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Putting 'Dopamine Overdose' To The Test: A Psychopharmacological Investigation in Parkinson's Disease and Healthy Volunteers

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Abstract

Dopaminergic therapy prescribed to address motor symptoms in Parkinson's disease (PD) is done at the expense of some cognition functions. It has been hypothesized that whether a given function is improved or impaired by medication depends on the baseline dopamine levels within underlying brain regions. Areas most affected by PD and severely dopamine depleted are predicted to benefit from dopaminergic therapy. Regions with less dopamine deficiency are predicted to worsen from excessive dopamine stimulation. This theoretical framework is known as the dopamine overdose hypothesis. The central aim of this thesis was to critically test the straightforward predictions put forward by this overdose account. First, I examined the effects of dopaminergic therapy on stimulus-reward and reversal learning in groups of PD patients that differed in severity of their disease and extent of dopamine deficiency. Learning impairments were found in late-stage PD at baseline and in early-stage PD with dopaminergic therapy, replicating previous findings. Predicted medication-related improvements in late-stage PD were not found, however. Next, I tested the effects of a dopamine challenge with L-dopa on reward learning in groups of healthy volunteers differentially affected by age-related dopamine decline. I found age-related baseline learning impairments in older compared to younger adults. L-dopa worsened learning similarly in both age groups, however. Last, I explored the effects of L-dopa on learning and associated brain activity in a sample of healthy young volunteers who are presumed to have optimal endogenous dopamine levels. Learning and associated brain activity was reduced following L-dopa administration, but decision enactment was unaffected. Taken together, these studies provide partial support for the dopamine overdose hypothesis but suggest a less straightforward scenario than initially predicted.

Keywords

Parkinson's disease; dopamine; dopaminergic therapy; striatum; functional MRI; cognition; cognitive impairment, reversal learning; reward learning; L-dopa

Lay Abstract

Parkinson's disease is marked by the loss of brain cells that produce the neurochemical dopamine, giving rise to motor symptoms such as tremor and rigidity. Dopaminergic therapy is prescribed to address this dopamine deficiency and improve motor function; however, this is done at the expense of some cognitive functions. The dopamine overdose hypothesis predicts that functions of brain regions with low dopamine levels will be improved by medication whereas those with high dopamine levels will worsen. The central aim of this thesis was to critically test this claim by comparing the effects of dopaminergic therapy on cognitive function in groups of participants that differed in their degree of dopamine deficiency. First, I tested how more severe dopamine depletion in late- compared to early-stage Parkinson's disease influenced the effects of medication on reward-based learning. Next, I examined how normal age-related declines in dopamine affected reward learning and responses to dopaminergic therapy in healthy older versus younger adults. Last, I explored how learning, decision-making, and associated brain activity were impacted by dopaminergic therapy when administered in healthy young adults with optimal dopamine levels. Across these three separate studies, I found only partial support for the dopamine overdose hypothesis. The effects of dopaminergic therapy on cognition are far more complex and less straightforward than initially predicted by this theoretical framework. Understanding these nuances will help clinicians guide treatment strategies in Parkinson's disease towards improving patient care and quality of life.

Co-Authorship Statement

All chapters of this dissertation were written by AV, with input and revisions from PAM. Each experiment was designed in collaboration with PAM and KNS. Data collection was performed by AV, with technical support from KNS. Statistical analyses were carried out by AV, with input from PAM.

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List of Abbreviations

ANART	American National Adult Reading Test
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BOLD	blood oxygenation level dependent
DAT	dopamine transporter
DS	dorsal striatum
ePD	early-stage Parkinson's disease
fMRI	functional magnetic resonance imaging
HC	healthy controls
L-dopa	levodopa or L-3,4-dihydroxyphenylalanine
lPD	late-stage Parkinson's disease
MoCA	Montreal Cognitive Assessment
NAc	nucleus accumbens
OFC	orbitofrontal cortex
PD	Parkinson's disease
PET	positron emission tomography
PRL	probabilistic reversal learning
ROI	region of interest
SNc	substantia nigra pars compacta
VS	ventral striatum
VTA	ventral tegmental area

Chapter 1

General Introduction

1.1 Overview

The central aim of this dissertation is to investigate the effects of dopaminergic therapy on cognition. I present a series of experiments designed to critically test the dopamine overdose hypothesis, an explanatory framework for understanding the effects of Parkinson's disease (PD) and dopamine replacement therapy on brain function. This longstanding account proposes that the effects of dopaminergic therapy on functions mediated by a given brain region depend on the baseline dopamine levels within the region. Whereas medication is predicted to improve those functions ascribed to areas most depleted of dopamine, those mediated by relatively dopamine-replete areas are expected to worsen. Evidence for such a baseline dependency in determining the effect of exogenous dopamine on functions is largely limited to behavioural studies in early-stage PD that use repeated experimental designs within an invariable cohort.

Combining pharmacological manipulations and functional MRI in cohorts with circumscribed dopamine deficiencies, I tested the role of baseline endogenous dopamine levels in mediating the effects of dopaminergic therapy on cognition. In Chapter 2, medication effects on reward learning were examined in groups of early- versus late-stage PD patients that differed in the degree of dopamine deficiency as a function of disease severity. In Chapter 3, the effects of a dopamine challenge on reward learning were tested in young and older healthy adults who were differentially affected by age-related dopamine decline. In Chapter 4, the effects of a dopamine challenge on learning and associated brain activity were explored in a sample of healthy young volunteers who were expected to have optimal dopamine levels in all brain regions.

1.2 Literature Review

1.2.1 Cognitive impairment in Parkinson's disease

PD is a progressive, age-related, neurodegenerative disorder affecting approximately 1% of the population over age 60 and increasing to 3% of the population over age 80 (Reeves, Bench, & Howard, 2002; Tanner & Goldman, 1996). Often regarded as a movement disorder, PD is characterized by cardinal motor symptoms of tremor, rigidity and stiffness, bradykinesia (i.e., slowness of movement), and postural instability (Lang & Lozano, 1998). Beyond these more apparent motor-based deficits, however, is a complex array of non-motor symptoms that include cognitive and affective impairment, hyposmia (i.e., impaired sense of smell), autonomic dysfunction, sleep disturbances, and gastrointestinal complications (Chaudhuri, Healy, & Schapira, 2006).

Cognitive impairment is an undisputed non-motor disease feature in PD (Robbins & Cools, 2014). Dementia is estimated to occur in up to 40% of patients (Aarsland, Zaccai, & Brayne, 2005; Brown & Marsden, 1984; Emre, 2003). Although mild cognitive impairment and overt dementia are well-recognized in advancing PD, it is increasingly clear that subtler changes to cognition are frequently present in a significant proportion of patients (Kehagia, Barker, & Robbins, 2010; Monchi, Degroot, Mejia-Constain, & Bruneau, 2012). These milder cognitive symptoms appear even in the earliest stages of PD, becoming more pronounced and varied with increasing disease duration and severity. Early reports of cognitive abnormalities in PD were described as being 'frontal-like' because of their resemblance to those deficits observed in frontal lobe patients (Owen et al., 1992; Taylor, Saint-Cyr, & Lang, 1990). Such deficits are largely in executive functions, including attention, planning, problem-solving, and set-shifting (Dirnberger &

Jahanshahi, 2013). The profile of cognitive impairments in PD has since expanded to encompass problems in visuospatial processing (Boller et al., 1984), memory (Brønnick, Alves, Aarsland, Tysnes, & Larsen, 2011; Cohn, Moscovitch, & Davidson, 2010; Davidson, Anaki, Saint-Cyr, Chow, & Moscovitch, 2006; Taylor et al., 1990), and reward-based learning (Frank, Seeberger, & O'Reilly, 2004; Künig et al., 2000).

Unlike their motor counterparts, which are more easily discerned and characterized, cognitive impairments in PD are complex and their etiology is poorly understood. Some cognitive abnormalities might result from cortical atrophy, although such deficits can still present even in patients absent of cortical compromise, as confirmed by post-mortems (Adler et al., 2010; Jellinger, 2010). Lewy body dispersion has also been proposed as a cause of cognitive impairment in PD. Evidence for a correlation between Lewy body burden and dispersion in cortical regions remains controversial, however (Jellinger, 2008; 2009; Mattila, Rinne, Helenius, Dickson, & Röyttä, 2000; Parkkinen, Kauppinen, Pirttilä, Autere, & Alafuzoff, 2005; Weisman et al., 2007). A pathological feature common across PD patients is the degeneration of midbrain dopamine neurons (Kish, Shannak, & Hornykiewicz, 1988). Given the critical role of dopamine in various aspects of cognition and behaviour (Berridge & Robinson, 1998; Schultz, 2007), dopamine dysfunction may serve as a central mechanism for cognitive symptoms in PD, particularly at earlier disease stages. Alterations in other neurotransmitter systems, such as the cholinergic or serotonergic systems, likely also contribute to cognitive and psychiatric problems (Ray & Strafella, 2012; Scatton, Javoy-Agid, Rouquier, Dubois, & Agid, 1983).

Cognitive deficits disproportionately impair quality of life and are a significant predictor of institutionalization (Aarsland, Larsen, & Tandberg, 2000). Although

recognized as an important unmet need in PD, the proper management of these symptoms is constrained by poor assessment and treatment strategies. Our understanding of and ability to address cognitive symptoms is stifled by their complexity and the challenges associated with their study. Fortunately, refinements in neuropsychological tests of brain function in tandem with recent advancements in functional neuroimaging provide a unique opportunity to directly investigate cognitive impairments in PD and their underlying neural mechanisms.

1.2.2 Pathophysiology of Parkinson's disease

PD is marked by a profound loss of dopamine-producing cells in the substantia nigra pars compacta (SNc). In fact, by the time a patient presents to the clinic with motor complaints and is diagnosed with PD, more than 80% of their dopaminergic neurons in the SNc have been lost (Halliday & McCann, 2010; Kish et al., 1988). The brain region most affected by changes to the dopaminergic system is the striatum, the input region of a collection of subcortical nuclei known as the basal ganglia. A second hallmark pathology in PD is the accumulation of misfolded α-synuclein protein into Lewy pathologies (Braak et al., 2003). These aggregates first deposit in the lower brain stem and olfactory areas. Protein deposition then spreads to the midbrain, corresponding with the selective loss of SNc neurons, before migrating to limbic and temporal structures, and then to the frontal cortex by advanced disease stages. The spreading pattern of misfolded α -synuclein protein with disease progression is described by Braak's staging hypothesis (Braak et al., 2003).

Sources of dopamine, namely the SNc and the ventral tegmental area (VTA), originate in the midbrain (see Figure 1.1). These neuronal populations give rise to two major dopamine pathways: SNc projects to dorsal striatum (DS) giving rise to

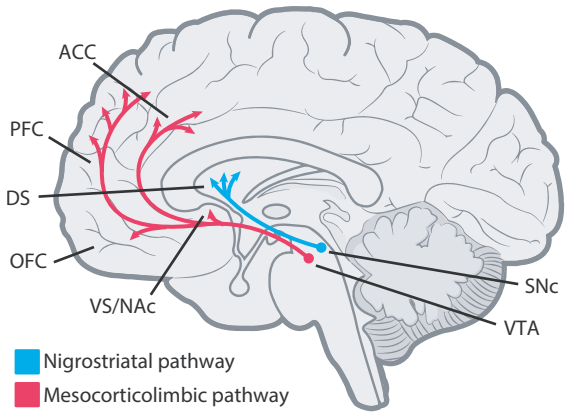

Figure 1.1: Dopaminergic pathways in the human brain. Dopaminergic neurons in the SNc project to and supply dopamine to DS, forming the nigrostriatal pathway (blue). Another population of dopaminergic neurons in the VTA innervates VS/NAc as well as other prefrontal and limbic cortices. This pathway is referred to collectively as the mesocorticolimbic pathway (red). ACC: anterior cingulate cortex; DS: dorsal striatum; PFC: prefrontal cortex; OFC: orbitofrontal cortex; SNc: substantia nigra pars compacta; VS/NAc: ventral striatum/nucleus accumbens; VTA: ventral tegmental area

the nigrostriatal pathway and VTA innervates ventral striatum (VS), limbic, and prefrontal cortices, forming the mesocorticolimbic pathway (Oades & Halliday, 1987). The DS is comprised of the bulk of the caudate nucleus and putamen whereas the VS constitutes the nucleus accumbens and the most ventral caudate and putamen. The pattern of dopamine dysfunction across these distinct pathways is not uniform in PD (Kish et al., 1988). At earlier disease stages, loss of dopaminergic neurons is confined to the ventrolateral SNc and decreased dopamine transmission is greatest in the caudal motor aspect of DS (Fearnley & Lees, 1991; Halliday & McCann, 2010). This results in the development of motor symptoms that typify PD. In contrast, those dopaminergic neurons in the dorsal SNc and VTA are relatively spared, and functions of their downstream targets are largely unperturbed. The asymmetry in dopamine dysfunction between nigrostriatal versus mesocorticolimbic pathways is maintained throughout the disease course, but becomes less pronounced at more advanced stages (Morrish, Sawle, & Brooks, 1996; Nandhagopal et al., 2009).

A key function of dopamine is to regulate the balance between two competing basal ganglia pathways, which in turn regulates thalamic and cortical activity (Frank, 2005); see Figure 1.2). The striatum receives input from the cortex and midbrain dopamine neurons. In the direct pathway, cortical activity and SNc dopamine activate D1 receptor-expressing neurons in the striatum, increasing the inhibition of the globus pallidus internal segment (GPi) and substantia nigra pars reticulata (SNr) output nuclei. In the indirect pathway, cortical activity increases and SNc dopamine inhibits D2 receptor-expressing neurons in the striatum, increasing inhibition of globus pallidus external segment (GPe), releasing subthalamic nucleus (STN), which drives activity of GPi/SNr output. The net effect of dopamine in both pathways is an overall decrease in thalamic inhibition,

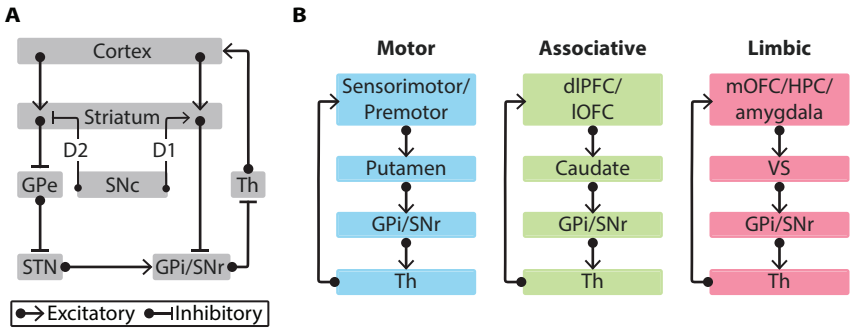

Figure 1.2: (A) Direct and indirect pathways of the basal ganglia. Midbrain dopamine regulates the balance between direct and indirect pathways. In PD, dopamine depletion in the striatum has opposing effects on these two competing pathways. The net effect is an over-inhibition of thalamic and motor cortex activity, resulting in poverty of movement that typifies the disease. **(B)** Parallel, segregated cortico-striatal loops. Dopamine depletion within different functional domains of the striatum produces circuit-specific dysfunction. dlPFC: dorsolateral prefrontal cortex; GPe: external segment of the globus pallidus; GPi: internal segment of the globus pallidus; HPC: hippocampus; l/mOFC: lateral/medial orbitofrontal cortex; SNc: substantia nigra pars compacta; SNr: substantia nigra pars reticulata; STN: subthalamic nucleus; Th: thalamus; VS: ventral striatum.

increasing cortical activity and completing a cortico-striatal loop. Loops from cortex to striatum and then back to cortex via the output nuclei of the basal ganglia (i.e., the globus pallidue and the SNr) and thalamus are topographically organized into discrete, parallel, segregated circuits (Alexander, DeLong, & Strick, 1986). Depending upon the functional domain of the striatum in which dopamine depletion develops, circuit-specific motor, cognitive, or limbic dysfunctions are produced. PD causes a reduction in dopamine transmission in the putamen. The consequent (a) decrease in direct pathway and (b) increase in indirect pathway activity both result in over-inhibition of the thalamus and of cortex, particularly the motor cortex. The inhibition of motor cortex leading to a decrease in motor activity characteristic of PD.

1.2.3 Dopamine replacement therapy

Dopamine replacement therapies are the mainstay treatment for motor symptoms in PD. They are prescribed to primarily redress the dopamine deficiency in DS and to normalize DS-mediated motor abnormalities. Dopaminergic therapy is commonly administered in PD via L-3,4-dihydroxyphenylalanine (L-dopa) or dopamine agonists.

Since its introduction, L-dopa has remained the gold standard treatment for motor symptoms in PD (LeWitt & Fahn, 2016). A dopamine precursor, it is taken up into dopaminergic neurons where it is decarboxylated into dopamine, stored in vesicles, and released from the presynaptic terminal. L-dopa is typically co-administered with a decarboxylase inhibitor, which itself cannot cross the blood-brain barrier, to minimize the conversion of L-dopa to dopamine in the periphery. Dopamine agonists are compounds that directly mimic the action of dopamine at post-synaptic receptors, mainly targeting D2 receptors. Because L-dopa (a) is absorbed and converted to dopamine via endogenous mechanisms, (b) non-

selectively acts on both D1 and D2 receptors, and (c) increases both phasic and tonic dopamine stimulation, it more closely approximates endogenous dopamine signalling compared to dopamine agonists.

Dopaminergic therapy alleviates motor symptoms in PD by redressing the dopamine depletion in DS and normalizing the balance between the direct and indirect basal ganglia pathways (see Figure 1.2). Recall that in PD, dopamine deficiency has opposing effects on these two competing circuits. Whereas activity in the direct 'Go' pathway is decreased, the activity in the indirect 'NoGo' pathway is increased. The net result is an over-inhibition of thalamic output and a consequent reduction in motor activity. Dopaminergic medications reverse this imbalance between direct and indirect pathways by driving excitatory and dampening inhibitory striatal outputs via D1 and D2 receptor stimulation, respectively.

1.2.4 Dopamine overdose hypothesis

Although dopaminergic therapy consistently improves motor symptoms in PD, its effects on cognitive functions are complex. Gotham et al. (1988) first noted paradoxical effects of medication on cognition in PD. The authors tested PD patients both on and off medication on a battery of cognitive tests that examined executive function, cognitive flexibility, working memory and attention, associative learning, and verbal fluency. PD patients were impaired on a word fluency task only when tested OFF medication. In contrast, performance on associative learning and self-ordered pointing tasks, which assess learning and working memory, were worsened in PD patients tested ON medication. Other tasks, such as the Wisconsin Card Sorting Task, were equally impaired in the OFF and ON states. These findings led to an early proposal that doses of dopaminergic

therapy prescribed to remedy functions of motor-related brain regions might 'overdose' other brain areas that support some cognitive functions.

The dopamine overdose hypothesis would later be formally proposed in the works of Swainson et al., (2000) and Cools et al., (2001a). This explanatory framework posits that the effects of dopaminergic therapy on a given brain region's function depends on the baseline dopamine levels within that region (see Figure 1.3). In PD, medication is predicted to improve those functions mediated by dopamine-deplete brain regions, whereas those ascribed to intact dopaminergic brain regions are detrimentally overdosed (Cools, 2006; P. A. MacDonald & Monchi, 2011). Such a relationship between dopamine levels and brain function is modelled by an inverted U-shaped function (Cools & D'Esposito, 2011).

Swainson et al., (2000) reported differential effects of PD and dopaminergic medication on short-term spatial memory and cognitive flexibility. The authors compared three groups of PD patients: a mild, unmedicated group, a mild, medicated group, and a severe, medicated group. On a test of short-term spatial memory, unmedicated PD patients demonstrated impairments not observed in those patients who were medicated. In a reversal learning task, the opposite pattern was noted, as both medicated PD groups were impaired whereas the unmedicated group showed intact learning. Although these findings appear to support the idea of a dopamine overdose at first glance, it should be noted that medicated patients in this study were more clinically disabled compared to *de novo* patients introducing a potential confound. In groups of PD patients better matched for disease severity, Cools and colleagues (2001a) compared task-switching and probabilistic reversal learning in PD patients tested either on or after overnight withdrawal of medication. Measures of task-switching were impaired in the OFF group but comparable to controls in the ON group,

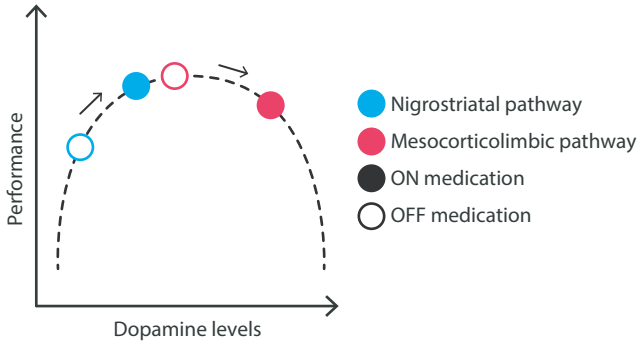

Figure 1.3: Illustration of the inverted U-shaped function described by the dopamine overdose hypothesis. The schematic illustrates the relationship between brain function and dopamine levels that are augmented by dopamine depletion and replacement. Whereas brain regions deplete in dopamine levels are impaired at baseline and improve with dopaminergic therapy (blue), those that are relatively dopamine-replete at baseline are worsened with medication (red), presumably through dopamine overdose.

suggesting a medication-related improvement. In contrast, unimpaired reversal learning in the OFF group was compromised in the ON group. These findings fully replicate the findings of Swainson et al., (2000).

The effects of PD and dopaminergic therapy on different cognitive functions described in the studies above can be understood based on (i) the brain regions known to mediate cognitive functions, (ii) the pathophysiology in PD, and (iii) the dopamine overdose hypothesis. Functions such as task-switching and spatial memory have been attributed to DS or its cortical partners (Aarts et al., 2014; 2010; Yehene, Meiran, & Soroker, 2008) whereas reversal learning has been ascribed to VS and ventral PFC (Cools, Clark, Owen, & Robbins, 2002; O'Doherty, Critchley, Deichmann, & Dolan, 2003; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). In PD, selective degeneration of SNc neurons produces a severe restriction of dopamine supply to DS, giving rise to motor and some cognitive symptoms. By contrast, those neurons in the VTA presumably are largely spared and functions of VTA-innervated brain regions are unaffected. Impaired spatial memory and task switching but unaffected reversal learning in PD patients OFF medication are reflective of this differential baseline impairment between DS versus VS, limbic and prefrontal cortical functions (Cools, Barker, Sahakian, & Robbins, 2001a; Swainson et al., 2000). Dopaminergic therapy is prescribed in PD to redress the dopamine deficiency in DS and normalize DS-mediated functions. Such doses of medication are proposed to overdose and worsen the functions of less dopamine-depleted VTA-innervated brain regions. Entirely in line with this prediction, spatial memory and task switching were improved but reversal learning was impaired in PD patients ON medication.

Since this initial work, the dopamine overdose hypothesis has guided the design of studies of cognition in PD over the past two decades. Behavioural studies

examining PD patients on versus off medication have revealed medication-related worsening in several functions, including: probabilistic associative learning (Jahanshahi et al., 2010; Torta, Castelli, Zibetti, Lopiano, & Geminiani, 2009), sequence learning (Feigin et al., 2003; Kwak, Müller, Bohnen, Dayalu, & Seidler, 2010; Seo, Seo, Beigi, Jahanshahi, & Averbeck, 2010; Tremblay et al., 2010), category learning (Shohamy et al., 2006), stimulus reward and reversal learning (Cools, Altamirano, & D'Esposito, 2006; Graef et al., 2010; A. A. MacDonald, Monchi, et al., 2013a; Swainson et al., 2000; Tomer, Aharon-Peretz, & Tsitrinbaum, 2007), stimulus-response learning (Vo et al., 2014), as well as explicit abstract figure and list learning (A. A. MacDonald, Seergobin, et al., 2013b), stimulus-stimulus facilitation (P. A. MacDonald et al., 2011), and learning from negative feedback (Frank & Claus, 2006). Similar effects are reported in healthy subjects following a dopamine challenge, further bolstering the dopamine overdose hypothesis (Breitenstein et al., 2006; Mehta, Swainson, Ogilvie, Sahakian, & Robbins, 2001; Pizzagalli et al., 2008; Santesso et al., 2009; Vo, Seergobin, & MacDonald, 2017; 2018; Vo, Seergobin, Morrow, & MacDonald, 2016). More recent work using functional neuroimaging, although scarce, seems to support the dopamine overdose account (Aarts et al., 2014; Argyelan et al., 2008; Cools, Lewis, Clark, Barker, & Robbins, 2007a; Feigin et al., 2003; Hiebert et al., 2019; Kwak, Müller, Bohnen, Dayalu, & Seidler, 2012; van Eimeren et al., 2009). These studies are discussed in greater detail in Sections 1.2.5 and 1.2.6.

The precise mechanism by which excess exogenous dopamine impairs cognitive functions in PD is not entirely understood. Reinforcement learning theory proposes that dopamine overstimulation might impede normal dopamine transmission by raising tonic and dampening phasic signals, thereby reducing the signal-to-noise ratio, in the striatum (Frank, 2005). It is well-understood that

midbrain dopamine neurons signal both positive and negative reward prediction errors with phasic bursts and dips, respectively (Bayer & Glimcher, 2005; Schultz, 1997). D2 receptor-expressing striatal projection neurons in the indirect pathway have (i) high affinity for dopamine and (ii) are activated by decreases in tonic dopamine. This primes their sensitivity to low concentrations of tonic dopamine and the ability to detect transient pauses in dopamine firing associated with negative prediction errors. In this way, the indirect pathway promotes avoidance and punishment-based learning. Dopaminergic therapy might 'overdose' normal functions by raising tonic dopamine levels that, in turn, occlude the phasic dips in dopamine, critical for signalling punishment. This notion has been supported experimentally in studies demonstrating that PD patients tested on medication show reduced punishment-based learning (Cools et al., 2006; Frank et al., 2004).

1.2.5 Effects of dopaminergic therapy in patients with Parkinson's disease

Early investigations of the effects of dopaminergic therapy on cognition in PD compared unmedicated, *de novo* to medicated PD patients. These results are confounded, however, by the fact that medicated PD patients are typically more disabled. Findings from studies that compare medicated PD patients to healthy age-matched controls fail to disambiguate disease from medication effects. More recent studies testing the same PD patient on and off dopaminergic therapy properly control for disease severity and treatment regimen effects. Although repeated testing in the same individual might introduce practice effects in the follow-up session, careful experimental design between sessions and a separate healthy control group also tested twice can help account for order and practice effects.

Cognitive functions improved by dopaminergic therapy in PD

Lange et al., (1992) found that the withdrawal of L-dopa in PD patients impaired performance on tests of spatial working memory and planning. Similar deficits in spatial working memory following medication withdrawal in PD have been noted by others (Beato et al., 2008; Lewis, Slabosz, Robbins, Barker, & Owen, 2005; Mattay et al., 2002; Mollion, Ventre-Dominey, Dominey, & Broussolle, 2003). L-dopa has also been found to selectively improve content manipulation in working memory (Cools, Miyakawa, Sheridan, & D'Esposito, 2010; Lewis et al., 2005; Slabosz et al., 2006). As previously mentioned, PD patients display baseline impairments in tests of set-shifting (Cools, Barker, Sahakian, & Robbins, 2001b; 2003) and response-switching (Hood et al., 2007; Shook, Franz, Higginson, Wheelock, & Sigvardt, 2005) that are improved by dopaminergic therapy. Aarts and colleagues (2014) tested PD patients on and off medication using a task-switching paradigm in fMRI. They found that medication-related improvement in switching behaviour was associated with enhanced switch-related activity in DS. Similarly, Hiebert et al., (2019) demonstrated the role of DS in decision-making and response selection processes in PD patients tested on and off their dopaminergic therapy. In the OFF session, patients showed poorer response selection and reduced DS activity relative to the ON session and compared to healthy controls. This baseline deficit in DS-mediated function was significantly improved when tested on medication. Fera et al. (2007) found that dopaminergic therapy improved interference in a colour-word Stroop task in PD. Accuracy on trials in which the stimulus dimensions were incongruent was enhanced in PD patients tested ON relative to OFF medication. This was correlated with increased activity in dorsolateral PFC and parietal lobes, cortical areas reciprocally connected to DS. Considering DS is the brain region most affected by dopamine depletion in PD, such improvements to DS-mediated functions and activity under the provision of medication are expected.

Cognitive functions worsened by dopaminergic therapy in PD

Numerous studies have reported the detrimental effects of dopaminergic therapy on cognition in PD. A review of the literature suggests that learning, in its various forms, is the cognitive operation most frequently overdosed. They include: probabilistic associative learning (Jahanshahi et al., 2010; Torta et al., 2009), sequence learning (Feigin et al., 2003; Kwak et al., 2010; Seo et al., 2010; Tremblay et al., 2010), category learning (Shohamy et al., 2006), reversal learning (Cools et al., 2006; Graef et al., 2010; A. A. MacDonald, Monchi, et al., 2013a; Swainson et al., 2000; Tomer et al., 2007), stimulus-response learning (Hiebert et al., 2019; Vo et al., 2014), implicit learning and learning from negative feedback (Frank & Claus, 2006). Dopaminergic therapy has also been shown to worsen the encoding of explicit abstract figures and lists (A. A. MacDonald, Seergobin, et al., 2013b). In a simple selection task, facilitation for consecutive, congruent stimulus-stimulus associations was reduced in PD patients on relative to off medication (P. A. MacDonald et al., 2011).

A small but growing literature examining dopaminergic therapy effects on cognition in PD using functional neuroimaging appear to support the dopamine overdose hypothesis (Aarts et al., 2014; Argyelan et al., 2008; Cools et al., 2007a; Feigin et al., 2003; Hiebert et al., 2019; Kwak et al., 2012; van Eimeren et al., 2009). Cools et al., (2007b) compared PD patients on and off medication on a probabilistic reversal learning task with fMRI. Briefly, participants learned stimulus-reward associations via probabilistic outcome feedback and adapted their stimulus-reward selections following unexpected contingency reversals. Though a behavioural effect between sessions was not observed, neuroimaging data revealed that dopaminergic therapy blunted NAc activity during final reversal errors that signalled behavioural switching on the subsequent trial. Kwak and

colleagues (2012) examined explicit motor sequence learning in PD patients tested on and off medication with fMRI. They found impaired sequence learning in PD patients on relative to off medication and compared to healthy controls. This behavioural deficit was related to reduced activity in VS. Taken together, these findings clearly demonstrate that functions mediated by VS, a VTA-innervated brain region that is less affected by dopamine depletion in early PD, is susceptible to the deleterious effects of dopaminergic therapy predicted by the dopamine overdose hypothesis. Others have also reported overdose effects in ventromedial PFC (Argyelan et al., 2008; 2018). Argylan et al., (2018) tested the effects of dopaminergic therapy on reward learning in early-stage PD compared to healthy controls with fMRI. Participants performed stimulus-reward selections during an anticipation phase before being presented with either reward or punishment outcomes in a feedback phase. During feedback processing, the authors found reduced BOLD responses in the bilateral putamen of PD patients tested on relative to off medication. When anticipating feedback, a medication-related decrease in activity within the ventromedial PFC was observed in PD patients. Finally, van Eimeren and colleagues (2009) found that BOLD responses in VS, thought to reflect a reward prediction error, were reduced in PD patients tested on L-dopa and the D2 agonist pramipexole during a probabilistic reward learning task. Only pramipexole was found to influence activity in the OFC, with hyperactivation in this region correlated with a behavioural risk-taking measure.

Though not the focus of this thesis and therefore not discussed in detail, it is important to note that dopaminergic therapy may enhance impulsivity in PD but to a pathological degree that manifests as maladaptive behaviours. Dopamine agonists are strongly linked to the occurrence of impulse control disorders. These behaviours include pathological gambling, hypersexuality, compulsive buying,

and binge eating (Evans, Strafella, Weintraub, & Stacy, 2009; Ray & Strafella, 2012; Weintraub et al., 2010). Similarly, some PD patients treated with L-dopa may endure dopamine dysregulation syndrome that involves compulsive overuse of their medications (Fenu, Wardas, & Morelli, 2009).

1.2.6 Effects of dopaminergic therapy in healthy volunteers

Testing the straightforward predictions of the dopamine overdose hypothesis in PD patients is mired in complexity. PD patients are heterogeneous in terms of disease severity and duration, the degree of asymmetry in midbrain dopamine degeneration, treatment regimens, and cognitive reserve. Loss of dopamine neurons not only reduces dopamine levels in downstream brain regions but also alters DAT concentration (Frost et al., 1993) and presynaptic dopamine auto-receptor signaling (Ekesbo et al., 1999). Chronic exposure to dopaminergic therapy in PD that might also affect post-synaptic dopamine receptor sensitivity (Bordet et al., 1997). It is difficult to conclude whether observed effects of dopaminergic therapy on cognition reflect a main effect of medication or a disease by medication interaction. Examining the effects of dopaminergic therapy and replicating overdose effects in healthy volunteers with normal dopamine systems can bolster conclusions drawn in PD.

Cognitive functions improved by dopaminergic therapy in healthy volunteers

Studies of dopaminergic therapy in healthy volunteers often focus on ameliorating cognitive changes associated with age-related dopamine decline (Chowdhury, Guitart-Masip, Bunzeck, Dolan, & Düzel, 2012; Chowdhury et al., 2013; Floel et al., 2008; Flöel et al., 2005). Floel et al., (2005) tested the effects of L-dopa on motor memory encoding of trained thumb movements in healthy young and older adults. They found poorer performance in older compared to young adults. When

tested on L-dopa, this age-related deficit in older adults was ameliorated to a level comparable to younger adults. In a follow-up study, Floel and colleagues (2008) showed that this enhanced motor memory encoding following treatment with L-dopa in older adults was associated with increased dopamine release in DS, as measured by positron emission tomography (PET) imaging. Lastly, Chowdhury et al., (2012) found that episodic memory tested with recall of studied scenes was enhanced by L-dopa in older adults in a dose-dependent manner.

In healthy young adults, Luciana et al., (1992) found that the D2 agonist bromocriptine enhanced the delayed recall of the spatial location of rapidly presented visual cues. The authors argued that this medication effect was specific to working memory processes, as immediate recall was not influenced by their pharmacological manipulation. Mehta and colleagues (2001) found a similar improvement of short-term spatial memory in younger adults following treatment with bromocriptine. Medication-related changes in working memory function might be related to baseline performance, as demonstrated by Kimberg et al., (1997). They reported that young adults with low working memory capacity showed improved performance following bromocriptine administration on a task battery thought to probe fronto-executive functions (e.g., Wisconsin Card Sorting Task, an associative memory test of complex sensitives, the Stroop task, and a spatial working memory task). Those individuals with high working memory capacity performed more poorly with dopamine stimulation. That young adults demonstrate improvements in the abovementioned studies seem at odds with the dopamine overdose hypothesis, which would predict that a bolus of exogenous dopamine would disrupt optimal dopamine function in this cohort even beyond slight inter-individual differences at baseline. This discrepancy might owe to the particular task demands being emphasized and probed, and the underlying brain

areas that are engaged. For example, working memory has long implicated the prefrontal cortex (Miller & Cohen, 2003). Exogenous dopamine might differentially affect this prefrontal versus striatum-mediated functions due to differences in receptor densities and regulation of dopamine levels between these regions (Akil et al., 2003; Cools & D'Esposito, 2011).

Knecht et al., (2004) and de Vries et al., (2010) reported enhanced pseudo-word and artificial grammar learning following treatment with L-dopa. Similarly, Shellshear and colleagues (2015) tested the effect of L-dopa on the acquisition of object and non-word pairings through observational learning. At first blush, these studies suggest that increasing dopamine levels in young adults improves learning. This is at odds with a larger literature reporting impaired learning with dopaminergic therapy in PD (Cools et al., 2006; Feigin et al., 2003; Frank & Claus, 2006; Graef et al., 2010; Hiebert et al., 2019; Jahanshahi et al., 2010; Kwak et al., 2010; A. A. MacDonald, Monchi, et al., 2013a; A. A. MacDonald, Seergobin, et al., 2013b; P. A. MacDonald et al., 2011; Seo et al., 2010; Shohamy et al., 2006; Swainson et al., 2000; Tomer et al., 2007; Torta et al., 2009; Tremblay et al., 2010; Vo et al., 2014) or a dopamine challenge in healthy volunteers (Breitenstein et al., 2006; Mehta et al., 2001; Pizzagalli et al., 2008; Santesso et al., 2009; Vo et al., 2016; 2017; 2018). Upon closer inspection, studies claiming improved learning with exogenous dopamine might instead reflect enhanced recollection and performance of learned associations rather than learning per se. Learning paradigms typically confound learning (i.e., the acquisition of associations among stimuli, responses, and outcomes) with performance (i.e., the recall, selection, and enactment of decisions based on prior learning). Enhancements in either of these processes can give the appearance of improved learning (Atallah, Lopez-Paniagua, Rudy, & O'Reilly, 2007). In each of the abovementioned studies,

learning was acquired over multiple sessions on separate days. If L-dopa enhanced learning, we would expect maximal effects during the earliest session, when learning was most challenged. Instead, L-dopa-related improvements in task performance were significant only when tested during later experimental sessions, when learning had plateaued and demands on retrieval and decision processes were emphasized.

Finally, Pessigilone et al. (2006) found that reward choice was enhanced in young adults by L-dopa relative to haloperidol, a dopamine antagonist. Participants learned to consistently select the stimulus in a pair that maximized rewards in a gain condition and minimized punishments in a loss condition. The authors claimed that L-dopa improved reward selections but did not affect loss avoidance relative to haloperidol. It is important to consider that no proper placebo condition was included, thus observed effects could reflect either improved or impaired reward performance due to L-dopa or haloperidol, respectively. Further, responses in this task were enacted by either providing or withholding key-press responses, introducing additional complex decision-making and response inhibition demands that confound straightforward interpretations of L-dopa's effect on reward choices. Chowdhury and colleagues (2013) reported abnormal reward learning in older adults that was restored by L-dopa. This study used a two-armed bandit task, during which participants selected between two fractal images that predicted the delivery or omission of reward feedback. On a trial-by-trial basis, the probability of obtaining reward varied based on a Gaussian random walk function, thus placing greater emphasis on decisions in a noisy environment rather than incremental learning per se. In this way, improved performance with L-dopa more likely reflects an amelioration of decision-making rather than reward learning processes.

Cognitive functions worsened by dopaminergic therapy in healthy volunteers

In support of the dopamine overdose hypothesis, several studies have found detrimental effects of dopaminergic therapy on cognition in healthy volunteers (Breitenstein et al., 2006; Mehta et al., 2001; Pizzagalli et al., 2008; Santesso et al., 2009; Vo et al., 2016; 2017; 2018). We recently tested the effects of L-dopa on probabilistic reversal learning in a sample of healthy young adults (Vo et al., 2016). Participants completed two separate sessions, during which they received either L-dopa or placebo in a double-blind procedure. We found that participants made more errors after treatment with L-dopa relative to placebo. Follow-up analyses showed that L-dopa impaired learning from both reward and punishment feedback. We also previously reported impairment of stimulus-response learning in young adults following treatment with L-dopa (Vo et al., 2017) as well as pramipexole (Gallant, Vo, Seergobin, & MacDonald, 2016).

Similar impairments following treatment with various dopamine agonists have been reported in young adults (Breitenstein et al., 2006; Cools et al., 2009; Mehta et al., 2001; Pizzagalli et al., 2008; Santesso et al., 2009). Mehta et al., (2001) found that a dose of bromocriptine impaired reversal learning in young adults. Breitenstein and colleagues (2006) (Breitenstein et al., 2006) showed that associative learning of a novel word list over repeated training sessions was reduced following treatment with pergolide. Pizzagalli et al., (2008) and Santesso et al., (2009) investigated the effects of pramipexole on reward learning in young adults. D2 receptor stimulation reduced selection of the more probabilistically rewarded stimulus in a pair compared to placebo. Frank et al., (Frank & O'Reilly, 2006) found a similarly reduction in learning from reward outcomes following cabergoline administration.

In summary, impaired learning following a dopamine challenge in healthy volunteers is consistent with findings for dopaminergic therapy in PD and in line with the dopamine overdose hypothesis. This behavioural pattern is thought to reflect the overdose of dopamine-replete VTA-innervated brain regions, which are known to support learning (Cools et al., 2002; Hiebert et al., 2014; Pennartz, Ito, Verschure, Battaglia, & Robbins, 2011; Reiss et al., 2005). Providing support for this view using fMRI, Riba et al., (2008) found that pramipexole increased risky decision making in young adults during a gambling task, which corresponded with a medication-related reduction in VS activity. Cools and colleagues (2009) showed that bromocriptine-related reversal learning impairments were greatest in those individuals with the highest dopamine synthesis capacity in the striatum, as measured by PET imaging. This is consistent with the notion of a baseline dependency effect.

1.2.6 Magnetic Resonance Imaging (MRI)

Structural MRI

MRI is a non-invasive imaging technique that produces high-resolution, three-dimensional images of tissues and organs. When a subject is moved into the center of a scanner's magnetic bore, hydrogen dipoles within water molecules (found in abundance within the body) will align with the magnetic field in a low energy state. A transient radio pulse is applied to excite these atoms out of phase and into a high energy state. As the perturbed hydrogen atoms re-orient to the magnetic field and return to a lower energy state, the energy emitted during this relaxation time is recorded by receiver coils. The rate of relaxation depends on the properties of the tissue type being imaged (e.g., fat versus cerebrospinal fluid). The resulting effects on the measured MRI signal are used to visualize different tissue structures.

Functional MRI

Functional MRI is a widely used method for mapping brain function. Given its high spatial and modest temporal resolution, fMRI can track dynamic changes in regional brain activity while a participant is either engaged in a task or remains at rest. When a brain region is active, increased local energy demands are met with increased local blood flow and oxygen delivery, a process termed the hemodynamic response. Oxygen is bound to hemoglobin in the blood. The magnetic properties of hemoglobin differ depending on whether or not it is bound to oxygen. Local increases in oxygenated blood produce a net decrease in deoxygenated blood. The resulting changes in regional concentrations of oxyhemoglobin versus deoxyhemoglobin—and the differences in their magnetic susceptibilities—are measured as a blood oxygenation level-dependent (BOLD) signal (Glover, 2011; Kwong et al., 1992; Ogawa, Lee, Kay, & Tank, 1990).

Although fMRI has undoubtedly transformed the field of cognitive neuroscience, it is important to recognize and consider its caveats. The BOLD signal measures changes in blood oxygenation levels as a proxy for neuronal activity and is thus an indirect measure that should be interpreted with caution. It also only provides relative measures of brain activity to one condition compared to another. FMRI suffers from relatively low temporal resolution. Whereas action potentials at the cellular level proceed on the scale of a few milliseconds, the hemodynamic response is slow and takes several seconds to peak. Despite these limitations, careful design of behavioural tasks combined with optimal acquisition parameters and elegant analysis techniques allow fMRI to be a powerful tool for studying brain function in humans.

Pharmacological MRI

Evidence provided by fMRI for the involvement of a brain region in a given

function is correlational. As a participant engages in a specific mental function inside an MRI scanner, observing regional increases in BOLD signal does not necessarily imply that such changes in brain activity are caused by that function per se. To draw stronger, more causal inferences, manipulation techniques (e.g., psychopharmacological agents, transcranial magnetic stimulation, lesion patients) can be used to alter brain function and measure the resulting effects on behaviour (Vaidya, Pujara, Petrides, Murray, & Fellows, 2019).

Pharmacological MRI combines fMRI with the administration or withdrawal of different drugs to map the effects of pharmacological agents on brain activity (Honey & Bullmore, 2004; Jenkins, 2012; Leslie & James, 2000). Different drugs modulate activity within distinct large-scale brain networks, such as the dopaminergic or serotonergic systems (Honey & Bullmore, 2004). Unlike lesion studies, drug manipulations produce temporary and reversible effects (Vaidya et al., 2019). For example, the precursor amino acid L-dopa can be used to transiently enhance dopaminergic function given its fast action and relatively short half-life (Contin & Martinelli, 2010). Drug studies are also clinically relevant, particularly to the study of disorders affecting specific neurotransmitter systems such as the dopaminergic system in PD or schizophrenia. Pharmacological MRI is not without its limitations, however. Given that we are measuring the effect of a drug on the BOLD signal, observed changes could reflect drug effects not only on underlying neuronal activity but also changes in vascular responses (Murphy, Murphy, Mackay, & Mackay, 2011). Similarly, we are not directly mapping the specific receptor binding of the drug and therefore localized changes in BOLD signal could represent either direct or remote (via functional connections) drug effects on a given brain region (Wandschneider & Koepp, 2016). It is critical that findings from pharmacological MRI experiments are interpreted with careful consideration of

drug pharmacodynamics and known receptor distributions in the brain, as well as inclusion of physiological control measures. Nonetheless, this technique is a powerful tool that allows stronger inferences about brain-behaviour relationships than could be achieved by traditional fMRI alone given the experimental manipulation of neurochemistry.

1.3 Summary

The effects of dopaminergic therapy on cognition in PD are complex. Whereas some functions improve with exogenous dopamine, others worsen. The dopamine overdose hypothesis has provided an important theoretical framework for understanding the effects of PD and dopaminergic therapy on behavior and brain function. It proposes that the effects of dopaminergic therapy on the function of a given brain region depend on the baseline dopamine levels within that region. Those functions ascribed to dopamine-deplete areas will improve with exogenous dopamine whereas those associated with relatively dopamine-replete areas are expected to worsen. Although this has provided a framework for understanding the effects of dopamine on motor and cognitive functions in PD for the past two decades, thorough and direct tests of the predictions are still needed. Supporting evidence is largely limited to behavioural studies in early-stage PD that use either between-group or repeated measures experimental designs.

Here, the primary aim is to critically test the predictions of the dopamine overdose hypothesis. I test the role of baseline endogenous dopamine levels on the effects of dopaminergic therapy on cognition and neural activity using (i) pharmacological manipulations of the dopamine system, (ii) fMRI, and (iii)

participant groups that differ in dopamine deficiency.

In Experiment 1, I examined the effects of dopaminergic therapy on reward learning in groups of PD patients that differed in the degree of dopamine deficiency as a function of disease severity and duration. Early- and late-stage PD patients were tested off relative to on half their usual dose of dopaminergic medication and compared to healthy age-matched controls. According to the dopamine overdose hypothesis, baseline learning impairments predicted at baseline in late- but not early-stage PD patients relative to healthy controls. These effects are expected due to a developing endogenous dopamine deficit in VTA-innervated brain areas with PD evolution. In early-stage PD, dopaminergic therapy is predicted to overestimate the modest degree of dopamine deficiency in VTA-innervated brain regions, resulting in impaired function. In late-stage PD, dopaminergic therapy theoretically improves baseline impairments by redressing the dopamine deficit in VTA-innervated brain regions. The latter is expected only if the dosage of exogenous dopamine matches the VTA and not the SNc deficiency. Dopamine doses titrated to the DS-mediated motor symptoms are expected to continue to overestimate the dopamine depletion that occurs in VTA-innervated brain regions.

In Experiment 2, I tested the effects of a dopamine challenge on reward learning in groups of healthy volunteers who are differentially affected by age-related dopamine decline. In a placebo-controlled, double-blind, crossover design, younger and older adults were compared following administration of L-dopa. In the placebo session, impaired learning for the older compared to young adult group was expected due to aging-related, baseline dopamine deficiency. L-dopa was predicted to improve baseline learning impairments in older adults by addressing age-related dopamine deficiency. This was provided that the

exogenous dopamine dose matched the endogenous deficit. In contrast, exogenous dopamine is expected to worsen learning performance in healthy young controls due to overdosing normal baseline dopamine systems in young adults.

In Experiment 3, I explored the effects of a dopamine challenge on learning and associated brain activity in a sample of healthy young volunteers who are presumed to have optimal baseline dopamine function. Participants performed a stimulus-response learning task inside an MRI scanner following administration of either L-dopa or a placebo. The task was designed to dissociate stimulus-response acquisitions during feedback processing from stimulus-response decisions, which have been shown previously to differentially engage VS versus DS activity (Hiebert et al., 2014). The dopamine overdose account predicts that optimal baseline dopamine levels across these brain regions makes them vulnerable to overdosed by exogenous dopamine, independent of PD pathology. Impoverished learning and response selection in the L-dopa condition is expected to correlate with depressed BOLD signal in brain regions that mediate learning.

1.4 References

Aarsland, D., Larsen, J. P., & Tandberg, E. (2000). Predictors of nursing home placement in Parkinson's disease: A population-based, prospective study. *Journal of the American …*, *48*(8), 938–942. http://doi.org/10.1111/j.1532-5415.2000.tb06891.x

Aarsland, D., Zaccai, J., & Brayne, C. (2005). A systematic review of prevalence studies of dementia in Parkinson's disease. *Movement Disorders*, *20*(10), 1255–1263. http://doi.org/10.1002/mds.20527

Aarts, E., Nusselein, A. A. M., Smittenaar, P., Helmich, R. C., Bloem, B. R., & Cools, R. (2014). Greater striatal responses to medication in Parkinson's disease are associated with better task-switching but worse reward performance. *Neuropsychologia*, *62*, 390–397. http://doi.org/10.1016/j.neuropsychologia.2014.05.023

Aarts, E., Roelofs, A., Franke, B., Rijpkema, M., Fernandez, G., Helmich, R. C., & Cools, R. (2010). Striatal dopamine mediates the interface between motivational and cognitive control in humans: evidence from genetic imaging. *Neuropsychopharmacology*, *35*(9), 1943–1951. http://doi.org/10.1038/npp.2010.68

Adler, C. H., Connor, D. J., Hentz, J. G., Sabbagh, M. N., Caviness, J. N., Shill, H. A., et al. (2010). Incidental Lewy body disease: clinical comparison to a control cohort. *Mov Disord*, *25*(5), 642–646. http://doi.org/10.1002/mds.22971

Akil, M., Akil, M., Kolachana, B. S., Rothmond, D. A., Rothmond, D. A., Hyde, T. M., et al. (2003). Catechol-O-methyltransferase genotype and dopamine regulation in the human brain. *J Neurosci*, *23*(6), 2008–2013.

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci*, *9*(1), 357–381. http://doi.org/10.1146/annurev.ne.09.030186.002041

Argyelan, M., Carbon, M., Ghilardi, M.-F., Feigin, A., Mattis, P., Tang, C., et al. (2008). Dopaminergic suppression of brain deactivation responses during sequence learning. *J Neurosci*, *28*(42), 10687–10695. http://doi.org/10.1523/JNEUROSCI.2933-08.2008

Argyelan, M., Herzallah, M., Sako, W., DeLucia, I., Sarpal, D., Vo, A., et al. (2018). Dopamine modulates striatal response to reward and punishment in patients with Parkinson's disease: a pharmacological challenge fMRI study. *Neuroreport*, *29*(7), 532–540. http://doi.org/10.1097/WNR.0000000000000970

Atallah, H. E., Lopez-Paniagua, D., Rudy, J. W., & O'Reilly, R. C. (2007). Separate neural substrates for skill learning and performance in the ventral and dorsal striatum. *Nat Neurosci*, *10*(1), 126–131. http://doi.org/10.1038/nn1817

Bayer, H. M., & Glimcher, P. W. (2005). Midbrain Dopamine Neurons Encode a Quantitative Reward Prediction Error Signal. *Neuron*, *47*(1), 129–141. http://doi.org/10.1016/j.neuron.2005.05.020

Beato, R., Levy, R., Pillon, B., Vidal, C., Montcel, du, S. T., Deweer, B., et al. (2008). Working memory in Parkinson's disease patients: clinical features and response to levodopa. *Arquivos De Neuro-Psiquiatria*, *66*(2A), 147–151. http://doi.org/10.1590/s0004-282x2008000200001

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research. Brain Research Reviews*, *28*(3), 309–369. Retrieved from http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=9858756&retmode=ref&cmd=prlinks

Boller, F., Passafiume, D., Keefe, N. C., Rogers, K., Morrow, L., & Kim, Y. (1984). Visuospatial Impairment in Parkinson's Disease: Role of Perceptual and Motor Factors. *JAMA Neurology*, *41*(5), 485–490. http://doi.org/10.1001/archneur.1984.04050170031011

Bordet, R., Bordet, R., Ridray, S., Ridray, S., Carboni, S., Carboni, S., et al. (1997). Induction of dopamine D3 receptor expression as a mechanism of behavioral sensitization to levodopa. *Proceedings of the National Academy of Sciences*, *94*(7), 3363–3367. http://doi.org/10.1073/pnas.94.7.3363

Braak, H., Del Tredici, K., Rüb, U., de Vos, R. A. I., Jansen Steur, E. N. H., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging*, *24*(2), 197–211. http://doi.org/10.1016/s0197-4580(02)00065-9

Breitenstein, C., Korsukewitz, C., Flöel, A., Kretzschmar, T., Diederich, K., & Knecht, S. (2006). Tonic dopaminergic stimulation impairs associative learning in healthy subjects. *Neuropsychopharmacology*, *31*(11), 2552–2564. http://doi.org/10.1038/sj.npp.1301167

Brown, R. G., & Marsden, C. D. (1984). How common is dementia in Parkinson's disease? *The Lancet*, *324*(8414), 1262–1265. http://doi.org/10.1016/S0140-6736(84)92807-1

Brønnick, K., Alves, G., Aarsland, D., Tysnes, O.-B., & Larsen, J. P. (2011). Verbal memory in drug-naive, newly diagnosed Parkinson's disease. The retrieval deficit hypothesis revisited. *Neuropsychology*, *25*(1), 114–124. http://doi.org/10.1037/a0020857

Chaudhuri, K. R., Healy, D. G., & Schapira, A. H. (2006). Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurology*, *5*(3), 235–245. http://doi.org/10.1016/S1474-4422(06)70373-8

Chowdhury, R., Guitart-Masip, M., Bunzeck, N., Dolan, R. J., & Düzel, E. (2012). Dopamine modulates episodic memory persistence in old age. *J Neurosci*, *32*(41), 14193–14204. http://doi.org/10.1523/JNEUROSCI.1278-12.2012

Chowdhury, R., Guitart-Masip, M., Lambert, C., Dayan, P., Huys, Q., Düzel, E., & Dolan, R. J. (2013). Dopamine restores reward prediction errors in old age. *Nat Neurosci*, *16*(5), 648–653. http://doi.org/10.1038/nn.3364

Cohn, M., Moscovitch, M., & Davidson, P. S. R. (2010). Double dissociation between familiarity and recollection in Parkinson's disease as a function of

encoding tasks. *Neuropsychologia*, *48*(14), 4142–4147. http://doi.org/10.1016/j.neuropsychologia.2010.10.013

Contin, M., & Martinelli, P. (2010). Pharmacokinetics of levodopa. *J Neurol*, *257*(Suppl 2), S253–61. http://doi.org/10.1007/s00415-010-5728-8

Cools, R. (2006). Dopaminergic modulation of cognitive function-implications for l-DOPA treatment in Parkinson's disease. *Neurosci Biobehav Rev*, *30*(1), 1–23. http://doi.org/10.1016/j.neubiorev.2005.03.024

Cools, R., & D'Esposito, M. (2011). Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biol Psychiatry*, *69*(12), e113–25. http://doi.org/10.1016/j.biopsych.2011.03.028

Cools, R., Altamirano, L., & D'Esposito, M. (2006). Reversal learning in Parkinson's disease depends on medication status and outcome valence. *Neuropsychologia*, *44*(10), 1663–1673. http://doi.org/10.1016/j.neuropsychologia.2006.03.030

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001a). Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cereb Cortex*, *11*(12), 1136–1143. http://doi.org/10.1093/cercor/11.12.1136

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001b). Mechanisms of cognitive set flexibility in Parkinson's disease. *Brain*, *124*(12), 2503–2512. http://doi.org/10.1093/brain/124.12.2503

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2003). l-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia*, *41*(11), 1431–1441. http://doi.org/10.1016/S0028-3932(03)00117-9

Cools, R., Clark, L., Owen, A. M., & Robbins, T. W. (2002). Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging. *J Neurosci*, *22*(11), 4563–4567.

Cools, R., Frank, M. J., Gibbs, S. E., Miyakawa, A., Jagust, W., & D'Esposito, M. (2009). Striatal dopamine predicts outcome-specific reversal learning and its sensitivity to dopaminergic drug administration. *J Neurosci*, *29*(5), 1538–1543. http://doi.org/10.1523/JNEUROSCI.4467-08.2009

Cools, R., Lewis, S. J. G., Clark, L., Barker, R. A., & Robbins, T. W. (2007a). L-DOPA disrupts activity in the nucleus accumbens during reversal learning in Parkinson's disease. *Neuropsychopharmacology*, *32*(1), 180–189. http://doi.org/10.1038/sj.npp.1301153

Cools, R., Miyakawa, A., Sheridan, M., & D'Esposito, M. (2010). Enhanced frontal function in Parkinson's disease. *Brain*, *133*(Pt 1), 225–233. http://doi.org/10.1093/brain/awp301

Cools, R., Sheridan, M., Jacobs, E., & D'Esposito, M. (2007b). Impulsive personality predicts dopamine-dependent changes in frontostriatal activity during component processes of working memory. *J Neurosci*, *27*(20), 5506–5514. http://doi.org/10.1523/JNEUROSCI.0601-07.2007

Davidson, P. S. R., Anaki, D., Saint-Cyr, J. A., Chow, T. W., & Moscovitch, M. (2006). Exploring the recognition memory deficit in Parkinson's disease: estimates of recollection versus familiarity. *Brain*, *129*(Pt 7), 1768–1779. http://doi.org/10.1093/brain/awl115

de Vries, M. H., Ulte, C., Zwitserlood, P., Szymanski, B., & Knecht, S. (2010). Increasing dopamine levels in the brain improves feedback-based procedural learning in healthy participants: an artificial-grammar-learning experiment. *Neuropsychologia*, *48*(11), 3193–3197. http://doi.org/10.1016/j.neuropsychologia.2010.06.024

Dirnberger, G., & Jahanshahi, M. (2013). Executive dysfunction in Parkinson's disease: a review. *Journal of Neuropsychology*, *7*(2), 193–224. http://doi.org/10.1111/jnp.12028

Ekesbo, A., Rydin, E., Torstenson, R., Sydow, O., Låengström, B., & Tedroff, J. (1999). Dopamine autoreceptor function is lost in advanced Parkinson's disease. *Neurology*, *52*(1), 120–125. http://doi.org/10.1212/wnl.52.1.120

Emre, M. (2003). Dementia associated with Parkinson's disease. *Lancet Neurology*, *2*(4), 229–237.

Evans, A. H., Strafella, A. P., Weintraub, D., & Stacy, M. (2009). Impulsive and compulsive behaviors in Parkinson's disease. *Mov Disord*, *24*(11), 1561–1570. http://doi.org/10.1002/mds.22505

Fearnley, J. M., & Lees, A. J. (1991). Ageing and parkinson's disease: substantia nigra regional selectivity. *Brain*, *114*(5), 2283–2301. http://doi.org/10.1093/brain/114.5.2283

Feigin, A., Ghilardi, M. F., Carbon, M., Edwards, C., Fukuda, M., Dhawan, V., et al. (2003). Effects of levodopa on motor sequence learning in Parkinson's disease. *Neurology*, *60*(11), 1744–1749. http://doi.org/10.1212/01.WNL.0000072263.03608.42

Fenu, S., Wardas, J., & Morelli, M. (2009). Impulse control disorders and dopamine dysregulation syndrome associated with dopamine agonist therapy in Parkinson's disease. *Behav Pharmacol*, *20*(5-6), 363–379. http://doi.org/10.1097/FBP.0b013e32833109a0

Fera, F., Nicoletti, G., Cerasa, A., Romeo, N., Gallo, O., Gioia, M. C., et al. (2007). Dopaminergic modulation of cognitive interference after pharmacological washout in Parkinson's disease. *Brain Research Bulletin*, *74*(1-3), 75–83. http://doi.org/10.1016/j.brainresbull.2007.05.009

Floel, A., Garraux, G., Xu, B., Breitenstein, C., Knecht, S., Herscovitch, P., & Cohen, L. G. (2008). Levodopa increases memory encoding and dopamine release in the striatum in the elderly. *Neurobiology of Aging*, *29*(2), 267–279. http://doi.org/10.1016/j.neurobiolaging.2006.10.009

Flöel, A., Breitenstein, C., Hummel, F., Celnik, P., Gingert, C., Sawaki, L., et al. (2005). Dopaminergic influences on formation of a motor memory. *Ann Neurol*, *58*(1), 121–130. http://doi.org/10.1002/ana.20536

Frank, M. J. (2005). Dynamic dopamine modulation in the basal ganglia: a neurocomputational account of cognitive deficits in medicated and nonmedicated Parkinsonism. *J Cogn Neurosci*, *17*(1), 51–72. http://doi.org/10.1162/0898929052880093

Frank, M. J., & Claus, E. D. (2006). Anatomy of a decision: striato-orbitofrontal interactions in reinforcement learning, decision making, and reversal. *Psychol Rev*, *113*(2), 300–326. http://doi.org/10.1037/0033-295X.113.2.300

Frank, M. J., & O'Reilly, R. C. (2006). A mechanistic account of striatal dopamine function in human cognition: psychopharmacological studies with cabergoline and haloperidol. *Behav Neurosci*, *120*(3), 497–517. http://doi.org/10.1037/0735-7044.120.3.497

Frank, M. J., Seeberger, L. C., & O'Reilly, R. C. (2004). By carrot or by stick: cognitive reinforcement learning in parkinsonism. *Science*, *306*(5703), 1940–1943. http://doi.org/10.1126/science.1102941

Frost, J. J., Rosier, A. J., Reich, S. G., Smith, J. S., Ehlers, M. D., Snyder, S. H., et al. (1993). Positron emission tomographic imaging of the dopamine transporter with 11C-WIN 35,428 reveals marked declines in mild Parkinson's disease. *Ann Neurol*, *34*(3), 423–431. http://doi.org/10.1002/ana.410340331

Gallant, H., Vo, A., Seergobin, K. N., & MacDonald, P. A. (2016). Pramipexole Impairs Stimulus-Response Learning in Healthy Young Adults. *Frontiers in Neuroscience*, *10*(784), 390. http://doi.org/10.3389/fnins.2016.00374

Glover, G. H. (2011). Overview of functional magnetic resonance imaging. *Neurosurgery Clinics of North America*, *22*(2), 133–9– vii. http://doi.org/10.1016/j.nec.2010.11.001

Gotham, A. M., Brown, R. G., & Marsden, C. D. (1988). 'Frontal'cognitive function in patients with Parkinson's disease 'on'and 'off'levodopa. *Brain*, *111*(2), 299–321. http://doi.org/10.1093/brain/111.2.299

Graef, S., Biele, G., Krugel, L. K., Marzinzik, F., Wahl, M., Wotka, J., et al. (2010). Differential influence of levodopa on reward-based learning in Parkinson's disease. *Frontiers in Human Neuroscience*, *4*, 169. http://doi.org/10.3389/fnhum.2010.00169

Halliday, G. M., & McCann, H. (2010). The progression of pathology in Parkinson's disease. *Ann N Y Acad Sci*, *1184*(1), 188–195. http://doi.org/10.1111/j.1749-6632.2009.05118.x

Hiebert, N. M., Owen, A. M., Ganjavi, H., Mendonça, D., Jenkins, M. E., Seergobin, K. N., & MacDonald, P. A. (2019). Dorsal striatum does not mediate feedback-based, stimulus-response learning: An event-related fMRI study in patients with Parkinson's disease tested on and off dopaminergic therapy. *NeuroImage*, *185*, 455–470. http://doi.org/10.1016/j.neuroimage.2018.10.045

Hiebert, N. M., Vo, A., Hampshire, A., Owen, A. M., Owen, A. M., Seergobin, K. N., & MacDonald, P. A. (2014). Striatum in stimulus-response learning via feedback and in decision making. *NeuroImage*, *101*, 448–457. http://doi.org/10.1016/j.neuroimage.2014.07.013

Honey, G., & Bullmore, E. (2004). Human pharmacological MRI. *Trends Pharmacol Sci*, *25*(7), 366–374. http://doi.org/10.1016/j.tips.2004.05.009

Hood, A. J., Amador, S. C., Cain, A. E., Briand, K. A., Al-Refai, A. H., Schiess, M. C., & Sereno, A. B. (2007). Levodopa slows prosaccades and improves antisaccades: an eye movement study in Parkinson's disease. *J Neurol Neurosurg Psychiatry*, *78*(6), 565–570. http://doi.org/10.1136/jnnp.2006.099754

Jahanshahi, M., Wilkinson, L., Gahir, H., Dharmaindra, A., Dharmarinda, A., Dharminda, A., & Lagnado, D. A. (2010). Medication impairs probabilistic classification learning in Parkinson's disease. *Neuropsychologia*, *48*(4), 1096–1103. http://doi.org/10.1016/j.neuropsychologia.2009.12.010

Jellinger, K. A. (2008). A critical reappraisal of current staging of Lewy-related pathology in human brain. *Acta Neuropathol*, *116*(1), 1–16. http://doi.org/10.1007/s00401-008-0406-y

Jellinger, K. A. (2009). A critical evaluation of current staging of alpha-synuclein pathology in Lewy body disorders. *Biochimica Et Biophysica Acta*, *1792*(7), 730–740. http://doi.org/10.1016/j.bbadis.2008.07.006

Jellinger, K. A. (2010). Neuropathology in Parkinson's disease with mild cognitive impairment. *Acta Neuropathol*, *120*(6), 829–30– author reply 831. http://doi.org/10.1007/s00401-010-0755-1

Jenkins, B. G. (2012). Pharmacologic magnetic resonance imaging (phMRI): imaging drug action in the brain. *NeuroImage*, *62*(2), 1072–1085. http://doi.org/10.1016/j.neuroimage.2012.03.075

Kehagia, A. A., Barker, R. A., & Robbins, T. W. (2010). Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. *The Lancet Neurology*, *9*(12), 1200–1213. http://doi.org/10.1016/S1474-4422(10)70212-X

Kimberg, D. Y., Kimberg, D. Y., D'Esposito, M., D'Esposito, M., Farah, M. J., &

Farah, M. J. (1997). Effects of bromocriptine on human subjects depend on working memory capacity. *Neuroreport*, *8*(16), 3581–3585. http://doi.org/10.1097/00001756-199711100-00032

Kish, S. J., Shannak, K., & Hornykiewicz, O. (1988). Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. *N Engl J Med*, *318*(14), 876–880. http://doi.org/10.1056/NEJM198804073181402

Knecht, S., Breitenstein, C., Bushuven, S., Wailke, S., Kamping, S., Flöel, A., et al. (2004). Levodopa: faster and better word learning in normal humans. *Ann Neurol*, *56*(1), 20–26. http://doi.org/10.1002/ana.20125

Künig, G., Leenders, K. L., Martin-Sölch, C., Missimer, J., Magyar, S., & Schultz, W. (2000). Reduced reward processing in the brains of Parkinsonian patients. *Neuroreport*, *11*(17), 3681–3687. http://doi.org/10.1097/00001756-200011270-00019

Kwak, Y., Müller, M. L. T. M., Bohnen, N. I., Dayalu, P., & Seidler, R. D. (2010). Effect of dopaminergic medications on the time course of explicit motor sequence learning in Parkinson's disease. *J Neurophysiol*, *103*(2), 942–949. http://doi.org/10.1152/jn.00197.2009

Kwak, Y., Müller, M. L. T. M., Bohnen, N. I., Dayalu, P., & Seidler, R. D. (2012). l-DOPA changes ventral striatum recruitment during motor sequence learning in Parkinson's disease. *Behavioural Brain Research*, *230*(1), 116–124. http://doi.org/10.1016/j.bbr.2012.02.006

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, B. P., et al. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Sciences*, *89*(12), 5675–5679. http://doi.org/10.1073/pnas.89.12.5675

Lang, A. E., & Lozano, A. M. (1998). Parkinson's disease. First of two parts. *N Engl J Med*, *339*(15), 1044–1053. http://doi.org/10.1056/NEJM199810083391506

Lange, K. W., Robbins, T. W., Marsden, C. D., James, M., Owen, A. M., & Paul, G. M. (1992). L-Dopa Withdrawal in Parkinsons-Disease Selectively Impairs Cognitive Performance in Tests Sensitive to Frontal-Lobe Dysfunction. *Psychopharmacology (Berl)*, *107*(2-3), 394–404. http://doi.org/10.1007/BF02245167

Leslie, R. A., & James, M. F. (2000). Pharmacological magnetic resonance imaging: a new application for functional MRI. *Trends Pharmacol Sci*, *21*(8), 314–318. http://doi.org/10.1016/S0165-6147(00)01507-8

Lewis, S. J. G., Slabosz, A., Robbins, T. W., Barker, R. A., & Owen, A. M. (2005). Dopaminergic basis for deficits in working memory but not attentional set-shifting in Parkinson's disease. *Neuropsychologia*, *43*(6), 823–832. http://doi.org/10.1016/j.neuropsychologia.2004.10.001

LeWitt, P. A., & Fahn, S. (2016). Levodopa therapy for Parkinson disease: A look backward and forward. *Neurology*, *86*(14 Suppl 1), S3–12. http://doi.org/10.1212/WNL.0000000000002509

Luciana, M., Depue, R. A., Arbisi, P., & Leon, A. (1992). Facilitation of working memory in humans by a d2 dopamine receptor agonist. *J Cogn Neurosci*, *4*(1), 58–68. http://doi.org/10.1162/jocn.1992.4.1.58

MacDonald, A. A., Monchi, O., Seergobin, K. N., Ganjavi, H., Tamjeedi, R., & MacDonald, P. A. (2013a). Parkinson's disease duration determines effect of dopaminergic therapy on ventral striatum function. *Mov Disord*, *28*(2), 153–160. http://doi.org/10.1002/mds.25152

MacDonald, A. A., Seergobin, K. N., Owen, A. M., Owen, A. M., Tamjeedi, R., Monchi, O., et al. (2013b). Differential effects of Parkinson's disease and

dopamine replacement on memory encoding and retrieval. *PLoS One*, *8*(9), e74044. http://doi.org/10.1371/journal.pone.0074044

MacDonald, P. A., & Monchi, O. (2011). Differential effects of dopaminergic therapies on dorsal and ventral striatum in Parkinson's disease: implications for cognitive function. *Parkinsons Dis*, *2011*(8414), 572743–18. http://doi.org/10.4061/2011/572743

MacDonald, P. A., MacDonald, A. A., Seergobin, K. N., Tamjeedi, R., Ganjavi, H., Provost, J. S., & Monchi, O. (2011). The effect of dopamine therapy on ventral and dorsal striatum-mediated cognition in Parkinson's disease: support from functional MRI. *Brain*, *134*(Pt 5), 1447–1463. http://doi.org/10.1093/brain/awr075

Mattay, V. S., Tessitore, A., Callicott, J. H., Bertolino, A., Goldberg, T. E., Chase, T. N., et al. (2002). Dopaminergic modulation of cortical function in patients with Parkinson's disease. *Ann Neurol*, *51*(2), 156–164.

Mattila, P. M., Rinne, J. O., Helenius, H., Dickson, D. W., & Röyttä, M. (2000). Alpha-synuclein-immunoreactive cortical Lewy bodies are associated with cognitive impairment in Parkinson's disease. *Acta Neuropathol*, *100*(3), 285–290. http://doi.org/10.1007/s004019900168

Mehta, M. A., Swainson, R., Ogilvie, A. D., Sahakian, J., & Robbins, T. W. (2001). Improved short-term spatial memory but impaired reversal learning following the dopamine D(2) agonist bromocriptine in human volunteers. *Psychopharmacology (Berl)*, *159*(1), 10–20. http://doi.org/10.1007/s002130100851

Miller, E. K., & Cohen, J. D. (2003). An Integrative Theory of Prefrontal Cortex Function. *Dx.Doi.org*, *24*(1), 167–202.

Mollion, H., Ventre-Dominey, J., Dominey, P. F., & Broussolle, E. (2003). Dissociable effects of dopaminergic therapy on spatial versus non-spatial working memory in Parkinson's disease. *Neuropsychologia*, *41*(11), 1442–1451.

Monchi, O., Degroot, C., Mejia-Constain, B., & Bruneau, M.-A. (2012). Neuroimaging studies of different cognitive profiles in Parkinson's disease. *Parkinsonism Relat Disord*, *18 Suppl 1*, S77–9. http://doi.org/10.1016/S1353-8020(11)70025-6

Morrish, P. K., Sawle, G. V., & Brooks, D. J. (1996). An [18F]dopa-PET and clinical study of the rate of progression in Parkinson's disease. *Brain*, *119 (Pt 2)*(2), 585–591. http://doi.org/10.1093/brain/119.2.585

Murphy, S. E., Murphy, S. E., Mackay, C. E., & Mackay, C. E. (2011). Using MRI to measure drug action: caveats and new directions. *Journal of Psychopharmacology (Oxford, England)*, *25*(9), 1168–1174. http://doi.org/10.1177/0269881110372547

Nandhagopal, R., Kuramoto, L., Schulzer, M., Mak, E., Cragg, J., Lee, C. S., et al. (2009). Longitudinal progression of sporadic Parkinson's disease: a multi-tracer positron emission tomography study. *Brain*, *132*(Pt 11), 2970–2979. http://doi.org/10.1093/brain/awp209

O'Doherty, J., Critchley, H., Deichmann, R., & Dolan, R. J. (2003). Dissociating Valence of Outcome from Behavioral Control in Human Orbital and Ventral Prefrontal Cortices. *The Journal of Neuroscience*, *23*(21), 7931–7939.

O'Doherty, J., Kringelbach, M. L., Rolls, E. T., Hornak, J., & Andrews, C. (2001). Abstract reward and punishment representations in the human orbitofrontal cortex. *Nat Neurosci*, *4*(1), 95–102. http://doi.org/10.1038/82959

Oades, R. D., & Halliday, G. M. (1987). Ventral Tegmental (A10) System - Neurobiology .1. Anatomy and Connectivity. *Brain Res*, *12*(2), 117–165. http://doi.org/10.1016/0165-0173(87)90011-7

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences*, *87*(24), 9868–9872. http://doi.org/10.1073/pnas.87.24.9868

Owen, A. M., James, M., Leigh, P. N., Summers, B. A., Marsden, C. D., Quinn, N. P., et al. (1992). Fronto-striatal cognitive deficits at different stages of parkinson's disease. *Brain*, *115*(6), 1727–1751. http://doi.org/10.1093/brain/115.6.1727

Parkkinen, L., Kauppinen, T., Pirttilä, T., Autere, J. M., & Alafuzoff, I. (2005). Alpha-synuclein pathology does not predict extrapyramidal symptoms or dementia. *Ann Neurol*, *57*(1), 82–91. http://doi.org/10.1002/ana.20321

Pennartz, C. M. A., Ito, R., Verschure, P. F. M. J., Battaglia, F. P., & Robbins, T. W. (2011). The hippocampal-striatal axis in learning, prediction and goal-directed behavior. *Trends Neurosci*, *34*(10), 548–559. http://doi.org/10.1016/j.tins.2011.08.001

Pessiglione, M., Seymour, B., Flandin, G., Dolan, R. J., & Frith, C. D. (2006). Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature*, *442*(7106), 1042–1045. http://doi.org/10.1038/nature05051

Pizzagalli, D. A., Evins, A. E., Schetter, E. C., Frank, M. J., Pajtas, P. E., Santesso, D. L., & Culhane, M. (2008). Single dose of a dopamine agonist impairs reinforcement learning in humans: behavioral evidence from a laboratory-based measure of reward responsiveness. *Psychopharmacology (Berl)*, *196*(2), 221–232. http://doi.org/10.1007/s00213-007-0957-y

Ray, N. J., & Strafella, A. P. (2012). The neurobiology and neural circuitry of cognitive changes in Parkinson's disease revealed by functional neuroimaging. *Mov Disord*, *27*(12), 1484–1492. http://doi.org/10.1002/mds.25173

Reeves, S., Bench, C., & Howard, R. (2002). Ageing and the nigrostriatal dopaminergic system. *Int J Geriatr Psychiatry*, *17*(4), 359–370. http://doi.org/10.1002/gps.606

Reiss, J. P., Campbell, D. W., Leslie, W. D., Paulus, M. P., Stroman, P. W., Polimeni, J. O., et al. (2005). The role of the striatum in implicit learning: a functional magnetic resonance imaging study. *Neuroreport*, *16*(12), 1291–1295. http://doi.org/10.1097/01.wnr.0000175615.93312.1a

Riba, J., Krämer, U. M., Heldmann, M., Richter, S., & Münte, T. F. (2008). Dopamine agonist increases risk taking but blunts reward-related brain activity. *PLoS One*, *3*(6), e2479. http://doi.org/10.1371/journal.pone.0002479

Robbins, T. W., & Cools, R. (2014). Cognitive deficits in Parkinson's disease: a cognitive neuroscience perspective. *Mov Disord*, *29*(5), 597–607. http://doi.org/10.1002/mds.25853

Santesso, D. L., Evins, A. E., Frank, M. J., Schetter, E. C., Bogdan, R., & Pizzagalli, D. A. (2009). Single dose of a dopamine agonist impairs reinforcement learning in humans: evidence from event-related potentials and computational modeling of striatal-cortical function. *Human Brain Mapping*, *30*(7), 1963–1976. http://doi.org/10.1002/hbm.20642

Scatton, B., Javoy-Agid, F., Rouquier, L., Dubois, B., & Agid, Y. (1983). Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. *Brain Res*, *275*(2), 321–328.

Schultz, W. (1997). Dopamine neurons and their role in reward mechanisms. *Curr Opin Neurobiol*, *7*(2), 191–197. http://doi.org/10.1016/S0959-4388(97)80007-4

Schultz, W. (2007). Multiple dopamine functions at different time courses. *Annu Rev Neurosci*, *30*(1), 259–288. http://doi.org/10.1146/annurev.neuro.28.061604.135722

Seo, Seo, M., Beigi, M., Jahanshahi, M., & Averbeck, B. B. (2010). Effects of dopamine medication on sequence learning with stochastic feedback in Parkinson's disease. *Front Syst Neurosci*, *4*. http://doi.org/10.3389/fnsys.2010.00036

Shellshear, L., MacDonald, A. D., Mahoney, J., Finch, E., McMahon, K., Silburn, P., et al. (2015). Levodopa enhances explicit new-word learning in healthy adults: a preliminary study. *Human Psychopharmacology*, *30*(5), 341–349. http://doi.org/10.1002/hup.2480

Shohamy, D., Shohamy, D., Myers, C. E., Myers, C. E., Geghman, K. D., Geghman, K. D., et al. (2006). L-dopa impairs learning, but spares generalization, in Parkinson's disease. *Neuropsychologia*, *44*(5), 774–784. http://doi.org/10.1016/j.neuropsychologia.2005.07.013

Shook, S. K., Franz, E. A., Higginson, C. I., Wheelock, V. L., & Sigvardt, K. A. (2005). Dopamine dependency of cognitive switching and response repetition effects in Parkinson's patients. *Neuropsychologia*, *43*(14), 1990–1999. http://doi.org/10.1016/j.neuropsychologia.2005.03.024

Slabosz, A., Lewis, S. J. G., Smigasiewicz, K., Szymura, B., Barker, R. A., & Owen, A. M. (2006). The role of learned irrelevance in attentional set-shifting impairments in Parkinson's disease. *Neuropsychology*, *20*(5), 578–588. http://doi.org/10.1037/0894-4105.20.5.578

Swainson, R., Rogers, R. D., Sahakian, B. J., Summers, B. A., Polkey, C. E., & Robbins, T. W. (2000). Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. *Neuropsychologia*, *38*(5), 596–612. http://doi.org/10.1016/S0028-3932(99)00103-7

Tanner, C. M., & Goldman, S. M. (1996). Epidemiology of Parkinson's disease. *Neurologic Clinics*, *14*(2), 317–335.

Taylor, A. E., Saint-Cyr, J. A., & Lang, A. E. (1990). Memory and learning in early Parkinson's disease: evidence for a "frontal lobe syndrome". *Brain and Cognition*, *13*(2), 211–232.

Tomer, R., Aharon-Peretz, J., & Tsitrinbaum, Z. (2007). Dopamine asymmetry interacts with medication to affect cognition in Parkinson's disease. *Neuropsychologia*, *45*(2), 357–367. http://doi.org/10.1016/j.neuropsychologia.2006.06.014

Torta, D. M. E., Castelli, L., Zibetti, M., Lopiano, L., & Geminiani, G. (2009). On the role of dopamine replacement therapy in decision-making, working memory, and reward in Parkinson's disease: does the therapy-dose matter? *Brain and Cognition*, *71*(2), 84–91. http://doi.org/10.1016/j.bandc.2009.04.003

Tremblay, P.-L., Bedard, M.-A., Langlois, D., Blanchet, P. J., Lemay, M., & Parent, M. (2010). Movement chunking during sequence learning is a dopamine-dependant process: a study conducted in Parkinson's disease. *Exp Brain Res*, *205*(3), 375–385. http://doi.org/10.1007/s00221-010-2372-6

Vaidya, A. R., Pujara, M. S., Petrides, M., Murray, E. A., & Fellows, L. K. (2019). Lesion Studies in Contemporary Neuroscience. *Trends in Cognitive Sciences*, *23*(8), 653–671. http://doi.org/10.1016/j.tics.2019.05.009

van Eimeren, T., Ballanger, B., Pellecchia, G., Miyasaki, J. M., Lang, A. E., & Strafella, A. P. (2009). Dopamine agonists diminish value sensitivity of the orbitofrontal cortex: a trigger for pathological gambling in Parkinson's disease? *Neuropsychopharmacology*, *34*(13), 2758–2766. http://doi.org/10.1038/sj.npp.npp2009124

Vo, A., Hiebert, N. M., Seergobin, K. N., Solcz, S., Partridge, A., & MacDonald, P. A. (2014). Dopaminergic medication impairs feedback-based stimulus-response learning but not response selection in Parkinson's disease. *Frontiers in Human Neuroscience*, *8*(169), 784. http://doi.org/10.3389/fnhum.2014.00784

Vo, A., Seergobin, K. N., & MacDonald, P. A. (2017). Effects of levodopa on stimulus-response learning versus response selection in healthy young adults. *Behavioural Brain Research*, *317*, 553–561. http://doi.org/10.1016/j.bbr.2016.10.019

Vo, A., Seergobin, K. N., & MacDonald, P. A. (2018). Independent effects of age and levodopa on reversal learning in healthy volunteers. *Neurobiology of Aging*, *69*, 129–139. http://doi.org/10.1016/j.neurobiolaging.2018.05.014

Vo, A., Seergobin, K. N., Morrow, S. A., & MacDonald, P. A. (2016). Levodopa impairs probabilistic reversal learning in healthy young adults. *Psychopharmacology (Berl)*, *233*(14), 2753–2763. http://doi.org/10.1007/s00213-016-4322-x

Wandschneider, B., & Koepp, M. J. (2016). Pharmaco fMRI: Determining the functional anatomy of the effects of medication. *NeuroImage: Clinical*, *12*, 691–697. http://doi.org/10.1016/j.nicl.2016.10.002

Weintraub, D., Koester, J., Potenza, M. N., Siderowf, A. D., Stacy, M., Voon, V., et al. (2010). Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol*, *67*(5), 589–595. http://doi.org/10.1001/archneurol.2010.65

Weisman, D., Cho, M., Taylor, C., Adame, A., Thal, L. J., & Hansen, L. A. (2007). In dementia with Lewy bodies, Braak stage determines phenotype, not Lewy body distribution. *Neurology*, *69*(4), 356–359. http://doi.org/10.1212/01.wnl.0000266626.64913.0f

Yehene, E., Meiran, N., & Soroker, N. (2008). Basal Ganglia Play a Unique Role in Task Switching within the Frontal-Subcortical Circuits: Evidence from Patients with Focal Lesions. *J Cogn Neurosci*, *20*(6), 1079–1093. http://doi.org/10.1162/jocn.2008.20077

Chapter 2

Evolution of ventral striatum-mediated cognition and response to dopamine replacement therapy in Parkinson's disease

2.1 Introduction

The dopamine overdose hypothesis has been offered as an explanatory framework for understanding the effects of dopaminergic therapy in PD (Cools, Barker, Sahakian, & Robbins, 2001; Gotham, Brown, & Marsden, 1988; Swainson et al., 2000). Central to this hypothesis is the notion of a baseline dependency effect. That is, whether exogenous dopamine improves or impairs the function of a given brain region depends on underlying baseline dopamine levels (Cools, 2006; P. A. MacDonald & Monchi, 2011). Functions mediated by regions low in dopamine are expected to improve with dopaminergic therapy whereas those ascribed to regions with normal or high dopamine levels are predicted to worsen, in an inverted U-shaped function (Cools & D'Esposito, 2011).

In PD, degeneration of dopamine-producing cells is presumably greatest in the SNc compared to the lesser-affected VTA (Fearnley & Lees, 1991; Haber, Haber, Fudge, & Fudge, 1997; Kish, Shannak, & Hornykiewicz, 1988; Vaillancourt, Spraker, Prodoehl, Zhou, & Little, 2012). As a result, mostly functions related to the SNc-innervated DS are impaired whereas those ascribed to VTA-innervated brain regions, such as VS, prefrontal, and limbic cortices, are relatively spared in comparison. Dopaminergic therapy is prescribed in PD to improve motor symptoms by redressing the severe dopamine-depletion in DS. Such doses of medication are hypothesized to overestimate the minimal degree of dopamine deficiency in VTA-innervated brain regions, especially at earlier disease stages, resulting in an overdose and impairment of functions (see Figure 2.1b).

As PD progresses, continued SNc degeneration and worsening of DS-mediated motor symptoms occurs. Also predicted is an emerging baseline dopamine deficit (Morrish, Sawle, & Brooks, 1996) and functional impairment in initially-spared,

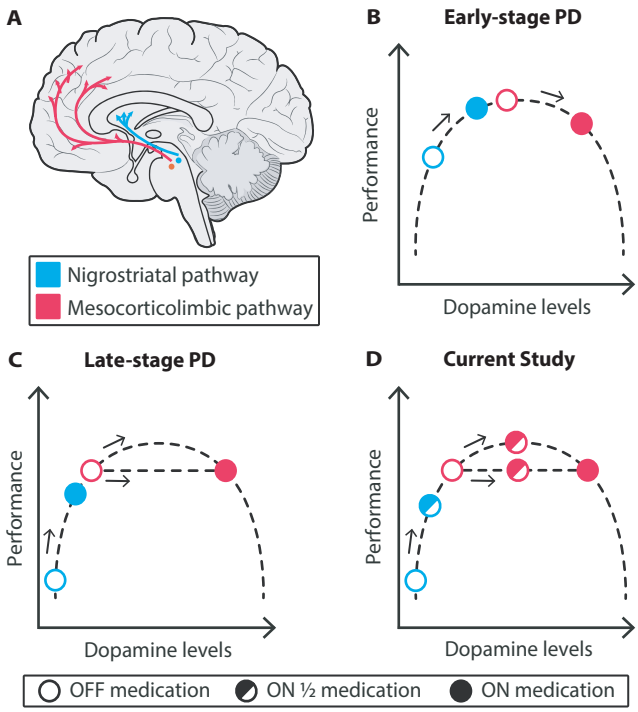

Figure 2.1: Hypothesized effects of Parkinson's disease (PD) and dopaminergic therapy on brain function within the framework of the dopamine overdose hypothesis. **(A)** Depiction of the major dopaminergic pathways in the human brain. **(B)** In the early PD, the nigrostriatal pathway is more severely dopamine-depleted than the mesocorticolimbic pathway, resulting in a baseline impairment in the former and relative sparing in the latter. When patients are treated with dopaminergic therapies, functions of dopamine-deplete brain regions are improved whereas those of less-affected areas are worsened, presumably via overdose. **(C)** As PD progresses, continued decline in the nigrostriatal pathway and an emerging deficit in the mesocorticolimbic pathway are expected. Whereas continued improvement of substantia nigra-innervated brain regions is evident, the effects of dopaminergic therapy on mesocorticolimbic functions at more advanced disease stages is less clear. If the dose of medication, titrated primarily in response to severely impaired dorsal striatum-mediated motor symptoms, overestimates the degree of dopamine depletion in mesocorticolimbic areas, a persistent overdose is possible. An alternative prediction is that mesocorticolimbic regions are not adapted to benefit from dopaminergic therapy and will neither improve nor worsen with treatment at later disease stages. **(D)** The present study aimed to disentangle competing interpretations of dopaminergic therapy effects on cognition in late-stage PD by comparing functions OFF versus ON ½ dose of medication.

VTA-innervated brain regions. Dopaminergic therapy continues to improve DS functions even late into the disease course and might similarly improve VTA-innervated brain functions by redressing the developing dopamine deficiency (see Figure 2.1c). This predicted shift from deleterious to beneficial medication effects on VTA-innervated brain function remains largely untested, however. Studies that have investigated the dopamine overdose framework in PD were performed almost exclusively in early, mild-to-moderately severe PD cohorts. This bias is likely motivated by the fact that the degree of asymmetry between SNc versus VTA dopamine depletion is thought to be greatest earlier in the disease course. We argue that a critical test of the straightforward predictions offered by the overdose hypothesis involves contrasting the effects of dopaminergic therapy on VTA-innervated brain function in PD patients that vary in the degree of dopamine deficiency in these regions as a function of disease duration and severity.

Peterson and colleagues (2009) first investigated the effect of dopamine depletion resulting from advanced PD on cognition. They examined probabilistic reversal learning in a sample of late PD patients after withdrawal of their dopaminergic medications compared to healthy controls. Participants learned through trial and error, which of two stimuli was associated with reward versus punishment and to consistently select the rewarding cue. After many stimulus-reward acquisition trials, this stimulus-reward contingency would unexpectedly reverse such that the participant was required to re-learn the new stimulus-reward association and adapt their selections accordingly. Late PD patients demonstrated poorer re-learning of the stimulus-reward probabilities post-reversal. This study demonstrated that advanced PD produces a deficit in reward learning, thought to reflect the loss of dopamine neurons in underlying brain regions. It is unclear, however, whether this reflects a disease or disease severity effect, as no early PD

group was examined. How this baseline dopamine deficit in PD might interact with dopaminergic therapy is also uncertain. MacDonald et al., (2013a) offer one of the first and few investigations into the evolution of cognition and responses to dopaminergic therapy in progressing PD. They compared stimulus-reward reversal learning in early (i.e., < 5 years disease duration) versus late (i.e., > 5 years disease duration) PD patients, tested on versus off dopaminergic medication, compared to age-matched healthy controls. The task version used involved serial reversals of stimulus-reward contingencies at multiple points throughout each session. The number of trials to reach pre-defined learning criteria throughout the experiment was used a measure of learning, with more trials denoting poorer learning performance. At baseline, in the OFF session, late PD patients learned more poorly than both early PD patients and healthy controls, whereas early PD patients learned comparably to controls. This pattern of normal learning in early but impaired learning in late PD at baseline is consistent with a developing endogenous dopamine deficit in brain regions that support learning. Examining the effects of dopaminergic therapy, early PD patients displayed poorer reward learning on relative to off medication. Their learning efficiency in the ON state was also impaired relative to that of healthy controls. This finding is entirely consistent with the predicted medication overdose of relatively dopamine-replete brain regions. Although this pattern of results in early PD patients provided strong support for the dopamine overdose hypothesis, and for the idea of a baseline dependency, the lack of improvement of baseline learning impairments in late PD patients tested on medication was at odds with this account. Reward and reversal learning were not impaired by dopaminergic therapy in late PD patients either.

Two competing explanations account for the absence of medication effects on

reward learning in late PD. Doses of medication titrated to motor symptoms mediated by the more severely-impaired SNc-innervated DS will continue to overestimate the degree of dopamine depletion in VTA-innervated brain regions, despite a developing endogenous dopamine deficit in these areas as PD progresses. The result is persistent dopamine overdose of VTA-innervated brain regions even in late PD (see Figure 2.1c). Alternatively, VTA-innervated brain regions, such as VS, might not be adapted to benefit from exogenous dopamine, even when endogenous dopamine deficiency does develop. This might occur due to particular differences in dopamine signalling and synaptic dopamine regulation in regions such as VS compared to DS. Comprised of fewer and smaller neurons with widely-spaced dendrites and spines, stimulation of VS with dopamine appears to produce a slower, more graded, and varied response compared to DS that displays maximal receptor stimulation across a wide range of firing frequencies (Wickens, Budd, Hyland, & Arbuthnott, 2007; Zhang et al., 2009). A reliance on more incremental dopamine signals, integrated over longer periods in VS could be more affected by an increase in baseline dopamine tone that is expected by bolus, exogenous dopamine. In contrast, a binary response to dopamine above a relatively-low threshold in DS seems to adapt this region to benefit from a larger range of dopamine concentrations. VS also expresses a lower concentration of dopamine transporters (DAT)–the protein responsible for clearing dopamine at the synapse in the striatum (Wickens et al., 2007), compared to DS. The fact that VS has slower and less efficient clearance of synaptic dopamine might increase its susceptibility to overdose by exogenous dopamine whereas superior dopamine regulation in DS is expected to act as a buffer against excess dopamine.

The present study aimed to test these competing explanations for the evolution of

cognitive changes and responses to dopaminergic therapy in PD. In a cross-sectional design, we investigated stimulus-reward and reversal learning in early- versus late-stage PD patients, OFF versus ON ½ dose of their usual dopaminergic medication, compared to learning in age-matched healthy controls. The reversal learning paradigm has previously been shown to correlate with activity in VTA-innervated brain regions, including VS and ventromedial PFC such as the orbitofrontal cortex (OFC; Cools, Clark, Owen, & Robbins, 2002; Cools, Lewis, Clark, Barker, & Robbins, 2007). Further, reversal learning appears to depend upon integrity of OFC (Fellows & Farah, 2003). Treating patients on a partial dose of dopaminergic medication, as opposed to a full dose as done by others (A. A. MacDonald, Monchi, et al., 2013a), could allow us to distinguish competing accounts of medication effects in early but especially late-stage PD (see Figure 2.1d). At baseline, when tested OFF medication, we predicted that early-stage PD patients would perform comparably to healthy controls whereas late-stage PD patients would demonstrate a baseline learning impairment compared to both early-stage PD and healthy controls, in line with what has already been shown (A. A. MacDonald, Monchi, et al., 2013a). This pattern would reflect an initial sparing and later decline of VTA-innervated brain functions in early- versus later-stage PD patients, respectively, with PD progression. Next, we predicted reduced learning efficiency in early-stage PD patients even when tested ON ½ dose relative to OFF medication and compared to healthy controls. This is due to the fact that in early PD, VTA is essentially spared and functions of VTA-innervated brain regions that are dopamine replete are worsened by dopamine overdose. Due to persistent asymmetry in SNc and VTA degeneration throughout the disease course in PD, doses of dopaminergic medication titrated to DS-mediated motor symptoms will continue to exceed the degree of dopamine depletion in VTA-innervated brain regions, even at later stages of PD. If VTA-innervated brain regions can benefit

from dopamine remediation, we expect that a partial dose of dopaminergic therapy, more matched to the baseline VTA dopamine deficit, should improve baseline reward and reversal learning deficits in late-stage PD patients. In contrast, if differences in dopamine signalling and regulation in VTA-innervated areas poorly adapts them to benefit from dopaminergic therapy, even when dopamine dosage more closely parallels the dopamine deficiency in late-stage PD, no improvements and perhaps even worsening of function will result.

2.2 Methods

2.2.1 Participants

Twenty-seven patients with PD and 18 age- and education-matched healthy controls (HCs) participated in the present study. PD patients were recruited through the Movement Disorders Clinic at London Health Sciences Centre. Patients were classified as being either early- (ePD) or late-stage (lPD) based on the severity of their motor symptoms, as measured by the motor sub-scale score of the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) in the OFF medication state. Cut-off points between mild/moderate PD were chosen based on previous proposals (Martinez Martin et al., 2015). This resulted in 16 ePD patients and 11 lPD patients. One subject from each PD subgroup was excluded from data analyses due to their failure to reach a pre-defined learning criterion in the behavioural task, resulting in 15 ePDs and 10 lPDs in the final patient sample.

All PD patients were previously diagnosed by a licensed neurologist, had no coexisting diagnosis of dementia or another neurological or psychiatric disease,

and met core assessment criteria for surgical interventional therapy and the UK Brain Bank for the diagnosis of idiopathic PD (Hughes, Daniel, & Kilford, 1992). HCs were free of neurological and psychiatric illness. All PD patients and no HCs were treated with dopaminergic therapy. Participants with a history of alcohol, prescription, or illegal drug abuse, or taking cognitive-enhancing drugs (including Aricept, Excelon, Reminyl, Exela, and/or memantine) were excluded from participating. All participants provided informed written consent prior to beginning the experiment in accordance with the Declaration of Helsinki (World Medical, 2013). This study was approved by the Health Sciences Research Ethics Board of the University of Western Ontario.

2.2.2 Experimental Design

All participants completed two testing sessions on different days. Sessions were separated by no more than one week. PD patients completed one session OFF medication and the other session ON ½ of their usual dopaminergic medication dosage. Sessions were counterbalanced across participants to control for order, practice, and fatigue effects. That is, half of PD patients completed Session 1 OFF medication and Session 2 ON ½ medication, and the other half performed Session 1 ON ½ medication and Session 2 OFF medication. For OFF testing sessions, PD patients abstained from taking dopaminergic precursors (i.e., levodopa/carbidopa) for a minimum of 12 to a maximum of 18 hours, as well as dopamine agonists (e.g., pramipexole, ropinirole, pergolide), monoamine oxidase inhibitors (e.g., rasagiline and selegiline), catechol-O-methyltransferase (COMT) inhibitors (e.g., entacapone), and amantadine for a minimum of 16 to a maximum of 20 hours, prior to the start of testing. For ON ½ testing sessions, PD patients took only half of their usual doses of dopaminergic medication on the day of testing. All PD patients confirmed that they complied with these instructions at

the start of each testing session. HCs did not take any medications in either session, but their data were analyzed to correspond to the OFF-ON medication order of the PD patient to whom they were matched to control for order, practice, and fatigue effects.

At the beginning of each session, participants completed a battery of cognitive and psychiatric control measures (see Table 2.1), including the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Starkstein Apathy Scale (SAS), and American National Adult Reading Test (ANART). The Montreal Cognitive Assessment (MoCA) was administered in the ON ½ session only for PD and HC participants. The motor sub-scale of the UPDRS was scored by a licensed neurologist with subspecialty training in movement disorders to assess disease severity for PD patients in both the OFF and ON ½ testing sessions. These scores were then converted to the MDS-UPDRS for the purposes of patient group classification, based on the formula: (UPDRS Part III × 1.2) + 2.3 (Goetz, Stebbins, & Tilley, 2012). HCs were also screened to rule out undiagnosed neurological illness. Daily L-dopa equivalents (LED) for each PD patient was calculated based on the theoretical equivalence to L-dopa (mg) as follows: L-dopa dose (mg) × 1 + L-dopa controlled release (mg) × 0.75 + L-dopa (mg) × 0.33 if on entacapone (mg) + amantadine (mg) × 0.5 + bromocriptine (mg) × 10 + cabergoline (mg) × 50 + pergolide (mg) × 100 + pramipexole (mg) × 67 + rasagiline (mg) × 100 + ropinirole (mg) × 16.67 + selegiline (mg) × 10 (Wüllner et al., 2010).

2.2.3 Behavioural Task

During each testing session, participants completed a probabilistic reversal learning (PRL) task. This task measured participants' ability to i) learn initial stimulus-reward associations, and ii) subsequently update these associations in response to changes in stimulus-reward contingencies, based on trial and error,

through feedback (see Figure 2.2). Stimulus-reward reversal learning has been previously shown to preferentially engage VTA-innervated brain regions such as VS and ventromedial PFC, specifically OFC (Cools et al., 2002; 2007). Further, PRL is impaired in patients with lesions in the ventromedial PFC (Fellows & Farah, 2003).

On every trial, participants were asked to select one card from a pair, presented side-by-side in the center of the computer screen. The left-right location of the cards was randomly switched between trials to prevent a deck from becoming associated with a consistent location or key-press response. Each card in the pair comes from a separate deck: one red and the other blue. Participants were instructed that a) one deck contained more winning than losing cards (i.e., the probabilistically favourable deck) whereas the other deck contained more losing than winning cards (i.e., the probabilistically unfavourable deck), and b) the probabilistically favourable deck could change at any point throughout the task without notice. They were not made aware of the exact reinforcement probabilities, however. The object of the task was to select the card that was most likely to be the winner (i.e., from the probabilistically favourable deck) on each trial. Participants were not told which deck was associated with the more favourable outcome at the outset. The initial stimulus-reward contingency and subsequent contingency reversals were therefore discerned by participants through trial and error. Participants selected the card on the left- or right-hand side of the screen using a button-press corresponding to either the index or middle finger, respectively, of their right hand. Feedback was provided at the end of each trial. Selecting the winning card resulted in a $50 increase in total play-money winnings whereas selecting the losing card resulted in a $50 decrease in total play-money winnings.

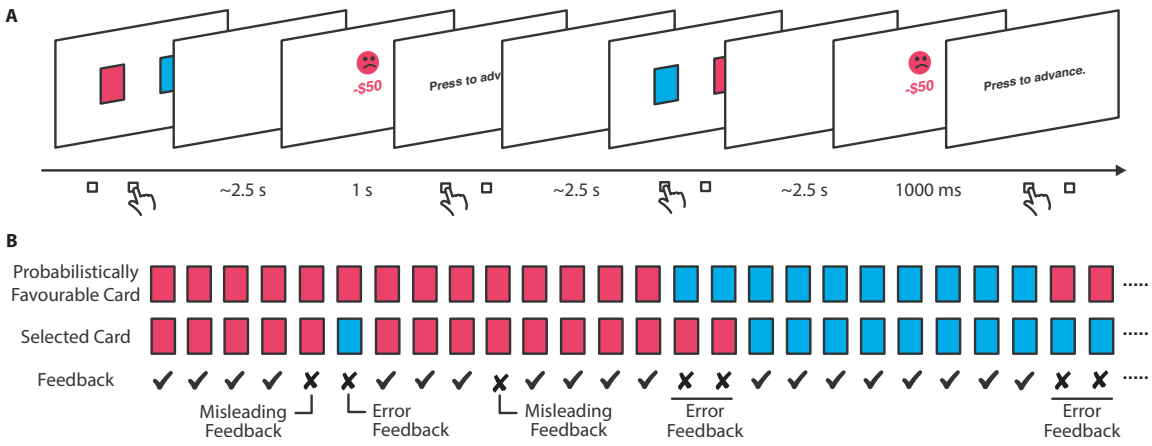

Figure 2.2: Probabilistic reversal learning trial structure and task design. **(A)** Trials proceeded as follows: i) a red card and a blue card were presented, side by side, and remained in the center of the screen until the participant provided a button-press response; ii) a blank screen appeared for an average inter-stimulus interval (ISI) of 2500 ms (taken from an exponential distribution ranging from 525 to 7000 ms); iii) outcome feedback (i.e., "Correct" or "Incorrect" and reward/punishment feedback (i.e., "+$50" or "-$50") appeared for 1000 ms; iv) a prompt appeared and remained in the center of the screen until the participant provided a secondary button-press to advance to the next trial; v) a blank screen for an average ITI of 2500 ms (taken from an exponential distribution ranging from 525 to 7000 ms) separated trials. **(B)** Selection of the probabilistically favourable card resulted in reward feedback on 90% of trials and misleading punishment feedback on 10% of trials (vice versa for selection of the unfavourable card). After the favourable card is selected on 8 consecutive trials, a reversal of the stimulus-reward contingencies occurs, requiring participants to select the new probabilistically favourable card. Additional reversals occurred after the participant selected the probabilistically favourable card, based on the new stimulus-reward contingency, on another 8 consecutive trials.

Trials proceeded as follows: i) a red card and a blue card were presented, side by side, and remained in the center of the screen until the participant provided a button-press response; ii) a blank screen for an average inter-stimulus interval (ISI) of 2500 ms, randomly taken from an exponential distribution ranging from 525 to 7000 ms, separated participant choices from outcome presentations; iii) outcome feedback (i.e., "Happy face" or "Sad face" and reward/punishment feedback of +$50 or -$50) appeared for 1000 ms; iv) a prompt required participants to provide a button-press to advance to the next trial; v) a blank screen for an average inter-trial interval (ITI) of 2500 ms, randomly taken from an exponential distribution ranging from 525 to 7000 ms, separated trials.

At the outset, either the red or blue deck was randomly assigned to be the probabilistically favourable deck. If the card from this deck was selected, positive feedback was provided for 90% of trials and negative feedback was given for 10% of trials. In contrast, if a card from the probabilistically unfavourable deck was chosen, positive feedback was given on only 10% of trials and negative feedback was provided on 90% of trials. Therefore, 10% of trials presented participants with misleading feedback. This a) increased the task difficulty but remained appropriate for a patient population, b) encouraged perseverative responding, and c) reduced participants anticipation of when contingency reversals would occur. Once the card from the probabilistically favourable deck was selected on eight consecutive trials, irrespective of feedback given to the participant, a contingency reversal occurred. This resulted in a switch of stimulus-reward relations between decks, such that the previously favourable deck became unfavourable and the previously unfavourable deck became favourable. Once the card from the probabilistically favourable deck, based on the new stimulus-reward contingency, was selected on eight consecutive trials, another contingency reversal

occurred. Participants continued the task until a total of eight successful reversals were achieved, until they reached a 200-trial deadline, or if they failed to complete the first stimulus-reward reversal prior to 120 trials.

2.2.4 Behavioural Measures and Statistical Analyses

Total number of errors during the PRL task was used as an index of learning performance, with more errors indicating poorer and less efficient learning. In addition to the total learning per session, we also examined learning separated into a) the initial stimulus-reward acquisition, and b) the stimulus-reward reversal learning phases. The acquisition period was defined as the initial trial until the first reversal. All trials thereafter were considered as being part of the reversal phase. We also examined the influence of reinforcement from the immediately-preceding trial on participants' selections (Lesage et al., 2017). Win-Stay and Lose-Shift probabilities refer to the proportion of trials on which participants stayed following a reward or shifted following a punishment, respectively.

The effect of disease severity, independent of dopaminergic therapy, was assessed in a one-way ANOVA contrasting Group (ePD vs. lPD vs. HC) in the OFF session. This was followed by *a priori* planned analyses to investigate the effects of PD (ePD OFF vs. HC and lPD OFF vs. HC) and PD severity (lPD OFF vs. ePD OFF). The effect of dopaminergic therapy on learning was first examined using a one-way ANOVA contrasting Group (ePD vs. lPD vs. HC) in the ON ½ dose session. We then performed *a priori* planned analyses to test medication effects (ePD ON ½ vs. HC, lPD ½ vs. HC, and ePD ON ½ vs. lPD ON ½). Finally, within-subject paired *t*-tests, contrasting OFF and ON ½ sessions, were conducted for each group separately. These frequentist statistics were followed by analogous Bayesian statistics. A critical *a priori* prediction in the present study was that medication would neither improve nor worsen learning in lPD patients. Traditional

frequentist approaches to statistical analysis are not well-suited for testing such predicted null effects due to a high 20% rate of rejecting a true null effect (i.e., Type II error) simply by chance. Bayesian statistics better equate error levels when contrasting evidence for the null and alternative hypotheses, allowing more direct comparisons of the relative model fit of the data (Dienes, 2014; Quintana & Williams, 2018). Here, a Bayes factor (BF_{01}) of greater than 3 strongly supports the null hypothesis, indicating that the observed data are at least 3 times more likely under the null than the alternative hypothesis. BF_{01} less than $1/3$ suggests evidence in favour of the alternative hypothesis and those falling between $1/3$ and 3 are considered anecdotal-level evidence.

2.3 Results

Two PD patients were unable to complete the first stimulus-reward reversal before the 120-trial deadline during their first testing session and their data were excluded from further analyses. Recall that although HC measures were analyzed to correspond to the OFF-ON order of the PD patient to whom they were matched, HC participants did not actually receive dopaminergic therapy in any session.

2.3.1 Control Measures

Demographic and clinical measures are presented in Table 2.1. Groups were well-matched in terms of age ($F_{2,42} = 1.923$, $p = 0.159$), years of education ($F_{2,42} = 1.069$, $p = 0.353$), estimated verbal IQ ($F_{2,42} = 0.102$, $p = 0.904$), and MoCA score ($F_{2,42} = 0.389$, $p = 0.680$).

Paired *t*-tests were used to compare clinical measures in the OFF and ON ½ sessions for each Group separately. In ePDs, MDS-UPDRS scores were

significantly greater in the OFF compared to ON ½ session (t_{14} = -10.395, p < 0.001), indicating increased motor symptom severity in patients tested OFF relative to ON ½ dose of dopaminergic therapy. No within-subject differences were found for BDI (t_{14} = -0.086, p = 0.932), BAI (t_{14} = 1.712, p = 0.109), or SAS (t_{14} = -0.725, p = 0.481) scores. In lPDs, MDS-UPDRS scores were significantly greater in the OFF compared to ON ½ session (t_9 = -5.420, p < 0.001). BDI (t_9 = -0.802, p = 0.443), BAI (t_9 = 0.949, p = 0.368), and SAS (t_9 = -1.555, p = 0.154) scores did not significantly differ between sessions, however. In HCs, no OFF and ON ½ differences were found for BDI (t_{17} = -0.205, p = 0.840), BAI (t_{17} = 0.079, p = 0.938), or SAS (t_{17} = 0.460, p = 0.651) scores.

Disease duration was significantly greater in the lPD compared to ePD group (t_{23} = -4.167, p < 0.001), as was LED (t_{23} = -3.378, p = 0.003), unsurprisingly. Significant Group effects were found for MDS-UPDRS OFF ($F_{2,42}$ = 370.940, p < 0.001), BDI OFF ($F_{2,42}$ = 9.603, p < 0.001), BAI OFF ($F_{2,42}$ = 5.718, p = 0.007), but not for SAS OFF ($F_{2,42}$ = 2.939, p = 0.064) scores. MDS-UPDRS OFF scores were significantly greater in the ePD compared to the HC (p < 0.001) group and lPD compared to the HC (p < 0.001) group. As MDS-UPDRS motor sub-scale in the OFF state was used to form ePD and lPD groups, this contrast was excluded. BDI OFF scores were significantly greater in the ePD (p < 0.001) and lPD (p = 0.003) compared to HC groups, but did not differ between PD groups (p = 0.727). BAI OFF scores were significantly greater in the ePD (p = 0.006) and lPD (p = 0.010) compared to HC groups, but did not differ between PD groups (p = 0.907). In the ON ½ session, we found significant Group effects for MDS-UPDRS ($F_{2,42}$ = 260.209, p < 0.001), BDI ($F_{2,42}$ = 11.291, p < 0.001), BAI ($F_{2,42}$ = 9.075, p = 0.001), but not SAS ($F_{2,42}$ = 2.520, p = 0.093) scores. UPDRS ON ½ scores were significantly greater in the ePD compared to the HC group (p < 0.001), and greater in the lPD compared to both ePD (p <

Table 2.1: Demographic and clinical measures for early- and late-stage Parkinson's disease patients and healthy controls.

Group	Age	Education	Duration	LED (mg)	DA (n)	UPDRS OFF	UPDRS ON	MoCA
ePD	66.40 (1.57)	15.00 (0.59)	4.87 (0.78)	534.45 (53.30)	5	25.5 (1.12)	21.66 (1.08)	27.87 (0.44)
lPD	70.90 (1.74)	15.40 (0.92)	10.50 (1.18)	883.68 (98.80)	7	36.26 (1.64)	32.17 (1.96)	27.40 (0.69)
HC	66.78 (1.51)	16.67 (1.01)	-	-	-	-	0.64 (0.18)	28.00 (0.36)

Group	BDI OFF	BDI ON	BAI OFF	BAI ON	SAS OFF	SAS ON	ANART
ePD	9.13 (1.91)	9.07 (1.68)	6.87 (1.76)	8.13 (1.80)	14.07 (1.97)	13.53 (1.52)	126.28 (1.20)
lPD	8.40 (1.29)	7.60 (1.24)	7.10 (1.36)	8.10 (1.14)	12.10 (2.08)	10.90 (1.79)	125.60 (1.93)
HC	1.94 (.65)	1.83 (0.60)	1.89 (0.64)	1.94 (0.51)	8.94 (0.98)	9.22 (1.20)	126.60 (1.43)

Values are reported as means ±SEM. Clinical measures were completed ON ½ medication unless noted otherwise. **Education:** number of years of formal education; **Duration:** number of years since PD diagnosis; **LED (mg):** L-dopa equivalent dose in mg; **DA:** number of PD patients on dopamine agonists in addition to l-dopa; **UPDRS OFF:** Movement Disorders Society-Unified Parkinson's Disease Rating Scale motor score in the OFF session; **UPDRS ON:** Movement Disorders Society-Unified Parkinson's Disease Rating Scale motor score in the ON ½ session; **MoCA:** Montreal Cognitive Assessment (out of 30); **BDI OFF:** Beck Depression Inventory score measure during the OFF session; **BDI ON:** Beck Depression Inventory score measure during the ON ½ session; **BAI OFF:** Beck Anxiety Inventory score measure during the OFF session; **BAI ON:** Beck Anxiety Inventory score measure during the ON ½ session; **SAS OFF:** Starkstein Apathy Scale score measure during the OFF session; **SAS ON:** Starkstein Apathy Scale score measure during the ON ½ session; **ANART:** Adult National American Reading Test IQ Estimation (Nelson & Willison, 1991).

0.001) and HC ($p < 0.001$) groups. BDI ON ½ scores were significantly greater in the ePD ($p < 0.001$) and lPD ($p = 0.003$) compared to HC groups, but did not differ between PD groups ($p = 0.438$). BAI ON ½ scores were significantly greater in the ePD ($p = 0.001$) and lPD ($p = 0.002$) compared to HC groups, but did not differ between PD groups ($p = 0.986$).

2.3.2 Behavioural Measures

Mean number of errors for total sessions, initial acquisitions, and stimulus-reward reversals for each Group (ePD vs. lPD vs. HC) and Session (OFF vs. ON ½) are presented in Figure 2.3a-c. Win-Stay and Lose-Shift probabilities are presented in Figure 2.4a-b.

Stimulus-reward acquisition and reversal errors

In the OFF session, a one-way ANOVA did not reach significance in terms of errors overall ($F_{2,42} = 2.872$, $p = 0.068$) or during either the acquisition ($F_{2,42} = 0.193$, $p = 0.825$) or reversal ($F_{2,42} = 2.198$, $p = 0.124$) phases separately (see Figure 2.3a-c). Planned group contrasts revealed significantly more errors in the lPD compared to ePD ($p = 0.035$) and HC ($p = 0.039$) groups, but ePDs and HCs did not differ ($p = 0.979$), in the total session. During stimulus-reward acquisitions, patients and controls made similar number of errors (all $p > 0.05$). Examining the reversal phase, we found the lPD group tended to commit more errors compared to both HC ($p = 0.055$) and ePD groups ($p = 0.083$), although this did not reach significance. Finally, ePDs and HCs performed similarly well ($p = 0.849$).

In the ON ½ medication session, a one-way, between-group ANOVA reached significance for number of errors ($F_{2,42} = 3.444$, $p = 0.042$) overall and during stimulus-reward reversals ($F_{2,42} = 4.462$, $p = 0.018$), but not for stimulus-reward acquisitions ($F_{2,42} = 1.396$, $p = 0.260$; see Figure 2.3a-c). Pairwise comparisons

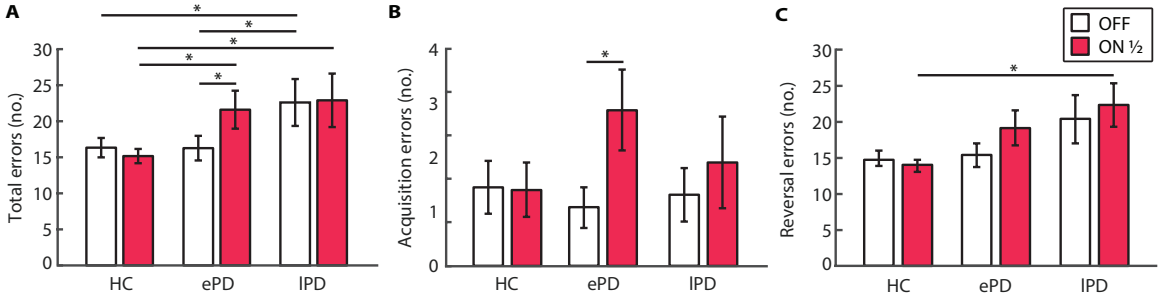

Figure 2.3: Mean error rates for each Group (ePD vs. lPD vs. HC) and Session (OFF vs. ON ½) for **(A)** total sessions, **(B)** initial stimulus-reward acquisitions, and **(C)** stimulus-reward reversals. * indicates $p < .05$. Error bars represent standard error.

revealed significantly more errors overall in the ePD ($p = 0.040$) and lPD ($p = 0.029$) groups compared to HCs, but no group differences between PD groups ($p = 0.715$). No significant differences were found between groups during the acquisition phase (all $p < 0.05$). In the reversal phase, ePDs tended to make more errors than HCs ($p = 0.052$) and lPDs made significantly more errors than HCs ($p = 0.007$), but no group differences were found comparing patient groups ($p = 0.310$).

Finally, separate paired *t*-tests revealed significantly more errors ON ½ compared to OFF medication in the ePD group ($t_{14} = 2.710$, $p = 0.017$) but in neither the lPD ($t_9 = 1.144$, $p = 0.889$) nor HC ($t_{17} = -0.666$, $p = 0.514$) groups across the total session (see Figure 2.3a). Recall that HCs were not actually treated with exogenous dopamine, though their data were analyzed to correspond to the OFF-ON order of the PD patients to whom they were matched to control for order, practice, and fatigue. Cohen's *d* was 0.700, suggesting a medium-to-large effect size for the worsening of stimulus-reward reversal learning in ePD patients in ON ½ session. Examining the acquisition phase, we found significantly more errors ON ½ relative to OFF medication only in the ePD group ($t_{14} = 2.685$, $p = 0.018$; see Figure 2.3b). A similar OFF-ON ½ pattern was found for stimulus-reward reversals in ePDs, however this did not reach significance ($t_{14} = 1.868$, $p = 0.083$; see Figure 2.3c). No OFF-ON ½ differences were observed for either the lPD (acquisitions: $t_9 = 0.557$, $p = 0.591$; reversals: $t_9 = 0.858$, $p = 0.413$; see Figure 2.3b-c) or HC (acquisitions: $t_{17} = -0.078$, $p = 0.939$; reversals: $t_{17} = -0.910$, $p = 0.375$; see Figure 2.3b-c) groups during either phase.

Win-Stay and Lose-Shift probabilities

In the OFF session, a one-way ANOVA revealed significant group differences with respect to Win-Stay probability ($F_{2,42} = 3.725$, $p = 0.033$; see Figure 2.4a), but not for Lose-Shift probability ($F_{2,42} = 1.203$, $p = 0.311$; see Figure 2.4b). Pairwise

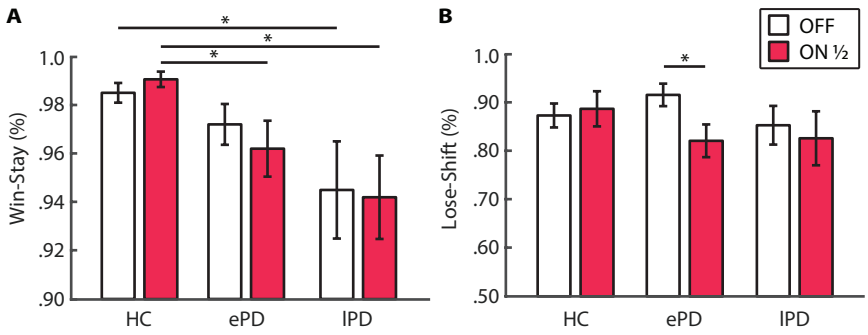

Figure 2.4: Mean **(A)** win-stay and **(B)** lose-shift probabilities for each Group (ePD vs. lPD vs. HC) and Session (OFF vs. ON ½). * indicates $p < .05$. Error bars represent standard error.

comparisons showed that lPDs tended towards less win-stay choices compared to ePDs (p = 0.069) and significantly less so compared to HCs (p = 0.010), but no differences were found between ePD and HC groups (p = 0.383). Planned contrasts of Lose-Shift probability did not reveal any significant between-group differences (all $p > 0.05$).

In the ON ½ session, we again found a significant Group effect for Win-Stay probability ($F_{2,42}$ = 6.786, p = 0.006; see Figure 2.4a), but not for Lose-Shift probability ($F_{2,42}$ = 0.932, p = 0.402; see Figure 2.4b). Simple effects analyses showed that lPDs (p = 0.002) and ePDs (p = 0.036) were significantly less likely to stay following reward feedback compared to HCs but did not significantly differ from one another (p = 0.200). Planned comparisons of Lose-Shift probability found no significant group differences in lose-shift choices (all $p > 0.05$).

Using separate paired t-tests to explore within-subject, OFF-ON differences, we did not observe medication effects for ePD (t_{14} = -1.502, p = 0.155), lPD (t_7 = -0.212, p = 0.837), or HC (t_{17} = 1.281, p = 0.217) groups in terms of Win-Stay probabilities (see Figure 2.4a). We did find, however, significant OFF-ON ½ differences in terms of Lose-Shift behaviour but only in ePD patients (t_{14} = -2.906, p = 0.012), and in neither lPD (t_7 = -0.528, p = 0.610) nor HC (t_{17} = 0.306, p = 0.763) groups (see Figure 2.4b). This reflected less frequent response shifting following punishment feedback in ePD patients tested ON ½ relative to OFF medication. We estimated a medium-large effect size with Cohen's d as 0.750 for this significant OFF-ON difference.

Bayesian analysis of predicted null effects

Given the absence of apparent medication effects on reversal learning in the lPD group, Bayesian paired t-tests were used to evaluate the likelihood of these data

given the null versus alternative hypotheses. In the lPD group, we found BF_{01} of 3.238 and 3.156 for total errors and Win-Stay probability, respectively, strongly in favour of the null hypothesis that performance in lPD is equivalent OFF and ON ½ dose dopaminergic therapy. Evidence in support of the null over alternative hypothesis for Lose-Shift probability did not reach the level of strong support but, rather, was considered anecdotal (BF_{01} = 2.848). For stimulus-reward acquisition and reversal errors, we found BF_{01} of 2.838 and 2.385, respectively, providing anecdotal evidence in favour of the null hypothesis of no within-subject differences in lPD. In contrast, for the ePD group, BF_{01} of 0.276 for total errors and 0.210 for Lose-Shift probability offered strong support for the alternative hypothesis, further bolstering significant OFF-ON effects from our frequentist analyses described above. Support in favour of the alternative hypothesis was found during the acquisition (BF_{01} = 0.287) but not reversal (BF_{01} = 0.955) phases. Finally, anecdotal-level evidence for within-subject medication effects on Win-Stay behaviour was in favour of the null hypothesis in ePD (BF_{01} = 1.721).

2.4 Discussion

2.4.1 Summary

In the present study, we provide a critical test of the dopamine overdose hypothesis and the notion of baseline dependency. Stimulus-reward reversal learning was examined in early- versus late-stage PD patients, OFF versus ON ½ medication, compared to healthy controls. We found evidence for an emerging deficit in reversal learning related to disease severity. At baseline, in the OFF session, ePDs and HCs performed equally well whereas lPD patients were more prone to errors and less likely of win-staying after reward outcomes compared to

both ePD patients and HCs. This pattern was found when examining errors in the total learning session and during stimulus-reward reversals, but not at the time of initial acquisition. We also found evolving effects of dopaminergic therapy on reversal learning in PD. In the ON ½ session, both ePD and lPD patients learned more poorly than HCs, indicated by increased errors and decreased win-stay behaviour. Medication-related worsening of learning in ePD compared to HC was evident whether examining the total session or in the reversal phase, but not during stimulus-reward acquisitions. That reversal learning in ePD patients was comparable to HCs at baseline but impaired when tested on dopaminergic medication to a degree equivocal to lPD patients is consistent with the dopamine overdose hypothesis. Direct OFF-ON contrasts for each group separately revealed more error-prone learning and reduced lose-shifting in the ON ½ relative to the OFF session for the ePD group only, partially supporting the overdose account. Critically, reversal learning performance was equivalent across sessions in both the lPD and HC groups. This pattern was observed whether examining errors across total sessions, during acquisitions, or during reversals. Dopaminergic therapy, even when administered as a partial dose, failed to remedy baseline learning impairments in lPD despite a developing endogenous dopamine deficit in initially-spared VTA-innervated brain regions. Complementary analyses based on Bayesian statistics provided support for the null medication effect on reversal learning observed in lPD patients.

We frequently observed effects of disease severity and dopaminergic therapy on error rates when examining overall sessions and during reversal phases, but less so in the acquisition phases. Although this might suggest a selective effect of PD and medication on stimulus-reward reversals, it is more likely the case that initial stimulus-reward learning was not sufficiently tested in order to observe a

behavioural effect. Recall that reward feedback during the PRL task was delivered on a 90:10 reinforcement probability. During early learning trials before the first reversal, participants would have encountered few probabilistic and no reversal errors, resulting in near ceiling performance across groups. Only after participants successfully completed initial stimulus-reward acquisitions and began the reversal phase was learning adequately challenged. In addition, we found contrasting disease severity and dopaminergic therapy effects depending on whether between- or within-group differences, respectively, were examined. Maximizing between-group differences in disease severity (i.e., at baseline in the OFF session) versus within-group differences in dopaminergic therapy (i.e., direct OFF-ON ½ session contrasts) revealed specific effects on win-staying and lose-shifting. We discuss these patterns in the following sections.

Patient groups differed in disease severity, confirmed by greater UPDRS scores in the lPD compared to ePD group in both the OFF and ON ½ sessions. This was mirrored by larger doses of dopaminergic therapy used to treat lPD compared to ePD group, which is to be expected given these medications are titrated in proportion to greater motor symptom severity in lPD patients. Given advanced PD is often associated with presence of mild cognitive impairment or dementia, we ensured our patient groups were cognitively "normal" with careful screening using cognitive and psychiatric tests. No participants met the cut-off criteria for cognitive impairment on the MoCA and these scores did not differ between groups. We also found a disease-related increase in self-reported depression and anxiety in patients compared to HCs that neither improved nor worsened with medication.

2.4.2 Parkinson's disease severity worsens reversal learning at baseline

As PD progresses, continued degeneration of SNc and worsening DS-mediated motor symptoms is expected. Motor symptom severity, as measured by UPDRS scores, was greater in lPD compared to ePD patients. Also predicted with increasing disease severity is the development of dopamine deficiency within initially-spared VTA-innervated brain regions (Morrish et al., 1996). This prediction was supported by our finding of poorer learning in lPD compared to ePD patients and HCs, but comparable performance between ePD patients and HCs.

Increased errors in lPD patients at baseline corresponded with decreased win-staying. This reduction in sensitivity of reward outcomes on choice behaviour likely reflects a decline in endogenous dopamine levels associated with increasing disease severity. Cools et al., (2006) tested such an influence of dopamine levels on reward- and punishment-based learning in PD. Using a task in which PD patients learned to associate stimuli with positive and negative outcomes, the authors found that patients off medication showed reduced reward- relative to punishment-based learning. This bias was reversed when patients were tested on medication. In a separate study using PET imaging, Cools and colleagues (2009) found that individuals with lower dopamine synthesis capacity in the striatum learned more poorly from unexpected rewards relative to punishment feedback, whereas the reverse pattern was seen in those individuals with high dopamine levels. Taken together, lower baseline dopamine levels related to PD and PD severity, as well as individual differences in endogenous dopamine, appears to reduce reward-based learning.

2.4.3 Dopaminergic therapy impairs reversal learning in early- but not late-stage Parkinson's disease

We found that dopaminergic therapy impaired stimulus-reward and reversal

learning, replicating previous findings in PD patients (Cools et al., 2001; 2006; Cools, Barker, Sahakian, & Robbins, 2003; A. A. MacDonald, Monchi, et al., 2013a; Swainson et al., 2000) as well as in healthy volunteers (Mehta, Swainson, Ogilvie, Sahakian, & Robbins, 2001; Vo, Seergobin, Morrow, & MacDonald, 2016). Both within- and between-subject analyses revealed that learning in ePD patients was better than lPD patients and comparable to HCs at baseline, but worsened with medication to an extent comparable to baseline impairments in lPD patients. This pattern reflects an initial sparing of VTA-innervated functions in ePD that are impaired by overdose of this region by dopaminergic therapy. Such an overdose effect was specific to the ePD group, as baseline reversal learning impairments in lPD patients neither improved nor worsened when tested on medication, replicating previous results (A. A. MacDonald, Monchi, et al., 2013a). This was supported with Bayesian analysis. We discuss this finding in greater detail in Section 2.4.4.

Medication-related reversal learning deficits in ePD patients were marked by more errors and less probability of shifting choices after receiving 'loss' feedback. These findings suggest that dopaminergic therapy might disrupt learning by reducing sensitivity to punishment feedback. It is well established in the reinforcement learning literature that midbrain dopamine neurons signal reward and punishment outcomes, especially when this feedback is surprising or unexpected (Bayer & Glimcher, 2005; Robinson, Frank, Sahakian, & Cools, 2010), via phasic bursts and/or pauses in firing (Bayer & Glimcher, 2005; Schultz, 1997). Exogenous dopamine is hypothesized to increase tonic dopamine levels in the striatum such that transient dips in dopamine levels critical for signalling punishment could be occluded (Frank, 2005). Impaired punishment-based learning by dopaminergic therapy has been demonstrated in a number of studies in both PD patients (Bódi

et al., 2009; Cools et al., 2001; 2007; Frank, Seeberger, & O'Reilly, 2004; Swainson et al., 2000) and healthy volunteers (Mehta et al., 2001; Moustafa, Cohen, Sherman, & Frank, 2008; Vo et al., 2016).

A small literature has investigated the effects of dopaminergic therapy on learning using neuroimaging in early PD (Aarts et al., 2014; Cools et al., 2007; Hiebert et al., 2019; Kwak, Müller, Bohnen, Dayalu, & Seidler, 2012; van Eimeren et al., 2009). Cools et al., (2007) showed that dopaminergic therapy specifically disrupted VS activity during a PRL task in a sample of early PD patients, though it should be noted that no behavioural effect of dopaminergic therapy was found. To elaborate, VS activity during final reversal errors that preceded an appropriate response shift (i.e., lose-shift) was reduced on relative to off medication in early PD patients. This effect was specific to VS, as examination of activity in DS among other control regions did not reveal any treatment effects. Similarly, Kwak et al. (2012) examined explicit motor sequence learning in PD patients tested off and on medication with fMRI. Patients were required to learn a sequence of key-presses over repeated training blocks, with reduced error rates and response times over time used as a measure of learning efficiency. The authors found that medication impaired learning during the early phase of training and this deficit corresponded with reduced signal change in VS. In a recent study by Hiebert et al. (2019), the effects of dopaminergic therapy on stimulus-response learning were investigated in PD patients compared to healthy controls. Participants learned to associate abstract stimuli with specific key-presses through trial-and-error via feedback. The authors found that learning rate of stimulus-response associations was correlated with activity in VS and this signal was attenuated when patients were tested on relative to off dopaminergic medication. Collectively, these studies demonstrate that medication-related worsening of learning performance is related

to reduced activity in VTA-innervated brain regions, VS in particular. Others have reported overdose effects in ventromedial PFC. Argylan et al., (2018) tested the effects of dopaminergic therapy on reward learning in early-stage PD compared to healthy controls with fMRI. Participants performed stimulus-reward selections during an anticipation phase before being presented with either reward or punishment outcomes in a feedback phase. During feedback processing, the authors found reduced BOLD responses in the bilateral putamen of PD patients tested on relative to off medication. When anticipating feedback, a medication-related decrease in activity within the ventromedial PFC was reported in PD patients.

2.4.4 Testing the dopamine overdose hypothesis

The dopamine overdose hypothesis posits that whether dopaminergic therapy improves or impairs a given brain region function is dependent on the baseline endogenous dopamine levels within that region. In PD, dopaminergic neurons in SNc are significantly degenerated whereas those in VTA are relatively spared. This results in a baseline impairment of SNc-innervated DS functions and less affected VTA-innervated brain functions. Dopaminergic therapy titrated in response to DS-mediated motor symptom severity overestimates the modest degree of dopamine-depletion to VTA-innervated areas, leading to impaired functions. Support for this overdose account, however, relies to a significant extent on studies in early-stage PD patients tested off versus on dopaminergic therapy either using behavioural results alone (Cools et al., 2006; Feigin et al., 2003; Frank & Claus, 2006; Graef et al., 2010; Jahanshahi et al., 2010; Kwak, Müller, Bohnen, Dayalu, & Seidler, 2010; A. A. MacDonald, Monchi, et al., 2013a; A. A. MacDonald, Seergobin, et al., 2013b; P. A. MacDonald et al., 2011; Seo, Seo, Beigi, Jahanshahi, & Averbeck, 2010; Shohamy et al., 2006; Swainson et al., 2000; Tomer,

Aharon-Peretz, & Tsitrinbaum, 2007; Torta, Castelli, Zibetti, Lopiano, & Geminiani, 2009; Tremblay et al., 2010; Vo et al., 2014) or behavioural results correlated with changes in neural activity assessed with neuroimaging (Aarts et al., 2014; Argyelan et al., 2018; Cools et al., 2007; Hiebert et al., 2019; Kwak et al., 2012). To a lesser extent, this hypothesis has also been investigated in healthy volunteers following a dopamine challenge (Breitenstein et al., 2006; Gallant, Vo, Seergobin, & MacDonald, 2016; Mehta et al., 2001; Pizzagalli et al., 2008; Santesso et al., 2009; Vo et al., 2016; Vo, Seergobin, & MacDonald, 2017; 2018; Yang, Glizer, Vo, Seergobin, & MacDonald, 2016).

Progressive degeneration of SNc and concordant worsening of DS-mediated motor symptoms is expected in later stages of PD. Also predicted is the emergence of a dopamine deficiency in initially-spared VTA-innervated brain regions. Dopaminergic therapy continues to reliably improve DS functions and might similarly be expected to benefit now impaired VTA-innervated brain functions at later-stages—although empirical support for this prediction is lacking at present. MacDonald and colleagues (2013a) compared reward learning in early versus late PD patients tested off versus on medication. At baseline, they found spared learning in early PD patients but impaired learning in late PD compared to healthy controls. This finding suggested there was a developing dopamine deficit in initially-spared brain regions. Dopaminergic therapy worsened learning in early PD patients but neither improved nor worsened baseline learning impairments in late PD, only partially supporting the dopamine overdose hypothesis. We replicated this pattern of behavioural findings in the present study though PD patients were tested on ½ their usual dose of dopaminergic therapy, which we expected would more closely parallel the dopamine deficiency in the VTA-innervated brain regions at later-stages of PD.

Two competing explanations are offered for understanding the lack of apparent medication effects on VTA-innervated brain function despite a developing endogenous dopamine deficit in late PD. Dopaminergic therapy is titrated to worsening DS-mediated motor symptoms that occur in proportion to the advancing DS dopamine depletion. Such doses of medication might continually exceed the degree of dopamine deficiency in VTA-innervated brain regions and consequently persistently overdose functions performed by these brain regions. Alternatively, VTA-innervated brain regions like VS might simply not be adapted to benefit from exogenous dopamine. In contrast to DS, VS is composed of smaller more widely-spaced medium spiny neurons that respond in a graded fashion to stimulation (Wickens et al., 2007; Zhang et al., 2009). This finely-tuned, gradient, and more slowly-integrating response in VS would be more susceptible to boluses of exogenous dopamine that could alter the tonic-to-phasic dopamine ratio at synapses in a way that does not reflect psychological events and experiences. DS, on the other hand, features maximal receptor stimulation across a wide range of firing frequencies that might tune this region to benefit from a broader range of dopamine concentrations.

Here we attempted to distinguish between these opposing predictions by testing early- versus late-stage PD patients on *a half dose of their usual dopaminergic medication*. If VTA-innervated brain functions are persistently overdosed by doses of dopaminergic therapy titrated to DS-mediated motor symptoms, a half dose was predicted to (i) overdose and impair spared functions in early PD but (ii) improve baseline deficits in late PD. If instead VTA-innervated brain regions do not benefit from exogenous dopamine, we predicted that a half dose would (i) disrupt spared functions in early PD but (ii) fail to improve or even further worsen baseline deficits in late PD. We show that even after reducing medication dosages

by half, learning was still impaired by dopaminergic therapy in early-stage PD patients. Further, a reduced dose of dopaminergic medication that should better approximate the VTA-dopamine deficiency did not benefit baseline impairments in late-stage PD patients. This finding is at odds with the notion that persistent overdose of VTA-innervated brain regions by dopamine medication doses determined by levels of DS dopamine impairments explains previous findings (A. A. MacDonald, Monchi, et al., 2013a). Our results seem more in line with the view that VTA-innervated brain regions, VS and potentially OFC in light of previous studies of the brain regions underlying PRL, are not adapted to benefit from exogenous dopamine even once dopamine depletion occurs. Of course, this is only a first step toward exploring these competing hypotheses. Future studies that compare different doses of dopamine within-subject in both early and later-staged PD patients would clarify this issue further. Lack of relation across dosing ranges and performance in these groups of PD patients would provide strong support. Correlating these behavioural findings with brain activation using neuroimaging would also be elucidatory.

It is possible that our analyses on performance of the lPD group was simply underpowered to reveal true, significant medication effects on reversal learning using frequentist statistics. To test this possibility, we used a Bayesian approach to assess the OFF-ON differences. Mirroring our findings with frequentist statistics, our Bayesian analyses strongly supported the null hypothesis that there were no performance differences between learning in the OFF and ON ½ dose sessions. Further, our null finding in the lPD group could not have resulted from inadequate medication effects more generally because DS-mediated motor symptoms, measured by UPDRS scores, were significantly improved by dopaminergic therapy.

2.4.5 Conclusions

We offer a critical investigation of the dopamine overdose hypothesis. We tested straightforward predictions regarding the role of baseline endogenous dopamine levels on cognitive function and responses to dopaminergic therapy. First, we compared PD patients at different stages of the disease course to test how progressive decline in baseline dopamine levels affect brain region function. Second, we tested PD patients OFF and ON ½ medication to contrast competing theories regarding exogenous dopamine effects in later disease stages, discussed in detail below.

EPD patients learned equally well to HCs at baseline but this learning was impaired when tested on half-doses of dopaminergic medication. This supports the dopamine overdose hypothesis. Examining the effect of disease progression and dopaminergic medication in lPD patients revealed a less tidy scenario than would be predicted by the overdose account, however. At baseline, lPD patients learned more poorly compared to ePD patients. This baseline impairment in learning for lPD relative to ePD patients and healthy controls is consistent with the predicted degeneration of VTA with PD progression, producing impaired function in VTA-innervated brain functions. However, there was no improvement in reward learning upon introducing a reduced dose of dopaminergic therapy that was expected to more closely resemble the dopamine-deficiency in these brain regions and to avoid persistent overdosing. In fact, dopaminergic therapy had no effect on learning in the lPD group. These findings call into question whether VTA-innervated brain regions like VS can benefit from exogenous dopamine. Unlike DS, whose functions improve with broad ranges of dopaminergic therapy at all stages of PD, distinct dopamine signalling and regulation properties in VS and other VTA-innervated brain regions might be intolerant to effects on tonic-to-

phasic dopamine ratios created by boluses of oral exogenous dopamine at any point along the disease course.

With increasing life expectancies, the prevalence of PD among other age-related neurodegenerative diseases is expected to rise. With improving pharmacological, surgical, and rehabilitative interventions, more patients will live longer and progress into advanced disease stages. Later in the PD course, cognitive impairments and overt dementia become the significant hindrance to quality of life and greatest predictor of institutionalization (Aarsland, Larsen, & Tandberg, 2000; Aarsland, Zaccai, & Brayne, 2005). This research contributes to a growing literature on the underlying causes of cognitive decline in PD, which will help guide future care and management of these complex symptoms. This line of research along with future studies intended to explore ranges of dopaminergic therapy doses within-subject in early and late-stage PD patients could inform treatment strategies in the clinic, prompting clinicians to consider cognitive profile and disease stage when prescribing treatment.

2.5 References

Aarsland, D., Larsen, J. P., & Tandberg, E. (2000). Predictors of nursing home placement in Parkinson's disease: A population-based, prospective study. *Journal of the American …*, *48*(8), 938–942. http://doi.org/10.1111/j.1532-5415.2000.tb06891.x

Aarsland, D., Zaccai, J., & Brayne, C. (2005). A systematic review of prevalence studies of dementia in Parkinson's disease. *Movement Disorders*, *20*(10), 1255–1263. http://doi.org/10.1002/mds.20527

Aarts, E., Nusselein, A. A. M., Smittenaar, P., Helmich, R. C., Bloem, B. R., & Cools, R. (2014). Greater striatal responses to medication in Parkinson's disease are associated with better task-switching but worse reward performance. *Neuropsychologia*, *62*, 390–397. http://doi.org/10.1016/j.neuropsychologia.2014.05.023

Argyelan, M., Herzallah, M., Sako, W., DeLucia, I., Sarpal, D., Vo, A., et al. (2018). Dopamine modulates striatal response to reward and punishment in patients with Parkinson's disease: a pharmacological challenge fMRI study. *Neuroreport*, *29*(7), 532–540. http://doi.org/10.1097/WNR.0000000000000970

Bayer, H. M., & Glimcher, P. W. (2005). Midbrain Dopamine Neurons Encode a Quantitative Reward Prediction Error Signal. *Neuron*, *47*(1), 129–141. http://doi.org/10.1016/j.neuron.2005.05.020

Bódi, N., Kéri, S., Nagy, H., Moustafa, A., Myers, C. E., Daw, N., et al. (2009). Reward-learning and the novelty-seeking personality: a between- and within-subjects study of the effects of dopamine agonists on young Parkinson's patients. *Brain*, *132*(Pt 9), 2385–2395. http://doi.org/10.1093/brain/awp094

Breitenstein, C., Korsukewitz, C., Flöel, A., Kretzschmar, T., Diederich, K., & Knecht, S. (2006). Tonic dopaminergic stimulation impairs associative learning in healthy subjects. *Neuropsychopharmacology*, *31*(11), 2552–2564. http://doi.org/10.1038/sj.npp.1301167

Cools, R. (2006). Dopaminergic modulation of cognitive function-implications for l-DOPA treatment in Parkinson's disease. *Neurosci Biobehav Rev*, *30*(1), 1–23. http://doi.org/10.1016/j.neubiorev.2005.03.024

Cools, R., & D'Esposito, M. (2011). Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biol Psychiatry*, *69*(12), e113–25. http://doi.org/10.1016/j.biopsych.2011.03.028

Cools, R., Altamirano, L., & D'Esposito, M. (2006). Reversal learning in Parkinson's disease depends on medication status and outcome valence. *Neuropsychologia*, *44*(10), 1663–1673. http://doi.org/10.1016/j.neuropsychologia.2006.03.030

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001). Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cereb Cortex*, *11*(12), 1136–1143. http://doi.org/10.1093/cercor/11.12.1136

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2003). l-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia*, *41*(11), 1431–1441. http://doi.org/10.1016/S0028-3932(03)00117-9

Cools, R., Clark, L., Owen, A. M., & Robbins, T. W. (2002). Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging. *J Neurosci*, *22*(11), 4563–4567.

Cools, R., Frank, M. J., Gibbs, S. E., Miyakawa, A., Jagust, W., & D'Esposito, M. (2009). Striatal dopamine predicts outcome-specific reversal learning and its sensitivity to dopaminergic drug administration. *J Neurosci*, *29*(5), 1538–1543. http://doi.org/10.1523/JNEUROSCI.4467-08.2009

Cools, R., Lewis, S. J. G., Clark, L., Barker, R. A., & Robbins, T. W. (2007). L-DOPA disrupts activity in the nucleus accumbens during reversal learning in Parkinson's disease. *Neuropsychopharmacology*, *32*(1), 180–189. http://doi.org/10.1038/sj.npp.1301153

Dienes, Z. (2014). Using Bayes to get the most out of non-significant results. *Front Psychol*, *5*(e33400), 781. http://doi.org/10.3389/fpsyg.2014.00781

Fearnley, J. M., & Lees, A. J. (1991). Ageing and parkinson's disease: substantia nigra regional selectivity. *Brain*, *114*(5), 2283–2301. http://doi.org/10.1093/brain/114.5.2283

Feigin, A., Ghilardi, M. F., Carbon, M., Edwards, C., Fukuda, M., Dhawan, V., et al. (2003). Effects of levodopa on motor sequence learning in Parkinson's disease. *Neurology*, *60*(11), 1744–1749. http://doi.org/10.1212/01.WNL.0000072263.03608.42

Fellows, L. K., & Farah, M. J. (2003). Ventromedial frontal cortex mediates affective shifting in humans: evidence from a reversal learning paradigm. *Brain*, *126*(Pt 8), 1830–1837. http://doi.org/10.1093/brain/awg180

Frank, M. J. (2005). Dynamic dopamine modulation in the basal ganglia: a neurocomputational account of cognitive deficits in medicated and nonmedicated Parkinsonism. *J Cogn Neurosci*, *17*(1), 51–72. http://doi.org/10.1162/0898929052880093

Frank, M. J., & Claus, E. D. (2006). Anatomy of a decision: striato-orbitofrontal interactions in reinforcement learning, decision making, and reversal. *Psychol Rev*, *113*(2), 300–326. http://doi.org/10.1037/0033-295X.113.2.300

Frank, M. J., Seeberger, L. C., & O'Reilly, R. C. (2004). By carrot or by stick: cognitive reinforcement learning in parkinsonism. *Science*, *306*(5703), 1940–1943. http://doi.org/10.1126/science.1102941

Gallant, H., Vo, A., Seergobin, K. N., & MacDonald, P. A. (2016). Pramipexole Impairs Stimulus-Response Learning in Healthy Young Adults. *Frontiers in Neuroscience*, *10*(784), 390. http://doi.org/10.3389/fnins.2016.00374

Goetz, C. G., Stebbins, G. T., & Tilley, B. C. (2012). Calibration of unified Parkinson"s disease rating scale scores to Movement Disorder Society-unified Parkinson"s disease rating scale scores. *Mov Disord*, *27*(10), 1239–1242. http://doi.org/10.1002/mds.25122

Gotham, A. M., Brown, R. G., & Marsden, C. D. (1988). 'Frontal'cognitive function in patients with Parkinson's disease 'on'and 'off'levodopa. *Brain*, *111*(2), 299–321. http://doi.org/10.1093/brain/111.2.299

Graef, S., Biele, G., Krugel, L. K., Marzinzik, F., Wahl, M., Wotka, J., et al. (2010). Differential influence of levodopa on reward-based learning in Parkinson's disease. *Frontiers in Human Neuroscience*, *4*, 169. http://doi.org/10.3389/fnhum.2010.00169

Haber, S. N., Haber, S. N., Fudge, J. L., & Fudge, J. L. (1997). The primate substantia nigra and VTA: integrative circuitry and function. *Critical Reviews™ in Neurobiology*, *11*(4), 323–342. http://doi.org/10.1615/CritRevNeurobiol.v11.i4.40

Hiebert, N. M., Owen, A. M., Ganjavi, H., Mendonça, D., Jenkins, M. E., Seergobin, K. N., & MacDonald, P. A. (2019). Dorsal striatum does not mediate feedback-based, stimulus-response learning: An event-related fMRI study in patients with Parkinson's disease tested on and off dopaminergic therapy. *NeuroImage*, *185*, 455–470. http://doi.org/10.1016/j.neuroimage.2018.10.045

Hughes, A. J., Daniel, S. E., & Kilford, L. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol*, *55*(3), 181–184. http://doi.org/10.1136/jnnp.55.3.181

Jahanshahi, M., Wilkinson, L., Gahir, H., Dharmaindra, A., Dharmarinda, A., Dharminda, A., & Lagnado, D. A. (2010). Medication impairs probabilistic classification learning in Parkinson's disease. *Neuropsychologia*, *48*(4), 1096–1103. http://doi.org/10.1016/j.neuropsychologia.2009.12.010

Kish, S. J., Shannak, K., & Hornykiewicz, O. (1988). Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease.

Pathophysiologic and clinical implications. *N Engl J Med*, *318*(14), 876–880. http://doi.org/10.1056/NEJM198804073181402

Kwak, Y., Müller, M. L. T. M., Bohnen, N. I., Dayalu, P., & Seidler, R. D. (2010). Effect of dopaminergic medications on the time course of explicit motor sequence learning in Parkinson's disease. *J Neurophysiol*, *103*(2), 942–949. http://doi.org/10.1152/jn.00197.2009

Kwak, Y., Müller, M. L. T. M., Bohnen, N. I., Dayalu, P., & Seidler, R. D. (2012). l-DOPA changes ventral striatum recruitment during motor sequence learning in Parkinson's disease. *Behavioural Brain Research*, *230*(1), 116–124. http://doi.org/10.1016/j.bbr.2012.02.006

Lesage, E., Aronson, S. E., Sutherland, M. T., Ross, T. J., Salmeron, B. J., & Stein, E. A. (2017). Neural Signatures of Cognitive Flexibility and Reward Sensitivity Following Nicotinic Receptor Stimulation in Dependent Smokers: A Randomized Trial. *JAMA Psychiatry*, *74*(6), 632–640. http://doi.org/10.1001/jamapsychiatry.2017.0400

MacDonald, A. A., Monchi, O., Seergobin, K. N., Ganjavi, H., Tamjeedi, R., & MacDonald, P. A. (2013a). Parkinson's disease duration determines effect of dopaminergic therapy on ventral striatum function. *Mov Disord*, *28*(2), 153–160. http://doi.org/10.1002/mds.25152

MacDonald, A. A., Seergobin, K. N., Owen, A. M., Owen, A. M., Tamjeedi, R., Monchi, O., et al. (2013b). Differential effects of Parkinson's disease and dopamine replacement on memory encoding and retrieval. *PLoS One*, *8*(9), e74044. http://doi.org/10.1371/journal.pone.0074044

MacDonald, P. A., & Monchi, O. (2011). Differential effects of dopaminergic therapies on dorsal and ventral striatum in Parkinson's disease: implications for cognitive function. *Parkinsons Dis*, *2011*(8414), 572743–18. http://doi.org/10.4061/2011/572743

MacDonald, P. A., MacDonald, A. A., Seergobin, K. N., Tamjeedi, R., Ganjavi, H., Provost, J. S., & Monchi, O. (2011). The effect of dopamine therapy on ventral and dorsal striatum-mediated cognition in Parkinson's disease: support from functional MRI. *Brain*, *134*(Pt 5), 1447–1463. http://doi.org/10.1093/brain/awr075

Martinez Martin, P., Rodríguez-Blázquez, C., Mario Alvarez, Arakaki, T., Arillo, V. C., Chaná, P., et al. (2015). Parkinson"s disease severity levels and MDS-Unified Parkinson"s Disease Rating Scale. *Parkinsonism Relat Disord*, *21*(1), 50–54. http://doi.org/10.1016/j.parkreldis.2014.10.026

Mehta, M. A., Swainson, R., Ogilvie, A. D., Sahakian, J., & Robbins, T. W. (2001). Improved short-term spatial memory but impaired reversal learning following the dopamine D(2) agonist bromocriptine in human volunteers. *Psychopharmacology (Berl)*, *159*(1), 10–20. http://doi.org/10.1007/s002130100851

Morrish, P. K., Sawle, G. V., & Brooks, D. J. (1996). An [18F]dopa-PET and clinical study of the rate of progression in Parkinson's disease. *Brain*, *119 (Pt 2)*(2), 585–591. http://doi.org/10.1093/brain/119.2.585

Moustafa, A. A., Cohen, M. X., Sherman, S. J., & Frank, M. J. (2008). A role for dopamine in temporal decision making and reward maximization in parkinsonism. *J Neurosci*, *28*(47), 12294–12304. http://doi.org/10.1523/JNEUROSCI.3116-08.2008

Nelson, H. E., & Willison, J. (1991). National Adult Reading Test (NART). *Int J Geriatr Psychiatry*, *7*(7), 533–533. http://doi.org/10.1002/gps.930070713

Peterson, D. A., Elliott, C., Song, D. D., Makeig, S., Sejnowski, T. J., & Poizner, H. (2009). Probabilistic reversal learning is impaired in Parkinson's disease. *Neuroscience*, *163*(4), 1092–1101. http://doi.org/10.1016/j.neuroscience.2009.07.033

Pizzagalli, D. A., Evins, A. E., Schetter, E. C., Frank, M. J., Pajtas, P. E., Santesso, D. L., & Culhane, M. (2008). Single dose of a dopamine agonist impairs reinforcement learning in humans: behavioral evidence from a laboratory-based measure of reward responsiveness. *Psychopharmacology (Berl)*, *196*(2), 221–232. http://doi.org/10.1007/s00213-007-0957-y

Quintana, D. S., & Williams, D. R. (2018). Bayesian alternatives for common null-hypothesis significance tests in psychiatry: a non-technical guide using JASP. *BMC Psychiatry*, *18*(1), 178. http://doi.org/10.1186/s12888-018-1761-4

Robinson, O. J., Frank, M. J., Sahakian, B. J., & Cools, R. (2010). Dissociable responses to punishment in distinct striatal regions during reversal learning. *NeuroImage*, *51*(4), 1459–1467. http://doi.org/10.1016/j.neuroimage.2010.03.036

Santesso, D. L., Evins, A. E., Frank, M. J., Schetter, E. C., Bogdan, R., & Pizzagalli, D. A. (2009). Single dose of a dopamine agonist impairs reinforcement learning in humans: evidence from event-related potentials and computational modeling of striatal-cortical function. *Human Brain Mapping*, *30*(7), 1963–1976. http://doi.org/10.1002/hbm.20642

Schultz, W. (1997). Dopamine neurons and their role in reward mechanisms. *Curr Opin Neurobiol*, *7*(2), 191–197. http://doi.org/10.1016/S0959-4388(97)80007-4

Seo, Seo, M., Beigi, M., Jahanshahi, M., & Averbeck, B. B. (2010). Effects of dopamine medication on sequence learning with stochastic feedback in Parkinson's disease. *Front Syst Neurosci*, *4*. http://doi.org/10.3389/fnsys.2010.00036

Shohamy, D., Shohamy, D., Myers, C. E., Myers, C. E., Geghman, K. D., Geghman, K. D., et al. (2006). L-dopa impairs learning, but spares generalization, in Parkinson's disease. *Neuropsychologia*, *44*(5), 774–784. http://doi.org/10.1016/j.neuropsychologia.2005.07.013

Swainson, R., Rogers, R. D., Sahakian, B. J., Summers, B. A., Polkey, C. E., & Robbins, T. W. (2000). Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. *Neuropsychologia*, *38*(5), 596–612. http://doi.org/10.1016/S0028-3932(99)00103-7

Tomer, R., Aharon-Peretz, J., & Tsitrinbaum, Z. (2007). Dopamine asymmetry interacts with medication to affect cognition in Parkinson's disease. *Neuropsychologia*, *45*(2), 357–367. http://doi.org/10.1016/j.neuropsychologia.2006.06.014

Torta, D. M. E., Castelli, L., Zibetti, M., Lopiano, L., & Geminiani, G. (2009). On the role of dopamine replacement therapy in decision-making, working memory, and reward in Parkinson's disease: does the therapy-dose matter? *Brain and Cognition*, *71*(2), 84–91. http://doi.org/10.1016/j.bandc.2009.04.003

Tremblay, P.-L., Bedard, M.-A., Langlois, D., Blanchet, P. J., Lemay, M., & Parent, M. (2010). Movement chunking during sequence learning is a dopamine-dependant process: a study conducted in Parkinson's disease. *Exp Brain Res*, *205*(3), 375–385. http://doi.org/10.1007/s00221-010-2372-6

Vaillancourt, D. E., Spraker, M. B., Prodoehl, J., Zhou, X. J., & Little, D. M. (2012). Effects of aging on the ventral and dorsal substantia nigra using diffusion tensor imaging. *Neurobiology of Aging*, *33*(1), 35–42. http://doi.org/10.1016/j.neurobiolaging.2010.02.006

van Eimeren, T., Ballanger, B., Pellecchia, G., Miyasaki, J. M., Lang, A. E., & Strafella, A. P. (2009). Dopamine agonists diminish value sensitivity of the orbitofrontal cortex: a trigger for pathological gambling in Parkinson's disease? *Neuropsychopharmacology*, *34*(13), 2758–2766. http://doi.org/10.1038/sj.npp.npp2009124

Vo, A., Hiebert, N. M., Seergobin, K. N., Solcz, S., Partridge, A., & MacDonald, P. A. (2014). Dopaminergic medication impairs feedback-based stimulus-response learning but not response selection in Parkinson's disease. *Frontiers in Human Neuroscience*, *8*(169), 784. http://doi.org/10.3389/fnhum.2014.00784

Vo, A., Seergobin, K. N., & MacDonald, P. A. (2017). Effects of levodopa on stimulus-response learning versus response selection in healthy young adults. *Behavioural Brain Research*, *317*, 553–561. http://doi.org/10.1016/j.bbr.2016.10.019

Vo, A., Seergobin, K. N., & MacDonald, P. A. (2018). Independent effects of age and levodopa on reversal learning in healthy volunteers. *Neurobiology of Aging*, *69*, 129–139. http://doi.org/10.1016/j.neurobiolaging.2018.05.014

Vo, A., Seergobin, K. N., Morrow, S. A., & MacDonald, P. A. (2016). Levodopa impairs probabilistic reversal learning in healthy young adults. *Psychopharmacology (Berl)*, *233*(14), 2753–2763. http://doi.org/10.1007/s00213-016-4322-x

Wickens, J. R., Budd, C. S., Hyland, B. I., & Arbuthnott, G. W. (2007). Striatal contributions to reward and decision making: making sense of regional variations in a reiterated processing matrix. *Ann N Y Acad Sci*, *1104*(1), 192–212. http://doi.org/10.1196/annals.1390.016

World Medical, A. (2013). World Medical Association Declaration of Helsinki. *Jama*, *310*(20), 2191–2194. http://doi.org/10.1001/jama.2013.281053

Wüllner, U., Kassubek, J., Odin, P., Schwarz, M., Naumann, M., Häck, H.-J., et al. (2010). Transdermal rotigotine for the perioperative management of Parkinson's disease. *Journal of Neural Transmission (Vienna, Austria : 1996)*, *117*(7), 855–859. http://doi.org/10.1007/s00702-010-0425-4

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*, 523–13. http://doi.org/10.3389/fnhum.2016.00523

Zhang, T., Zhang, L., Liang, Y., Siapas, A. G., Zhou, F.-M., & Dani, J. A. (2009). Dopamine signaling differences in the nucleus accumbens and dorsal striatum exploited by nicotine. *J Neurosci*, *29*(13), 4035–4043. http://doi.org/10.1523/JNEUROSCI.0261-09.2009

Chapter 3

Independent effects of aging and L-dopa on reversal learning in healthy volunteers

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3.1 Introduction

The dopamine overdose hypothesis provides an explanatory framework for understanding the effects of dopaminergic therapy on cognition in PD (Cools, Barker, Sahakian, & Robbins, 2001; Gotham, Brown, & Marsden, 1988; Swainson et al., 2000). It posits that whether medication improves or impairs given functions depends on the baseline endogenous dopamine levels in the brain regions that support them (Cools, 2006; P. A. MacDonald & Monchi, 2011). Although the notion of dopamine overdose has guided several investigations of cognition in PD over the past two decades, this hypothesis requires greater exploration. Here, we investigated whether age-related changes in baseline dopamine levels would modulate the effects of dopaminergic therapy on reward learning.

In healthy aging, declines in the dopaminergic system are recognized. An estimated 50% loss of dopamine neurons in the SNc/VTA occurs across the normal adult lifespan (P. L. McGeer, McGeer, & Suzuki, 1977). This is also marked by reduced DAT concentrations (Allard & Marcusson, 1989; Braskie et al., 2008; De Keyser, Ebinger, & Vauquelin, 1990; Erixon-Lindroth et al., 2005; Eusebio et al., 2012; Ishibashi et al., 2009; van Dyck, Seibyl, Malison, & Laruelle, 2002; Volkow et al., 1996; 1994; Zelnik, Angel, Paul, & Kleinman, 1986), declines in dopamine synthesis capacity (Dreher, Meyer-Lindenberg, Kohn, & Berman, 2008), and dopamine depletion in SNc- and VTA-innervated brain regions (Bunzeck et al., 2007). Postsynaptic changes in striatal D1 and D2 receptor densities are also noted with age (Antonini et al., 1993; De Keyser et al., 1990; Ishibashi et al., 2009; Suhara et al., 1991; Volkow et al., 1998; Wang et al., 1998), with more pronounced declines in the caudate nucleus and putamen compared to VS, mirroring what occurs in PD (Kim et al., 2011).

Indeed, changes in VTA in early PD seem comparable to those changes that occur in normal healthy aging (Bunzeck et al., 2007), consistent with the pathophysiological predictions that VTA is relatively spared in early PD. This is supported by numerous demonstrations of equivalent performance between PD patients in the OFF state and age-matched controls in functions mediated by VTA-supplied brain regions (Cools et al., 2001; Cools, Altamirano, & D'Esposito, 2006; Cools, Barker, Sahakian, & Robbins, 2003; Cools, Lewis, Clark, Barker, & Robbins, 2007; Feigin et al., 2003; Frank, Seeberger, & O'Reilly, 2004; Graef et al., 2010; Hiebert, Seergobin, Vo, Ganjavi, & MacDonald, 2014; Jahanshahi et al., 2010; Kwak, Müller, Bohnen, Dayalu, & Seidler, 2010; A. A. MacDonald, Monchi, et al., 2013a; A. A. MacDonald, Seergobin, et al., 2013b; P. A. MacDonald & Monchi, 2011; Seo, Seo, Beigi, Jahanshahi, & Averbeck, 2010; Swainson et al., 2000; Tomer, Aharon-Peretz, & Tsitrinbaum, 2007; Torta, Castelli, Zibetti, Lopiano, & Geminiani, 2009; Tremblay et al., 2010; Vo et al., 2014). Here, we tested healthy older volunteers both on a low-dose of dopaminergic therapy (i.e., 100 mg of L-dopa) relative to placebo, and compared to a group of healthy younger volunteers who have optimal dopaminergic systems.

The predictions for younger adults according to the dopamine overdose hypothesis are clear. At baseline, we expect younger adults will learn stimulus-reward associations and reversals normally whereas exogenous dopamine should worsen learning. In fact, we have previously demonstrated this pattern (Vo, Seergobin, Morrow, & MacDonald, 2016). In healthy older controls, however, we expect dopamine deficiency will develop owing to aging. As others have found (Mell et al., 2005; Weiler, Bellebaum, & Daum, 2008) and also have attributed to age-related functional changes in the dopaminergic system (Eppinger, Schuck, Nystrom, & Cohen, 2013; Samanez-Larkin et al., 2007; Schott et al., 2007; Vink,

Kleerekooper, van den Wildenberg, & Kahn, 2015), we expect poorer stimulus-reward and/or reward-reversal learning in the baseline state for the older relative to younger controls. A single dose of L-dopa might improve reward learning in this older adult group given this baseline deficit. If this low dose of L-dopa, however, still overestimates the deficiency that arises in the VTA due to normal aging, L-dopa might worsen performance—though lesser overdose effects are expected for older compared to younger volunteers.

In the current experiment, by using the same dose of exogenous dopamine in both experimental groups, who are predicted to differ in endogenous dopamine levels related to aging (Kish, Shannak, Rajput, Deck, & Hornykiewicz, 1992), we can test predictions of the dopamine overdose hypothesis directly. In studies with PD patients, within-group differences in degree of dopamine deficiency related to disease stage as well as differences in treatment regimens administered in L-dopa session render the interpretation of results less straightforward. Because a) we have prior evidence that the dopaminergic systems are impaired as part of the natural aging process, b) we will estimate the function of this dopaminergic system at baseline in older compared to younger volunteers in the OFF state, and c) we have equated the dosage of dopaminergic therapy across both groups, this study presents a powerful opportunity for critically testing notions about dopamine overdose that have been applied broadly to understand cognitive processes in PD (Cools, 2006; P. A. MacDonald & Monchi, 2011).

3.2 Methods

3.2.1 Participants

Twenty-six healthy younger adults and 34 healthy older adults participated in the

present study (see Table 3.1). All participants were screened for pre-existing neurological and psychiatric illness, history of drug or alcohol abuse, and contraindications for L-dopa. Three older adults scored below 26 (out of 30) on the Montreal Cognitive Assessment (MoCA) screening measure and another 2 older adults failed to reach the criteria of learning the first stimulus-reward association within 70 trials. Their data were therefore excluded from our analyses. The final sample consisted of 26 younger (M_{age} ± SEM = 21.08 ± 0.29) and 29 older (M_{age} ± SEM = 66.83 ± 1.24) adults. The data generated by the 26 younger controls have previously been described (Vo et al., 2016). All participants provided informed written consent prior to beginning the experiment in accordance with the Declaration of Helsinki (World Medical, 2013). This study was approved by the Health Sciences Research Ethics Board at the University of Western Ontario.

3.2.2 Experimental Design

All participants completed two testing sessions in a randomized, double-blind, placebo-controlled, crossover design. They received 100 mg of L-dopa (L-3,4-dihyroxyphenylalanine), a dopamine precursor, with 25 mg of carbidopa, a decarboxylase inhibitor, in one session and an equal volume of placebo in the other. The dose used here is the same as has been implemented in previous investigations (Flöel et al., 2005; Knecht et al., 2004; Onur, Piefke, Lie, Thiel, & Fink, 2011; Vo et al., 2016; Vo, Seergobin, & MacDonald, 2017). Both drug and placebo were delivered orally in identical capsules to achieve double-blindness. The order of drug-placebo administration was counterbalanced across participants to account for order, practice, and fatigue effects. In other words, half of the participants completed the first testing session on L-dopa (i.e., L/P), whereas the other half completed the first testing session on placebo (i.e., P/L). Participants were instructed to abstain from caffeine, alcohol, and nicotine on days of testing.

Furthermore, all participants were tested at least one hour after a meal to minimize interference with L-dopa absorption by protein-containing food. Cognitive testing began approximately 45 minutes following capsule administration to allow time for peak plasma L-dopa levels (Olanow, Schapira, & Rascol, 2000). Testing sessions were separated by a washout period of seven days for total drug clearance. At the beginning and end of each testing session, participants reported their subjective level of alertness using the Bond-Lader visual analogue scale (Bond & Lader, 1974) and their heart rate and blood pressure were recorded (see Table 3.1).

3.2.3 Behavioural Task

In each testing session, participants completed a probabilistic reversal learning task (see Figure 3.1). In this task, participants were required to select between a pair of cards dealt from two decks: one red and the other blue. On each trial, a card from each deck was presented side-by-side in the center of the computer screen. The left-right location of the cards was randomly switched between trials to prevent a deck from becoming associated with a consistent location or key-press response. Participants were instructed that one deck contained more winning than losing cards (probabilistic favourable) whereas the other deck contained more losing than winning cards (probabilistically unfavourable) and that the probabilistically favourable deck could change at any point throughout the task without notice. They were not made aware of the exact reinforcement probabilities, however. The object of the task was to select the card that was most likely to be the winner (i.e., from the probabilistically favourable deck) on each trial. Participants were not told which deck was associated with the more favourable outcome. The initial stimulus-reward contingency and subsequent contingency reversals were therefore discerned through trial and error.

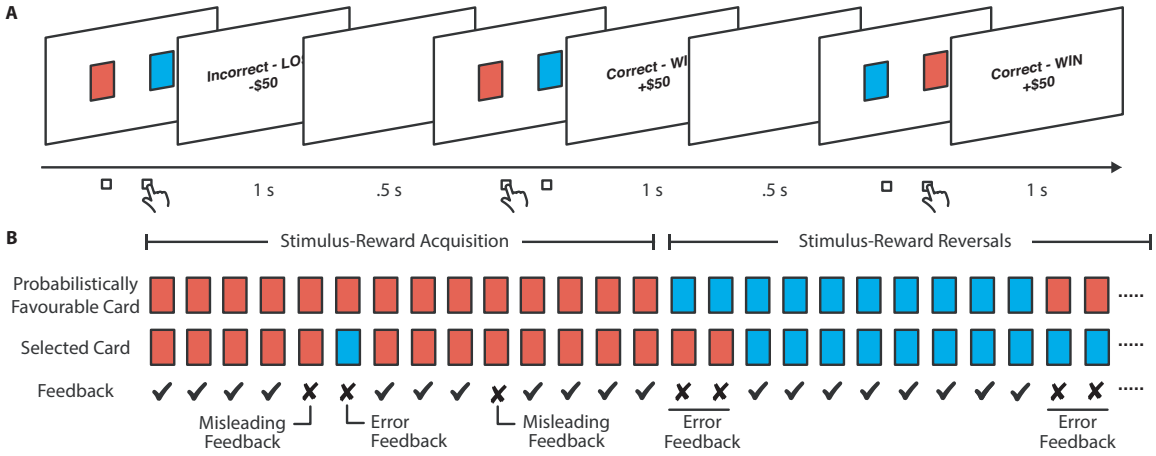

Figure 3.1: (A) Example of the trial structure. Each trials proceeded as follows: (i) a red card and a blue card were presented, side by side, in the centre of the computer screen until the participant provided a button-press response, either 'Z' or '/' keys; (ii) feedback, either "Correct - WIN (+$50)" or "Incorrect - LOSE (-$50)", was presented for 1000 ms; (iii) a blank screen for 500 ms separated trials. **(B)** Illustration of the task design. Reversals occurred once the probabilistically favorable card was selected by the participant on 8 consecutive trials. The task ended once the participant completed 8 reversal stages or reached a 500-trial deadline.

Participants pressed the "Z" key to select the card appearing on the left and the "/" key to select the card appearing on the right. Feedback was provided at the end of each trial. Selecting the winning card resulted in a $50 increase whereas selecting the losing card resulted in a $50 decrease in total winnings.

All trials proceeded as follows: (i) a red card and a blue card were presented, side by side, in the center of the computer screen until the participant provided a key-press response, either "Z" or "/" keys; (ii) feedback, either "Correct – WIN (+$50)" or "Incorrect - LOSE (-$50)", was presented for 1000 ms; (iii) a blank screen for 500 ms separated trials (see Figure 3.1a).At the outset, either the red or blue deck was randomly assigned to be the probabilistically favourable deck. If the card from this deck was selected, positive feedback was provided for 80% of trials and negative feedback was given for 20% of trials. In contrast, if a card from the probabilistically unfavourable deck was chosen, positive feedback was given on only 20% of trials and negative feedback was provided on 80% of trials. Therefore, 20% of trials (4 random trials in every 20 trials) presented participants with misleading feedback. This increased the task difficulty, encouraged perseverative responding, and prevented participants from anticipating when an actual contingency reversal would occur. Once the card from the probabilistically favourable deck was selected on eight consecutive trials, irrespective of feedback given to the participant, a contingency reversal occurred. This resulted in a switch of stimulus-reward relations between decks, such that the previously favourable deck became unfavourable and the previously unfavourable deck become favourable. Once the card from the probabilistically favourable deck, based on the new stimulus-reward contingency, was selected on eight consecutive trials, another contingency reversal occurred. Participants continued the task until a total of eight successful reversals were achieved or until they reached a 500-trial

deadline. Two older adults failed to learn the first stimulus-reward association before the 70-trial limit and their data were excluded from analysis. Figure 3.1b presents the experimental design.

3.2.4 Behavioural Measures

We first examined error rates. We analyzed the data in terms of: (a) total learning session, (b) initial stimulus-reward acquisition period, and (c) stimulus-reward reversal learning phase (see Figure 3.1b). Initial stimulus-reward acquisition was comprised of the initial trial until the first reversal. All trials thereafter were considered as part of the stimulus-reward reversal learning phase. The total number of errors committed during each of these learning periods was used as a behavioural measure of stimulus-reward learning, with more errors corresponding to poorer learning. For each learning phase, we ran separate 2 × 2 × 2 mixed analyses of variance (ANOVAs), with Group (Older vs. Younger) and Order (L/P vs. P/L) as the between-subject factors and Treatment (L-dopa vs. Placebo) as the within-subject variable. Because we anticipated practice effects across testing Sessions 1 and 2, a between-subjects factor of Order was included in our analyses. In each instance of a significant interaction effect with Order, we conducted follow-up 2 × 2 between-subject ANOVAs on Session 1 scores only, to assess the effects of Group and/or Treatment uncontaminated by practice effects.

In addition, we explored how participants' selections were influenced by reinforcement from the immediately-preceding trial (Lesage et al., 2017). Lose-Shift describes the likelihood of shifting a response across consecutive trials following punishment feedback whereas Win-Stay refers to the probability of repeating a selection from the previous trial after reward feedback was provided. Analogous to our initial analysis of error rates, we ran 2 × 2 × 2 mixed ANOVAs, with Group (Older vs. Younger) and Order (L/P vs. P/L) as the between-subject

factors and Treatment (L-dopa vs. Placebo) as the within-subject variable.

3.3 Results

3.3.1 Control Measures

We compared demographic measures between age groups using separate independent t-tests. Groups were matched in terms of years of education (t_{53} = 1.548, p = .128) and estimated verbal IQ scores (t_{53} = 1.878, p = 0.066). Judgment of whether drug or placebo was administered in each testing session was at chance (53.8%), suggesting that subjective effects of L-dopa and placebo were equivalent across sessions in both groups of participants.

Change-from-baseline physiological and subjective ratings of alertness are found in Table 3.1. For each measure, we performed separate 2 × 2 mixed ANOVAs with Group (Older vs. Younger) as the between-subject factor and Treatment (L-dopa vs. Placebo) as the within-subject variable. For change in heart rate, we found a significant main effect of Treatment ($F_{1,53}$ = 5.006, p = 0.029) that reflected a larger decrease from baseline heart rate in the placebo relative to the L-dopa session. There was neither a significant main effect of Group ($F_{1,53}$ = 3.816, p = 0.056) nor a Group × Treatment interaction effect (F < 1) on heart rate, however. For blood pressure, there was a significant main effect of Group for change in both systolic ($F_{1,53}$ = 25.059, p < 0.001) and diastolic ($F_{1,53}$ = 22.706, p < 0.001) blood pressure. Younger adults demonstrated a larger decrease from baseline in systolic and diastolic blood pressure compared to older adults from baseline to post-treatment. We did not observe a significant main effect of Treatment (Fs < 1) or a Group × Treatment interaction effect (Fs < 1) on blood pressure, however. For alertness, there was no significant main effect of treatment ($F_{1,53}$ = 2.099, p = 0.153) or Group

Table 3.1: Affective, physiological, and subjective report of alertness measures in young and older adults on L-dopa versus placebo.

	Young Adult (n=26)		**Older Adult (n=29)**	
	L-dopa	**Placebo**	**L-dopa**	**Placebo**
ΔHR	8.65 (1.54)	11.62 (1.45)	5.31 (1.54)	7.92 (1.45)
ΔSys	6.08 (1.96)	8.23 (2.03)	-3.85 (1.96)	-1.92 (2.03)
ΔDia	1.73 (1.42)	3.35 (1.05)	-2.96 (1.42)	-4.27 (1.05)
ΔAlert	-1.99 (2.67)	-0.26 (2.26)	14.59 (2.67)	9.60 (2.26)

Values reported are means (±SEM). **ΔHR** = Change-from-baseline in heart rate (bpm); **ΔSys** = Change-from-baseline in systolic blood pressure (mmHg); **ΔDia** = Change-from-baseline in diastolic blood pressure (mmgHg); **ΔAlert** = Change-from-baseline in subjective report of alertness (Bond & Lader, 1974).

($F_{1,53}$ = 0.600, p = 0.442), or a Group × Treatment interaction effect ($F_{1,53}$ = 0.086, p = 0.771). That is, participants rated their subjective alertness as equivalent in the L-dopa and Placebo sessions. This is important for the interpretation of our findings.

3.3.2 Behavioural Measures

Overall error rates

Mean number of errors for each learning phase (i.e., total session, acquisition of initial stimulus-response association phase, reversal of stimulus-response association phase) are presented in Figure 3.2a-f. Greater number of errors denoted poorer learning for each phase of learning.

Separate 2 × 2 × 2 mixed ANOVAs were conducted on the total number of errors in a) the total session, including both the initial and reversal phases, b) the initial stimulus- response association acquisition phase, and c) the stimulus-response association reversal phase. Group (Older vs. Younger) and Order (L/P vs. P/L) were the between-subject factors whereas Treatment (L-dopa vs. Placebo) was the within-subject variable. We found a significant main effect of Group across the total learning session ($F_{1,51}$ = 9.886, p = 0.003) and during the stimulus-reward reversal learning phase ($F_{1,51}$ = 8.804, p = 0.005), but the Group effect for initial stimulus-reward acquisitions did not reach significance ($F_{1,51}$ = 9.886, p = 0.078; see Figure 3.2a-c). In each instance, older adults produced a greater number of errors compared to younger adults. We also found a significant main effect of Treatment for total learning session ($F_{1,51}$ = 4.274, p = 0.004) and a trend towards significance for stimulus-reward reversals ($F_{1,51}$ = 3.918, p = 0.053), but not for initial stimulus-reward acquisitions ($F_{1,51}$ = 1.487, p = 0.228; see Figure 3.2a-c). Participants made more errors when tested on L-dopa compared to placebo. There was a main effect of Order on errors committed during the initial stimulus-reward acquisition phase

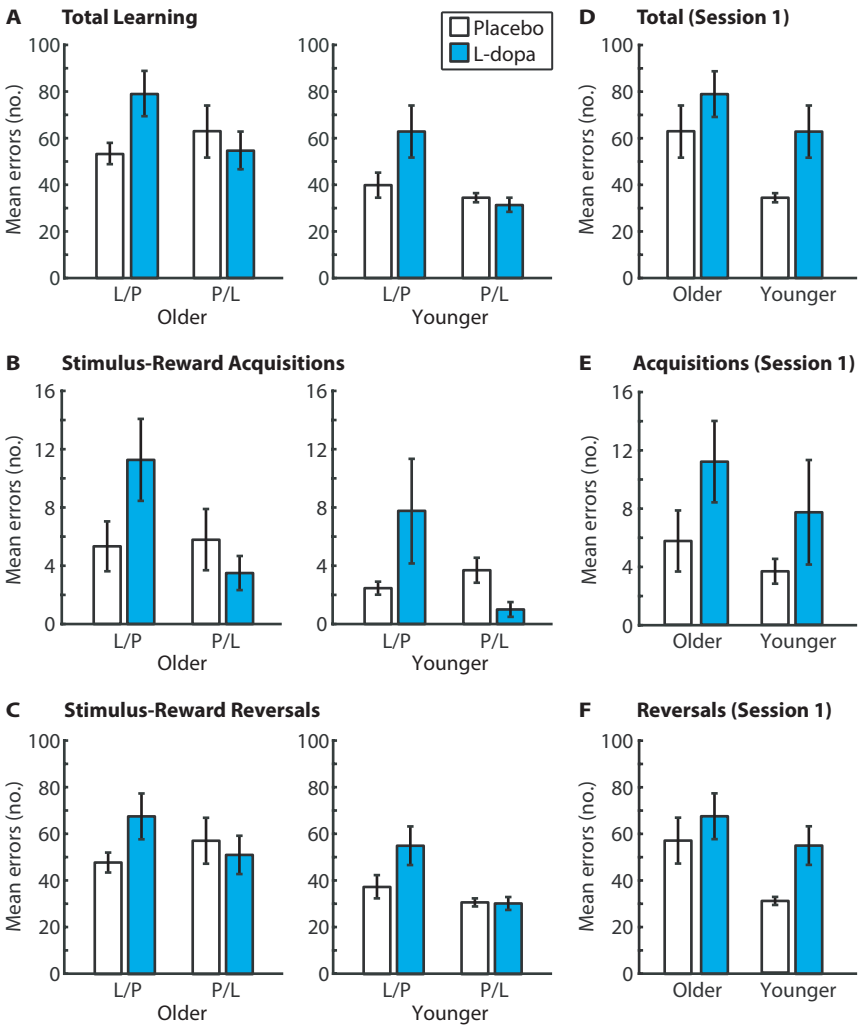

Figure 3.2: Effects of Order (L/P vs. P/L) and Treatment (L-dopa vs. Placebo) for each Group (Older vs. Younger) on mean number of errors during **(A)** total learning session, **(B)** stimulus-reward acquisitions, **(C)** stimulus-reward reversals, **(D)** total learning session (Session 1 only), **(E)** stimulus-reward acquisitions (Session 1 only), and **(F)** stimulus-reward reversals (Session 1 only). Error bars represent standard error.

($F_{1,51}$ = 4.436, p = 0.040) and a trend towards significance for total errors across the entire session ($F_{1,51}$ = 3.952, p = 0.052). These main effects reflected more errors in the L/P order compared to the P/L order. There was no main effect of Order on errors during the stimulus-reward reversal phase ($F_{1,51}$ = 2.645, p = 0.110). Finally, our analyses revealed a significant Order × Treatment interaction effect for the total learning session ($F_{1,51}$ = 11.197, p = 0.002), initial stimulus-reward acquisition period ($F_{1,51}$ = 9.974, p = 0.003), and stimulus-reward reversal phase ($F_{1,51}$ = 7.923, p = 0.007). Post-hoc pairwise comparisons revealed significantly more errors in the L-dopa relative to placebo session in the L/P order (all $p < 0.05$) but not in the P/L order (all $p > 0.05$). In no learning phase were there significant Group × Treatment (all Fs < 1), Group × Order ($F_{1,51}$ = 0.752, p = 0.390 for total learning session; $F_{1,51}$ = 0.085, p = 0.772, for initial stimulus-reward acquisitions; $F_{1,51}$ = 1.042, p = 0.312 for stimulus-reward reversals), or 3-way interactions (all Fs < 1).

Overall error rates in Session 1 only

Though we found significant main effects of Group and Treatment, we further explored the significant Order × Treatment interaction. We performed subsequent 2 × 2 between-subject ANOVAs on errors in Session 1 only for each learning phase. Constraining our analyses to the first testing session allowed us to investigate the effect of age group and L-dopa on learning, independent of the expected practice effects. We found a significant main effect of Group for total learning session ($F_{1,51}$ = 5.458, p = 0.023) and during stimulus-reward reversals ($F_{1,51}$ = 5.421, p = 0.024) but not for initial stimulus-reward acquisitions ($F_{1,51}$ = 1.182, p = 0.282; see Figure 3.2d-f). Older adults produced more errors compared to younger adults during stimulus-reward reversals. We also found a significant main effect of Treatment for total learning session ($F_{1,51}$ = 5.383, p = 0.024) and during stimulus-reward reversals ($F_{1,51}$ = 4.298, p = 0.043) but the contrast for initial stimulus-reward

acquisitions did not reach significance ($F_{1,51}$ = 3.454, p = 0.069; see Figure 3.2d-f). For all measures, participants treated with L-dopa made more errors compared to those treated with placebo. Finally, there were no Group × Treatment interaction effects for any learning phase (all Fs < 1).

Bayesian Analysis of overall error rates in the Group × Treatment interaction

Somewhat surprisingly, we did not find a significant Group × Treatment interaction effect in any learning phase. To determine whether Treatment (i.e., L-dopa vs. Placebo) had a similar effect on both younger and older participants, we calculated the Bayes Factors (BF_{10}) with particular interest in the Group × Treatment interaction effects in 2 × 2 × 2 Bayesian mixed ANOVAs on error rates with Group and Order as the between-subject factors and Treatment as the within-subject variable. To perform multiple-model comparisons, we divided the sum of the posterior probabilities of models containing our term of interest but no interactions with the term of interest by the sum of the posterior probabilities of models without the term of interest. We found BF_{10} of 0.314, 0.306, and 0.291 for the total learning session, stimulus-reward reversal phase, and stimulus-reward acquisition phase, respectively. In each case, the null hypothesis that there was no interaction between Group and Treatment was strongly supported (Dienes, 2014).

Lose-Shift and Win-Stay probabilities

Examining the influence of the immediately-preceding trial on performance, we investigated the Lose-Shift and Win-Stay probabilities. Lose-Shift describes the likelihood of shifting responses across consecutive trials following punishment feedback whereas Win-Stay refers to the probability of repeating a response across consecutive trials when reward feedback was provided on the first in the pair. These trial types are displayed in Figure 3.3a-b. Larger percentages of each trial type suggest greater propensity for being affected by the immediately-preceding

outcomes, resulting in more stay responses after reward and more shift responses following punishment. The percentage of Lose-Shift and Win-Stay responses when the immediately-preceding feedback was inappropriate given the larger context (i.e., misleading feedback) versus the percentage of Lose-Shift and Win-Stay responses when the feedback on the immediately-preceding trial was congruent with the larger context (i.e., non-misleading feedback), provided an additional measure of learning efficacy.

In a 2 × 2 × 2 mixed ANOVA on Lose-Shift probability, we found a significant main effect of Group ($F_{1,51}$ = 8.121, p = 0.006) that reflected greater lose-shifting in older compared to younger adults (see Figure 3.3a). There were no significant main effects either of Treatment ($F_{1,51}$ = 0.198, p = 0.658) or Order ($F_{1,51}$ = 3.468, p = 0.068). Further, we did not find significant Group × Treatment ($F_{1,51}$ = 1.575, p = 0.215), Order × Treatment, or three-way interaction effects (both Fs < 1).

To better understand the differences in Lose-Shift strategy between age groups, we performed a 2 × 2 × 2 mixed ANOVA with Group (Older vs. Younger) as the between-subject factor, and Treatment (L-dopa vs. Placebo) and Context (Misleading vs. Non-Misleading feedback) as within-subject variables. We found significant main effects of Group ($F_{1,53}$ = 8.279, p = 0.006) and Context ($F_{1,53}$ = 57.297, p < 0.001), which reflected greater lose-shifting in older compared to younger adults and following non-misleading relative to misleading negative feedback. There was also a significant Group × Context interaction effect ($F_{1,53}$ = 9.959, p = 0.003). Post-hoc pairwise comparisons demonstrated greater probability of lose-shifting in older compared to younger adults following misleading punishment feedback (p = 0.002) though there was no Group difference in percentage of lose-shift responses for non-misleading (p = 0.074) punishment feedback. There was no significant main effect of Treatment ($F_{1,53}$ = 0.214, p = 0.646), Group × Treatment

($F_{1,53}$ = 1.911, p = 0.173), Treatment × Context ($F_{1,53}$ = 0.726, p = 0.398), or 3-way ($F_{1,53}$ = 2.024, p = 0.161) interaction effects.

A 2 × 2 × 2 mixed ANOVA on Win-Stay rates revealed a significant main effect of Order ($F_{1,51}$ = 5.756, p = 0.020) but not Group ($F_{1,51}$ = 2.189, p = 0.145) or Treatment ($F_{1,51}$ = 2.530, p = 0.118; see Figure 3.3b). Participants tested in the L/P order were less likely to stay after a reward than those in the P/L order. We also found a significant Order × Treatment interaction effect ($F_{1,51}$ = 5.819, p = 0.019). Post-hoc pairwise comparisons demonstrated that the Win-Stay rate was lower in the L-dopa compared to placebo session (p = 0.008) for the L/P order but not the P/L order (p = 0.542). There were no significant Group × Order ($F_{1,51}$ = 2.035, p = 0.160), Group × Treatment, or three-way interaction effects (both Fs < 1).

We further explored Win-Stay strategies by considering the context in which reward feedback was delivered. A 2 × 2 × 2 mixed ANOVA with Group (Older vs. Younger) as the between-subject factor, and Treatment (L-dopa vs. Placebo) and Context (Misleading vs. Non-Misleading feedback) as within-subject variables revealed a significant main effect of Context ($F_{1,53}$ = 9.230, p = 0.004). This main effect reflected greater Win-Stay responses after non-misleading relative to misleading feedback. We did not find significant main effects of Treatment (F < 1) or Group (F < 1), or significant Group × Treatment (F < 1), Group × Context (F1,53 = 1.734, p = 0.194), Treatment × Context (F1,53 = 1.829, p = 0.182), or 3-way (F < 1) interaction effects.

Win-Stay probability in Session 1 only

Given an Order and Order × Treatment interaction, we examined Win-Stay trial percentage in Session 1 only in a 2 × 2 between-subject ANOVA. We found a significant main effect of Treatment ($F_{1,51}$ = 5.997, p = 0.018), with the L-dopa group

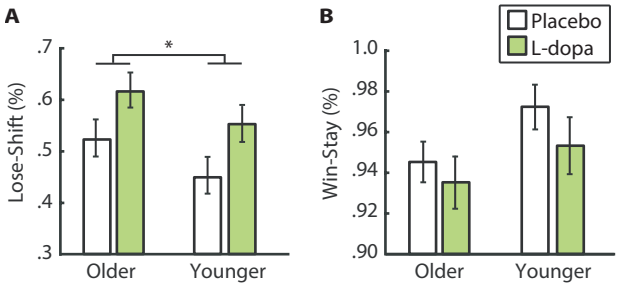

Figure 3.3: Mean proportion of **(A)** Lose-Shift and **(B)** Win-Stay trials for L-dopa versus Placebo in young versus older adults. * indicates $p < 0.05$. Error bars represent standard error.

being less likely to stay after reward feedback compared to the placebo group in Session 1. There was neither a significant main effect of Group ($F_{1,51}$ = 1.203, p = 0.278) nor a Group × Treatment interaction effect ($F_{1,51}$ = 1.628, p = 0.208), however.

3.4 Discussion

3.4.1 Summary

In the present study, we found evidence for effects of Group and Treatment on stimulus-reward and reversal learning. Older adults learned more poorly than younger adults across the total learning session and during the stimulus-reward reversal learning phase. This was evidenced by significantly more errors overall as well as by a greater propensity to shift responses after misleading punishment feedback for older relative to younger participants.

After controlling for practice effects by either considering Order (L/P vs. P/L) or examining Session 1 only, learning was also impaired following treatment with L-dopa during the total learning session and the stimulus-reward reversal learning phase. The detrimental effect of L-dopa was equivalent for younger and older age groups on stimulus-reward reversal learning, as Group and Treatment effects were independent. In fact, using Bayesian analysis, the null hypothesis that Group and Treatment did not interact in producing error rates was strongly supported in each the a) total learning session, b) stimulus-reward association acquisition phase, and c) stimulus-reward reversal phase. With finer-grained analyses, we also found that L-dopa reduced the propensity to stay with a response that was rewarded on the immediately-preceding trial for participants in the L/P order. The effect of L-dopa on stimulus-reward learning was not explained by changes in

attention or alertness nor due to expectancy effects. Although the reduction in heart rate from baseline to end of the experimental session was slightly less in the L-dopa than in the Placebo session, L-dopa otherwise produced no changes in physiological control measures or in subjective reports of alertness. Participants were also at chance level in correctly predicting whether or not they had received drug or placebo. These findings suggest that the detrimental effects of L-dopa on stimulus-reward association learning were specific.

Given our crossover design that involved testing participants on L-dopa and placebo across two sessions, we anticipated robust practice effects to interact with expected effects of L-dopa. This has been shown previously (Vo et al., 2016). We found significant Order × Treatment interactions providing further evidence that L-dopa interferes with stimulus-reward learning. The Order × Treatment interactions reflected a) significantly more errors and b) lower propensity to stay with a response that was rewarded on the immediately-preceding trial on L-dopa relative to placebo but only for participants tested in the L/P order. This pattern of findings illustrates the combined influences of the beneficial effect of practice and the adverse effects of L-dopa on learning (see Figure 3.4). In the L/P order, the effects of practice and L-dopa act in the same direction with the former bolstering performance in Session 2 and the latter impairing learning in Session 1 for a net effect of clearly superior learning in Session 2 (see Figure 3.4a). The opposite is true for the P/L order, where practice and L-dopa effects are acting in opposite directions, presumably cancelling each other. This point is highlighted by the fact that performance did not improve in Session 2 in the P/L order, presumably due to the adverse impact of L-dopa on learning (see Figure 3.4b), despite robust beneficial effects of experience and practice being anticipated based on previous literature (Vo et al., 2016). To bolster this interpretation of our data, we considered

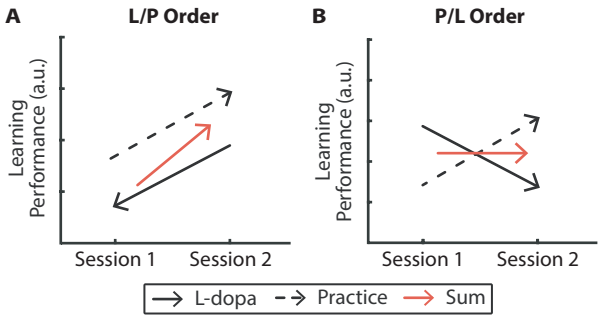

Figure 3.4: Schematic of the combined effects of L-dopa and practice on learning performance in each Order (L/P vs. P/L). **(A)** In the L/P order, the benefits of practice and withdrawal of levodopa from session 1 to 2 work in the same direction. **(B)** In the P/L, the benefits of practice and administration of levodopa from session 1 to 2 work in opposing directions.

Session 1 only, in which learning performance was uncontaminated by practice and order effects and we could isolate the impact of L-dopa. We found significantly impoverished learning in the total learning session and during stimulus-reward reversals for participants receiving L-dopa compared to those treated with placebo. More specifically, we found that L-dopa reduced the propensity to stay with a response that was rewarded on the immediately-preceding trial relative to placebo in Session 1. Findings from these Session 1 analyses, when practice effects can be eliminated, are entirely supportive of the effects of Treatment in the full 3-way mixed ANOVAs.

3.4.2 Effects of age group on reversal learning

We found that older adults learned more poorly compared to younger adults based on greater numbers of errors overall and during stimulus-reward reversals. These findings are in line with previous studies (Mell et al., 2005; Weiler et al., 2008; Worthy, Davis, Gorlick, Cooper, Bakkour, Mumford, et al., 2015a). Mell et al. (2005) showed that older adults learned more poorly than younger adults on a probabilistic object reversal task, requiring more trials to achieve a learning criterion and completing fewer experimental blocks.

In addition to overall increased error rates in older adults, they also had a significantly higher probability than younger adults of abruptly switching following misleading relative to non-misleading error feedback. This was indicative in the older adults of poorer learning of the probabilistic nature of the task and the stimulus-reward probabilities over the longer term. The performance of older adults suggested that most recent feedback was overrepresented. This finding is consistent with previous reports of a decision-making bias in older adults towards greater reliance on more recent events (Eppinger & Kray, 2011; Eppinger, Haemmerer, & Li, 2011; Worthy, Davis, Gorlick, Cooper, Bakkour,

Mumford, et al., 2015a; Worthy, Otto, Doll, Byrne, & Maddox, 2015b). Using a two-choice decision making task, in which the reward cues differed in average reward value and variability of reward magnitudes, Worthy et al. (2015b) observed age-related differences in sensitivity to recent negative feedback. Older adults demonstrated a particular sensitivity to recent negative outcomes, abruptly switching their choices following sudden, steep declines in reward. This reactive choice behaviour in older compared to younger adults proved disadvantageous for performance in the present study, leading to premature lose-shifting in response to misleading error feedback despite the stimulus still being associated with a greater probability of reward in the greater context.

Stimulus-reward reversal learning is a cognitive function frequently ascribed to dopaminergic brain regions including the VS, orbitofrontal cortex, and ventromedial prefrontal cortex (Cools et al., 2007; Cools, Clark, Owen, & Robbins, 2002; Fellows & Farah, 2007). Although the exact mechanism underlying age-related impairment in reward learning is not clear, the degeneration of the dopaminergic system in normal aging is an intuitive explanation (Eppinger et al., 2013; Samanez-Larkin et al., 2007; Schott et al., 2007; Vink et al., 2015). Across the adult lifespan, reductions in a) number of dopamine neurons in the SNc/VTA (P. L. McGeer et al., 1977), b) DAT concentrations (Allard & Marcusson, 1989; Braskie et al., 2008; De Keyser et al., 1990; Erixon-Lindroth et al., 2005; Eusebio et al., 2012; Ishibashi et al., 2009; van Dyck et al., 2002; Volkow et al., 1994; 1996; Zelnik et al., 1986), and c) dopamine synthesis capacity (Bunzeck et al., 2007; Dreher et al., 2008) are clearly observed. Changes to postsynaptic dopamine receptors also occur with aging (Antonini et al., 1993; De Keyser et al., 1990; Ishibashi et al., 2009; Suhara et al., 1991; Volkow et al., 1998; Wang et al., 1998). These impairments in the dopaminergic system have been proposed to mediate age-related declines in

reward learning (Backman et al., 2000; Mell, 2009; Schott et al., 2007; Volkow et al., 1998). Schott et al. (2007) report differential patterns of activation for anticipation versus receipt of reward outcomes between younger and older adults. A shift in VS activity was observed. Older adults showed higher VS activation for receipt rather than anticipation of reward whereas younger adults show higher VS activation during reward prediction relative to reward delivery (Eppinger et al., 2013; Mell, 2009; Samanez-Larkin et al., 2007; Vink et al., 2015). Based on this literature, the pattern of age-related impairment in the dopaminergic system is expected to adversely impact association learning, potentially accounting for our age group effects.

3.4.3 Effects of L-dopa on reversal learning

In analyses that controlled for Order and practice effects, we demonstrate this detrimental effect of L-dopa on stimulus-reward association learning and stimulus-reward reversals as discussed above in the Summary of Results section. Participants made more errors following treatment with L-dopa compared to placebo. This finding is consistent with previous investigations of dopaminergic therapy effects in healthy young volunteers (Breitenstein et al., 2006; Frank & O'Reilly, 2006; Vo et al., 2016; 2017). The magnitude of the medication-associated impairment on stimulus-reward learning was equivalent for both age groups, confirmed with Bayesian analyses, strongly supporting the null hypothesis that there was no Group × Treatment interaction. These detrimental effects of L-dopa were equivalent for younger and older participants, though the latter group overall and at baseline, made more errors in stimulus-response learning in keeping with less effective learning.

Investigating the effect of L-dopa on specific trial types defined by outcomes on immediately-preceding trials (i.e., Lose-Shift and Win-Stay behaviour), we found

that L-dopa significantly reduced participants' propensity to repeat a response that was rewarded on the immediately-preceding trial (i.e., reduced Win-Stay). In our mixed ANOVA, this pattern was only significant in participants who performed in the L/P order. Ruling out the possibility that this disadvantageous propensity arose simply as an idiosyncratic effect of Order, assessing Session 1 data only, participants treated with L-dopa experienced lower Win-Stay percentages than their counterparts receiving placebo. These findings suggest that L-dopa impairs stimulus-reward association and reversal learning and particularly it seems to promote inappropriate switching away from responses that were previously rewarded. Pizzagalli et al. (2008) also found a reduction of Win-Stay strategies in healthy volunteers following administration of pramipexole, a dopamine agonist. In a probabilistic reward task, they found that pramipexole reduced the likelihood of a participant correctly selecting a more frequently rewarded stimulus when it had been rewarded on the immediately-preceding trial. The authors suggested that enhancing endogenous dopamine levels leads to increased inhibitory auto-receptor binding on pre-synaptic dopamine neurons, reducing instructive, phasic dopamine reward signals.

3.4.4 Testing the dopamine overdose hypothesis

Here, we exploit the fact that degeneration in the dopaminergic system occurs with normal aging (Backman et al., 2000) to investigate the dopamine overdose hypothesis. According to this hypothesis, the degree of dysfunction related to exogenous dopamine should be proportional to baseline endogenous dopamine. An identical dose of L-dopa was administered to our younger and older control groups. This produced equivalent impairment in overall errors in reward learning, irrespective of differences in baseline dopaminergic tone between our age groups. That is, despite an expected developing endogenous dopamine deficit

in our older adults, and an established baseline reward-learning impairment in the OFF state in this group, the same dose of L-dopa impaired learning performance to a similar degree in our older and younger adults.

Despite our predictions, both age groups demonstrated a similar magnitude of medication-related learning impairment relative to baseline confirmed with a Bayesian analysis. This suggests that VTA-innervated brain regions might not be adapted to benefit from exogenous dopaminergic therapy irrespective of baseline dopaminergic tone/deficits (A. A. MacDonald, Monchi, et al., 2013a). Potentially any benefit in terms of behaviour only appears when exogenous dopamine therapy closely matches the endogenous dopamine deficit in VTA-innervated brain regions or perhaps there exists a more complex relation between endogenous dopamine levels and exogenous dopamine dose than is implied by the dopamine overdose hypothesis in the VTA. Either way, the prospect of supplementing dopamine to remedy deficits in VTA-innervated brain regions seems poor based on this study and others (A. A. MacDonald, Monchi, et al., 2013a). Alternatively, even though exogenous dopaminergic therapy interferes with stimulus-reward reversal learning, the age-related worsening of these functions could be mediated by a different mechanism such as disruptions to other neurotransmitter systems (e.g., cholinergic, serotonergic) or due to cortical and limbic dysfunction (Pirker et al., 2000; Schliebs & Arendt, 2006). Were this the case, dopamine supplementation would not be expected to improve performance.

Age group and L-dopa produce different types of errors when Lose-Shift and Win-Stay trial types were investigated separately. This potentially explains our lack of interaction between Group and Treatment. Older adults were more likely to switch when a stimulus-reward response was paired with misleading punishment on the immediately-preceding trial, discounting the influence of the larger context

and the average stimulus-reward association. Older adults were more likely to switch despite the fact that this response for a particular stimulus was paired with rewarding feedback 80% of the time in the larger context. Older and younger participants were equally likely to shift responses immediately following punishment feedback for responses, when this outcome information was congruent (i.e., not misleading) with the larger context, however. By contrast, L-dopa reduced the propensity to repeat or stay with a response that was rewarded on an immediately-preceding trial. This potentially owes to the fact that L-dopa blunts instructive, phasic dopaminergic responses, in effect reducing the impact or experience of reward. The fact that these variables affect different error types could explain the observed independent effects of Group and Treatment on our measures of learning efficacy. Previous investigations on the effects of dopamine agonists in reward learning reveal similar reductions in reward-related behaviour as we show here (Frank & O'Reilly, 2006; Pizzagalli et al., 2008; Santesso et al., 2009). Replicating these patterns of results in an independent cohort, and investigating the mechanisms underlying these effects of age and L-dopa on reward learning using neuroimaging seems an important next step.

3.4.5 Conclusions

We found that age group and L-dopa independently disrupted stimulus-reward reversal learning. Older adults learned more poorly than younger adults. After controlling for order and practice effects, L-dopa also worsened learning though this effect did not interact with the impact of age group. That is, though there was evidence of a baseline impairment in stimulus-reward reversal learning in our older control group, they experienced impairment proportional to that of younger controls in stimulus-reward and reward-reversal learning related to an identical, single-dose of L-dopa. These effects of dopaminergic therapy on cognition seem

not as straightforward as the predictions of the highly intuitive dopamine overdose hypothesis, with the possibility that unlike DS, VTA-innervated brain regions such as VS, might not be adapted to benefit as simply from exogenous dopamine even when baseline dopamine levels are reduced. Alternative interpretations of these data should also be investigated, including the possibility that age group learning deficits arise from neurodegeneration in non-dopaminergic systems or structural changes in cortical or limbic regions that are also known to occur with aging (Pirker et al., 2000; Schliebs & Arendt, 2006). These baseline deficits would not be expected to resolve with dopamine supplementation under these alternative scenarios. Based on a large body of evidence regarding the effects of aging on the dopaminergic system, however, dopamine overdose effects on learning were expected to be lesser for older relative to younger participants. This did not occur, however, casting some doubts on the straightforward predictions of the dopamine overdose hypothesis.

Finally, age group and levodopa seemed to have independent effects on different error types. Age group increased the propensity for shifting a response from one trial to the next when that stimulus-specific response elicited a negative outcome (i.e., lose feedback) on the immediately preceding trial. This increased tendency to shift after negative feedback in elderly participants occurred even when this feedback was misleading and although this response was more frequently rewarded (i.e., approximately 80%) within the larger, probabilistic learning context. By contrast, participants on levodopa were less likely than those treated with placebo to stay with the response that was rewarded (i.e., win feedback) on the immediately preceding trials, when Order effects and Order interactions were removed. These effects are consistent with a small number of studies showing disruption of rewarding feedback, with reduced impact of reward on subsequent

behaviors after treatment with exogenous dopamine. Further investigations are required to replicate these intriguing patterns as well as to clarify the neural basis of these cognitive effects, related to aging, PD, and exogenous dopaminergic therapy.

3.5 References

Allard, P., & Marcusson, J. O. (1989). Age-correlated loss of dopamine uptake sites labeled with [3 H] GBR-12935 in human putamen. *Neurobiology of Aging*, *10*(6), 661–664. http://doi.org/10.1016/0197-4580(89)90001-8

Antonini, A., Leenders, K. L., Reist, H., Thomann, R., Beer, H. F., & Locher, J. (1993). Effect of Age on D2 Dopamine Receptors in Normal Human Brain Measured by Positron Emission Tomography and 11C-Raclopride. *Arch Neurol*, *50*(5), 474–480. http://doi.org/10.1001/archneur.1993.00540050026010

Backman, L., Ginovart, N., Dixon, R. A., Wahlin, T. B., Wahlin, A., Halldin, C., & Farde, L. (2000). Age-related cognitive deficits mediated by changes in the striatal dopamine system. *American Journal of Psychiatry*, *157*(4), 635–637. http://doi.org/10.1176/ajp.157.4.635

Bond, A., & Lader, M. (1974). The use of analogue scales in rating subjective feelings. *British Journal of Medical Psychology*, *47*(3), 211–218. http://doi.org/10.1111/j.2044-8341.1974.tb02285.x

Braskie, M. N., Wilcox, C. E., Landau, S. M., O'Neil, J. P., Baker, S. L., Madison, C. M., et al. (2008). Relationship of striatal dopamine synthesis capacity to age and cognition. *J Neurosci*, *28*(52), 14320–14328. http://doi.org/10.1523/JNEUROSCI.3729-08.2008

Breitenstein, C., Korsukewitz, C., Flöel, A., Kretzschmar, T., Diederich, K., & Knecht, S. (2006). Tonic dopaminergic stimulation impairs associative learning in healthy subjects. *Neuropsychopharmacology*, *31*(11), 2552–2564. http://doi.org/10.1038/sj.npp.1301167

Bunzeck, N., Schütze, H., Stallforth, S., Kaufmann, J., Düzel, S., Heinze, H.-J., & Düzel, E. (2007). Mesolimbic novelty processing in older adults. *Cereb Cortex*, *17*(12), 2940–2948. http://doi.org/10.1093/cercor/bhm020

Cools, R. (2006). Dopaminergic modulation of cognitive function-implications for l-DOPA treatment in Parkinson's disease. *Neurosci Biobehav Rev*, *30*(1), 1–23. http://doi.org/10.1016/j.neubiorev.2005.03.024

Cools, R., Altamirano, L., & D'Esposito, M. (2006). Reversal learning in Parkinson's disease depends on medication status and outcome valence. *Neuropsychologia*, *44*(10), 1663–1673. http://doi.org/10.1016/j.neuropsychologia.2006.03.030

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001). Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cereb Cortex*, *11*(12), 1136–1143. http://doi.org/10.1093/cercor/11.12.1136

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2003). l-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia*, *41*(11), 1431–1441. http://doi.org/10.1016/S0028-3932(03)00117-9

Cools, R., Clark, L., Owen, A. M., & Robbins, T. W. (2002). Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging. *J Neurosci*, *22*(11), 4563–4567.

Cools, R., Lewis, S. J. G., Clark, L., Barker, R. A., & Robbins, T. W. (2007). L-DOPA disrupts activity in the nucleus accumbens during reversal learning in

Parkinson's disease. *Neuropsychopharmacology*, *32*(1), 180–189. http://doi.org/10.1038/sj.npp.1301153

De Keyser, J., Ebinger, G., & Vauquelin, G. (1990). Age-related changes in the human nigrostriatal dopaminergic system. *Ann Neurol*, *27*(2), 157–161. http://doi.org/10.1002/ana.410270210

Dreher, J.-C., Meyer-Lindenberg, A., Kohn, P., & Berman, K. F. (2008). Age-related changes in midbrain dopaminergic regulation of the human reward system. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(39), 15106–15111. http://doi.org/10.1073/pnas.0802127105

Eppinger, B., & Kray, J. (2011). To choose or to avoid: age differences in learning from positive and negative feedback. *J Cogn Neurosci*, *23*(1), 41–52. http://doi.org/10.1162/jocn.2009.21364

Eppinger, B., Haemmerer, D., & Li, S.-C. (2011). Neuromodulation of reward-based learning and decision making in human aging. *Ann N Y Acad Sci*, *1235*(1), 1–17. http://doi.org/10.1111/j.1749-6632.2011.06230.x

Eppinger, B., Schuck, N. W., Nystrom, L. E., & Cohen, J. D. (2013). Reduced striatal responses to reward prediction errors in older compared with younger adults. *J Neurosci*, *33*(24), 9905–9912. http://doi.org/10.1523/JNEUROSCI.2942-12.2013

Erixon-Lindroth, N., Farde, L., Robins Wahlin, T.-B., Sovago, J., Halldin, C., & Bäckman, L. (2005). The role of the striatal dopamine transporter in cognitive aging. *Psychiatry Research: Neuroimaging*, *138*(1), 1–12. http://doi.org/10.1016/j.pscychresns.2004.09.005

Eusebio, A., Azulay, J.-P., Ceccaldi, M., Girard, N., Mundler, O., & Guedj, E. (2012). Voxel-based analysis of whole-brain effects of age and gender on dopamine transporter SPECT imaging in healthy subjects. *Eur J Nucl Med Mol Imaging*, *39*(11), 1778–1783. http://doi.org/10.1007/s00259-012-2207-8

Feigin, A., Ghilardi, M. F., Carbon, M., Edwards, C., Fukuda, M., Dhawan, V., et al. (2003). Effects of levodopa on motor sequence learning in Parkinson's disease. *Neurology*, *60*(11), 1744–1749. http://doi.org/10.1212/01.WNL.0000072263.03608.42

Fellows, L. K., & Farah, M. J. (2007). The Role of Ventromedial Prefrontal Cortex in Decision Making: Judgment under Uncertainty or Judgment Per Se? *Cereb Cortex*, *17*(11), 2669–2674. http://doi.org/10.1093/cercor/bhl176

Flöel, A., Breitenstein, C., Hummel, F., Celnik, P., Gingert, C., Sawaki, L., et al. (2005). Dopaminergic influences on formation of a motor memory. *Ann Neurol*, *58*(1), 121–130. http://doi.org/10.1002/ana.20536

Frank, M. J., & O'Reilly, R. C. (2006). A mechanistic account of striatal dopamine function in human cognition: psychopharmacological studies with cabergoline and haloperidol. *Behav Neurosci*, *120*(3), 497–517. http://doi.org/10.1037/0735-7044.120.3.497

Frank, M. J., Seeberger, L. C., & O'Reilly, R. C. (2004). By carrot or by stick: cognitive reinforcement learning in parkinsonism. *Science*, *306*(5703), 1940–1943. http://doi.org/10.1126/science.1102941

Gotham, A. M., Brown, R. G., & Marsden, C. D. (1988). 'Frontal'cognitive function in patients with Parkinson's disease 'on'and ‘off’levodopa. *Brain*, *111*(2), 299–321. http://doi.org/10.1093/brain/111.2.299

Graef, S., Biele, G., Krugel, L. K., Marzinzik, F., Wahl, M., Wotka, J., et al. (2010). Differential influence of levodopa on reward-based learning in Parkinson's disease. *Frontiers in Human Neuroscience*, *4*, 169. http://doi.org/10.3389/fnhum.2010.00169

Hiebert, N. M., Seergobin, K. N., Vo, A., Ganjavi, H., & MacDonald, P. A. (2014). Dopaminergic therapy affects learning and impulsivity in Parkinson's

disease. *Annals of Clinical and Translational Neurology*, *1*(10), 833–843. http://doi.org/10.1002/acn3.128

Ishibashi, K., Ishii, K., Oda, K., Kawasaki, K., Mizusawa, H., & Ishiwata, K. (2009). Regional analysis of age-related decline in dopamine transporters and dopamine D2-like receptors in human striatum. *Synapse*, *63*(4), 282–290. http://doi.org/10.1002/syn.20603

Jahanshahi, M., Wilkinson, L., Gahir, H., Dharmaindra, A., Dharmarinda, A., Dharminda, A., & Lagnado, D. A. (2010). Medication impairs probabilistic classification learning in Parkinson's disease. *Neuropsychologia*, *48*(4), 1096–1103. http://doi.org/10.1016/j.neuropsychologia.2009.12.010

Kim, J.-H., Son, Y.-D., Kim, H.-K., Lee, S.-Y., Cho, S.-E., Kim, Y.-B., & Cho, Z.-H. (2011). Effects of age on dopamine D2 receptor availability in striatal subdivisions: a high-resolution positron emission tomography study. *European Neuropsychopharmacology : the Journal of the European College of Neuropsychopharmacology*, *21*(12), 885–891. http://doi.org/10.1016/j.euroneuro.2011.03.009

Kish, S. J., Shannak, K., Rajput, A., Deck, J. H., & Hornykiewicz, O. (1992). Aging produces a specific pattern of striatal dopamine loss: implications for the etiology of idiopathic Parkinson's disease. *J Neurochem*, *58*(2), 642–648. http://doi.org/10.1111/j.1471-4159.1992.tb09766.x

Knecht, S., Breitenstein, C., Bushuven, S., Wailke, S., Kamping, S., Flöel, A., et al. (2004). Levodopa: faster and better word learning in normal humans. *Ann Neurol*, *56*(1), 20–26. http://doi.org/10.1002/ana.20125

Kwak, Y., Müller, M. L. T. M., Bohnen, N. I., Dayalu, P., & Seidler, R. D. (2010). Effect of dopaminergic medications on the time course of explicit motor sequence learning in Parkinson's disease. *J Neurophysiol*, *103*(2), 942–949. http://doi.org/10.1152/jn.00197.2009

MacDonald, A. A., Monchi, O., Seergobin, K. N., Ganjavi, H., Tamjeedi, R., & MacDonald, P. A. (2013a). Parkinson's disease duration determines effect of dopaminergic therapy on ventral striatum function. *Mov Disord*, *28*(2), 153–160. http://doi.org/10.1002/mds.25152

MacDonald, A. A., Seergobin, K. N., Owen, A. M., Owen, A. M., Tamjeedi, R., Monchi, O., et al. (2013b). Differential effects of Parkinson's disease and dopamine replacement on memory encoding and retrieval. *PLoS One*, *8*(9), e74044. http://doi.org/10.1371/journal.pone.0074044

MacDonald, P. A., & Monchi, O. (2011). Differential effects of dopaminergic therapies on dorsal and ventral striatum in Parkinson's disease: implications for cognitive function. *Parkinsons Dis*, *2011*(8414), 572743–18. http://doi.org/10.4061/2011/572743

McGeer, P. L., McGeer, E. G., & Suzuki, J. S. (1977). Aging and Extrapyramidal Function. *Arch Neurol*, *34*(1), 33–35. http://doi.org/10.1001/archneur.1977.00500130053010

Mell, T. (2009). Altered function of ventral striatum during reward-based decision making in old age. *Frontiers in Human Neuroscience*, *3*. http://doi.org/10.3389/neuro.09.034.2009

Mell, T., Heekeren, H. R., Marschner, A., Wartenburger, I., Villringer, A., & Reischies, F. M. (2005). Effect of aging on stimulus-reward association learning. *Neuropsychologia*, *43*(4), 554–563. http://doi.org/10.1016/j.neuropsychologia.2004.07.010

Olanow, W., Schapira, A. H., & Rascol, O. (2000). Continuous dopamine-receptor stimulation in early Parkinson's disease. *Trends Neurosci*, *23*(10 Suppl), S117–26. http://doi.org/10.1016/S1471-1931(00)00030-6

Onur, Ö. A., Piefke, M., Lie, C.-H., Thiel, C. M., & Fink, G. R. (2011). Modulatory effects of levodopa on cognitive control in young but not in older subjects: a

pharmacological fMRI study. *J Cogn Neurosci*, *23*(10), 2797–2810. http://doi.org/10.1162/jocn.2011.21603

Pirker, W., Asenbaum, S., Hauk, M., Kandlhofer, S., Tauscher, J., Willeit, M., et al. (2000). Imaging serotonin and dopamine transporters with 123I-beta-CIT SPECT: binding kinetics and effects of normal aging. *Journal of Nuclear Medicine : Official Publication, Society of Nuclear Medicine*, *41*(1), 36–44.

Pizzagalli, D. A., Evins, A. E., Schetter, E. C., Frank, M. J., Pajtas, P. E., Santesso, D. L., & Culhane, M. (2008). Single dose of a dopamine agonist impairs reinforcement learning in humans: behavioral evidence from a laboratory-based measure of reward responsiveness. *Psychopharmacology (Berl)*, *196*(2), 221–232. http://doi.org/10.1007/s00213-007-0957-y

Samanez-Larkin, G. R., Gibbs, S. E. B., Khanna, K., Nielsen, L., Carstensen, L. L., & Knutson, B. (2007). Anticipation of monetary gain but not loss in healthy older adults. *Nat Neurosci*, *10*(6), 787–791. http://doi.org/10.1038/nn1894

Santesso, D. L., Evins, A. E., Frank, M. J., Schetter, E. C., Bogdan, R., & Pizzagalli, D. A. (2009). Single dose of a dopamine agonist impairs reinforcement learning in humans: evidence from event-related potentials and computational modeling of striatal-cortical function. *Human Brain Mapping*, *30*(7), 1963–1976. http://doi.org/10.1002/hbm.20642

Schliebs, R., & Arendt, T. (2006). The significance of the cholinergic system in the brain during aging and in Alzheimer's disease. *Journal of Neural Transmission*, *113*(11), 1625–1644. http://doi.org/10.1007/s00702-006-0579-2

Schott, B. H., Niehaus, L., Wittmann, B. C., Schütze, H., Seidenbecher, C. I., Heinze, H.-J., & Düzel, E. (2007). Ageing and early-stage Parkinson's disease affect separable neural mechanisms of mesolimbic reward processing. *Brain*, *130*(Pt 9), 2412–2424. http://doi.org/10.1093/brain/awm147

Seo, Seo, M., Beigi, M., Jahanshahi, M., & Averbeck, B. B. (2010). Effects of dopamine medication on sequence learning with stochastic feedback in Parkinson's disease. *Front Syst Neurosci*, *4*. http://doi.org/10.3389/fnsys.2010.00036

Suhara, T., Fukuda, H., Inoue, O., Itoh, T., Suzuki, K., Yamasaki, T., & Tateno, Y. (1991). Age-related changes in human D1 dopamine receptors measured by positron emission tomography. *Psychopharmacology (Berl)*, *103*(1), 41–45. http://doi.org/10.1007/BF02244071

Swainson, R., Rogers, R. D., Sahakian, B. J., Summers, B. A., Polkey, C. E., & Robbins, T. W. (2000). Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. *Neuropsychologia*, *38*(5), 596–612. http://doi.org/10.1016/S0028-3932(99)00103-7

Tomer, R., Aharon-Peretz, J., & Tsitrinbaum, Z. (2007). Dopamine asymmetry interacts with medication to affect cognition in Parkinson's disease. *Neuropsychologia*, *45*(2), 357–367. http://doi.org/10.1016/j.neuropsychologia.2006.06.014

Torta, D. M. E., Castelli, L., Zibetti, M., Lopiano, L., & Geminiani, G. (2009). On the role of dopamine replacement therapy in decision-making, working memory, and reward in Parkinson's disease: does the therapy-dose matter? *Brain and Cognition*, *71*(2), 84–91. http://doi.org/10.1016/j.bandc.2009.04.003

Tremblay, P.-L., Bedard, M.-A., Langlois, D., Blanchet, P. J., Lemay, M., & Parent, M. (2010). Movement chunking during sequence learning is a dopamine-dependant process: a study conducted in Parkinson's disease. *Exp Brain Res*, *205*(3), 375–385. http://doi.org/10.1007/s00221-010-2372-6

van Dyck, C. H., Seibyl, J. P., Malison, R. T., & Laruelle, M. (2002). Age-related decline in dopamine transporters: analysis of striatal subregions, nonlinear

effects, and hemispheric asymmetries. *The American Journal of …*, *10*(1), 36–43. http://doi.org/10.1097/00019442-200201000-00005

Vink, M., Kleerekooper, I., van den Wildenberg, W. P. M., & Kahn, R. S. (2015). Impact of aging on frontostriatal reward processing. *Human Brain Mapping*, *36*(6), 2305–2317. http://doi.org/10.1002/hbm.22771

Vo, A., Hiebert, N. M., Seergobin, K. N., Solcz, S., Partridge, A., & MacDonald, P. A. (2014). Dopaminergic medication impairs feedback-based stimulus-response learning but not response selection in Parkinson's disease. *Frontiers in Human Neuroscience*, *8*(169), 784. http://doi.org/10.3389/fnhum.2014.00784

Vo, A., Seergobin, K. N., & MacDonald, P. A. (2017). Effects of levodopa on stimulus-response learning versus response selection in healthy young adults. *Behavioural Brain Research*, *317*, 553–561. http://doi.org/10.1016/j.bbr.2016.10.019

Vo, A., Seergobin, K. N., Morrow, S. A., & MacDonald, P. A. (2016). Levodopa impairs probabilistic reversal learning in healthy young adults. *Psychopharmacology (Berl)*, *233*(14), 2753–2763. http://doi.org/10.1007/s00213-016-4322-x

Volkow, N. D., Ding, Y. S., Fowler, J. S., Wang, G. J., Logan, J., Gatley, S. J., et al. (1996). Dopamine transporters decrease with age. *J Nucl Med*, *37*(4), 554–559.

Volkow, N. D., Fowler, J. S., Wang, G. J., Logan, J., Schlyer, D., Macgregor, R., et al. (1994). Decreased dopamine transporters with age in health human subjects. *Ann Neurol*, *36*(2), 237–239. http://doi.org/10.1002/ana.410360218

Volkow, N. D., Gur, R. C., Wang, G. J., Fowler, J. S., Moberg, P. J., Ding, Y. S., et al. (1998). Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. *American Journal of Psychiatry*, *155*(3), 344–349. http://doi.org/10.1176/ajp.155.3.344

Wang, Y., Chan, G. L., Holden, J. E., Dobko, T., Mak, E., Schulzer, M., et al. (1998). Age-dependent decline of dopamine D1 receptors in human brain: a PET study. *Synapse (New York, N.Y.)*, *30*(1), 56–61. http://doi.org/10.1002/(SICI)1098-2396(199809)30:1<56::AID-SYN7>3.0.CO;2-J

Weiler, J. A., Bellebaum, C., & Daum, I. (2008). Aging affects acquisition and reversal of reward-based associative learning. *Learn Mem*, *15*(4), 190–197. http://doi.org/10.1101/lm.890408

World Medical, A. (2013). World Medical Association Declaration of Helsinki. *Jama*, *310*(20), 2191–2194. http://doi.org/10.1001/jama.2013.281053

Worthy, D. A., Davis, T., Gorlick, M. A., Cooper, J. A., Bakkour, A., Mumford, J. A., et al. (2015a). Neural correlates of state-based decision-making in younger and older adults. *NeuroImage*. http://doi.org/10.1016/j.neuroimage.2015.12.004

Worthy, D. A., Otto, A. R., Doll, B. B., Byrne, K. A., & Maddox, W. T. (2015b). Older Adults are Highly Responsive to Recent Events During Decision-Making. *Decisions*, *2*(1), 27–38. http://doi.org/10.1037/dec0000018

Zelnik, N., Angel, I., Paul, S. M., & Kleinman, J. E. (1986). Decreased density of human striatal dopamine uptake sites with age (Vol. 126, pp. 175–176). European journal of …. http://doi.org/10.1016/0014-2999(86)90758-2

Chapter 4

L-dopa blunts ventral striatum activity during stimulus-response learning in healthy volunteers

4.1 Introduction

In PD, dopaminergic therapy is prescribed to address motor symptoms, which result from dopamine depletion to DS. The correction of motor symptoms is done at the expense of some cognitive functions, however (Cools, 2006; P. A. MacDonald & Monchi, 2011; Vaillancourt, Schonfeld, Kwak, Bohnen, & Seidler, 2013). Deleterious effects of dopaminergic therapy on learning have previously been described by the dopamine overdose hypothesis (Cools, Barker, Sahakian, & Robbins, 2001; Gotham, Brown, & Marsden, 1988; Swainson et al., 2000). It proposes that baseline endogenous dopamine levels within a given brain region determines whether exogenous dopamine improves or impairs function (Cools, 2006; P. A. MacDonald & Monchi, 2011). In PD, dopaminergic neurons in SNc are severely degenerated whereas those within VTA are presumed to be relatively less affected by comparison (Fearnley & Lees, 1991; Haber, Haber, Fudge, & Fudge, 1997; Kish, Shannak, & Hornykiewicz, 1988; Vaillancourt, Spraker, Prodoehl, Zhou, & Little, 2012). The SNc-innervated DS is more significantly dopamine-depleted. In contrast, regions supplied by VTA, including VS, prefrontal, and limbic cortices, are largely spared or only modestly deplete of dopamine at early to mid-stages of PD. Whereas dopaminergic therapy improves functions of the dopamine-deplete DS, it is hypothesized to exceed baseline dopamine levels in VTA-innervated brain regions, resulting in a so-called "overdose" and explaining impaired functions.

A review of the literature suggests that learning, in its various forms, is the cognitive function most frequently worsened by dopaminergic therapy in PD (P. A. MacDonald & Monchi, 2011). Studies of PD patients, tested on compared to off their dopaminergic therapies, have reported impairments in probabilistic

associative (Jahanshahi et al., 2010; Torta, Castelli, Zibetti, Lopiano, & Geminiani, 2009), sequence (Feigin et al., 2003; Kwak, Müller, Bohnen, Dayalu, & Seidler, 2010; Seo, Seo, Beigi, Jahanshahi, & Averbeck, 2010; Tremblay et al., 2010), stimulus-reward and reversal (Cools, Altamirano, & D'Esposito, 2006; Graef et al., 2010; A. A. MacDonald, Monchi, et al., 2013a; Swainson et al., 2000; Tomer, Aharon-Peretz, & Tsitrinbaum, 2007), stimulus-stimulus association (P. A. MacDonald et al., 2011), as well as explicit abstract figure and list (A. A. MacDonald, Seergobin, et al., 2013b) learning. Finally, several examples demonstrate dopaminergic medication-related impairment of learning from negative feedback (Bódi et al., 2009; Frank, Seeberger, & O'Reilly, 2004; McCoy, Jahfari, Engels, Knapen, & Theeuwes, 2019).

Further bolstering the dopamine overdose hypothesis are studies in healthy young adults. This cohort has normal endogenous dopamine levels across SNc- and VTA-innervated brain regions, free of PD- and age-related deficiencies. Replicating previous findings in PD, a dopamine challenge has been shown reduce learning in healthy young adults. Reversal learning impairments have been found following administration of either L-dopa (Vo, Seergobin, Morrow, & MacDonald, 2016) or bromocriptine (Mehta, Swainson, Ogilvie, Sahakian, & Robbins, 2001) compared to placebo. Breitenstein and colleagues (2006) showed that associative learning of a novel word list over repeated training sessions was impaired by pergolide. Examining the effects of pramipexole on reward-based learning, Pizzagalli et al., (Pizzagalli et al., 2008) and Santesso et al., (Santesso et al., 2009) found decreased bias towards a probabilistically rewarded choice. Frank et al., (Frank & O'Reilly, 2006) found a similar reduction in learning from reward outcomes following cabergoline administration. Given dopamine levels are optimal in healthy young adults, impaired cognition resulting from excess dopamine in brain regions with normal dopamine function is predicted by the

dopamine overdose hypothesis. At odds with this view, others have claimed that dopaminergic therapy improves learning in PD (Beigi, Wilkinson, Gobet, Parton, & Jahanshahi, 2016; Mollion, Ventre-Dominey, Dominey, & Broussolle, 2003; Shohamy et al., 2005) and healthy adults (Chowdhury et al., 2013; de Vries, Ulte, Zwitserlood, Szymanski, & Knecht, 2010; Knecht et al., 2004; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006; Shellshear et al., 2015). The discrepancy between these two conflicting literatures can be explained by the fact that learning (i.e., the acquisition of associations among stimuli, response, and outcomes) and performance (i.e., the recall, selection, and enactment of decisions based on prior learning) are often confounded in traditional learning paradigms (Jessup, Jessup, O'Doherty, & O'Doherty, 2011; McDonald & White, 2013). Improved task performance with dopaminergic therapy could reflect enhancements in either of these processes, but is labeled as improved learning nonetheless (Atallah, Lopez-Paniagua, Rudy, & O'Reilly, 2007). Indeed, upon closer inspection of these studies, we find that (i) task designs placed greater emphasis on working memory, recollection, and/or response selection, and (ii) effects of medication were maximal only in later phases, after learning had plateaued and response decisions instead were most challenged as opposed to earlier phases when learning demands were greatest. In this way, a dopaminergic therapy-related improvement in performing response decisions would give the impression of improved learning.

We have previously shown how separating a stimulus-response paradigm into its learning and decision-making components can help to clarify the specific effects of dopaminergic therapy (Hiebert et al., 2019; Vo et al., 2014; Vo, Seergobin, & MacDonald, 2017). Vo et al., (Vo et al., 2014) tested stimulus-response learning in PD patients on and off their dopaminergic medications across two separate sessions. Participants first learned associations among abstract stimuli and

specific key-press responses through trial and error via outcome feedback in a training session and later performed these trained stimulus-response selections without feedback in a separate test session. Dopaminergic therapy reduced learning rates in those PD patients tested on compared to off medication but did not affect performance at test. Using the same task in healthy young adults administered L-dopa, we replicated this pattern of impaired stimulus-response learning but spared performance (Vo et al., 2017). Hiebert et al., (Hiebert et al., 2019; 2014) demonstrated with fMRI how separating individual task trials into stimulus-response (SR) and feedback (FB) phases differentially engaged DS and VS activity, respectively. Others have also used this approach of separating learning from decision making events (Aron et al., 2004; Daniel & Pollmann, 2014; Haruno & Kawato, 2006; Hélie, Waldschmidt, & Ashby, 2010; Rodriguez, 2009; Waldschmidt & Ashby, 2011). Testing PD patients on versus off medication in fMRI, Hiebert et al., (Hiebert et al., 2019) showed that dopaminergic therapy impaired stimulus-response learning and attenuated BOLD responses in VS during FB events but improved stimulus-response decisions and enhanced DS activity during SR events.

Irrespective of whether exogenous dopamine enhances learning or response decisions in young adults, that either of these striatum-mediated functions is possibly improved in this cohort is not predicted by the dopamine overdose hypothesis. Young adults have optimal endogenous dopamine levels across the dopaminergic system, absent of PD- or age-related declines. As such, VS-mediated learning and DS-mediated decisions are expected to worsen similarly following a dopamine challenge. As mentioned, learning in young adults is reduced by dopamine precursors (Breitenstein et al., 2006; Vo et al., 2016; 2017; Vo, Seergobin, & MacDonald, 2018) as well as dopamine agonists (Frank & O'Reilly,

2006; Gallant, Vo, Seergobin, & MacDonald, 2016; Mehta et al., 2001; Pizzagalli et al., 2008; Santesso et al., 2009). Far fewer cases have examined these effects on response decisions and DS activity (Winkel et al., 2012). We sought to address this gap by testing VS-mediated learning and DS-associated response decisions following L-dopa administration in healthy young adults.

Using (i) a dopamine challenge in healthy young adults with (ii) a task that separated trials into SR and FB events and (iii) fMRI, we tested the effects of L-dopa on learning, decision-making, and activity in the brain regions that mediate them. Dopaminergic tone and regulation are optimal in healthy young adults (Dreher, Meyer-Lindenberg, Kohn, & Berman, 2008; van Dyck, Seibyl, Malison, & Laruelle, 2002; Volkow & Fowler, 2000). Consequently, this cohort provides a straightforward model for testing the dopamine overdose hypothesis. We predicted that measures of learning will correlate with activity in VS during FB events whereas measures of decision enactment will correlate with DS activity during SR events. In young adults with optimal baseline dopamine levels across these brain regions, L-dopa should impair both learning and decision enactment measures as well as to attenuate corresponding activity in VS and DS, respectively.

4.2 Methods

4.2.1 Participants

Thirty-two healthy volunteers participated in the present study (M_{age} ± SEM = 22.38 ± 0.46 years; 17 females). All participants were free of neurological and psychiatric illnesses, history of alcohol, prescription, or illicit drug abuse, and contraindications to L-dopa and MRI. Two participants were excluded from data analysis. One participant withdrew early from the study due to discomfort being

inside the MRI scanner, whereas a second participant's data were unusable due to equipment failure. All participants gave informed written consent prior to beginning the experiment in accordance with the Declaration of Helsinki (World Medical, 2013). This study was approved by the Health Sciences Research Ethics Board of the University of Western Ontario.

4.2.2 Experimental Design

All participants completed a single experimental session during which they performed a stimulus-response learning task inside a MRI scanner following administration of either 100/25 mg of L-dopa/carbidopa or an equal volume of placebo determined by random assignment. Both drug and placebo were administered in identical gel capsules in a double-blind procedure. The dose used here is the same as has been implemented in previous investigations (Flöel et al., 2005; Knecht et al., 2004; Onur, Piefke, Lie, Thiel, & Fink, 2011; Vo et al., 2016; 2017). To equate L-dopa absorption rates across individuals as much as possible, participants were instructed to: (i) abstain from caffeine, alcohol, and nicotine on the day of testing; (ii) consume only light, non-protein containing meals on the day of testing; and (iii) not consume a meal within an hour of the start of testing. Cognitive testing began approximately 45 minutes following capsule administration to allow time for peak plasma L-dopa levels (Olanow, Schapira, & Rascol, 2000). To control for potential non-specific peripheral effects of L-dopa, physiological control measures (i.e., heart rate and blood pressure) and subjective mood ratings (Bond & Lader, 1974) were acquired immediately before capsule administration (i.e., pre) and following the wait period but before entering the MRI scanner (i.e., post). We computed change-from-baseline scores by subtracting pre- and post- measurements, weighting potential changes to heart rate, blood pressure, and subjective alertness to individuals' own baseline. Finally,

participants' verbal IQs were estimated using the American Adult National Reading Test (ANART; (Nelson & Willison, 1991).

4.2.3 Behavioural Task

Participants performed a version of the stimulus-response learning task we have previously used (Hiebert et al., 2014; 2019; Vo et al., 2014; 2017). During the task, associations among abstract stimuli and key-press responses were acquired through trial and error. Abstract stimuli were generated using Groboto (Braid Art Labs, Colorado Springs, USA). A total of nine different abstract stimuli were used in the experiment (see Figure 4.1), with three stimuli assigned to each of three possible key-press responses corresponding to the participant's index, middle, and ring fingers of their right hand.

During each trial, an abstract stimulus was presented and remained in the center of the screen until the participant made a key-press response (see Figure 4.2). This was defined as the stimulus-response (SR) event. Feedback regarding the accuracy of participants' selections (i.e., either 'Correct' or 'Incorrect') was provided after each response for 1000 ms. Participants were then prompted to press the button corresponding with their thumb to move on to the next trial. This was defined as the feedback (FB) event. An average interstimulus interval (ISI) of 2500 ms, randomly taken from an exponential distribution ranging from 525 to 7000 ms, was used to separate participant responses to the green object from the visual, feedback presentation. In this way, brain responses specific to SR and FB events were examined separately. An intertrial interval (ITI) of 2500ms, also randomly sampled from an exponential distribution ranging from 525 to 7000 ms, separated the thumb button press from trial N-1 to the fixation point starting trial N.

During each block, the same nine abstract shapes were presented twice in random

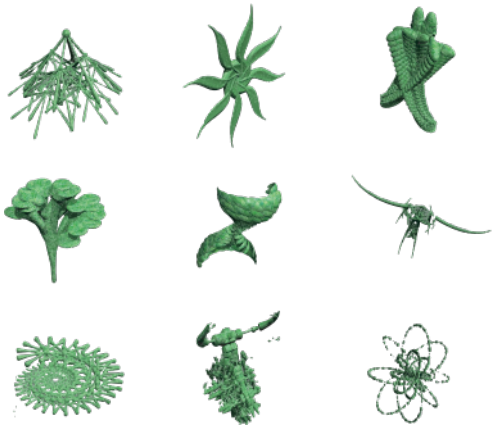

Figure 4.1: Abstract stimulus set presented during the stimulus-response learning task. Stimuli were generated using Groboto (Braid Art Labs, Colorado Springs, USA). A total of nine different abstract stimuli were used in the experiment, with three stimuli assigned to each of three possible key-press responses corresponding to the participant's index, middle, and ring fingers of their right hand.

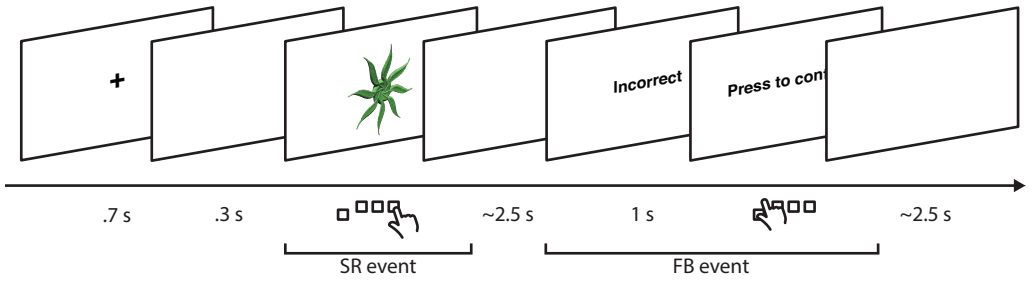

Figure 4.2: Stimulus-response learning trial structure. Trials proceeded as follows: (i) a fixation cross appeared for 700 ms; (ii) a blank screen appeared for 300 ms; (iii) an abstract stimulus was presented and remained in the center of the screen until the participant made one of three possible key-press responses; (iv) a blank screen appeared for an average ISI of 2500 ms (randomly taken from an exponential distribution ranging from 525 to 7000 ms); (v) feedback regarding the accuracy of the participants' selection (i.e., either 'Correct' or 'Incorrect') was provided after each response for 1000 ms; (vi) the participant provided a button-press with their thumb to advance to the next trial; (vii) a blank screen for an average ITI of 2500 ms (randomly taken from an exponential distribution ranging from 525 to 7000 ms) separated trials. Stimulus-response (SR) events were defined as the onset of a stimulus to the participant's response whereas feedback (FB) events were fixed to the presentation of feedback to the button-press that advanced to the next trial.

order for a total of 18 trials. Participants completed six experimental blocks for a total of 108 trials. At the end of each block, a percent accuracy score summarizing their performance was briefly displayed. All participants completed six total runs, corresponding to each of the six learning blocks, each lasting approximately 3 mins.

4.2.4 Behavioural Measures and Statistical Analyses

Our main dependent measure was the percent accuracy achieved across the six learning blocks, with greater scores denoting superior learning performance. Learning scores were submitted to a 2 × 6 mixed ANOVA with Group (L-dopa vs. Placebo) as the between-subject factor and Block (1 vs. 2 vs. 3 vs. 4 vs. 5 vs. 6) as the within-subject variable. Significant interaction effects were further investigated with Bonferroni-corrected pairwise comparisons. We also computed and contrasted the learning curve slopes between groups in a two-sample *t*-test, with greater scores indicating more efficient acquisition of stimulus-response relations. Learning curves were computed in R based on linear regression using accuracy scores across the 6 learning blocks. To explore potential influences of L-dopa on decisions, we examined RTs for correct decisions in an analogous 2 × 6 mixed ANOVA. Shorter RTs were taken to reflect greater certainty in response selection and enactment of stimulus-response decisions.

4.2.5 Imaging Data Acquisition

Functional data were acquired in a 3 Tesla Siemens Prisma Fit MRI scanner (Siemens, Erlangen, Germany) with a 32-channel head coil at the Centre for Functional and Metabolic Mapping, Robarts Research Institute. All participants completed a total of six runs, each lasting approximately 3 minutes in duration. Functional data were collected using an echo-planar pulse (EPI) sequence (TR = 2.5 s, TE = 30 ms, matrix size = 88 × 88 pixels, 43 slices, voxel size = 2.5×2.5×2.5 mm^3,

flip angle = 90°). A high-resolution T1-weighted MPRAGE (magnetization-prepared rapid-acquisition gradient echo) sequence (voxel size = 1×1×1 mm^3, 192 slices) was also acquired for full brain coverage.

4.2.6 Imaging Data Analysis

Functional data were analyzed using Statistical Parametric Mapping version 12 (SPM12; Wellcome Department of Imaging Neuroscience, London, United Kingdom) in conjunction with Matrix Laboratory (MATLAB; MathWorks, Inc., Natick, Massachusetts, United States). The first 4 functional volumes (i.e., 10 s) of each run were discarded to minimize T1 equilibrium effects. Functional images underwent standard preprocessing procedures, including slice time correction, reorientation for participant motion, spatial normalization to the standard Montreal Neurological Institute (MNI) template, spatial smoothing with an 8 mm full-width half-maximum Gaussian kernel.

At the first-level analysis, we fit a GLM to model brain responses to the onset and duration of (i) Feedback (FB) and (ii) Stimulus-Response (SR) events. As previously mentioned, the FB event was defined as the onset of feedback until the participant's button-press that advanced to the next trial. The SR event encompassed the onset of the abstract stimulus until the participant's response. In this way, both the FB and SR events were matched in terms of their motor response demands. We additionally examined Correct and Incorrect trials separately. Regressors were formed by convolving events with the canonical hemodynamic response function. Six realignment parameters that described rigid-body movement (x, y, z, pitch, roll, yaw) were included as nuisance regressors. Data were high-pass filtered (128 s) to remove low frequency drifts.

Both FB and SR events were estimated against the implicit baseline. To further

explore brain activity related to feedback processing, we formed an additional contrast of interest comparing Correct versus Incorrect FB events. We expected regions involved in learning to be more sensitive to correct relative to incorrect feedback. A similar approach has been used previously (Hiebert et al., 2014). Therefore, our contrasts of interest were: (i) FB versus implicit baseline, (ii) Correct versus Incorrect FB, and (iii) SR versus implicit baseline. These contrasts were then taken to a second-level group analysis. We first examined task-related brain responses during our contrasts of interest using one-sample *t*-tests collapsed across groups. Next, we directly compared brain responses during our contrast of interest using two-sample *t*-tests between L-dopa and Placebo groups. Small volume correction (SVC) within a bilateral VS and DS mask of interest, for which we had *a priori* hypotheses informed by prior studies (Hiebert et al., 2014; 2019), was applied at a threshold of $p < 0.05$ (FWE-corrected for multiple comparisons at the voxel level). See below for details on region-of-interest specifications.

Given our *a priori* hypotheses regarding the brain regions correlated with FB and SR events, based on previous work (Hiebert et al., 2014; 2019), we focused our analyses on striatal ROIs. VS and DS ROIs in the present study were the same as used previously (Hiebert et al., 2014), consisting of spheres with radii of 6 mm. VS ROIs were centered on the nucleus accumbens (x = ±10, y = 8, z = -4) whereas DS ROIs were placed on the dorsal head of the caudate nucleus (x = ±18, y = 24, z = 6) and dorsal putamen (x = ±29, y = 9, z = 6). Mean β estimates from each ROI and contrast of interest were extracted using the MarsBaR toolbox (Brett, Anton, Valabregue, & Poline, 2002). To test for significant activation of VS and DS ROIs during our contrasts of interest, we submitted mean β estimates collapsed across groups to a one-sample *t*-test compared to a value of zero. We then contrasted β estimates in a 2 × 4 mixed ANOVA with Group (L-dopa vs. Placebo) as the

between-subject factor and ROI (Left VS, Right VS, Left DS, Right DS) as the within-subject variable. Finally, we examined brain-behaviour correlations across all participants collapsed across groups. Pearson correlation analyses were performed between mean β estimates for each ROI with behavioural measures of learning (i.e., learning curve slopes) and stimulus-response decisions (i.e., mean RTs for correct trials).

4.3 Results

4.3.1 Control Measures

Control measures are summarized in Table 4.1. Both L-dopa and Placebo groups were well-matched in terms of age (t_{28} = -1.676, p = 0.105), years of education (t_{28} = -1.105, p = 0.278), and estimated verbal IQ as measured by the ANART (t_{28} = 0.814, p = 0.422). Change-from-baseline for HR, systolic and diastolic blood pressure, and subjective ratings of alertness (as measured by the Bond-Lader visual analogue scale) were calculated and compared between experimental groups using two-sample *t*-tests. There were no significant differences in change-from-baseline scores for HR (t_{28} = 0.098, p = 0.923), systolic (t_{28} = 1.686, p = 0.103) or diastolic (t_{28} = 1.653, p = 0.110) blood pressure, or alertness reports (t_{28} = -0.080, p = 0.936). Further, participants were at chance when asked to predict to which condition they were assigned during the experiment. Together, these control findings suggest that significant effects of our drug manipulation were specific to our cognitive task and not explained by general physiological changes.

4.3.2 Behavioural Measures

Figure 4.3ab presents the mean accuracy scores and RTs for correct trials across

Table 4.1: Demographic, physiological, and subjective report of alertness measures in L-dopa and Placebo groups.

Measure	L-dopa (n = 15)	Placebo (n = 15)
Age	21.73 (0.61)	23.27 (0.68)
Education	15.40 (0.43)	16.20 (0.58)
Verbal IQ	125.17 (1.18)	126.70 (1.46)
ΔHR	7.53 (2.00)	7.27 (1.87)
ΔSys	2.00 (1.25)	-1.67 (1.78)
ΔDia	0.87 (1.89)	-2.87 (1.24)
ΔAlert	10.59 (4.59)	11.07 (3.82)

Values reported are means (±SEM). ΔHR = Change-from-baseline in heart rate (bpm); ΔSys = Change-from-baseline in systolic blood pressure (mmHg); ΔDia = Change-from-baseline in diastolic blood pressure (mmgHg); ΔAlert = Change-from-baseline in subjective report of alertness (Bond & Lader, 1974).

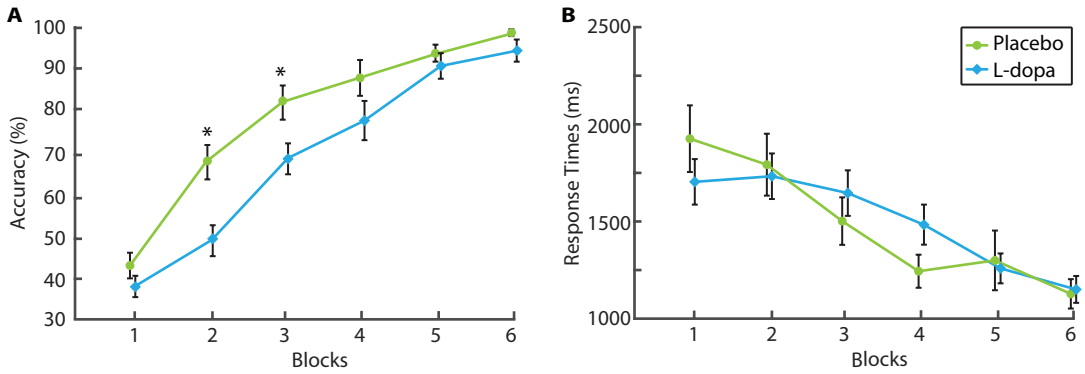

Figure 4.3: Mean **(A)** accuracy scores and **(B)** RTs for correct trials across learning blocks for L-dopa (blue) and Placebo (green) groups. Accuracy scores were lower in the L-dopa compared to Placebo group on average and in Blocks 2 and 3. RTs for correct decisions were faster in Blocks 4-6 relative to Blocks 1-3 but did not differ between groups. * indicates $p < 0.05$. Error bars represent standard error.

each learning block for each group separately. A 2 × 6 mixed ANOVA with Group (L-dopa vs. Placebo) as the between-subject factor and Block (1-6) as the within-subject variable revealed significant main effects of both Group ($F_{1,28}$ = 6.670, p = 0.015) and Block ($F_{5,140}$ = 145.816, p < 0.001). Overall, accuracy scores were significantly lower in the L-dopa compared to the Placebo group, demonstrating lesser learning following a dopamine challenge. The proportion of correct responses significantly improved across each of the six learning blocks (all p-values < 0.05), demonstrating that stimulus-response learning was achieved, increasing from 40.4% (±2.0) in Block 1 to 96.8% (±1.4) in Block 6 (see Figure 4.3a). We also found a significant Group × Block interaction effect ($F_{5,140}$ = 3.147, p = 0.010). Post-hoc pairwise comparisons revealed lower accuracy scores in the L-dopa compared to Placebo group in Blocks 2 (p = 0.002) and 3 (p = 0.021) only. Learning curve slopes did not significantly differ between the L-dopa (0.120 ± 0.007) and Placebo (0.104 ± 0.006) groups (t_{28} = 1.579, p = 0.126). A Bayesian two-sample t-test with a BF_{10} of 1.555 provided anecdotal evidence for the alternative hypothesis.

In an analogous 2 × 6 mixed ANOVA on RTs for correct trials, we found a main effect of Block ($F_{5,140}$ = 20.238, p < 0.001). Post-hoc pairwise comparisons revealed that RTs were significantly faster during Blocks 4 to 6 relative to Blocks 1 to 3 (see Figure 4.3b). There was no main effect of Group ($F_{1,28}$ = 0.016, p = 0.901) or a Group × Block interaction effect ($F_{5,140}$ = 1.850, p = 0.107). A Bayesian two-sample t-test comparing mean RTs for correct trials between the L-dopa and Placebo groups reported a BF_{10} of 0.346, providing support for the null hypothesis of no between-group differences in this measure.

4.3.3 Imaging Results

Table 4.2 presents whole-brain results for each contrasts of interest, collapsed across groups in a one-sample t-test and directly contrasting groups in two-sample

Table 4.2: Brain regions showing significant activation for contrasts of interest

Anatomical region	Voxels	*t*-stat	$p_{SVC\text{-}FWE}$	x	y	z
FB > Implicit Baseline						
All participants						
R ventral putamen	10	4..99	0.002	15	8	-1
L ventral caudate/accumbens	8	4.14	0.003	-12	11	-1
R dorsal putamen	17	5.87	<0.001	24	8	5
R dorsal caudate	10	4.99	0.002	18	17	5
Placebo > L-dopa						
No suprathreshold activations	-	-	-	-	-	-
L-dopa > Placebo						
No suprathreshold activations	-	-	-	-	-	-
FB Correct > Incorrect						
All participants						
R ventral caudate/accumbens	20	4.26	0.004	12	11	-4
Placebo > L-dopa						
No suprathreshold activations	-	-	-	-	-	-
L-dopa > Placebo						
No suprathreshold activations	-	-	-	-	-	-
FB Incorrect > Correct						
All participants						
No suprathreshold activations	-	-	-	-	-	-
SR > Implicit Baseline						
All participants						
L dorsal putamen	5	3.95	0.023	-24	5	5
R dorsal putamen	2	3.84	0.030	24	11	5
Placebo > L-dopa						
No suprathreshold activations	-	-	-	-	-	-
L-dopa > Placebo						
No suprathreshold activations	-	-	-	-	-	-

All voxel locations are reported in MNI coordinates. FWE: family-wise error; SVC: small volume correction. Activations thresholded at $p_{SVC\text{-}FWE} < .05$ within a striatal volume of interest

t-tests. Our contrasts of interest were (i) FB > baseline, (ii) Correct > Incorrect FB and (iii) SR > baseline. Results were corrected at $p < 0.05$, FWE-corrected for multiple comparisons at the voxel-level within a striatal mask of interest.

In the FB > implicit baseline contrast, we found significant activity in the right ventral putamen ($t = 4.99$; $k = 10$; $p_{FWE\text{-}SVC} = 0.002$; *peak coordinates:* 15, 8, -1) and left ventral caudate extending into the NAc ($t = 4.14$; $k = 8$; $p_{FWE\text{-}SVC} = 0.003$; *peak coordinates:* -12, 11, -1). We also observed activity in the right dorsal putamen ($t = 5.87$; $k = 17$; $p_{FWE\text{-}SVC} < 0.001$; *peak coordinates:* 24, 8, 5) and caudate ($t = 4.93$; $k = 10$; $p_{FWE\text{-}SVC} = 0.002$; *peak coordinates:* 18, 17, 5). No regions were significantly active for the reverse contrast. Further exploring brain activity related to FB events, the Correct > Incorrect FB contrast revealed a significant cluster encompassing the right accumbens ($t = 4.16$; $k = 11$; $p_{FWE\text{-}SVC} = 0.018$; *peak coordinates:* 9, 11, -4) and extending into the right putamen ($t = 4.11$; $k = 2$; $p_{FWE\text{-}SVC} = 0.020$; *peak coordinates:* 21, 20, 2). The reverse contrast did not reveal any significant activations. In the SR > baseline contrast, significant activity arose in left ($t = 3.95$; $k = 5$; $p_{FWE\text{-}SVC} = 0.023$; *peak coordinates:* -24, 5, 5) and right ($t = 3.84$; $k = 2$; $p_{FWE\text{-}SVC} = 0.030$; *peak coordinates:* 24, 11, 5) dorsal putamen. No regions were significantly active for the reverse contrast. In each of our contrasts of interest, two-sample *t*-tests did not reveal preferential activity in either the L-dopa > Placebo or the Placebo > L-dopa contrasts.

Separate one-sample *t*-tests collapsed across groups compared mean β estimates extracted from each ROI during our contrasts of interest to a value of zero (see Figure 4.4B). In the Correct > Incorrect FB contrast, activity in the left ($t_{29} = 2.316$, $p = 0.028$) and right ($t_{29} = 3.524$, $p = 0.001$) VS ROI was significantly greater than zero. Importantly, we did not find activation significantly above zero in either left ($t_{29} = 0.563$, $p = 0.578$) or right ($t_{29} = 1.784$, $p = 0.085$) DS ROI. Next, a 2 × 4 mixed ANOVA contrasting mean β estimates within each VS and DS ROI between L-dopa and

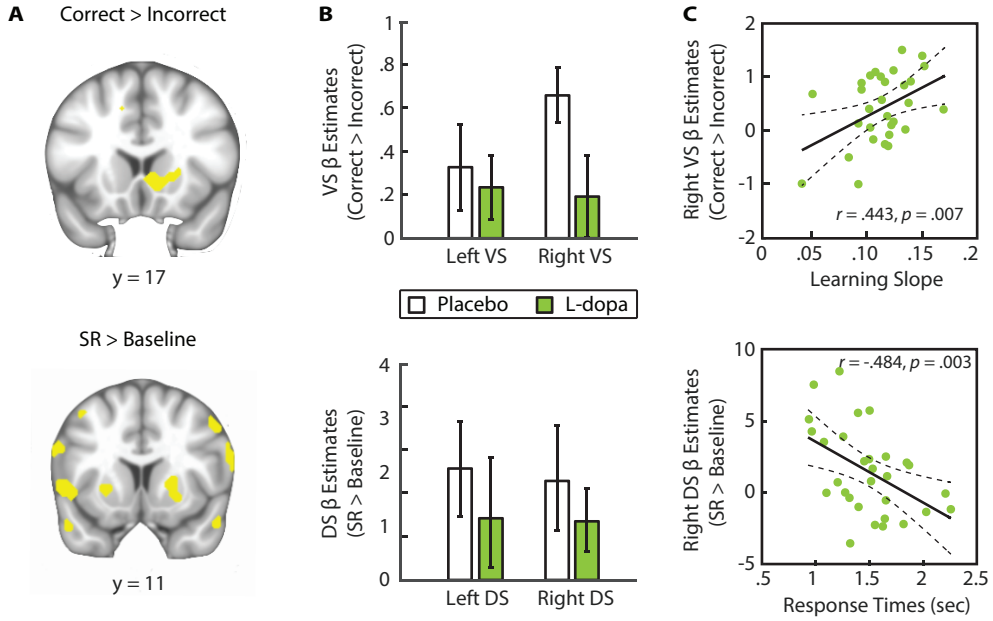

Figure 4.4: (A) *Top:* Ventral striatum activity was more sensitive to Correct versus Incorrect feedback events collapsed across groups (image threshold: $p < .001$ uncorrected for display). *Bottom:* Dorsal striatum activity was correlated with stimulus-response events. **(B)** Mean β estimates extracted from left and right ventral (*top*) and dorsal (*bottom*) striatal ROIs. Right ventral striatal activation observed in the Placebo group was blunted in the L-dopa group (error bars represent standard error). **(C)** *Top:* Greater activity in the right ventral striatum during feedback processing predicted superior learning rates. *Bottom:* Larger DS responses during stimulus-response events were related to faster RTs for correct decisions. Lines depict group-level linear effects 95% confidence interval.

Placebo groups. We found a significant main effect of ROI ($F_{3,84}$ = 5.222, p = 0.002) but not Group ($F_{1,28}$ = 0.185, p = 0.670). Activity in the right VS ROI was significantly greater than both left (p = 0.012) and right (p = 0.039) DS ROIs, but not left VS ROI (p = 1.000). No significant differences were evident between both DS ROIs and left VS ROI (all p > 0.05). There was also a significant Group × ROI interaction effect ($F_{3,84}$ = 3.890 p = 0.022). Post-hoc pairwise comparisons revealed lower activity in the L-dopa compared to Placebo group in the right VS ROI, although this did not reach statistical significance (p = 0.052). No group differences were found in any of the other ROIs (all p > 0.05).

Examining activity during SR events, one-sample t-tests collapsed across groups revealed activity significantly above zero in both left (t_{29} = 3.085, p = 0.004) and right (t_{29} = 2.629, p = 0.014) DS ROIs. No VS ROI was significantly activated during SR events (all p > 0.05), however. A 2 × 4 mixed ANOVA contrasting mean β estimates within each ROI between Groups did not reveal significant main effects of either ROI ($F_{3,84}$ = 0.227, p = 0.877) or Group ($F_{1,28}$ = 0.956, p = 0.337), or a Group × ROI interaction effect ($F_{3,84}$ = 0.416, p = 0.742).

Finally, we examined brain-behaviour correlations between mean β estimates from each ROI and behavioural measures of stimulus-response learning (i.e., learning curve slopes) and decision making (i.e., mean RTs for correct trials). During the Correct > Incorrect FB contrast, we found a positive correlation between the right VS ROI and learning rate (r = 0.443, p = 0.007; see Figure 4.4c). Greater VS activity predicted more efficient acquisition of stimulus-response associations. Left VS activity and learning curves were not significantly correlated (r = 0.079, p = 0.339). Similarly, neither left (r = 0.091, p = 0.317) nor right (r = 0.112, p = 0.277) DS ROI was significantly related to our learning measure. During the SR > baseline contrast, activity in both the left (r = -0.547, p = 0.001) and right (r = -

0.484, $p = 0.003$) DS ROIs negatively correlated with mean RTs for correct decisions (see Figure 4.4c). Greater DS activity corresponded with faster RTs during the enactment of stimulus-response decisions. Activity in our VS ROIs were not significantly correlated with our measure of decision-making (both $p > 0.05$).

4.4 Discussion

4.4.1 Summary

In the present study, we investigated the effects of L-dopa on stimulus-response learning in healthy young adults with fMRI. We specifically tested whether optimal baseline dopamine levels within brain regions previously shown to mediate the learning and enactment of stimulus-response associations would be at similar risk of overdose effects, as predicted by the dopamine overdose hypothesis. Behaviourally, we found that L-dopa worsened the learning of stimulus-response associations. This effect was greatest during earlier learning blocks (i.e., Blocks 2 and 3), when demands placed on acquiring associations among stimuli and responses were presumably greatest. L-dopa did not, however, influence the speed with which participants enacted correct stimulus-response decisions—our measure of certainty in decision making. Brain imaging data revealed preferential VS activity during FB events, the point at which stimulus-response associations were learned and reinforced. Further, VS activation was greater for correct compared to incorrect feedback events. VS signals were also positively correlated with individual learning curve slopes, such that greater VS activity predicted more efficient stimulus-response learning. Critically, this activity was attenuated in participants treated with L-dopa compared to those administered a placebo. Preferential DS activity was found

during SR events, when stimulus-response decisions were performed. DS activity during SR events correlated with mean RTs for correct trials, with greater DS signal predicting faster RTs. Decision-related activity in DS did not differ between L-dopa and Placebo groups, however. Taken together, our results only partially support the dopamine overdose hypothesis. L-dopa worsened learning efficiency and reduced VS activity, replicating previous findings (Cools, Lewis, Clark, Barker, & Robbins, 2007; Hiebert et al., 2019; Kwak, Müller, Bohnen, Dayalu, & Seidler, 2012). L-dopa neither worsened nor improved decision certainty as indexed by RT for stimulus-specific response selections. Further, L-dopa neither depressed nor enhanced DS activity that arose preferentially in SR events and negatively correlated with RT for response selections. Contrary to the effects of L-dopa on learning and VS activity, its effect on decision certainty and DS activity in young adults was at odds with the overdose framework. We discuss these more nuanced results in the following sections.

Our finding of impaired learning performance following L-dopa administration could not be explained by confounding physiological side-effects resulting from peripheral dopamine action. Groups did not differ in control measures of heart rate, blood pressure, or subjective reports of alertness. Participants were also at chance level in their accuracy of predicting to which experimental group they were assigned.

4.4.2 L-dopa impairs stimulus-response learning

We found that administration of L-dopa impaired stimulus-response learning in healthy young adults, replicating our previous findings in both PD patients tested on and off dopaminergic medication as well as healthy volunteers following a dopamine challenge (Hiebert et al., 2019; Vo et al., 2014; 2017). In an earlier experiment, PD patients learned stimulus-response associations more poorly

when tested on compared to off their usual dopaminergic medication (Vo et al., 2014). This effect of medication was specific to learning, as dopaminergic therapy has no impact on the accuracy of stimulus-specific response selections in a test phase after a threshold of 75% accuracy was achieved. Using the same task in a sample of healthy young adults, following a single treatment with L-dopa, we reported analogous medication-associated impairments in stimulus-response learning but no effect of medication on response selections (Vo et al., 2017).

Unlike in our previous studies, we did not include an explicit test phase to isolate stimulus-specific response decisions from feedback-based learning. This limited conclusions regarding the specificity of our observed medication effects on learning processes. The differences in learning curves between L-dopa and Placebo groups reveal significant group differences early in the learning task, when demands to learn novel associations among stimuli and responses are greatest (see Figure 4.2a). By the final learning blocks, learning had been achieved to a high level with accuracies of greater than 90% in both groups. In the final block, evidenced by little change in accuracy or RT from the penultimate block, performance reflected predominantly response selection processes informed by previous learning. In the final blocks, there was no effect of L-dopa on accuracy as both L-dopa and Placebo groups performed comparably. Further, in contrast to the L-dopa-associated worsening of learning, we did not find a similar impairment in our behavioural measure of decision-making. Groups did not differ in their mean RTs for selecting the correct stimulus-specific responses, supported by both frequentist and Bayesian analyses. Our findings mirror previously reported null effects of exogenous dopamine on decision-making in healthy young adults when a separate test phase, more clearly isolating decision making from learning processes, was performed (Vo et al., 2014; 2017).

Our results add to a growing literature showing learning to be the cognitive function most frequently worsened by dopaminergic therapy in PD and healthy adults. In addition to stimulus-response learning, studies comparing PD patients on relative to off medication have also demonstrated impairments in probabilistic associative (Jahanshahi et al., 2010; Torta et al., 2009), sequence (Feigin et al., 2003; Kwak et al., 2010; Seo et al., 2010; Tremblay et al., 2010), stimulus-reward and reversal learning (Cools et al., 2006; Graef et al., 2010; A. A. MacDonald, Monchi, et al., 2013a; Swainson et al., 2000; Tomer et al., 2007), as well as explicit abstract figure and list learning (A. A. MacDonald, Seergobin, et al., 2013b), stimulus-stimulus facilitation (P. A. MacDonald et al., 2011), and learning from negative feedback (Frank & Claus, 2006). Further bolstering these findings in PD, a dopamine challenge in healthy young adults has been shown to impair reversal learning (Mehta et al., 2001; Vo et al., 2016), associative learning of novel word lists (Breitenstein et al., 2006), and probabilistic reward learning (Frank & O'Reilly, 2006; Pizzagalli et al., 2008; Santesso et al., 2009).

Contrary to this view, several studies have reported enhanced learning with dopaminergic therapy in PD patients (Beigi et al., 2016; Mollion et al., 2003; Shohamy et al., 2005) and healthy adults (Chowdhury et al., 2013; de Vries et al., 2010; Knecht et al., 2004; Pessiglione et al., 2006; Shellshear et al., 2015). We reconcile these competing literatures by considering that traditional learning paradigms often confound learning and decision-making (Jessup et al., 2011; McDonald & White, 2013). Changes in task performance could reflect an influence of exogenous dopamine on either of these processes (Atallah et al., 2007) but are labeled as an effect on learning. In young adults, Knecht et al., (2004) and de Vries et al., (2010) found enhanced pseudo-word and artificial grammar learning with L-dopa. Shellshear and colleagues (2015) showed that associative learning of

object and non-word pairings was also facilitated by L-dopa. In each of these studies, learning took place over multiple sessions on separate days. If dopaminergic therapy enhanced learning, we would expect maximal effects during the earliest session, when demands to acquire associations among stimuli were greatest. Instead, improvements related to exogenous dopamine were maximal in later sessions, after learning had plateaued and recollection of learned associations were emphasized. Pessigilone et al. (2006) found that reward choice was enhanced in young adults by L-dopa relative to haloperidol, a dopamine antagonist. Participants learned to consistently select the stimulus in a pair that maximized rewards in a gain condition and minimized punishments in a loss condition. The authors claimed that L-dopa improved reward selections but did not affect loss avoidance relative to haloperidol. It is important to consider that no proper placebo condition was included, thus observed effects could reflect either improved or impaired reward performance due to L-dopa or haloperidol, respectively. Further, responses in this task were enacted by either providing or withholding key-press responses, introducing additional complex decision-making and response inhibition demands that confound straightforward interpretations of L-dopa's effect on reward choices. Finally, Chowdhury and colleagues (2013) reported abnormal reward learning in older adults that was restored by L-dopa. This study used a two-armed bandit task, during which participants selected between two fractal images that predicted the delivery or omission of reward feedback. On a trial-by-trial basis, the probability of obtaining reward varied based on a Gaussian random walk function, thus placing greater emphasis on decisions in a noisy environment rather than incremental learning per se. In this way, improved performance with L-dopa more likely reflects an amelioration of decision-making rather than reward learning processes.

4.4.3 L-dopa blunts VS activity during feedback but has no effect on DS activity during decision making

We used a task design that decomposed trials into FB and SR events to allow separate assessment of brain activity related to learning and decision-making processes, respectively. FB events, during which participants learned and reinforced associations between stimuli and responses, correlated with VS and not DS activity. The level of VS activation was related to correct versus incorrect feedback. This learning-related activity in VS was blunted in participants treated with L-dopa compared to those who received placebo. Preferential DS activity arose during SR events, when stimulus-response decisions were recalled and enacted, and correlated with faster decision RTs. In contrast to VS, responses in DS were not modulated by L-dopa.

Our findings are in line with a small literature reporting similar overdose effects of VTA-innervated brain regions in PD patients using neuroimaging (Aarts et al., 2014; Argyelan et al., 2018; Cools et al., 2007; Hiebert et al., 2019; Kwak et al., 2012). Hiebert et al., (2019) used a similar stimulus-response learning paradigm to assess the effects of dopaminergic therapy on striatal activity in PD. Patients were tested both on and off their dopaminergic medication across two experimental sessions. During each session, they were first required to associate a set of abstract stimuli to specific button-press responses via trial and error (i.e., learning phase) before performing these learned associations in the absence of any further feedback-based learning (i.e., test phase). In the learning phase of each session, trials were separated into stimulus-response and feedback events. The authors found that dopaminergic therapy impaired stimulus-response learning but improved response selection accuracy in PD. This behavioural pattern was mirrored by their imaging results, as dopaminergic medication attenuated VS activity related to

feedback events during the learning phase, but enhanced DS activity during stimulus-specific response selection events in both the learning and test phases. Similarly, others have reported dopaminergic medication-related attenuation of VS activity during probabilistic reversal learning (Cools et al., 2007), stimulus-reward selections (Argyelan et al., 2018), reward anticipation (Aarts et al., 2014), and motor sequence learning (Kwak et al., 2012).

Young healthy adults tested in this study have optimal dopamine levels in DS as well as in VTA-innervated brain regions. Consequently, DS-mediated functions like VS-associated learning were predicted to worsen following a dopamine challenge. We did not find such an effect, however. Previous investigations of exogenous dopamine effects on DS function in healthy volunteers have focused on addressing cognitive changes associated with age-related dopamine decline in older adults (Chowdhury, Guitart-Masip, Bunzeck, Dolan, & Düzel, 2012; Floel et al., 2008; Flöel et al., 2005). In healthy young adults, Winkel et al., (2012) examined the effects of bromocriptine on perceptual decision-making in young adults with fMRI. Participants performed a version of the random dot motion task, during which they were cued to make either fast or accurate judgements regarding the direction of motion of a cloud of dots presented on a computer screen. The authors found that exogenous dopamine did not affect decision thresholds between speed and accuracy during the task, with support from Bayesian analyses. Activity in DS and pre-supplementary motor cortex was found to correlate with response preparation elicited by cues prompting speed relative to accurate responses. This activation was not affected by bromocriptine, however. In a test of perceptual decision-making that minimized explicit learning requirements, that exogenous dopamine neither improved nor worsened DS-mediated function in young adults appears consistent with our findings.

4.4.4 Dopamine overdose hypothesis

The notion that baseline dopaminergic tone determines the response to exogenous dopamine is the central tenet of the dopamine overdose hypothesis. Functions of dopamine-deplete brain regions are predicted to improve whereas those of dopamine-replete brain areas are expected to worsen with dopaminergic therapy. This hypothesis has been largely supported by studies in early-stage PD, in which severe dopamine deficiency in DS is contrasted with relatively spared dopamine levels in VTA-innervated brain regions. Treatment with dopaminergic therapy improves functions of the dopamine-deplete DS but impairs those functions of dopamine-replete VTA-innervated brain regions. Critical tests of this theory in healthy young volunteers, who have optimal baseline dopamine levels, have yielded results supportive of the dopamine overdose hypothesis. Mirroring the findings in PD, exogenous dopamine has been found to impair reversal learning (Mehta et al., 2001; Vo et al., 2016), stimulus-response learning (Gallant et al., 2016; Vo et al., 2017), learning from probabilistic reward (Frank & O'Reilly, 2006; Pizzagalli et al., 2008; Santesso et al., 2009), as well as associative learning of novel word lists (Breitenstein et al., 2006).

In the present study, healthy young adults displayed impaired learning and attenuated VS signal following administration with L-dopa. Our findings are in line with predictions of dopamine-replete VTA-innervated brain functions in accordance with the dopamine overdose hypothesis. In addition, deleterious effects of exogenous dopamine observed in the present study could not be explained by PD-related reductions in regulation of synaptic dopamine via DATs (Frost et al., 1993) or due to post-synaptic receptor sensitization following chronic treatment with dopaminergic therapy (Bordet et al., 1997). These possibilities obviously could not be rule out in previous PD studies. Rather, our results appear

to support the notion that high baseline dopamine levels in VTA-innervated brain regions of young adults are prone to overdose by exogenous dopamine.

Despite numerous demonstrations that dopaminergic therapy worsens functions mediated by VTA-innervated brain regions (Aarts et al., 2014; Argyelan et al., 2018; Cools et al., 2007; Feigin et al., 2003; Hiebert et al., 2019; Kwak et al., 2012; Riba, Krämer, Heldmann, Richter, & Münte, 2008; van Eimeren et al., 2009), evidence for medication-related impairment of DS functions are lacking. Many studies have focused on investigating whether dopaminergic therapy can address cognitive changes associated with age-related dopamine decline in older adults (Chowdhury et al., 2012; Floel et al., 2008; Flöel et al., 2005). In young adults, Luciana et al., (1992) found that bromocriptine enhanced the delayed but not immediate recall of the spatial location of rapidly presented visual cues. Mehta et al., (2001) also showed improved short-term spatial memory in young adults following treatment with bromocriptine. Working memory has long implicated PFC (Miller & Cohen, 2003), a region reciprocally connected to DS. Dopamine stimulation might have distinct effects on prefrontal versus striatum-mediated functions due to differences in D1- and D2-receptor densities and mechanisms of dopamine regulation between these regions (Akil et al., 2003; Cools & D'Esposito, 2011). Of the few studies that have explicitly tested a dopamine challenge on DS-mediated decision-making (Vo et al., 2017; Winkel et al., 2012), null effects were reported. A notable exception is a study by Kimberg et al., (1997), which found bromocriptine administration in young adults actually impaired performance on several tests of fronto-executive function that implicate DS, including the Wisconsin Card Sorting Task, an associative memory test of complex sensitives, the Stroop task, and a spatial working memory task similar to that used by Luciana et al., (1992). However, this deleterious effect of exogenous dopamine was only

noted in those subjects with high working memory capacity, which has been shown to positively correlate with endogenous dopamine synthesis capacity (Cools, Gibbs, Miyakawa, Jagust, & D'Esposito, 2008). There is clearly little consensus among the small literature investigating the effects of exogenous dopamine on DS-mediated functions in young adults. Further investigations are needed to provide a critical test of the overdose account.

Our finding that L-dopa did not impair DS-mediated decisions is at odds with the dopamine overdose hypothesis. In healthy young adults, dopamine levels are optimal across the striatum. The overdose account would predict that functions ascribed to DS would be impaired by exogenous dopamine in a similar fashion to that observed in VS functions. Average RT, our measure of decision certainty, was not impacted by L-dopa versus placebo. Further, DS activation in SR events was not altered by dopaminergic therapy. Finally, exogenous dopamine had no impact on the negative correlation between average RT and DS BOLD signal. DS is potentially better adapted to respond to exogenous dopamine with safeguards against overdose, even when baseline dopamine levels are optimal. DS consists of larger medium spiny neurons with more dendrites and spines, denser dopamine inputs, and higher expression of DAT (Wickens, Budd, Hyland, & Arbuthnott, 2007). DAT rapidly clears synaptic dopamine, which could play a critical role in dopamine overdose. In contrast, VS is comprised of smaller medium spiny neurons with fewer, more widely-spaced dendrites and spines, sparser dopamine supply, and lower DAT concentrations. Whereas DS displays maximal firing in response to receptor stimulation across a wide range of frequencies, VS expresses a more graded and incremental response to stimulation (Zhang et al., 2009). In this way, DS might be better tuned to reach threshold for firing across a broader range of dopamine concentrations compared to the more finely-tuned dopamine

signaling in VS. The latter would seem more easily perturbed by a bolus of exogenous dopamine. Further, differences in the expression of DAT between these brain regions might result in differential capacities to buffer against excess synaptic dopamine introduced by exogenous dopaminergic therapy. Further testing of the effects of exogenous dopamine on an array of DS-mediated functions and across a range of dopamine doses in healthy young volunteers is needed to investigate this alternative hypothesis.

4.4.5 Conclusions

We provide evidence in partial support of the dopamine overdose hypothesis and the straightforward prediction that a dopamine challenge should impair cognitive functions in healthy young adults by exceeding baseline optimal dopamine levels in underlying brain regions. In the present study, L-dopa was found to impair stimulus-response learning and to blunt learning-related activity in VS. Our measure of stimulus-specific response selection and associated activity in DS were not affected by this dopamine challenge, however. Our findings do not fit the straightforward predictions of the dopamine overdose hypothesis and suggest that factors other than baseline dopaminergic tone could determine response to dopamine. These proposals merit further explorations.

4.5 References

Aarts, E., Nusselein, A. A. M., Smittenaar, P., Helmich, R. C., Bloem, B. R., & Cools, R. (2014). Greater striatal responses to medication in Parkinson's disease are associated with better task-switching but worse reward performance. *Neuropsychologia*, *62*, 390–397. http://doi.org/10.1016/j.neuropsychologia.2014.05.023

Akil, M., Akil, M., Kolachana, B. S., Rothmond, D. A., Rothmond, D. A., Hyde, T. M., et al. (2003). Catechol-O-methyltransferase genotype and dopamine regulation in the human brain. *J Neurosci*, *23*(6), 2008–2013.

Argyelan, M., Herzallah, M., Sako, W., DeLucia, I., Sarpal, D., Vo, A., et al. (2018). Dopamine modulates striatal response to reward and punishment in patients with Parkinson's disease: a pharmacological challenge fMRI study. *Neuroreport*, *29*(7), 532–540. http://doi.org/10.1097/WNR.0000000000000970

Aron, A. R., Shohamy, D., Clark, J., Myers, C., Gluck, M. A., & Poldrack, R. A. (2004). Human midbrain sensitivity to cognitive feedback and uncertainty during classification learning. *J Neurophysiol*, *92*(2), 1144–1152. http://doi.org/10.1152/jn.01209.2003

Atallah, H. E., Lopez-Paniagua, D., Rudy, J. W., & O'Reilly, R. C. (2007). Separate neural substrates for skill learning and performance in the ventral and dorsal striatum. *Nat Neurosci*, *10*(1), 126–131. http://doi.org/10.1038/nn1817

Beigi, M., Wilkinson, L., Gobet, F., Parton, A., & Jahanshahi, M. (2016). Levodopa medication improves incidental sequence learning in Parkinson's disease. *Neuropsychologia*, *93*(Pt A), 53–60. http://doi.org/10.1016/j.neuropsychologia.2016.09.019

Bond, A., & Lader, M. (1974). The use of analogue scales in rating subjective feelings. *British Journal of Medical Psychology*, *47*(3), 211–218. http://doi.org/10.1111/j.2044-8341.1974.tb02285.x

Bordet, R., Bordet, R., Ridray, S., Ridray, S., Carboni, S., Carboni, S., et al. (1997). Induction of dopamine D3 receptor expression as a mechanism of behavioral sensitization to levodopa. *Proceedings of the National Academy of Sciences*, *94*(7), 3363–3367. http://doi.org/10.1073/pnas.94.7.3363

Bódi, N., Kéri, S., Nagy, H., Moustafa, A., Myers, C. E., Daw, N., et al. (2009). Reward-learning and the novelty-seeking personality: a between- and

within-subjects study of the effects of dopamine agonists on young Parkinson's patients. *Brain*, *132*(Pt 9), 2385–2395. http://doi.org/10.1093/brain/awp094

Breitenstein, C., Korsukewitz, C., Flöel, A., Kretzschmar, T., Diederich, K., & Knecht, S. (2006). Tonic dopaminergic stimulation impairs associative learning in healthy subjects. *Neuropsychopharmacology*, *31*(11), 2552–2564. http://doi.org/10.1038/sj.npp.1301167

Brett, M., Anton, J. L., Valabregue, R., & Poline, J.-B. (2002). Region of interest analysis using an SPM toolbox (Vol. 16). Presented at the 8th International Conference on Functinal Mapping of the Human Brain, Sendai, Japan.

Chowdhury, R., Guitart-Masip, M., Bunzeck, N., Dolan, R. J., & Düzel, E. (2012). Dopamine modulates episodic memory persistence in old age. *J Neurosci*, *32*(41), 14193–14204. http://doi.org/10.1523/JNEUROSCI.1278-12.2012

Chowdhury, R., Guitart-Masip, M., Lambert, C., Dayan, P., Huys, Q., Düzel, E., & Dolan, R. J. (2013). Dopamine restores reward prediction errors in old age. *Nat Neurosci*, *16*(5), 648–653. http://doi.org/10.1038/nn.3364

Cools, R. (2006). Dopaminergic modulation of cognitive function-implications for l-DOPA treatment in Parkinson's disease. *Neurosci Biobehav Rev*, *30*(1), 1–23. http://doi.org/10.1016/j.neubiorev.2005.03.024

Cools, R., & D'Esposito, M. (2011). Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biol Psychiatry*, *69*(12), e113–25. http://doi.org/10.1016/j.biopsych.2011.03.028

Cools, R., Altamirano, L., & D'Esposito, M. (2006). Reversal learning in Parkinson's disease depends on medication status and outcome valence. *Neuropsychologia*, *44*(10), 1663–1673. http://doi.org/10.1016/j.neuropsychologia.2006.03.030

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001). Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cereb Cortex*, *11*(12), 1136–1143. http://doi.org/10.1093/cercor/11.12.1136

Cools, R., Gibbs, S. E., Miyakawa, A., Jagust, W., & D'Esposito, M. (2008). Working memory capacity predicts dopamine synthesis capacity in the human striatum. *J Neurosci*, *28*(5), 1208–1212. http://doi.org/10.1523/JNEUROSCI.4475-07.2008

Cools, R., Lewis, S. J. G., Clark, L., Barker, R. A., & Robbins, T. W. (2007). L-DOPA disrupts activity in the nucleus accumbens during reversal learning in Parkinson's disease. *Neuropsychopharmacology*, *32*(1), 180–189. http://doi.org/10.1038/sj.npp.1301153

Daniel, R., & Pollmann, S. (2014). A universal role of the ventral striatum in reward-based learning: evidence from human studies. *Neurobiology of Learning and Memory*, *114*, 90–100. http://doi.org/10.1016/j.nlm.2014.05.002

de Vries, M. H., Ulte, C., Zwitserlood, P., Szymanski, B., & Knecht, S. (2010). Increasing dopamine levels in the brain improves feedback-based procedural learning in healthy participants: an artificial-grammar-learning experiment. *Neuropsychologia*, *48*(11), 3193–3197. http://doi.org/10.1016/j.neuropsychologia.2010.06.024

Dreher, J.-C., Meyer-Lindenberg, A., Kohn, P., & Berman, K. F. (2008). Age-related changes in midbrain dopaminergic regulation of the human reward system. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(39), 15106–15111. http://doi.org/10.1073/pnas.0802127105

Fearnley, J. M., & Lees, A. J. (1991). Ageing and parkinson's disease: substantia nigra regional selectivity. *Brain*, *114*(5), 2283–2301. http://doi.org/10.1093/brain/114.5.2283

Feigin, A., Ghilardi, M. F., Carbon, M., Edwards, C., Fukuda, M., Dhawan, V., et al. (2003). Effects of levodopa on motor sequence learning in Parkinson's disease. *Neurology*, *60*(11), 1744–1749. http://doi.org/10.1212/01.WNL.0000072263.03608.42

Floel, A., Garraux, G., Xu, B., Breitenstein, C., Knecht, S., Herscovitch, P., & Cohen, L. G. (2008). Levodopa increases memory encoding and dopamine release in the striatum in the elderly. *Neurobiology of Aging*, *29*(2), 267–279. http://doi.org/10.1016/j.neurobiolaging.2006.10.009

Flöel, A., Breitenstein, C., Hummel, F., Celnik, P., Gingert, C., Sawaki, L., et al. (2005). Dopaminergic influences on formation of a motor memory. *Ann Neurol*, *58*(1), 121–130. http://doi.org/10.1002/ana.20536

Frank, M. J., & Claus, E. D. (2006). Anatomy of a decision: striato-orbitofrontal interactions in reinforcement learning, decision making, and reversal. *Psychol Rev*, *113*(2), 300–326. http://doi.org/10.1037/0033-295X.113.2.300

Frank, M. J., & O'Reilly, R. C. (2006). A mechanistic account of striatal dopamine function in human cognition: psychopharmacological studies with cabergoline and haloperidol. *Behav Neurosci*, *120*(3), 497–517. http://doi.org/10.1037/0735-7044.120.3.497

Frank, M. J., Seeberger, L. C., & O'Reilly, R. C. (2004). By carrot or by stick: cognitive reinforcement learning in parkinsonism. *Science*, *306*(5703), 1940–1943. http://doi.org/10.1126/science.1102941

Frost, J. J., Rosier, A. J., Reich, S. G., Smith, J. S., Ehlers, M. D., Snyder, S. H., et al. (1993). Positron emission tomographic imaging of the dopamine transporter with 11C-WIN 35,428 reveals marked declines in mild Parkinson's disease. *Ann Neurol*, *34*(3), 423–431. http://doi.org/10.1002/ana.410340331

Gallant, H., Vo, A., Seergobin, K. N., & MacDonald, P. A. (2016). Pramipexole Impairs Stimulus-Response Learning in Healthy Young Adults. *Frontiers in Neuroscience*, *10*(784), 390. http://doi.org/10.3389/fnins.2016.00374

Gotham, A. M., Brown, R. G., & Marsden, C. D. (1988). 'Frontal'cognitive function in patients with Parkinson's disease 'on'and 'off'levodopa. *Brain*, *111*(2), 299–321. http://doi.org/10.1093/brain/111.2.299

Graef, S., Biele, G., Krugel, L. K., Marzinzik, F., Wahl, M., Wotka, J., et al. (2010). Differential influence of levodopa on reward-based learning in Parkinson's disease. *Frontiers in Human Neuroscience*, *4*, 169. http://doi.org/10.3389/fnhum.2010.00169

Haber, S. N., Haber, S. N., Fudge, J. L., & Fudge, J. L. (1997). The primate substantia nigra and VTA: integrative circuitry and function. *Critical Reviews™ in Neurobiology*, *11*(4), 323–342. http://doi.org/10.1615/CritRevNeurobiol.v11.i4.40

Haruno, M., & Kawato, M. (2006). Different neural correlates of reward expectation and reward expectation error in the putamen and caudate nucleus during stimulus-action-reward association learning. *J Neurophysiol*, *95*(2), 948–959. http://doi.org/10.1152/jn.00382.2005

Hélie, S., Waldschmidt, J. G., & Ashby, F. G. (2010). Automaticity in rule-based and information-integration categorization. *Attention, Perception & Psychophysics*, *72*(4), 1013–1031. http://doi.org/10.3758/APP.72.4.1013

Hiebert, N. M., Owen, A. M., Ganjavi, H., Mendonça, D., Jenkins, M. E., Seergobin, K. N., & MacDonald, P. A. (2019). Dorsal striatum does not mediate feedback-based, stimulus-response learning: An event-related fMRI study in patients with Parkinson's disease tested on and off dopaminergic therapy. *NeuroImage*, *185*, 455–470. http://doi.org/10.1016/j.neuroimage.2018.10.045

Hiebert, N. M., Vo, A., Hampshire, A., Owen, A. M., Owen, A. M., Seergobin, K. N., & MacDonald, P. A. (2014). Striatum in stimulus-response learning via feedback and in decision making. *NeuroImage*, *101*, 448–457. http://doi.org/10.1016/j.neuroimage.2014.07.013

Jahanshahi, M., Wilkinson, L., Gahir, H., Dharmaindra, A., Dharmarinda, A., Dharminda, A., & Lagnado, D. A. (2010). Medication impairs probabilistic classification learning in Parkinson's disease. *Neuropsychologia*, *48*(4), 1096–1103. http://doi.org/10.1016/j.neuropsychologia.2009.12.010

Jessup, R. K., Jessup, R. K., O'Doherty, J. P., & O'Doherty, J. P. (2011). Human dorsal striatal activity during choice discriminates reinforcement learning behavior from the gambler's fallacy. *J Neurosci*, *31*(17), 6296–6304. http://doi.org/10.1523/JNEUROSCI.6421-10.2011

Kimberg, D. Y., Kimberg, D. Y., D'Esposito, M., D'Esposito, M., Farah, M. J., & Farah, M. J. (1997). Effects of bromocriptine on human subjects depend on working memory capacity. *Neuroreport*, *8*(16), 3581–3585. http://doi.org/10.1097/00001756-199711100-00032

Kish, S. J., Shannak, K., & Hornykiewicz, O. (1988). Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. *N Engl J Med*, *318*(14), 876–880. http://doi.org/10.1056/NEJM198804073181402

Knecht, S., Breitenstein, C., Bushuven, S., Wailke, S., Kamping, S., Flöel, A., et al. (2004). Levodopa: faster and better word learning in normal humans. *Ann Neurol*, *56*(1), 20–26. http://doi.org/10.1002/ana.20125

Kwak, Y., Müller, M. L. T. M., Bohnen, N. I., Dayalu, P., & Seidler, R. D. (2010). Effect of dopaminergic medications on the time course of explicit motor sequence learning in Parkinson's disease. *J Neurophysiol*, *103*(2), 942–949. http://doi.org/10.1152/jn.00197.2009

Kwak, Y., Müller, M. L. T. M., Bohnen, N. I., Dayalu, P., & Seidler, R. D. (2012). l-DOPA changes ventral striatum recruitment during motor sequence learning in Parkinson's disease. *Behavioural Brain Research*, *230*(1), 116–124. http://doi.org/10.1016/j.bbr.2012.02.006

Luciana, M., Depue, R. A., Arbisi, P., & Leon, A. (1992). Facilitation of working memory in humans by a d2 dopamine receptor agonist. *J Cogn Neurosci*, *4*(1), 58–68. http://doi.org/10.1162/jocn.1992.4.1.58

MacDonald, A. A., Monchi, O., Seergobin, K. N., Ganjavi, H., Tamjeedi, R., & MacDonald, P. A. (2013a). Parkinson's disease duration determines effect of dopaminergic therapy on ventral striatum function. *Mov Disord*, *28*(2), 153–160. http://doi.org/10.1002/mds.25152

MacDonald, A. A., Seergobin, K. N., Owen, A. M., Owen, A. M., Tamjeedi, R., Monchi, O., et al. (2013b). Differential effects of Parkinson's disease and dopamine replacement on memory encoding and retrieval. *PLoS One*, *8*(9), e74044. http://doi.org/10.1371/journal.pone.0074044

MacDonald, P. A., & Monchi, O. (2011). Differential effects of dopaminergic therapies on dorsal and ventral striatum in Parkinson's disease: implications for cognitive function. *Parkinsons Dis*, *2011*(8414), 572743–18. http://doi.org/10.4061/2011/572743

MacDonald, P. A., MacDonald, A. A., Seergobin, K. N., Tamjeedi, R., Ganjavi, H., Provost, J. S., & Monchi, O. (2011). The effect of dopamine therapy on ventral and dorsal striatum-mediated cognition in Parkinson's disease: support from functional MRI. *Brain*, *134*(Pt 5), 1447–1463. http://doi.org/10.1093/brain/awr075

McCoy, B., Jahfari, S., Engels, G., Knapen, T., & Theeuwes, J. (2019). Dopaminergic medication reduces striatal sensitivity to negative outcomes in Parkinson’s disease. *Brain*, 445528. http://doi.org/10.1101/445528

McDonald, R. J., & White, N. M. (2013). A triple dissociation of memory systems: Hippocampus, amygdala, and dorsal striatum. *Behav Neurosci*, *127*(6), 835–853. http://doi.org/10.1037/a0034883

Mehta, M. A., Swainson, R., Ogilvie, A. D., Sahakian, J., & Robbins, T. W. (2001). Improved short-term spatial memory but impaired reversal learning following the dopamine D(2) agonist bromocriptine in human volunteers. *Psychopharmacology (Berl)*, *159*(1), 10–20. http://doi.org/10.1007/s002130100851

Miller, E. K., & Cohen, J. D. (2003). An Integrative Theory of Prefrontal Cortex Function. *Dx.Doi.org*, *24*(1), 167–202.

Mollion, H., Ventre-Dominey, J., Dominey, P. F., & Broussolle, E. (2003). Dissociable effects of dopaminergic therapy on spatial versus non-spatial working memory in Parkinson's disease. *Neuropsychologia*, *41*(11), 1442–1451.

Nelson, H. E., & Willison, J. (1991). National Adult Reading Test (NART). *Int J Geriatr Psychiatry*, *7*(7), 533–533. http://doi.org/10.1002/gps.930070713

Olanow, W., Schapira, A. H., & Rascol, O. (2000). Continuous dopamine-receptor stimulation in early Parkinson's disease. *Trends Neurosci*, *23*(10 Suppl), S117–26. http://doi.org/10.1016/S1471-1931(00)00030-6

Onur, Ö. A., Piefke, M., Lie, C.-H., Thiel, C. M., & Fink, G. R. (2011). Modulatory effects of levodopa on cognitive control in young but not in older subjects: a pharmacological fMRI study. *J Cogn Neurosci*, *23*(10), 2797–2810. http://doi.org/10.1162/jocn.2011.21603

Pessiglione, M., Seymour, B., Flandin, G., Dolan, R. J., & Frith, C. D. (2006). Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature*, *442*(7106), 1042–1045. http://doi.org/10.1038/nature05051

Pizzagalli, D. A., Evins, A. E., Schetter, E. C., Frank, M. J., Pajtas, P. E., Santesso, D. L., & Culhane, M. (2008). Single dose of a dopamine agonist impairs reinforcement learning in humans: behavioral evidence from a laboratory-

based measure of reward responsiveness. *Psychopharmacology (Berl)*, *196*(2), 221–232. http://doi.org/10.1007/s00213-007-0957-y

Riba, J., Krämer, U. M., Heldmann, M., Richter, S., & Münte, T. F. (2008). Dopamine agonist increases risk taking but blunts reward-related brain activity. *PLoS One*, *3*(6), e2479. http://doi.org/10.1371/journal.pone.0002479

Rodriguez, P. F. (2009). Stimulus-outcome learnability differentially activates anterior cingulate and hippocampus at feedback processing. *Learn Mem*, *16*(5), 324–331. http://doi.org/10.1101/lm.1191609

Santesso, D. L., Evins, A. E., Frank, M. J., Schetter, E. C., Bogdan, R., & Pizzagalli, D. A. (2009). Single dose of a dopamine agonist impairs reinforcement learning in humans: evidence from event-related potentials and computational modeling of striatal-cortical function. *Human Brain Mapping*, *30*(7), 1963–1976. http://doi.org/10.1002/hbm.20642

Seo, Seo, M., Beigi, M., Jahanshahi, M., & Averbeck, B. B. (2010). Effects of dopamine medication on sequence learning with stochastic feedback in Parkinson's disease. *Front Syst Neurosci*, *4*. http://doi.org/10.3389/fnsys.2010.00036

Shellshear, L., MacDonald, A. D., Mahoney, J., Finch, E., McMahon, K., Silburn, P., et al. (2015). Levodopa enhances explicit new-word learning in healthy adults: a preliminary study. *Human Psychopharmacology*, *30*(5), 341–349. http://doi.org/10.1002/hup.2480

Shohamy, D., Shohamy, D., Myers, C. E., Myers, C. E., Grossman, S., Grossman, S., et al. (2005). The role of dopamine in cognitive sequence learning: evidence from Parkinson's disease. *Behavioural Brain Research*, *156*(2), 191–199. http://doi.org/10.1016/j.bbr.2004.05.023

Swainson, R., Rogers, R. D., Sahakian, B. J., Summers, B. A., Polkey, C. E., & Robbins, T. W. (2000). Probabilistic learning and reversal deficits in patients

with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. *Neuropsychologia*, *38*(5), 596–612. http://doi.org/10.1016/S0028-3932(99)00103-7

Tomer, R., Aharon-Peretz, J., & Tsitrinbaum, Z. (2007). Dopamine asymmetry interacts with medication to affect cognition in Parkinson's disease. *Neuropsychologia*, *45*(2), 357–367. http://doi.org/10.1016/j.neuropsychologia.2006.06.014

Torta, D. M. E., Castelli, L., Zibetti, M., Lopiano, L., & Geminiani, G. (2009). On the role of dopamine replacement therapy in decision-making, working memory, and reward in Parkinson's disease: does the therapy-dose matter? *Brain and Cognition*, *71*(2), 84–91. http://doi.org/10.1016/j.bandc.2009.04.003

Tremblay, P.-L., Bedard, M.-A., Langlois, D., Blanchet, P. J., Lemay, M., & Parent, M. (2010). Movement chunking during sequence learning is a dopamine-dependant process: a study conducted in Parkinson's disease. *Exp Brain Res*, *205*(3), 375–385. http://doi.org/10.1007/s00221-010-2372-6

Vaillancourt, D. E., Schonfeld, D., Kwak, Y., Bohnen, N. I., & Seidler, R. (2013). Dopamine overdose hypothesis: evidence and clinical implications. *Mov Disord*, *28*(14), 1920–1929. http://doi.org/10.1002/mds.25687

Vaillancourt, D. E., Spraker, M. B., Prodoehl, J., Zhou, X. J., & Little, D. M. (2012). Effects of aging on the ventral and dorsal substantia nigra using diffusion tensor imaging. *Neurobiology of Aging*, *33*(1), 35–42. http://doi.org/10.1016/j.neurobiolaging.2010.02.006

van Dyck, C. H., Seibyl, J. P., Malison, R. T., & Laruelle, M. (2002). Age-related decline in dopamine transporters: analysis of striatal subregions, nonlinear effects, and hemispheric asymmetries. *The American Journal of …*, *10*(1), 36–43. http://doi.org/10.1097/00019442-200201000-00005

van Eimeren, T., Ballanger, B., Pellecchia, G., Miyasaki, J. M., Lang, A. E., & Strafella, A. P. (2009). Dopamine agonists diminish value sensitivity of the orbitofrontal cortex: a trigger for pathological gambling in Parkinson's disease? *Neuropsychopharmacology*, *34*(13), 2758–2766. http://doi.org/10.1038/sj.npp.npp2009124

Vo, A., Hiebert, N. M., Seergobin, K. N., Solcz, S., Partridge, A., & MacDonald, P. A. (2014). Dopaminergic medication impairs feedback-based stimulus-response learning but not response selection in Parkinson's disease. *Frontiers in Human Neuroscience*, *8*(169), 784. http://doi.org/10.3389/fnhum.2014.00784

Vo, A., Seergobin, K. N., & MacDonald, P. A. (2017). Effects of levodopa on stimulus-response learning versus response selection in healthy young adults. *Behavioural Brain Research*, *317*, 553–561. http://doi.org/10.1016/j.bbr.2016.10.019

Vo, A., Seergobin, K. N., & MacDonald, P. A. (2018). Independent effects of age and levodopa on reversal learning in healthy volunteers. *Neurobiology of Aging*, *69*, 129–139. http://doi.org/10.1016/j.neurobiolaging.2018.05.014

Vo, A., Seergobin, K. N., Morrow, S. A., & MacDonald, P. A. (2016). Levodopa impairs probabilistic reversal learning in healthy young adults. *Psychopharmacology (Berl)*, *233*(14), 2753–2763. http://doi.org/10.1007/s00213-016-4322-x

Volkow, N. D., & Fowler, J. S. (2000). Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cereb Cortex*, *10*(3), 318–325.

Waldschmidt, J. G., & Ashby, F. G. (2011). Cortical and striatal contributions to automaticity in information-integration categorization. *NeuroImage*, *56*(3), 1791–1802. http://doi.org/10.1016/j.neuroimage.2011.02.011

Wickens, J. R., Budd, C. S., Hyland, B. I., & Arbuthnott, G. W. (2007). Striatal contributions to reward and decision making: making sense of regional

variations in a reiterated processing matrix. *Ann N Y Acad Sci*, *1104*(1), 192–212. http://doi.org/10.1196/annals.1390.016

Winkel, J., van Maanen, L., Ratcliff, R., van der Schaaf, M. E., van Schouwenburg, M. R., Cools, R., & Forstmann, B. U. (2012). Bromocriptine does not alter speed-accuracy tradeoff. *Frontiers in Neuroscience*, *6*, 126. http://doi.org/10.3389/fnins.2012.00126

World Medical, A. (2013). World Medical Association Declaration of Helsinki. *Jama*, *310*(20), 2191–2194. http://doi.org/10.1001/jama.2013.281053

Zhang, T., Zhang, L., Liang, Y., Siapas, A. G., Zhou, F.-M., & Dani, J. A. (2009). Dopamine signaling differences in the nucleus accumbens and dorsal striatum exploited by nicotine. *J Neurosci*, *29*(13), 4035–4043. http://doi.org/10.1523/JNEUROSCI.0261-09.2009

Chapter 5

General Discussion

5.1 Summary of findings

The aim of this dissertation was to systematically test the dopamine overdose hypothesis, which posits that the effects of dopaminergic therapy on a given brain region's function depends on baseline dopamine levels within that region. It is predicted that regions with higher dopamine levels are more susceptible to overdose by exogenous dopamine whereas those with lower dopamine levels stand to benefit from dopamine replacement. In Chapter 2, I examined the effects of dopaminergic therapy on stimulus-reward acquisition and reversal learning in groups of PD patients that differed in the severity of their disease and correspondingly in the extent of dopamine deficiency (Morrish, Sawle, & Brooks, 1996). Performance in the reversal learning paradigm has previously been shown to correlate with activity in VTA-innervated brain regions (Cools, Clark, Owen, & Robbins, 2002; Cools, Lewis, Clark, Barker, & Robbins, 2007). Further, lesions in VTA-innervated brain regions impair reversal learning (Fellows & Farah, 2003). Early- and late-stage PD patients were tested OFF relative to ON ½ their usual dose of dopaminergic medication and compared to healthy age-matched controls. Early-stage PD patients learned equally well to controls at baseline, but this learning was impaired when tested on dopaminergic therapy. At baseline, late-stage PD patients learned more poorly compared to early-stage PD and controls, reflecting a decline in initially-spared VTA-innervated brain function with disease progression. Interestingly, no improvement in reward learning was found after introducing ½ the dose of their dopaminergic therapy which was expected to more closely match the dopamine deficit in VTA-innervated brain regions in this subgroup. In Chapter 3, I tested the effects of a dopamine challenge on reward learning in groups of healthy volunteers differentially affected by age-related dopamine decline. In a placebo-controlled, double-blind, crossover design,

younger and older adults were compared following administration of L-dopa. I found age-related baseline learning impairments in older compared to younger adults. L-dopa worsened learning similarly in both age groups, however. Finally, in Chapter 4, I explored the effects of a dopamine challenge on learning and associated brain activity in a sample of healthy young volunteers who are presumed to have optimal endogenous dopamine levels. Participants performed a stimulus-response learning task with fMRI, following administration of either L-dopa or a placebo. I showed that learning was impaired and associated BOLD signal in VS was blunted following L-dopa administration, however DS-associated decision enactment was unaffected. Taken together, these studies provide partial support for the dopamine overdose hypothesis but suggest a less straightforward scenario than initially predicted by this existing theoretical framework. These nuances and complexities are discussed in further detail below.

5.2 The Dopamine Overdose Hypothesis

5.2.1 Role of endogenous dopamine levels

Our findings only support a partial role of endogenous dopamine levels in determining the effects of dopaminergic therapy on cognition in PD. The dopamine overdose hypothesis predicts that in PD, medication will improve functions of the severely dopamine-deplete DS but will impair those functions associated with less dopamine deficient, VTA-innervated brain regions. In line with this view, we found that early-stage PD patients, with the greatest asymmetry in dopamine deficiency between DS and VTA-innervated brain areas, learned more poorly on relative to off medication (see Chapter 2). Similarly, healthy volunteers with normal dopamine systems evidenced overdose effects on learning

following treatment with L-dopa compared to placebo (see Chapters 3 and 4). Results from fMRI revealed that medication-related learning impairments are correlated with reduced activity in VS (Chapter 4). Taken together, these findings seem to suggest that dopaminergic therapy impairs learning by overdosing disease spared, VTA-innervated brain regions.

At odds with the overdose account, however, is the finding that late-stage PD patients, who demonstrated baseline impairments thought to reflect a developing endogenous dopamine deficiency in VTA-innervated brain regions related to disease progression, did not show improvement with dopaminergic medication (see Chapter 2). Further, reward learning in older adults was impaired by a dopamine challenge to an extent similar to that observed in young adults, despite an age-related dopamine decline and observed baseline learning impairments (see Chapter 3). We also did not find expected worsening of DS-mediated decision-making following a dopamine challenge despite normal dopamine levels in healthy young adults (Chapter 4).

In late-stage PD patients, the dopamine overdose hypothesis would predict that baseline dopamine deficits would be redressed by dopaminergic therapy leading to an improvement in functions. In elderly controls, the dopamine overdose hypothesis would predict lesser impairment relative to young controls with administration of the same dose of dopaminergic therapy. One possible explanation for our findings is that (i) the dose of medication used to treat worsening DS-mediated motor symptoms in late-stage PD and (ii) the standard minimal effective dose of L-dopa commonly used in pharmacological manipulation studies in healthy volunteers, might continually overestimate the degree of dopamine deficiency in VTA-innervated brain regions, resulting in a persistent overdose effect. Such a persistent overdose in cohorts with baseline

dopamine deficits were predicted to be smaller than that observed in their respective comparison groups (i.e., early-stage PD and young healthy adults) according to the dopamine overdose hypothesis. Late-stage PD patients should show lesser overdose than early-stage PD patients in the ON ½ session, yet no such group difference was found in this session. In fact, we used a half dose of dopaminergic therapy for the ON session with the explicit goal of minimizing potential persistent overdose effects but continued to find null medication effects in this advanced PD group. That is, a dose of dopaminergic medication that should have been more in line with the degree of dopamine deficiency in VTA-innervated brain regions did not seem to remedy the baseline dopamine deficit. In contrast to early PD patients, late-stage PD patients did not evidence a dopamine overdose effect, with no worsening of reward learning in the ON ½ dose condition relative to the OFF session. This was not due to a floor effect as late-stage PD patients reached pre-defined learning criteria of 8 stimulus-reward reversal stages before a 200-trial deadline. Although learning performance in this group was evidently less efficient compared to early-stage PD and healthy controls, learning was nonetheless achieved successfully. Along the same lines, older adults were impaired by L-dopa to a similar degree as a younger control group, demonstrating independent effects of age-related dopamine decline and L-dopa. In young adults, dopamine levels are optimal across VS and DS, which should render them equally susceptible to overdose by a dopamine challenge. Although we observed the predicted L-dopa-associated impairment of learning and blunting of activity, our measure of DS-mediated decision enactment was unaffected, despite peak dopaminergic tone. In short, baseline dopamine levels do not fully predict the response to dopaminergic therapy in our experiments.

We propose an alternative model that might better reconcile discordant evidence

for the dopamine overdose hypothesis. Central to this proposal is the notion that different brain regions may be differentially adapted to benefit from exogenous dopamine. DS is comprised of medium spiny neurons with more numerous dendrites and spines, denser dopamine inputs, and greater DAT expression (Wickens, Budd, Hyland, & Arbuthnott, 2007). In contrast, VS consists of medium spiny neurons with fewer, more widely-spaced dendrites and spines, more sparse dopamine supply, and lower DAT concentrations (Wickens et al., 2007). Recall that DAT regulates synaptic dopamine through uptake (Jaber, Jones, Giros, & Caron, 1997). These physiological distinctions translate to unique response profiles between these regions. Whereas maximal receptor stimulation across a wide range of firing frequencies is observed in DS, more variable and graded responses are found in VS (Zhang et al., 2009). Such a binary response to dopamine in DS might tune this region to benefit from a broader range of dopamine concentrations, whereas the more finely-tuned dopamine signalling in VS would be more impaired by boluses of dopamine that could raise tonic and phasic levels of dopamine differentially at the synapse. If VS relies more on the phasic-to-tonic ratio of dopamine at the synapse for firing, it will be more sensitive to overdose. In this way, dopaminergic therapy might (i) interfere with normal baseline VS function but (ii) fail to rescue impaired VS function even with a disease- or aging-related dopamine deficit and when doses of medication are titrated in proportion to this deficit. This 'dopamine adaptation' model accounts not only for medication-associated worsening of VTA-innervated functions observed in early-stage PD and healthy young adults, but also explains the failure of dopamine therapy to rescue baseline impairments in late-stage PD patients and healthy older adults or to overdose DS-mediated functions in healthy young adults. Further research is needed, however, to provide more direct evidence for this alternative hypothesis to the longstanding dopamine overdose framework.

Floresco (2013) proposed that the classic inverted U-shaped function describing the role of dopamine in brain function is not a one-size-fits-all but rather a collection of functions. Too little or too much dopamine can have differing effects across a range of cognitive tasks and on their underlying neural mechanisms. Different cognitive processes might rely on unique patterns of dopaminergic activity, endogenous mechanisms for which exogenous dopamine may or may not be well suited to replicate. Therefore, using a unitary framework for understanding dopamine function across the brain might limit our ability to capture the complexities of dopaminergic therapy effects on cognition.

5.2.2 Role of endogenous dopamine regulation

In addition to testing the predictions offered by the dopamine overdose hypothesis, our findings also rule out a competing explanation of dopaminergic therapy effects in PD referred to as the 'dopamine denervation' hypothesis. Kulisevsky et al., (1996) reported that cognitive performance (a) was improved by L-dopa in unmedicated *de novo* PD patients, (b) did not benefit from L-dopa in those PD patients with stable medication responses, and (c) was impaired in those PD patients with 'wearing-off' fluctuating responses to medication. Unstable medication responses were taken to indicate greater loss of midbrain dopamine neurons in these patients. This dopamine denervation results in a decline in the mechanisms that regulate dopamine signalling, such as DAT-mediated synaptic clearance or pre-synaptic auto-receptor inhibition. Further, higher and chronic doses of L-dopa prescribed in fluctuating patients might enhance post-synaptic receptor sensitivity. The authors argued that medication-related impairments in those PD patients with greater dopamine denervation are therefore a consequence of reduced dopamine regulation and increased receptor sensitivity.

In stark contrast to the dopamine overdose framework, the dopamine denervation hypothesis predicts that dopaminergic therapy will worsen the functions of those brain regions more greatly affected by midbrain dopamine loss. This prediction is not supported by either the PD pathophysiology or an extensive literature examining medication effects in PD. Recall that in PD, DS is more severely dopamine-depleted than largely spared VTA-innervated brain regions (Fearnley & Lees, 1991; Kish, Shannak, & Hornykiewicz, 1988). That DS functions consistently improve whereas VTA-innervated brain functions are frequently worsened with dopaminergic therapy in early-stage PD (Cools, 2006; P. A. MacDonald & Monchi, 2011) is entirely at odds with this view.

Our findings further challenge the dopamine denervation hypothesis. As PD progresses, loss of midbrain dopamine neurons and DS-mediated motor symptoms further worsen, and initially-spared VTA-innervated brain functions decline (A. A. MacDonald et al., 2013; Morrish et al., 1996). Deleterious effects of dopaminergic therapy are predicted to be more severe in late-stage relative to early-stage PD. However, we found no such pattern (see Chapter 2). Early-stage PD, with less severe dopamine denervation, was most impaired by medication whereas late-stage PD neither improved nor worsened with medication. In addition, findings from dopamine challenge studies in healthy volunteers with normally functioning dopamine systems also refute this denervation model. Young healthy adults have optimal baseline dopamine levels, efficient regulation of synaptic dopamine, and no receptor sensitization from chronic exposure to dopaminergic therapy. Older adults undergo age-related declines in their dopamine systems and regulation mechanisms (Bordet et al., 1997; De Keyser, Ebinger, & Vauquelin, 1990; Frost et al., 1993; Ishibashi et al., 2009; P. L. McGeer, McGeer, & Suzuki, 1977; van Dyck, Seibyl, Malison, & Laruelle, 2002), which is

predicted to predispose this group to greater medication-associated impairments compared to younger adults. Our findings that both young and older adults were comparably worsened by medication (see Chapter 3 and 4) would not be predicted by the dopamine denervation hypothesis.

5.3 Limitations

5.3.1 Chapter 2 Limitations

An important limitation of this study, one which commonly plagues patient studies, is our relatively small PD patient sample size. This stemmed from challenges in recruiting patients who were eligible and willing to participate, particularly those patients with more advanced PD. Caution should be taken when interpreting the generalizability of our results and future research should strive to replicate our findings in a larger cohort. To support our significant findings based on frequentist statistics, we also provide complementary Bayesian analyses that are less susceptible to biases introduced by different sample sizes.

We used a cross-sectional design to examine the role of PD severity on cognitive function at baseline and response to dopaminergic therapy. Though a longitudinal design examining the same patient over time would better control for between-subject variability and PD heterogeneity, such an approach presents its own inherent problems. The obvious constraint to longitudinal research is time. Attrition of the original recruitment cohort is also expected over time, due to either voluntary withdrawal from the study or mortality.

We stratified our PD patients into early- and late-stage subgroups based on disease severity, as measured by scores on the UPDRS and classified based on criteria

proposed by others (Martinez Martin et al., 2015). This clinical measure of motor symptom severity is an indirect proxy for PD severity as it is thought to reflect the degree of dopamine deficiency in DS. Arguably, a more accurate measure of disease severity is provided by PET imaging of the dopamine system as has been done by others (Kwak, Bohnen, Müller, Dayalu, & Seidler, 2013). However, this strategy is hampered by its invasiveness and expense. Another approach to patient group classification is based on disease duration (A. A. MacDonald et al., 2013). There is no agreed upon cut-off to distinguish early- and late-stage PD. This criterion can differ from study to study. Also, disease duration does not necessarily account for the rate of disease progression in a given patient. For example, a patient with short disease duration might present with a fast progressing form of PD whereas another patient with a longer disease duration might progress more gradually. Hence, we opted to use UPDRS to segregate our patients into early and late-stage PD.

Finally, our hypothesis that dopamine overdose should be minimized when VTA-dopamine deficiency is better matched could have been better tested using a range of dopaminergic therapy within the same subject. If learning performance in late-stage PD patients was invariant irrespective of dose of dopamine therapy (i.e., ¼, vs. ½, vs. ¾ dose), our conclusion that VTA-innervated brain regions do not benefit from dopaminergic therapy would have been more strongly supported. As it stands, the possibility that ½ dose of the usual dopaminergic regimen still exceeds the degree of VTA-dopamine deficiency remains. In addition, functional neuroimaging that directly measures dopamine changes in relation to baseline performance and after the introduction of exogenous dopamine with PET, using dopamine ligands would provide more compelling evidence and greater confidence in our interpretation of these behavioural findings.

5.3.2 Chapter 3 Limitations

A limitation of this study is the lack of evidence from functional neuroimaging to directly test our predictions related to dopaminergic therapy effects on specific regional brain functions. Our experiment is based on previous research demonstrating that a) stimulus-reward reversal learning is mediated by VTA-innervated brain regions, b) dopamine declines in normal healthy aging, and c) dopaminergic therapy overdoses less dopamine deficient brain regions. We found that learning was impaired in older compared to younger adults, and administration of L-dopa impaired learning in both groups similarly. Without support from brain imaging, however, we can only infer that age- and medication-related worsening of reversal learning owes to disruption of activity in VTA-innervated brain regions as predicted by the dopamine overdose hypothesis. To address this limitation and provide more direct support, we conducted an L-dopa challenge study in healthy young adults using fMRI in Chapter 4.

5.3.3 Chapter 4 Limitations

In this study, we used a between-subject design in which participants completed a single session on either L-dopa or placebo through random group assignment. This approach was motivated by our previous findings of clear practice effects in repeated-measure crossover studies (Vo, Seergobin, & MacDonald, 2018; Vo, Seergobin, Morrow, & MacDonald, 2016) that, depending on the order of testing, might work in the opposite direction of treatment effects across experimental sessions. One potential limitation of this between-subject design, however, is the potential for group differences owing to sampling bias rather than the independent variable of interest. We rule out this possibility by (i) sampling from a relatively homogeneous population of healthy undergraduate students, (ii) measuring and comparing groups on control measures (e.g., age, education level,

estimated verbal IQ, physiological changes, and subjective alertness reports) for which no significant differences were found, and (iii) equating L-dopa absorption across individuals by having participants adhere to a diet of light, non-protein containing meals on the day of testing.

Unlike in our previous studies, we did not include an explicit test phases to isolate stimulus-specific response decisions from feedback-based learning. This limited conclusions regarding the specificity of our observed medication effects on learning processes. However, inspection of the learning curves showed that L-dopa impaired performance early in the task, when learning demands were greatest. In the final blocks, when performance relied predominantly on response selections informed by prior learning, we did not observe any between-group differences in either accuracy or RTs. Bayesian analyses revealed evidence in favour of this null effect. This pattern is in keeping with previously reported null effects of exogenous dopamine on decision-making in healthy young adults when a separate test phase was performed to more clearly isolate stimulus-response decisions from learning processes (Gallant, Vo, Seergobin, & MacDonald, 2016; Vo, Seergobin, & MacDonald, 2017).

It is important to note that fMRI provides an indirect measure of brain activity by detecting localized changes in blood flow in response to stimuli, via the BOLD signal (Glover, 2011; Kwong et al., 1992; Ogawa, Lee, Kay, & Tank, 1990). Further, pharmacological MRI does not directly measure the specific receptor binding and molecular action of a drug, rather changes in the BOLD signal between experimental and placebo groups are assumed to reflect changes in dopamine signaling (Wandschneider & Koepp, 2016). We therefore interpreted our findings with care, considering the known pharmacodynamics of L-dopa in the brain (Contin & Martinelli, 2010). A more direct measure of neurochemical activity in

the brain is achieved with PET imaging, which uses radioligands that bind to specific classes of receptors. Relating behavioural and fMRI patterns to specific measures of endogenous dopamine signalling would greatly inform our understanding of the present findings.

5.4 Future directions

We investigated the dopamine overdose hypothesis by testing the effects of dopaminergic therapy in different cohorts recruited based on circumscribed dopamine deficiencies. Endogenous dopamine levels were indirectly manipulated by examining PD patients at different disease stages and healthy adults at different ages, and directly modulated by dopamine replacement therapy in PD or an L-dopa challenge in healthy volunteers. Dopamine levels in the human brain can also be manipulated via other approaches. Polymorphisms in the genes that govern the expression of proteins and receptors involved in regulating dopamine transmission might have important consequences on an individual's response to dopaminergic therapy. For example, the SLC6A3 gene codes for the DAT (Sano, Kondoh, Kakimoto, & Kondo, 1993). Compared to wildtype, carriers of the common 9R polymorphism express higher DAT concentrations and therefore lower baseline dopamine levels. Whether this polymorphism interacts with PD or aging to modulate the effects of dopaminergic therapy is not yet clear.

We used an L-dopa challenge in our studies with healthy volunteers to provide an analogous model of dopaminergic therapy and withdrawal in PD. The dopaminergic system can be pharmacologically manipulated by other

neurochemicals that block dopamine activity or dietary depletion of tyrosine/phenylalanine to effectively lower global dopamine synthesis. For example, sulpiride is a dopamine receptor antagonist that has been shown to attenuate adaptive prediction error coding in the midbrain and VS, impairing learning performance, in healthy subjects with fMRI (Diederen, Spencer, Vestergaard, Fletcher, & Schultz, 2016). Dietary dopamine depletion in healthy volunteers biases reversal learning performance towards punishment- relative to reward-based learning (Robinson, Standing, DeVito, Cools, & Sahakian, 2010). In each, manipulations that lower basal dopamine activity produces behavioural effects similar to that observed in PD patients at baseline. Future investigations using these manipulations to examine whether the produced baseline impairments can be redressed by L-dopa administration would provide an appealing test of the dopamine overdose hypothesis.

In order to better link behavioural, functional, and neurochemical processes, future research should aim to combine functional MRI with PET imaging. FMRI would allow measurement of brain activity correlated with behavioural in an event-related manner. PET using radioligands targeting the dopaminergic system, via dopamine receptors or DATs, would inform our assumptions regarding baseline dopamine levels in early- and late-stage PD and with aging (Cools et al., 2009; Lawrence, Brooks, & Whone, 2013). It would also allow more direct localization and measurement of endogenous dopamine function and exogenous dopamine action in the brain. Relating these imaging patterns to behavioural phenomena and BOLD signals would provide a powerful test of the hypotheses investigated in the present thesis.

5.5 Significance

The prevalence of PD is expected to rise given increasing life expectancies (Dorsey et al., 2007). Although effective pharmacological, surgical, and rehabilitative interventions exist for motor symptoms, we continue to lack proper treatments and strategies for managing complex cognitive symptoms that are prevalent in PD. Cognitive impairment disproportionately impacts the quality of life, especially at later disease stages, and is a major predictor of institutionalization (Aarsland, Larsen, & Tandberg, 2000; Aarsland, Zaccai, & Brayne, 2005). This research contributes to an increasing awareness and understanding of the causes of cognitive decline in PD, which will help guide future care and management of these complex symptoms. Clarifying the effects of dopaminergic therapy on cognition and their neural underpinnings will inform treatment strategies in the clinic. Clinicians will be prompted to factor in cognitive profile and disease stage in addition to motor symptomatology when prescribing treatment, striking a better balance between enhancing motor function and minimizing cognitive dysfunction.

5.6 Conclusion

In conclusion, this dissertation sought to critically investigate the dopamine overdose hypothesis. Across a series of psychopharmacological experiments in PD and healthy volunteers, I tested the notion that whether dopaminergic therapy improves or impairs a given regional brain function depends on the baseline dopamine levels within that region. In Chapter 2, I found that late-stage PD patients showed a baseline impairment in learning—a function frequently shown

to engage and depend on VTA-innervated brain regions—compared to early-stage PD patients and controls. Whereas dopaminergic medication worsened learning in early-stage PD, it neither improved nor worsened learning in later-staged PD patients, a finding not entirely in support of the dopamine overdose hypothesis. In Chapter 3, I showed age-related baseline learning impairments in older compared to younger adults. L-dopa worsened learning similarly in both age groups. In Chapter 4, I demonstrated that learning is impaired and associated BOLD signal in VS is blunted following L-dopa administration in healthy young adults. Decision-related responses in DS were unaffected, however. Collectively, my results are only partially explained by the straightforward predictions of the dopamine overdose hypothesis and the emphasized dependency on baseline dopamine levels. I offer a caveat to this model proposing that different brain regions may be differentially adapted to benefit from exogenous dopamine, reconciling discrepant patterns of observed medication effects from the studies here and the literature at large. In the end, I argue that although the dopamine overdose hypothesis has guided the study of cognition in PD for two decades, the effects of dopaminergic therapy on cognition are far more complex and not as tidy as initially implied.

5.7 References

Aarsland, D., Larsen, J. P., & Tandberg, E. (2000). Predictors of nursing home placement in Parkinson's disease: A population-based, prospective study. *Journal of the American …*, *48*(8), 938–942. http://doi.org/10.1111/j.1532-5415.2000.tb06891.x

Aarsland, D., Zaccai, J., & Brayne, C. (2005). A systematic review of prevalence studies of dementia in Parkinson's disease. *Movement Disorders*, *20*(10), 1255–1263. http://doi.org/10.1002/mds.20527

Bordet, R., Bordet, R., Ridray, S., Ridray, S., Carboni, S., Carboni, S., et al. (1997). Induction of dopamine D3 receptor expression as a mechanism of behavioral sensitization to levodopa. *Proceedings of the National Academy of Sciences*, *94*(7), 3363–3367. http://doi.org/10.1073/pnas.94.7.3363

Contin, M., & Martinelli, P. (2010). Pharmacokinetics of levodopa. *J Neurol*, *257*(Suppl 2), S253–61. http://doi.org/10.1007/s00415-010-5728-8

Cools, R. (2006). Dopaminergic modulation of cognitive function-implications for l-DOPA treatment in Parkinson's disease. *Neurosci Biobehav Rev*, *30*(1), 1–23. http://doi.org/10.1016/j.neubiorev.2005.03.024

Cools, R., Clark, L., Owen, A. M., & Robbins, T. W. (2002). Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging. *J Neurosci*, *22*(11), 4563–4567.

Cools, R., Frank, M. J., Gibbs, S. E., Miyakawa, A., Jagust, W., & D'Esposito, M. (2009). Striatal dopamine predicts outcome-specific reversal learning and its sensitivity to dopaminergic drug administration. *J Neurosci*, *29*(5), 1538–1543. http://doi.org/10.1523/JNEUROSCI.4467-08.2009

Cools, R., Lewis, S. J. G., Clark, L., Barker, R. A., & Robbins, T. W. (2007). L-DOPA disrupts activity in the nucleus accumbens during reversal learning in Parkinson's disease. *Neuropsychopharmacology*, *32*(1), 180–189. http://doi.org/10.1038/sj.npp.1301153

De Keyser, J., Ebinger, G., & Vauquelin, G. (1990). Age-related changes in the human nigrostriatal dopaminergic system. *Ann Neurol*, *27*(2), 157–161. http://doi.org/10.1002/ana.410270210

Diederen, K. M. J., Spencer, T., Vestergaard, M. D., Fletcher, P. C., & Schultz, W. (2016). Adaptive Prediction Error Coding in the Human Midbrain and Striatum Facilitates Behavioral Adaptation and Learning Efficiency. *Neuron*, *90*(5), 1127–1138. http://doi.org/10.1016/j.neuron.2016.04.019

Dorsey, E. R., Constantinescu, R., Thompson, J. P., Biglan, K. M., Holloway, R. G., Kieburtz, K., et al. (2007). Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology*, *68*(5), 384–386. http://doi.org/10.1212/01.wnl.0000247740.47667.03

Fearnley, J. M., & Lees, A. J. (1991). Ageing and parkinson's disease: substantia nigra regional selectivity. *Brain*, *114*(5), 2283–2301. http://doi.org/10.1093/brain/114.5.2283

Fellows, L. K., & Farah, M. J. (2003). Ventromedial frontal cortex mediates affective shifting in humans: evidence from a reversal learning paradigm. *Brain*, *126*(Pt 8), 1830–1837. http://doi.org/10.1093/brain/awg180

Floresco, S. B. (2013). Prefrontal dopamine and behavioral flexibility: shifting from an "inverted-U" toward a family of functions. *Frontiers in Neuroscience*, *7*, 62. http://doi.org/10.3389/fnins.2013.00062

Frost, J. J., Rosier, A. J., Reich, S. G., Smith, J. S., Ehlers, M. D., Snyder, S. H., et al. (1993). Positron emission tomographic imaging of the dopamine transporter with 11C-WIN 35,428 reveals marked declines in mild Parkinson's disease. *Ann Neurol*, *34*(3), 423–431. http://doi.org/10.1002/ana.410340331

Gallant, H., Vo, A., Seergobin, K. N., & MacDonald, P. A. (2016). Pramipexole Impairs Stimulus-Response Learning in Healthy Young Adults. *Frontiers in Neuroscience*, *10*(784), 390. http://doi.org/10.3389/fnins.2016.00374

Glover, G. H. (2011). Overview of functional magnetic resonance imaging. *Neurosurgery Clinics of North America*, *22*(2), 133–9– vii. http://doi.org/10.1016/j.nec.2010.11.001

Ishibashi, K., Ishii, K., Oda, K., Kawasaki, K., Mizusawa, H., & Ishiwata, K. (2009). Regional analysis of age-related decline in dopamine transporters and dopamine D2-like receptors in human striatum. *Synapse*, *63*(4), 282–290. http://doi.org/10.1002/syn.20603

Jaber, M., Jones, S., Giros, B., & Caron, M. G. (1997). The dopamine transporter: a crucial component regulating dopamine transmission. *Movement Disorders*, *12*(5), 629–633. http://doi.org/10.1002/mds.870120502

Kish, S. J., Shannak, K., & Hornykiewicz, O. (1988). Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. *N Engl J Med*, *318*(14), 876–880. http://doi.org/10.1056/NEJM198804073181402

Kulisevsky, J., Avila, A., Barbanoj, M., Antonijoan, R., Berthier, M. L., & Gironell, A. (1996). Acute effects of levodopa on neuropsychological performance in stable and fluctuating Parkinson's disease patients at different levodopa plasma levels. *Brain*, *119 (Pt 6)*(6), 2121–2132. http://doi.org/10.1093/brain/119.6.2121

Kwak, Y., Bohnen, N. I., Müller, M. L. T. M., Dayalu, P., & Seidler, R. D. (2013). Striatal denervation pattern predicts levodopa effects on sequence learning in Parkinson's disease. *Journal of Motor Behavior*, *45*(5), 423–429. http://doi.org/10.1080/00222895.2013.817380

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, B. P., et al. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Sciences*, *89*(12), 5675–5679. http://doi.org/10.1073/pnas.89.12.5675

Lawrence, A. D., Brooks, D. J., & Whone, A. L. (2013). Ventral striatal dopamine synthesis capacity predicts financial extravagance in Parkinson's disease. *Front Psychol*, *4*, 90. http://doi.org/10.3389/fpsyg.2013.00090

MacDonald, A. A., Monchi, O., Seergobin, K. N., Ganjavi, H., Tamjeedi, R., & MacDonald, P. A. (2013). Parkinson's disease duration determines effect of dopaminergic therapy on ventral striatum function. *Mov Disord*, *28*(2), 153–160. http://doi.org/10.1002/mds.25152

MacDonald, P. A., & Monchi, O. (2011). Differential effects of dopaminergic therapies on dorsal and ventral striatum in Parkinson's disease: implications for cognitive function. *Parkinsons Dis*, *2011*(8414), 572743–18. http://doi.org/10.4061/2011/572743

Martinez Martin, P., Rodríguez-Blázquez, C., Mario Alvarez, Arakaki, T., Arillo, V. C., Chaná, P., et al. (2015). Parkinson"s disease severity levels and MDS-Unified Parkinson"s Disease Rating Scale. *Parkinsonism Relat Disord*, *21*(1), 50–54. http://doi.org/10.1016/j.parkreldis.2014.10.026

McGeer, P. L., McGeer, E. G., & Suzuki, J. S. (1977). Aging and Extrapyramidal Function. *Arch Neurol*, *34*(1), 33–35. http://doi.org/10.1001/archneur.1977.00500130053010

Morrish, P. K., Sawle, G. V., & Brooks, D. J. (1996). An [18F]dopa-PET and clinical study of the rate of progression in Parkinson's disease. *Brain*, *119 (Pt 2)*(2), 585–591. http://doi.org/10.1093/brain/119.2.585

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences*, *87*(24), 9868–9872. http://doi.org/10.1073/pnas.87.24.9868

Robinson, O. J., Standing, H. R., DeVito, E. E., Cools, R., & Sahakian, B. J. (2010). Dopamine precursor depletion improves punishment prediction during reversal learning in healthy females but not males. *Psychopharmacology (Berl)*, *211*(2), 187–195. http://doi.org/10.1007/s00213-010-1880-1

Sano, A., Kondoh, K., Kakimoto, Y., & Kondo, I. (1993). A 40-nucleotide repeat polymorphism in the human dopamine transporter gene. *Human Genetics*, *91*(4), 405–406. http://doi.org/10.1007/BF00217369

van Dyck, C. H., Seibyl, J. P., Malison, R. T., & Laruelle, M. (2002). Age-related decline in dopamine transporters: analysis of striatal subregions, nonlinear effects, and hemispheric asymmetries. *The American Journal of …*, *10*(1), 36–43. http://doi.org/10.1097/00019442-200201000-00005

Vo, A., Seergobin, K. N., & MacDonald, P. A. (2017). Effects of levodopa on stimulus-response learning versus response selection in healthy young adults. *Behavioural Brain Research*, *317*, 553–561. http://doi.org/10.1016/j.bbr.2016.10.019

Vo, A., Seergobin, K. N., & MacDonald, P. A. (2018). Independent effects of age and levodopa on reversal learning in healthy volunteers. *Neurobiology of Aging*, *69*, 129–139. http://doi.org/10.1016/j.neurobiolaging.2018.05.014

Vo, A., Seergobin, K. N., Morrow, S. A., & MacDonald, P. A. (2016). Levodopa impairs probabilistic reversal learning in healthy young adults. *Psychopharmacology (Berl)*, *233*(14), 2753–2763. http://doi.org/10.1007/s00213-016-4322-x

Wandschneider, B., & Koepp, M. J. (2016). Pharmaco fMRI: Determining the functional anatomy of the effects of medication. *NeuroImage: Clinical*, *12*, 691–697. http://doi.org/10.1016/j.nicl.2016.10.002

Wickens, J. R., Budd, C. S., Hyland, B. I., & Arbuthnott, G. W. (2007). Striatal contributions to reward and decision making: making sense of regional variations in a reiterated processing matrix. *Ann N Y Acad Sci*, *1104*(1), 192–212. http://doi.org/10.1196/annals.1390.016

Zhang, T., Zhang, L., Liang, Y., Siapas, A. G., Zhou, F.-M., & Dani, J. A. (2009). Dopamine signaling differences in the nucleus accumbens and dorsal

striatum exploited by nicotine. *J Neurosci*, *29*(13), 4035–4043. http://doi.org/10.1523/JNEUROSCI.0261-09.2009

Western Research

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

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).

Andrew Vo

Education

2014-	Doctor of Philosophy – Psychology University of Western Ontario in London, Canada
2009-2013	Bachelor of Science (Honors) – Psychology & Physiology University of Western Ontario in London, Canada

Awards & Distinctions

2018	Academic Achievement Scholarship, PSAC 610
2018	Ontario Volunteer Service Award
2017	Best Poster, Clinical Neurological Sciences Research Day
2017-2018	Graduate Research Award, Parkinson Society Southwestern Ontario
2016-2018	NSERC Postgraduate Scholarship
2016-2018	Western Doctoral Excellence Research Award
2016-2017	Ontario Graduate Scholarship (declined)
2017	Academic Achievement Scholarship, PSAC 610
2015-2016	Ontario Graduate Scholarship
2015	University Finalist, 3 Minute Thesis
2013	Top 2% Abstract, World Parkinson Congress

Publications

Khan, A.R., Hiebert, N.M., **Vo, A.**, Wang, B.T., Owen, A.M., Seergobin, K.N., & MacDonald, P.A. (2019). Biomarkers of Parkinson's disease: Striatal sub-regional structural morphometry and diffusion MRI. *NeuroImage: Clinical*, *21*, 101597.

Vo, A., Seergobin, K.N., & MacDonald, P.A. (2018). Independent effects of age and levodopa on reversal learning in healthy volunteers. *Neurobiology of Aging, 69*, 129-139.

Vo, A., Ganjavi, H., & MacDonald, P.A. (2018) Levodopa has mood-enhancing effects in healthy elderly adults. *International Journal of Geriatric Psychiatry, 33*(4), 674–675.

Vo, A., Seergobin, K.N., & MacDonald, P.A. (2017) Effects of levodopa on stimulus-response learning versus response selection in healthy young adults. *Behavioural Brain Research, 317*, 553-561.

Vo, A., Seergobin, K.N., Morrow, S.A., & MacDonald, P.A. (2016) Levodopa impairs stimulus-reward learning and reversal learning in healthy young adults. *Psychopharmacology, 233*(14), 2753-2763.

Gallant, H.*, **Vo, A.***, Seergobin, K.N., & MacDonald, P.A. (2016) Pramipexole impairs

stimulus-response learning in healthy young adults. *Frontiers in Neuroscience, 10*, 374. *equal contributions

Yang, X., 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.

Hiebert, N.M., Seergobin, K.N., **Vo, A.**, Ganjavi, H., & MacDonald, P.A. (2014). Dopaminergic therapy affects learning and impulsivity in Parkinson's disease. *Annals of Clinical and Translational Neurology, 1*(10), 833-843.

Vo, A., Hiebert, N.M., Seergobin, K.N., Solcz, S., Partridge, A., & MacDonald, P.A. (2014). Dopaminergic medication impairs feedback-based stimulus-response learning but not response selection in Parkinson's disease. *Frontiers in Human Neuroscience, 8*, 784.

Hiebert, N.M., **Vo, A.**, Seergobin, K.N., Hampshire, A., Owen, A.M., & MacDonald, P.A. (2014). Striatum in stimulus-response learning via feedback and in decision making. *NeuroImage, 101*, 448-457.

Peer-Reviewed Abstracts

MacDonald, P.A., Hiebert, N.M., Kahn, A.R., **Vo, A.**, Wang, B.T., Owen, A.M., & MacDonald, P.A. (2018) Structural biomarkers of Parkinson's disease: Striatal sub-regional structural morphometry and diffusion MRI. *Annals of Neurology,* 84, S100-S101.

Vo, A., Seergobin, K.N., & MacDonald, P.A. (2016) Differential effects of levodopa on facilitation versus interference in healthy older adults. *Canadian Journal of Experimental Psychology-Revue Canadienne de Psychologie Experimentale, 70*(4), 423.

Vo, A., Seergobin, K.N., Jiang, S., & MacDonald, P.A. (2015) Effects of levodopa on cognition in healthy volunteers: Implications for Parkinson's disease. *Canadian Journal of Neurological Sciences, 42*, Supplement 1, S17.

Vo, A., Hiebert, N.M., Seergobin, K.N., Solcz, S., Partridge, A., & MacDonald, P.A. (2014). Dopaminergic medication impairs learning but not decision making in Parkinson's disease. *Canadian Journal of Experimental Psychology-Revue Canadienne de Psychologie Experimentale, 68*(4), 271.

MacDonald, P.A., **Vo, A.**, Hiebert, N.M., & Seergobin, K.N. (2014) Learning and decision making in Parkinson's disease. *Movement Disorders, 29*, Supplement 1, S614.

MacDonald, P.A., Hiebert, N.M., **Vo, A.**, Hampshire, A., Owen, A.M., Ganjavi, H., & Seergobin, K.N. (2014). Understanding the role of striatum in learning and decision-making using fMRI. *Movement Disorders, 29*, Supplement 1, S614.

Vo, A., Hiebert, N.M., Seergobin, K.N., Solcz, S., Owen, A.M., Partridge, A., &

MacDonald, P.A. (2013). Recasting the role of dorsal striatum in learning and decision-making: A study in Parkinson's disease. *Journal of Parkinson's Disease, 3*, Supplement 1, S236.

Hiebert, N.M., **Vo, A.**, Seergobin, K.N., Hampshire, A., Owen, A.M., & MacDonald, P.A. (2013). Dorsal and ventral striatum in stimulus-response learning via feedback and decision-making. *Journal of Parkinson's Disease, 3*, Supplement 1, S234.

Platform Presentations

Khan, A.R., Hiebert, N.M., **Vo, A.**, Wang, B.T., Owen, A.M., Seergobin, K.N., & MacDonald, P.A. Biomarkers of Parkinson's disease: Striatal sub-regional structural morphometry and diffusion MRI. Platform presentation at the Clinical Neurological Sciences Departmental Research Day, London, Canada, April 2017.

Vo, A., Seergobin, K.N., Jiang, S., & MacDonald, P.A. Effects of levodopa on ventral striatum-mediated cognition in healthy volunteers: Implications for Parkinson's disease. Platform presentation at the Clinical Neurological Sciences Departmental Research Day, London, Canada, March 2015.

Vo, A., Hiebert, N.M., Seergobin, K.N., Solcz, S., Partridge, A., & MacDonald, P.A. Dopaminergic medication impairs learning but not decision making in Parkinson's disease. Platform presentation at the Clinical Neurological Sciences Departmental Research Day, London, Canada, March 2014.

Vo, A., Hiebert N.M., Seergobin, K.N., Hampshire, A., Owen, A.M., MacDonald, P.A. Recasting the role of dorsal striatum in learning and decision-making: A study in Parkinson's disease. Featured "Hot Topics" talk at the 3rd World Parkinson Congress, Montréal, Canada, October 2013.

Poster Presentations

MacDonald, P.A., Hiebert, N.M., Khan, A.R., Naci, L., **Vo, A.**, Wang, B.T., Owen, A.M., & Seergobin, K.N. Structural and functional biomarkers of Parkinson's disease: Using structural and functional neuroimaging to identify the presence and severity of Parkinson's disease. Poster presented at the 48th annual meeting of the Society for Neuroscience, San Diego, USA, November 2018.

Khan, A.R., Hiebert, N.M., **Vo, A.**, Wang, B.T., Owen, A.M., Seergobin, K.N., & MacDonald, P.A. Biomarkers of Parkinson's disease: Striatal sub-regional structural morphometry and diffusion MRI. Poster presented at the 12th annual Canadian Association for Neuroscience, Vancouver, Canada, May 2018.

Vo, A., Seergobin, K.N., & MacDonald, P.A. Independent effects of age and levodopa on reversal learning in healthy volunteers. Poster presented at the 12th annual

Canadian Association for Neuroscience, Vancouver, Canada, May 2018.

Vo, A., Seergobin, K.N., & MacDonald, P.A. Aging and levodopa independently disrupt reversal learning in healthy volunteers. Poster presented at the Clinical Neurological Sciences Departmental Research Day, London, Canada, April 2017.

MacDonald, P.A., **Vo, A.**, & Seergobin, K.N. Levodopa impairs learning in healthy young adults: Implications for Levocarb in Parkinson's disease. Poster presented at the 20th International Congress of Parkinson's Disease and Movement Disorders, Berlin, Germany, June 2016.

MacDonald, P.A., **Vo, A.**, & Seergobin, K.N. Levodopa impairs learning in healthy young adults: Implications for Levocarb in Parkinson's disease. Poster presented at the 22nd Annual Meeting of the Organization for Human Brain Mapping, Geneva, Switzerland, June 2016.

Vo, A., Seergobin, K.N., & MacDonald, P.A. Levodopa impairs learning in healthy young adults: Implications for Levocarb in Parkinson's disease. Poster presented at the 10th annual Canadian Association for Neuroscience, Toronto, Canada, June 2016.

Vo, A., Seergobin, K.N., & MacDonald, P.A. Levodopa impairs reward learning in healthy young adults: Implications for Parkinson's disease. Poster presented at the Inaugural Brain and Mind Institute Symposium, London, Canada, September 2015.

Vo, A., Seergobin, K.N., Jiang, S., & MacDonald, P.A. Levodopa impairs reversal learning in healthy young adults. Poster presented at the 35th annual meeting of the Southern Ontario Neuroscience Association, Hamilton, Canada, May 2015.

Vo, A., Seergobin, K.N., Jiang, S., & MacDonald, P.A. Effects of levodopa on cognition in healthy young adults. Poster presented at the 44th annual meeting of the Lake Ontario Visionary Establishment, Niagara Falls, Canada, February 2015.

Vo, A., Hiebert, N.M., Seergobin, K.N., Solcz, S., Partridge, A., & MacDonald, P.A. Dopaminergic medication impairs learning but not decision making in Parkinson's disease. Poster presented at the 34th annual meeting of the Southern Ontario Neuroscience Association, London, Canada, May 2014.

Vo, A., Hiebert, N.M., Seergobin, K.N., Solcz, S., Partridge, A., & MacDonald, P.A. Dopaminergic medication impairs learning but not decision making in Parkinson's disease. Poster presented at the 43rd annual meeting of the Lake Ontario Visionary Establishment, Niagara Falls, Canada, February 2014.