the changes that occur in SNc- and VTA-innervated brain regions on and off dopaminergic therapy. Future investigations could incorporate functional MRI and an MRI-compatible version of the Go/No-go task.

## 4.8 Conclusions

Overall, the results of this study lend support for the role of dopaminergic therapy in decreasing motor impulsivity in PD. Our findings emphasize that impulsivity should be addressed as a multi-faceted construct rather than a single concept. We also highlight the importance of examining non-motor functions affected by dopaminergic medication in PD. These findings improve our understanding of how dopaminergic therapy affects cognition in PD. This knowledge will ultimately aid clinicians in developing optimal dopaminergic medication regimens for their PD patients, taking into account the different impacts on cognitive as well as motor functioning.

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[006X.46.1.139](https://doi.org/10.1037//0022-006X.46.1.139)



# Appendices

## Appendix A. Ethics approval notice.



**Date:** 30 November 2017

**To:** Penny MacDonald

**Project ID:** 102018

**Study Title:** Distinguishing the roles of ventral and dorsal striatum in cognition (REB #18517)

**Application Type:** Continuing Ethics Review (CER) Form

**Review Type:** Delegated

**Full Board Reporting Date:** December 5, 2017

**Date Approval Issued:** 30/Nov/2017

**REB Approval Expiry Date:** 29/Nov/2018

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Dear Penny MacDonald,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Kelly Patterson, Ethics Officer, on Behalf of Dr. Joseph Gilbert, HSREB Chair

*Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).*

## Appendix B. Bond-Lader Visual Analogue Scale (VAS).

<b>For administrator's use only</b>	Date (dd/mm/yy):	Session #:
Score:	Subject #:	Time:
	Medication:	


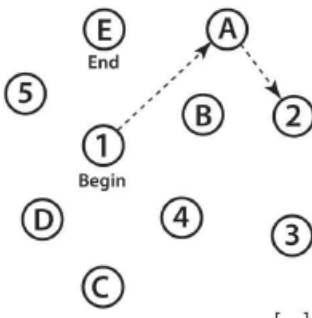
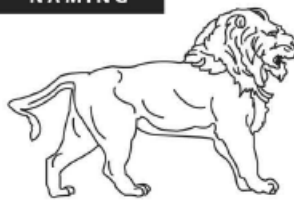
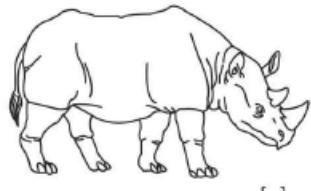
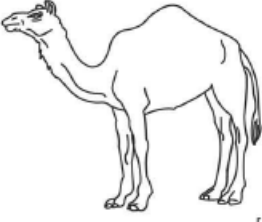
### Bond & Lader Visual Analogue Mood Scale

ALERT	_____	DROWSY	_____ mm
CALM	_____	EXCITED	_____ mm
STRONG	_____	FEEBLE	_____ mm
MUZZY	_____	CLEAR HEADED	_____ mm
WELL COORDINATED	_____	CLUMSY	_____ mm
LETHARGIC	_____	ENERGETIC	_____ mm
CONTENDED	_____	DISCONTENTED	_____ mm
TROUBLED	_____	TRANQUIL	_____ mm
MENTALLY SLOW	_____	QUICK WITTED	_____ mm
TENSE	_____	RELAXED	_____ mm
ATTENTIVE	_____	DREAMY	_____ mm
INCOMPENTENT	_____	PROFICIENT	_____ mm
HAPPY	_____	SAD	_____ mm
ANTAGONISTIC	_____	FRIENDLY	_____ mm
INTERESTED	_____	BORED	_____ mm
WITHDRAWN	_____	SOCIABLE	_____ mm

**Appendix C. American National Adult Reading Test (ANART).**

- |                 |                |               |
|-----------------|----------------|---------------|
| 1. ache         | 23. papyrus    | 45. caprice   |
| 2. debt         | 24. asthma     | 46. demesne   |
| 3. pint         | 25. hiatus     | 47. imbroglia |
| 4. depot        | 26. simile     | 48. hyperbole |
| 5. chord        | 27. blatant    | 49. syncope   |
| 6. bouquet      | 28. cellist    | 50. prelate   |
| 7. deny         | 29. zealot     |               |
| 8. capon        | 30. abstemious |               |
| 9. heir         | 31. meringue   |               |
| 10. aisle       | 32. placebo    |               |
| 11. subtle      | 33. façade     |               |
| 12. nausea      | 34. pugilist   |               |
| 13. gauge       | 35. virulent   |               |
| 14. naïve       | 36. worsted    |               |
| 15. thyme       | 37. détente    |               |
| 16. courteous   | 38. anise      |               |
| 17. algae       | 39. sieve      |               |
| 18. fetal       | 40. chassis    |               |
| 19. quadruped   | 41. beatify    |               |
| 20. epitome     | 42. scion      |               |
| 21. superfluous | 43. cabal      |               |
| 22. chamois     | 44. apropos    |               |

**Appendix D. Montreal Cognitive Assessment (MoCA).**

<b>MONTREAL COGNITIVE ASSESSMENT (MOCA)</b> Version 7.1 Original Version		NAME : Education : Sex :	Date of birth : DATE :
<b>VISUOSPATIAL / EXECUTIVE</b>		Copy cube 	Draw CLOCK (Ten past eleven) (3 points)
	[ ]	[ ]	[ ]    [ ]    [ ] Contour    Numbers    Hands
<b>NAMING</b>			
		[ ]	[ ]
<b>MEMORY</b>		Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.	
		FACE    VELVET    CHURCH    DAISY    RED	No points
		1st trial	[ ]    [ ]    [ ]    [ ]    [ ]
		2nd trial	[ ]    [ ]    [ ]    [ ]    [ ]
<b>ATTENTION</b>		Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4 Subject has to repeat them in the backward order [ ] 7 4 2	
Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors		[ ] FBACMNAAJKLBAFAKDEAAAJAMOF AAB	
Serial 7 subtraction starting at 100		[ ] 93    [ ] 86    [ ] 79    [ ] 72    [ ] 65	4 or 5 correct subtractions: <b>3 pts</b> , 2 or 3 correct: <b>2 pts</b> , 1 correct: <b>1 pt</b> , 0 correct: <b>0 pt</b>
<b>LANGUAGE</b>		Repeat : I only know that John is the one to help today. [ ] The cat always hid under the couch when dogs were in the room. [ ]	
Fluency / Name maximum number of words in one minute that begin with the letter F		[ ] _____ (N ≥ 11 words)	
<b>ABSTRACTION</b>		Similarity between e.g. banana - orange = fruit [ ] train - bicycle [ ] watch - ruler	
<b>DELAYED RECALL</b>		Has to recall words WITH NO CUE	Points for UNCUEd recall only
		FACE    VELVET    CHURCH    DAISY    RED	[ ]    [ ]    [ ]    [ ]    [ ]
<b>Optional</b>		Category cue	
		Multiple choice cue	
<b>ORIENTATION</b>		[ ] Date    [ ] Month    [ ] Year    [ ] Day    [ ] Place    [ ] City	
© Z.Nasreddine MD    www.mocatest.org    Normal ≥ 26 / 30		TOTAL    ___/30 Add 1 point if ≤ 12 yr edu	



## Appendix F. Barratt Impulsiveness Scale (BIS).

<b>For administrator's use only</b>	Date (dd/mm/yy):	Session #:
Score:	Subject #:	Time:
Sub-scores: A:    CI:    M:    P:    SC:    CC:	Medication:	

### Barratt Impulsiveness Scale (BIS-11)

**Directions:** People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an **X** on the appropriate circle on the right side of this page. **Do not** spend too much time on any statement. Answer quickly and honestly.

	1	2	3	4
	Rarely/Never	Occasionally	Often	Almost Always/Always
1. I plan tasks carefully.	1	2	3	4
2. I do things without thinking.	1	2	3	4
3. I make-up my mind quickly.	1	2	3	4
4. I am happy-go-lucky.	1	2	3	4
5. I don't "pay attention."	1	2	3	4
6. I have "racing" thoughts.	1	2	3	4
7. I plan trips well ahead of time.	1	2	3	4
8. I am self-controlled.	1	2	3	4
9. I concentrate easily.	1	2	3	4
10. I save regularly.	1	2	3	4
11. I "squirm" at plays or lectures.	1	2	3	4
12. I am a careful thinker.	1	2	3	4
13. I plan for job security.	1	2	3	4
14. I say things without thinking.	1	2	3	4
15. I like to think about complex problems.	1	2	3	4
16. I change jobs.	1	2	3	4
17. I act "on impulse."	1	2	3	4
18. I get easily bored when solving thought problems.	1	2	3	4
19. I act on the spur of the moment.	1	2	3	4
20. I am a steady thinker.	1	2	3	4
21. I change residences.	1	2	3	4
22. I buy things on impulse.	1	2	3	4
23. I can only think about one thing at a time.	1	2	3	4
24. I change hobbies.	1	2	3	4
25. I spend or charge more than I earn.	1	2	3	4
26. I often have extraneous thoughts when thinking.	1	2	3	4
27. I am more interested in the present than the future.	1	2	3	4
28. I am restless at the theatre or lectures.	1	2	3	4
29. I like puzzles.	1	2	3	4
30. I am future oriented.	1	2	3	4

## Appendix G. Sensation Seeking Scale (SSS).

<b>For administrator's use only</b>	Date (dd/mm/yy):	
Total: BS: D: ES: TAS:	Subject #:	Session #:
	Medication:	Time:

### Sensation Seeking Scale Form V

**Instructions:** Each of the items below contains two choices, A and B. Please indicate (circle) on your answer sheet which of the choices most describes your likes or the way you feel. In some cases you may find items in which both choices describe your likes or feelings. Please choose the one which better describes your likes or feelings.

In some cases you may find items in which you do not like either choice. In these cases mark the choice you dislike least. Please answer each item.

It is important you respond to all items with only one choice, A or B. We are interested only in your likes or feeling, not in how others feel about these things or how one is supposed to feel. There are no right or wrong answers as in other kinds of tests. Be frank and give your honest appraisal of yourself.

- |   |   |
|---|---|
| 1. A. I like "wild" uninhibited parties<br>B. I prefer quiet parties with good conversation   | 10. A. I would not like to try any drug which might produce strange and dangerous effects on me<br>B. I would like to try some of the new drugs that produce hallucinations |
| 2. A. There are some movies I enjoy seeing a second or even a third time<br>B. I can't stand watching a movie that I've seen before   | 11. A. A sensible person avoids activities that are dangerous<br>B. I sometimes like to do things that are a little frightening   |
| 3. A. I often wish I could be a mountain climber<br>B. I can't understand people who risk their necks climbing mountains  | 12. A. I dislike "swingers" (people who are uninhibited and free about sex)<br>B. I enjoy the company of real "swingers"  |
| 4. A. I dislike all body odors<br>B. I like some for the earthly body smells  | 13. A. I find that stimulants make me uncomfortable<br>B. I often like to get high (drinking liquor or smoking marijuana)   |
| 5. A. I get bored seeing the same old faces<br>B. I like to comfortable familiarity of everyday friends   | 14. A. I like to try new foods that I have never tasted before<br>B. I order the dishes with which I am familiar, so as to avoid disappointment and unpleasantness          |
| 6. A. I like to explore a strange city or section of town by myself, even if it means getting lost<br>B. I prefer a guide when I am in a place I don't know well                          | 15. A. I enjoy looking at home movies or travel slides<br>B. Looking at someone's home movies or travel slides bores me tremendously  |
| 7. A. I dislike people who do or say things just to shock or upset others<br>B. When you can predict almost everything a person will do and say he or she must be a bore                  | 16. A. I would like to take up the sport of water skiing<br>B. I would not like to take up water skiing   |
| 8. A. I usually don't enjoy a movie or play where I can predict what will happen in advance<br>B. I don't mind watching a movie or a play where I can predict what will happen in advance | 17. A. I would like to try surf boarding<br>B. I would not like to try surf boarding  |
| 9. A. I have tried marijuana or would like to<br>B. I would never smoke marijuana   |   |

18. A. I would like to take off on a trip with no preplanned or definite routes, or timetable  
B. When I go on a trip I like to plan my route and timetable fairly carefully
19. A. I prefer the "down to earth" kinds of people as friends  
B. I would like to make friends in some of the "far out" groups like artists or "punks"
20. A. I would not like to learn to fly an airplane  
B. I would like to learn to fly an airplane
21. A. I prefer the surface of the water to the depths  
B. I would like to go scuba diving
22. A. I would like to meet some persons who are homosexual (men or women)  
B. I stay away from anyone I suspect of being "gay or lesbian"
23. A. I would like to try parachute jumping  
B. I would never want to try jumping out of a plane with or without a parachute
24. A. I prefer friends who are excitingly unpredictable  
B. I prefer friends who are reliable and predictable
25. A. I am not interested in experience for its own sake  
B. I like to have new and exciting experiences and sensations even if they are a little frightening, unconventional, or illegal
26. A. The essence of good art is in its clarity, symmetry of form and harmony of colors  
B. I often find beauty in the "clashing" colors and irregular forms of modern paintings
27. A. I enjoy spending time in the familiar surroundings of home  
B. I get very restless if I have to stay around home for any length of time
28. A. I like to dive off the high board  
B. I don't like the feeling I get standing on the high board (or I don't go near it at all)
29. A. I like to date members of the opposite sex who are physically exciting  
B. I like to date members of the opposite sex who share my values
30. A. Heavy drinking usually ruins a party because some people get loud and boisterous  
B. Keeping the drinks full is the key to a good party
31. A. The worst social sin is to be rude  
B. The worst social sin is to be a bore
32. A. A person should have considerable sexual experience before marriage  
B. It's better if two married persons begin their sexual experience with each other
33. A. Even if I had the money I would not care to associate with flight rich persons like those in the "jet set"  
B. I could conceive of myself seeking pleasures around the world with the "jet set"
34. A. I like people who are sharp and witty even if they do sometimes insult others  
B. I dislike people who have their fun at the expense of hurting the feelings of others
35. A. There is altogether too much portrayal of sex in movies  
B. I enjoy watching many of the "sexy" scenes in movies
36. A. I feel best after taking a couple of drinks  
B. Something is wrong with people who need liquor to feel good
37. A. People should dress according to some standard of taste, neatness, and style  
B. People should dress in individual ways even if the effects are sometimes strange
38. A. Sailing long distances in small sailing crafts is foolhardy  
B. I would like to sail a long distance in a small but seaworthy sailing craft
39. A. I have no patience with dull or boring persons  
B. I find something interesting in almost every person I talk to
40. A. Skiing down a high mountain slope is a good way to end up on crutches  
B. I think I would enjoy the sensations of skiing very fast down a high mountain slope



## Appendix H. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS).

<b>For administrator's use only</b>	Date (dd/mm/yy):	Session:
Score:	Subject #:	Time:
	Medication:	

### Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS)

1. How much do you think about the following behaviors (such as having trouble keeping thoughts out of your mind or feeling guilty)?

Gambling?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Sex?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Buying?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Eating?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Performing tasks or hobbies?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Repeating simple activities?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Taking your PD medications?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)

2. Do you have urges or desires for the following behaviors that you feel are excessive or cause you distress (including becoming restless or irritable when unable to participate in them)?

Gambling?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Sex?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Buying?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Eating?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Performing tasks or hobbies?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Repeating simple activities?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Taking your PD medications?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)

3. Do you have difficulty controlling the following behaviors (such as increasing them over time, or having trouble cutting down or stopping them)?

Gambling?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Sex?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Buying?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Eating?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Performing tasks or hobbies?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Repeating simple activities?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Taking your PD medications?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)

4. Do you engage in activities specifically to continue the following behaviors (such as hiding what you are doing, lying, hoarding things, borrowing from others, accumulating debt, stealing, or being involved in illegal acts)?

Gambling?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Sex?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Buying?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Eating?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Performing tasks or hobbies?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Repeating simple activities?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Taking your PD medications?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)

**Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale  
(QUIP-RS)**

Subject: \_\_\_\_\_

Date: \_\_\_\_\_

**SCORING SHEET**

**A. Gambling** \_\_\_\_\_ **(0-16)**

**B. Sex** \_\_\_\_\_ **(0-16)**

**C. Buying** \_\_\_\_\_ **(0-16)**

**D. Eating** \_\_\_\_\_ **(0-16)**

**E. Hobbyism-Punding** \_\_\_\_\_ **(0-32)**

**F. PD Medication Use** \_\_\_\_\_ **(0-16)**

**Total ICD Score (A-D)** \_\_\_\_\_ **(0-64)**

**Total QUIP-RS Score (A-F)** \_\_\_\_\_ **(0-112)**

## Appendix I. New Freezing of Gait Questionnaire (NFOG).

<b>For administrator's use only</b>	Date (dd/mm/yy):	Session:
Score:	Subject #:	Time:
	Medication:	

### New Freezing of Gait Questionnaire

<p><b>Part I – Distinction Freezer – non-Freezer, over the past month</b></p> <p><b>1. Did you experience “freezing episodes” over the past month?</b></p> <p><i>Without video</i></p> <p><i>Freezing is the feeling that your feet are transiently glued to the floor while trying to initiate walking, making a turn or when walking through narrow spaces or in crowded places? Sometimes it can be accompanied with trembling of the legs and small shuffling steps.</i></p> <p><i>Additional instructions with video</i></p> <p><i>We will watch a short video together to see the many ways in which freezing can occur. Also, look carefully for how long these episodes last, as you can expect some questions on this later. (tester points out the clock on video clip)</i></p> <p>0. I have not experienced such a feeling or episode over the past month</p> <p>1. I have experienced such a feeling or episode over the past month</p> <p><b><i>If the answer is 1 (patient is a freezer) complete part II and III. The sum of part II and III is the final NFOG score.</i></b></p>
<p><b>Part II – Freezing severity</b></p> <p><b>2. How frequently do you experience freezing episodes?</b></p> <p>0. Less than once a week</p> <p>1. Not often, about once a week</p> <p>2. Often, about once a day</p> <p>3. Very often, more than once a day</p>
<p><b>3. How frequently do you experience freezing episodes during turning?</b></p> <p>0. Never</p> <p>1. Rarely, about one a month</p> <p>2. Not often, about once a week</p> <p>3. Often, about once a day</p> <p>4. Very often, more than once a day</p> <p><b>If the answer is 1 or more go to question #4. If the answer is 0, go directly to #5.</b></p>
<p><b>4. How long is your longest freezing episode during turning?</b></p> <p>1. Very short, 1 sec</p> <p>2. Short, 2 - 5 s.</p> <p>3. Long, between 5 and 30 s.</p> <p>4. Very long, unable to walk for more than 30 s.</p>

<p><b>5. How frequently do you experience episodes of freezing when initiating the first step?</b></p> <ul style="list-style-type: none"> <li>0. Never</li> <li>1. Rarely, about once a month</li> <li>2. Not often, about once a week</li> <li>3. Often, about once a day</li> <li>4. Very often, more than once a day</li> </ul> <p><b>If the answer 1 or more go to question #6. If the answer is 0, go directly to #7.</b></p>
<p><b>6. How long is your longest freezing episode when initiating the first step?</b></p> <ul style="list-style-type: none"> <li>1. Very short, 1 s.</li> <li>2. Short, 2-5 s.</li> <li>3. Long, between 5 and 30 s.</li> <li>4. Very long, unable to walk for more than 30 s.</li> </ul>
<p><b>Part III – Freezing impact on daily life</b></p>
<p><b>7. How disturbing are the freezing episodes for your daily walking?</b></p> <ul style="list-style-type: none"> <li>0. Not at all</li> <li>1. Very little</li> <li>2. Moderately</li> <li>3. Significantly</li> </ul>
<p><b>8. Do the freezing episodes cause feelings of insecurity and fear of falling?</b></p> <ul style="list-style-type: none"> <li>0. Not at all</li> <li>1. Very little</li> <li>2. Moderately</li> <li>3. Significantly</li> </ul>
<p><b>9. Are your freezing episodes affecting your daily activities?</b>  <b>(Rate the impact of freezing on daily activities only. Not the impact of the disease in general)</b></p> <ul style="list-style-type: none"> <li>0. Not at all, I continue doing things as normal</li> <li>1. Mildly, I avoid only few daily activities</li> <li>2. Moderately, I avoid a significant amount (about half) of daily activities</li> <li>3. Severely, I am very restricted in carrying out most daily activities</li> </ul>

## Appendix J. Starkstein Apathy Scale (SAS).

<b>For administrator's use only</b>	Date (dd/mm/yy):	Session #:
Score:	Subject #:	Time:
	Group:	

### Starkstein Apathy Scale

**Instructions:** For each question, indicate as "Not at all", "Slightly", "Some", or "A lot" with an 'X' while leaving the other spaces blank.

Questions	Not at all	Slightly	Some	A lot
1. Are you interested in learning new things?				
2. Does anything interest you?				
3. Are you concerned about your condition?				
4. Do you put much effort into things?				
5. Are you always looking for something to do?				
6. Do you have plans and goals for the future?				
7. Do you have motivation?				
8. Do you have the energy for daily activities?				
9. Does someone have to tell you what to do each day?				
10. Are you indifferent to things?				
11. Are you unconcerned with many things?				
12. Do you need a push to get started on things?				
13. Are you neither happy nor sad, just in between?				
14. Would you consider yourself apathetic?				

## Appendix K. Unified PD Rating Scale - Motor Subscale (UPDRS).

### UPDRS Protocol

Ask at the start *“which arm/hand do you have most difficulty with?”*

Always start with LESS impaired side

Only model for a few seconds, then stop

*“This is subject (PD/CTRL #), session #, (on/off) medication.”*

1. Film face at rest for a few seconds
2. Ask patient to speak one-two sentences (for dysarthria)
  - *“Today is a very nice day outside”*
  - *“I am at the University for an experiment”*
3. Evaluate resting tremor
  - a. hands relaxed on thighs
  - b. with cognitive stressing *“Close your eyes and name the months of the year backward from December”*
4. Evaluate tone
  - a. Bilateral upper extremities
5. Evaluate postural tremor
  - a. hands outstretched
  - b. fingertips apposed (forming wings with arms ensuring fingers are not touching)
6. Evaluate action tremor
  - a. Finger-to-nose (finger target should be arms-length away and in same position)
7. Evaluate bradykinesia
  - a. Finger taps (pinching) *“Big and fast”*
  - b. Hand opening-closing movements *“Big and fast”*
  - c. Pronation-supination movements *“Fast as you can”*
  - d. Toe-tapping (minimum 3 inches off ground)
8. Ask patient to rise from the chair without the assistance of his/her arms (arms crossed over chest) *“Fold your arms across and chest and stand up”*
9. Evaluate gait, ask to walk up and down hallway 2-3 times, with turns
10. Pull test *“Try to maintain your balance and limit yourself to one step backwards”*

## Curriculum Vitae

**Name:** Xue Qing Yang

**Post-secondary Education and Degrees:**

Western University  
 London, Ontario, Canada  
 Master of Science  
 Department of Psychology  
 Cognitive, Developmental and Brain Sciences  
 2016 – Present

Western University  
 London, Ontario, Canada  
 Bachelor of Medical Science  
 Department of Physiology and Pharmacology  
 Honours Specialization in Physiology, Minor in Psychology  
 2012 – 2016

**Honours and Awards:**

Canada Graduate Scholarship – Master’s Program  
 Canadian Institutes of Health Research  
 2017 – 2018

Ontario Graduate Scholarship (Offered)  
 2017

Undergraduate Student Research Award  
 Natural Sciences and Engineering Research Council of Canada (NSERC)  
 2015

Continuing Admission Scholarship  
 Western University  
 2012 – 2016

**Presentations**

Clinical Neurological Sciences Departmental Research Day  
*Effects of Dopaminergic therapy on delay and probability discounting in Parkinson’s disease*  
 Poster presentation  
 2017

Retiring with Strong Minds Community Seminar  
*Different forms of impulsivity in Parkinson’s disease*  
 Seminar presentation  
 2017

**Research  
Experience**

Master's degree  
MacDonald Lab, Western University  
*Investigating the effects of Dopaminergic therapy on motor  
planning and motor control in Parkinson's disease*  
2016 – 2018

Master's degree  
MacDonald Lab, Western University  
*Dopaminergic therapy increases Go Timeouts in the Go/No-Go  
task in patients with Parkinson's Disease*  
2016 – 2018

Fourth year undergraduate thesis project  
MacDonald Lab, Western University  
*Effect of pramipexole on motor impulsivity in young healthy  
volunteers*  
2015 – 2016

NSERC Undergraduate Student Research Award  
Peng Lab, York University  
*Role of Nodal and Versican in migration and invasion of epithelial  
ovarian cancer cells*  
2015

Research Assistant  
Neff Lab, Western University  
*Relationship between testosterone and immunity in bluegill sunfish*  
2014 – 2015

**Related Work**

Teaching Assistant  
Psychology 2043A  
Exceptional Children: Developmental Disorders  
2018

Teaching Assistant  
Psychology 1000  
Introduction to Psychology  
2016 – 2017

**Publications:**

Yang, X. Q., Glizer, D., Vo, A., Seergobin, K. N., & MacDonald, P. A. (2016).  
Pramipexole Increases Go Timeouts but Not No-go Errors in Healthy Volunteers.  
*Frontiers in Human Neuroscience, 10*, 523. <https://doi.org/10.3389/fnhum.2016.00523>



Yang, X. Q., Lauzon, B., Seergobin, K. N., & MacDonald, P. A. (2018). Dopaminergic Therapy Increases Go Timeouts in the Go/No-Go Task in Patients with Parkinson's Disease. *Frontiers in Human Neuroscience, 11*, 642.  
<https://doi.org/10.3389/fnhum.2017.00642>