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Is Online Motor Control Really Impaired In Parkinson's Disease?

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Abstract

Patients with Parkinson's disease (PD) are thought to be selectively impaired in consciously-mediated online automatic motor control, whereas the ability to perform subconscious online adjustments remains intact. This present study evaluates the hypothesis that the previously alleged deficits in online motor control in PD are not due to the consciousness of the correction, but rather are attributable to aspects of the prior experimental designs disproportionately penalizing patients for PD-related bradykinesia. Here, we implemented a modified traditional double-step paradigm to investigate consciously-mediated online motor control in PD, in a manner that would be unconfounded by disease-related bradykinesia. Further, we investigated the effects of dopamine-replacement therapy on performance. We found that PD patients (n=12) and healthy-matched controls (n=12) were equal in performing automatic online corrections whether or not these corrections were consciously perceived, and their performance was unaffected by dopaminergic therapy. These findings inform our understanding of automatic motor control in PD.

Keywords

Online Motor Control; Parkinson's Disease; Automaticity; Perception; Bradykinesia;
Dopaminergic Therapy

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Table of Contents

Abstract.....	ii
Acknowledgements.....	iii
Table of Contents.....	iv
List of Tables.....	vii
List of Figures.....	viii
List of Appendices.....	ix
List of Abbreviations.....	x
Chapter 1 Introduction.....	1
1.1 Summary of Online Motor Control.....	1
1.1.2 Psychophysics of Online Corrections.....	1
1.1.3 Automaticity of Online Corrections – ‘The Automatic Pilot’.....	3
1.1.4 Neural Substrates Involved in Online Motor Control.....	7
1.2 Parkinson’s Disease.....	11
1.2.1 Parkinson’s Disease Pathology and Aetiology.....	11
1.2.2 Symptomology of Parkinson’s Disease.....	14
1.2.3 Symptomatic Treatment of Parkinson’s Disease.....	15
1.2.4 Online Motor Control in Parkinson’s Disease.....	16
1.3 The Current Study.....	20

1.3.1 Rationale for Current Study.....	20
1.3.2 Objective.....	21
1.3.3 Predictions.....	22
Chapter 2 Methods.....	22
2.1 Participants.....	22
2.2. General Design.....	26
2.3 Apparatus and Stimuli.....	26
2.4 Procedure.....	28
2.4.1 Target Displacement Judgment Task.....	32
2.4.2 Double-Step Pointing Task.....	32
2.5 Data Processing and Analyses.....	34
2.5.1 Target Displacement Judgment.....	34
2.5.2 Double-Step Pointing.....	34
Chapter 3 Results.....	37
3.1 Target Displacement Judgment Task: Perceptual Awareness Results.....	37
3.2 Saccade Reaction Time and Target Jump Timing Results.....	39
3.3 Limb Movement Characteristics: Stationary Trials.....	40
3.4 Limb Movement Characteristics: Jumps Trials.....	41
Chapter 4 Discussion.....	49

4.1 General Summary of Results.....	49
4.2 Online Motor Control in Healthy Ageing and in Parkinson's Disease.....	51
4.3 Conscious Awareness and Online Corrections.....	54
4.4 Role of Striatum/Basal Ganglia in Movement Generation and Online Motor Control.....	56
4.5 Automaticity in Parkinson's Disease.....	60
4.6 Limitations and Future Directions.....	61
4.7 Conclusions.....	63
References.....	65
Appendices.....	90
Curriculum Vitae.....	113

List of Tables

Table 1: Demographic, clinical information and screening cognitive and affective measures for participants with PD and controls.....	25
Table 2: Detailed description of each condition type.....	31

List of Figures

Figure 1: Model of normal basal ganglia circuitry.....	12
Figure 2: Schematic of a hypothetical timeline for target displacement at hand movement onset.....	20
Figure 3: Schematic of experimental setup.....	28
Figure 4: Schematic of visual display for an example double-step trial.....	30
Figure 5: Timeline of trial events.....	33
Figure 6: Percentage of correct responses in target jump judgment two-alternative forced choice task	38
Figure 7: Primary saccade reaction time in response to initial target appearance.....	40
Figure 8: Primary hand reaction time in response to initial target appearance.....	43
Figure 9: Movement duration difference scores compared to zero.	44
Figure 10: Mean trajectory plots for reaches originally directed to T3.....	45
Figure 11: Mean trajectory plots for reaches originally directed to T5.....	46

List of Appendices

Appendix A: Participant Inclusion/Exclusion Criteria.....	90
Appendix B: Consent Form.....	92
Appendix C: Starkstein Apathy Scale.....	99
Appendix D: Montreal Cognitive Assessment.....	100
Appendix E: Montreal Cognitive Assessment Evaluation Scale.....	101
Appendix F: Bond & Lader Mood Scale.....	105
Appendix G: ANART.....	106
Appendix H: Health & Demographic Questionnaire.....	107
Appendix I: Levodopa Screening Questionnaire.....	109
Appendix J: UPDRS Protocol.....	110
Appendix K: Ethics Approval.....	112

List of Abbreviations

fMRI	Functional magnetic resonance imaging
FP	Fixation point
GABA	Gamma-aminobutyric acid
GPe	External globus pallidus
GPi	Internal globus pallidus
HD	Huntington's disease
IREC	Infrared emitting diode
LED	Light-emitting diode
Levodopa	l-3,4-Dihydroxyphenylalanine
MD	Movement duration
MoCA	Montreal Cognitive Assessment
MSN	Medium spiny neurons
PD	Parkinson's disease
PET	Positron emission topography
PPC	Posterior parietal cortex
RT	Reaction time
SB	Start button
SNc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulata
T1	Target 1

T2	Target 2
T3	Target 3
T4	Target 4
T5	Target 5
T6	Target 6
T7	Target 7
TMS	Transcranial magnetic stimulation
UPDRS	Unified Parkinson's disease rating scale
VTA	Ventral tegmental area

Chapter 1: Introduction

1.1 Summary of Online Motor Control

Fast and precise modifications to motor plans can be implemented while actions are occurring (i.e. online). This flexibility with respect to predefined motor plans is incredibly adaptive. Continuous real-time supervision of an ongoing movement is achieved through feedback loops comparing the limb and goal positions. Through this mechanism, motor error signals can be generated and adjustments in limb position can be promptly induced in response to changing task demands, such as when the target location changes, or simply when the initial motor plan is imperfect (Bard et al., 1999; Desmurget et al., 1999; Gréa et al., 2000).

Evidence validating the rapid online control of action has primarily stemmed from the use of a behavioral task known as the ‘double-step’ paradigm. In this experimental design, participants are instructed to point to a peripheral visual target, which depending on the trial, will either remain stationary or will unexpectedly change locations at hand movement onset. These target perturbations rapidly induce changes in limb trajectory away from its original path and toward the new goal location. Such unexpected target displacements provide a valuable opportunity to investigate how planned actions are adapted in real-time following their initiation.

1.1.2 Psychophysics of Online Corrections

Accurate and rapid online motor control relies heavily on the multisensory fusion of visual, proprioceptive, and vestibular modalities, as well as fast internal feed-forward and

feedback loops (Prablanc et al., 1979; Todorov & Jordan, 2002). To fully understand the mechanisms involved in online corrections, it is first important to break down the psychophysics of pointing movements directed at stationary targets.

Neurophysiological studies have identified a latency of 60-100 ms between the overt eye movement response and the overt arm movement response in a standard peripheral pointing task (Desmurget et al., 2001; Johnson-Frey, 2003; Prablanc & Martin, 1992). Ultimately, this delay translates into the gaze arriving at the target at approximately the same time as hand movement begins. However, it is critical to note that the initial EMG discharge for the eye and the hand is nearly synchronous (Biguer et al., 1982; Jeannerod, 1988). Increased latencies for the arm compared to the eye are reasoned to be attributable to increased inertial forces, rather than an actual delay in sensorimotor processing. This serial organization of the ocular-motor response helps explain how and why actions are modified online. In contrast to traditional theories of motor control, the hybrid model of online motor control posits an integrated two-step process (Desmurget & Grafton, 2000; Hoff & Arbib, 1993; Pélisson et al., 1986; Prablanc & Martin, 1992). First, a crude motor program for the arm, based on perifoveal information, is generated prior to limb movement onset. Given that this initial motor command is generated based on an imperfect approximation of the target position, it might only function to rapidly drive the effector into the general vicinity of the target. Once the primary ocular saccade has reached the target, the arm movement begins. Thus, to refine the action and optimize control, the arm's motor plan can be automatically updated online, after movement initiation, based on the new and improved foveal information.

Similarly, in the context of the 'double-step' paradigm, the central nervous system will continue to parse the visual scene and integrate novel information in accordance with

unexpected changes in task demands. In-flight modifications can be derived from a predictive feed-forward model of where the limb position should be relative to the target (Wolpert et al., 1995), to avoid inherent delays associated with sensory processing. When there is an unexpected change in target position, there will be a significant disparity between the actual and predicted sensory outcome of an ongoing action. An error signal will be detected and translated into a motor command aimed at adapting patterns of muscle activation to minimize the discrepancy. These adaptations in muscle activity proceed in a similar manner for double-step movements as they do for single-step movements. Changes in EMG activity occur approximately 100 ms after target perturbation and such EMG bursts precede actual deviations in limb kinematics (Fautrelle et al., 2010). It is through feed forward specification of motor commands and continuous feedback loops that the motor system is able to generate online corrections within ~150 ms of target displacement (Brenner & Smeets, 1997; Gritsenko et al., 2009; Izawa & Shadmehr, 2008; Paulignan et al., 1991; Prablanc & Martin, 1992; Soechting & Lacquaniti, 1983). Such rapid, real-time adjustments far surpass the temporal rates associated with sensory processing alone, which can often exceed ~250 ms (Frith et al., 2000).

1.1.3 Automaticity of Online Corrections - 'The Automatic Pilot'

Over the last few decades, accumulating evidence has prompted the online corrective system to be notably referred to in the literature as the hand's 'automatic pilot'. A variety of studies support the notion that online corrections involve little if any conscious iterative control (Day & Lyon et al., 2000; Diedrichsen et al., 2004; Johnson et al., 2002; McIntosh et al., 2010; Pisella et al., 2000). Online modifications in reach trajectories have been shown to occur well before the time at which the participant reports consciously perceiving these

adaptations. For example, Castiello et al. (1991) showed that limb trajectories could be modified within 120 ms of target perturbations – whereas it took participants greater than 400 ms to vocalize their conscious perception of the target jump. This lag was interpreted to reflect an inherent delay between action and perception, rather than simply an increase in the time needed to generate a vocal response. Moreover, it is well accepted that limb modifications can occur even in the absence of a conscious awareness of both one's own reach amendments and/or perturbations in target position. That is to say, the hand can be guided to a new target position regardless of any conscious perceptual awareness of the change and independent of intention. This has best been studied through the use of Goodale et al.'s (1986) modification of the traditional double-step design. Here, instead of a target perturbation being elicited at hand movement onset, a small target displacement was triggered while the participant performed their initial eye movement to the first appearing target. Although participants lacked a conscious awareness of the target being displaced, their hand trajectories appropriately diverged away from their original path to reach the new target position, without any additional delay. It was suggested that the participants' failure to perceive the second target displacement reflected the naturally occurring 'fine-tuning' of the human ocular system. Primary saccades often undershoot a target's position and require the refinement of a subsequent corrective saccade to accurately bring the target of interest directly onto the fovea. Therefore, triggering a relatively small target displacement (~10% of the movement amplitude) during the primary saccade would induce the same post-saccadic refinement as would occur in a single-step trial. The apparent correction that would occur due to the target perturbation would simply reflect that which normally follows a primary saccade to a stationary target in any case. Other groups have since replicated these findings and have suggested that errors can still be efficiently corrected by the motor system, even when these

errors are not consciously perceived by the participant (Chua & Enns, 2005; Desmurget et al., 2001; Pelisson et al., 1986; Prablanc & Martin, 1992). These results not only lend support for the automaticity of this corrective response, but also suggest that separate neural pathways might mediate perception and action (Milner & Goodale, 1995).

The notion that double-step-induced online corrections are largely automatic is also supported by studies finding comparable limb movement durations (MD) in reaching to targets that remain stationary versus to targets that moved to a final location while the action was underway. Namely, this online response mechanism results in the participant taking the same amount of time to point to a stationary target as it does for them to point to a target that ends in the same location, although its initial position had been different when the reaching movement was started. Thus, while limb trajectories are being modified to reach a new target position, no additional processing time is required. As alluded to earlier, this rapid processing indicates that the corrective system might be able to bypass the typical time course required for an afferent sensory signal to be translated into an efferent motor command. Furthermore, these findings suggest that a new motor command is not being completely reprogrammed, but rather online corrections induce rapid automatic modulations of the ongoing response and motor programme.

Although the consensus is that rapid, online corrections suggest a certain level of automatic processing, the degree to which these processes operate automatically remains less known. To address this knowledge gap, researchers have compared the corrective system against two additional standards required for highly automatic processes. First, the action should be fairly insensitive to conscious iterative control. That is, online corrections should function as ‘hard-wired’ processes that cannot be easily overridden. Compliance with this criterion has best been demonstrated in studies where participants are instructed to abort their

pointing action upon detection of a target displacement. Most notably, Pisella et al. (2000) demonstrated in a significant number of trials that regardless of their intention to do so, participants were unable to successfully interrupt their online correction. Furthermore, follow up studies have since modified Pisella et al.'s (2000) design by instructing participants to point in the opposite direction of a target jump, rather than inhibit or cancel their action outright. Comparably, participants were unable to repress motor corrections and reliably deviated their trajectory in the direction of the target jump despite the anti-point instruction (Day & Lyon, 2000; Johnson et al., 2002).

The second criterion for automaticity states that the action must remain unaffected by simultaneous cognitive load. A typical way to investigate this is through the use of a dual-task paradigm, in which participants are asked to perform two simultaneous tasks. Performing an action during single versus dual task conditions can be compared to investigate the efficiency and automaticity of the action. An automatic action should be performed equivalently under single or dual task conditions. Using this approach, Liu et al. (2008) demonstrated that a simultaneous object identification task interfered with the planning of an action, but not the online control of an already initiated action. Consequently, it was argued that whereas competing cognitive resources might disrupt the pre-programming of an action, online control of an already established action remains unaffected. McIntosh et al. (2010) further corroborated these findings by showing that both the speed and accuracy of online corrections are unaltered by the simultaneous performance of an auditory 1-back task. Collectively, these results have led to conclusions ascribing an extremely high level of automaticity and autonomy to online reach corrections.

1.1.4 Neural Substrates Involved in Online Motor Control

In addition to inputs from the extrastriate visual cortex, the posterior parietal cortex (PPC) receives input from a variety of other sensory modalities including the auditory and somatosensory regions (Fogassi & Luppino, 2005). The PPC's neuroanatomical connectivity and its integrative role concerning spatial representations of the body and target objects in the environment render it a prime candidate for specifying online context-dependent motor commands (Andersen et al., 1997). Despite the large body of evidence supporting the PPC as a well-positioned and likely component of online motor control, less is known about the exact nature of the underlying mechanisms mediating its involvement in rapid online motor adjustments. The strongest direct evidence comes from studies in patients with PPC lesions who exhibit significant impairments in double-step reaching tasks compared to single-step tasks. Desmurget et al. (1999) first reported disturbances in in-flight reach adjustments upon transcranial magnetic stimulation (TMS) of the left posterior parietal lobe. Similarly, MacDonald and Paus (2003) reported that the awareness of self-generated movements was disrupted when repetitive TMS was applied over the superior parietal lobe. These results have since been supplemented by a clinical case study of a patient with ischemic bilateral parietal lesions. This patient demonstrated selective impairments during a double-step pointing task requiring online reach adjustments, while retaining the ability to accurately point to stationary targets during a single-step condition (Pisella et al., 2000). More recently, Battaglia Mayer et al. (2013) found similar disturbances in reach adjustments upon deactivation of the parietal areas through the injection of gamma-aminobutyric acid (GABA)-A agonists in non-human primates.

In line with these results, neurophysiological studies have also identified changes in PPC activity 150 ms following target displacement and approximately 20 ms prior to changes in hand kinematics (Archambault et al., 2009; Archambault et al., 2011). Similarly, in a positron emission topography (PET) study, increased activity in the intraparietal sulcus was found during a double-step pointing task when compared to a single step task in which no online corrections were required (Desmurget et al., 2001). Taken together, the anatomical positioning and neurophysiological results have led researchers to hypothesize a fundamental role for the PPC as a “neural comparator” in online movement guidance. In this regard, the PPC might integrate sensory inflow and motor outflow, thereby computing the motor error between the target position and the predicted location of the hand. The PPC identifies to what extent the existing motor command is imprecise and how this error can be rectified through forward modelling of limb dynamics (Buneo & Andersen, 2006; Desmurget et al., 1999; Gréa et al., 2002).

Whereas the PPC is thought to be involved in identifying error signals, the anterior parasagittal cerebellar cortex is argued to be involved in converting these signals into corrective motor commands (Desmurget et al., 2001). Anatomical studies have identified a range of diverse connections between the cerebellum and cortical areas, including parietal, temporal, motor, and premotor cortices (Ramnani, 2006). It is through these connections that the anterior parasagittal cerebellar cortex generates an accurate corrective motor plan in response to the neural signals issued by the primary motor cortex. Subsequently, changes in muscle activation can be induced to redirect the limb in-flight to a modified trajectory path (Bastian et al., 1996; Day et al., 1998; Desmurget et al., 2001). Additionally, a strong line of evidence implicates the cerebellum in the feed-forward prediction of sensory consequences of movements (Blakemore et al., 2001; Miall et al., 1993). Congruent with these theories, a

PET imaging study showed increased activity of the anterior parasagittal cerebellar cortex following unexpected disturbances in target position requiring inflight reach amendments (Desmurget et al., 2001).

More recently, sub-cortical structures, including the basal ganglia, have been implicated in online motor control. The basal ganglia are a collection of subcortical nuclei, including the striatum as the input region, and the globus pallidus and substantia nigra reticularis (SNr) as the output regions, which have been extensively implicated in motor and cognitive functions (Blandini et al., 2000; DeLong, 2000; Graybiel, 2000; Parent & Hazrati, 1995). Scarce support for the basal ganglia in online motor control has primarily stemmed from clinical studies investigating patients with basal ganglia disorders, such as Huntington's disease (HD) and Parkinson's disease (PD). Smith et al. (2000) first reported that patients with HD have a diminished capacity to adapt their actions online in response to large, externally applied perturbations to their moving limb. It is important to note that in addition to basal ganglia degeneration, HD patients also suffer from significant cortical atrophy, which makes interpretation of their data difficult (Ciarmiello et al., 2006; Hedreen et al., 1991; Rosas et al., 2008). In contrast, studies in early PD are more specific tests of basal ganglia involvement in online motor control, given a significant and specific biochemical deficit to the striatum, compared to relative sparing of the cortex (Halliday et al., 2011; Hornykiewicz, 1998; Jellinger, 1991). Currently, to our knowledge, few studies have reported PD-related impairments in iterative online motor control in response to both target errors and execution errors (Desmurget et al., 2004; Tunik et al., 2004). The role of the basal ganglia in online motor control is further complicated by inconsistent results from neuroimaging studies. Diedrichsen et al. (2005) revealed increased striatal (i.e., putamen and caudate nuclei) activity exclusively during online corrections induced by target

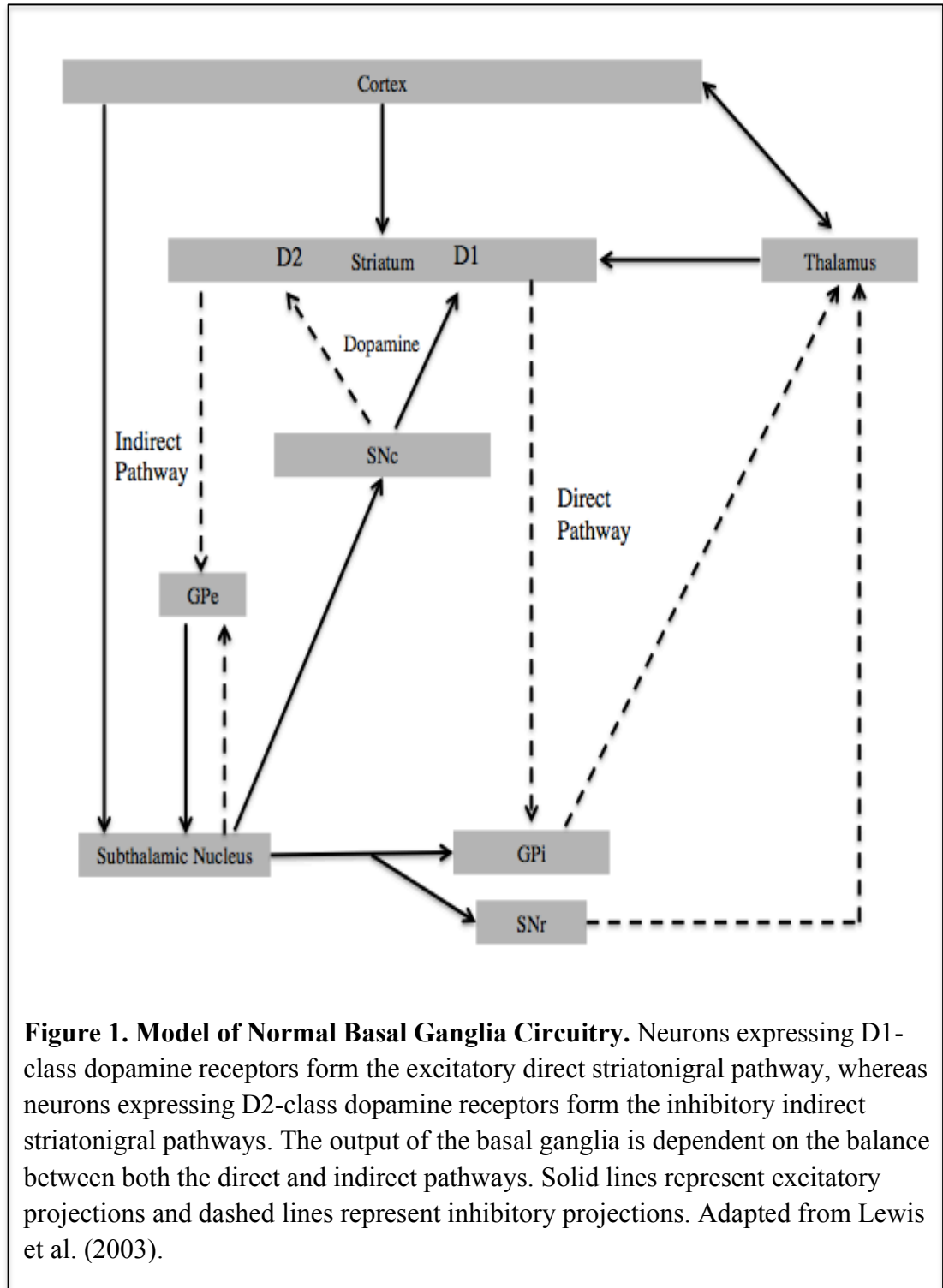
displacements, whereas no such elevation in striatal activity was reported for execution errors induced by mechanical limb perturbations. In contrast, other groups reported augmented basal ganglia activity only during the ‘pre-movement’ planning phase of self-initiated actions, as opposed to during the online execution of the action itself (Elsinger et al., 2006; Boecker et al., 2008). Furthermore, clinical reports speculate that the basal ganglia are involved in striatal-dopamine-mediated correction of *trial-to-trial* errors. The ambiguous use of the term “error correction” has perhaps resulted in unwarranted support for the basal ganglia in the automatic control of the in-flight error corrective system. Critically, Smith & Shadmeh (2000) have highlighted that it is essential to distinguish between the different mechanisms for adjusting to errors online compared to adapting to errors identified through trial-to-trial learning. Second, reports cite that patients with PD not only use visual feedback, but might actually rely more heavily on this visual information during reaching or pointing tasks. Increased reliance on continuous visual information might be an alternative strategy used to help compensate for PD-related deficits in the pre-programming of a motor plan (Flash et al., 1992; Klockgether et al., 1994). In theory, if the basal ganglia are truly implicated in online control, then dysfunction of this neural region should significantly disturb the use of visual feedback loops during an ongoing action. In subsequent chapters, I will further elaborate on online motor control in PD, along with the myriad of factors that possibly confound interpretation of previous work that has supported impairments in this function in this disease.

1.2. Parkinson's Disease

1.2.1 Parkinson's Disease Pathology & Aetiology

PD is the second most common neurodegenerative disorder worldwide. A central pathological change in PD, giving rise to its most recognizable motor symptoms, comprises the substantial degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) and, to a much lesser extent, in the ventral tegmental area (VTA). To understand the neuropathology of PD, it is first important to review normal basal ganglia circuitry. The basal ganglia are a collection of sub-cortical nuclei situated at the base of the prosencephalon. The striatum is the principal input structure of the basal ganglia, receiving afferent projections from virtually all functioning regions of the cerebral cortex, the thalamus, the SNc and the VTA. Cortico-striatal connections are functionally and topographically divided and provide excitatory glutamatergic input to the striatal medium spiny neurons (MSNs). In turn, the MSNs project to the two major output components of the basal ganglia, the globus pallidus and the SNr, through a direct and indirect pathway respectively. The striatal output of both pathways is inhibitory, with GABA being the principal neurotransmitter of the output streams. The pallidal complex and the SNr, in turn, provide inhibitory outputs to the thalamus, which then projects back, via excitatory connections, to the cortex. The direct and indirect basal ganglia pathways have antagonistic effects on thalamic and thus, target cortical structures. Excitation of the direct pathway results in net excitation of thalamic neurons, whereas excitation of the indirect pathway results in net inhibition of thalamic neurons (Alexander et al., 1986; Gerfen, 1996; Graybiel, 2000; Gurney et al., 2001; Haber, 2003; Haber & Calzvara, 2009; McHaffie et al., 2005; Parent, 1990; Parent & Hazrati, 1995). The thalamus has excitatory connections to the cortex and in this way the direct pathway

enhances cortical activity whereas the indirect pathway depresses it. Connectivity of the indirect and direct pathways is illustrated in Figure 1.



The direct and indirect basal ganglia pathways are modulated through dopaminergic striatonigral projections. Critically, there is differential expression of D1 and D2-class dopamine receptors in each of these two streams. MSNs in the direct pathway have high levels of D1-class receptors, which depolarize the neuron in response to dopamine. In contrast, the MSNs in the indirect pathway predominately express D2-class receptors, which hyperpolarize the neuron in response to dopamine. The functional antagonism between D1 and D2-class receptors translates into heightened dopamine levels stimulating the direct pathway, while simultaneously inhibiting the indirect pathway. Together, increased striatal dopamine results in an overall reduction in GPi and SNr activity and consequently an overall increase in thalamic and cortical activity (DeLong et al., 2007; Graybiel, 2000; Smith et al., 1998; Utter & Basso, 2008).

An appropriate balance between both the direct and indirect basal ganglia pathways is integral for proper psychomotor functioning. When this balance is interrupted, discharge patterns in the basal ganglia become abnormal and movement disorders prevail. In the case of PD, the SNc suffers the greatest dopaminergic neuron loss compared to other basal ganglia nuclei (Fahn, 2003; Greenfield & Bosanquet, 1953; Jellinger, 1991; Tanner & Goldman, 1996). Degeneration of the striatonigral dopaminergic pathway increases neuronal activity in the GPi and the SNr, and consequently results in over-inhibition of thalamo-cortical and brainstem motor systems (Transm, 1995). The hallmark features of PD – including poverty of voluntary movements and resting tremor – are primarily owed to excessive inhibition of these neural regions.

1.2.2 Symptomology of Parkinson's Disease

Striatal dopamine depletion leads to the predominant motor features of PD, including early bradykinesia, rigidity, resting tremor, as well as later postural and gait abnormalities. These early, main motor characteristics almost always present unilaterally at onset, though they eventually become bilateral with disease progression. Bradykinesia refers to slowness in movement and often occurs in conjunction with reduced spontaneous and hypometric movements, termed akinesia or hypokinesia. Bradykinesia can manifest as increased motor reaction times (RT), decreased acceleration, and reduced movement velocities. Such movement abnormalities have been suggested to arise due to a central deficit in the planning phase of motor control (Berardelli et al., 2001). In other words, deficits in pre-programming of motor plans are postulated to produce difficulties initiating movements and maintaining consistent force and speed (Sheridan et al., 1987).

Although primarily characterized by motor symptoms, non-motor symptoms are also commonly present in PD and include neuropsychiatric (Aarsland et al., 1999; Aarsland et al., 2009; Chaudhuri et al., 2009), cognitive (Dubois & Pillon, 1996; Green et al., 2002; Jankovic, 2008; Owen et al., 1992), autonomic (Goetz et al., 1986; Wakabayashi & Takahashi, 1997), gastrointestinal (Edwards et al., 1992; Pfeiffer, 2003), sensory, (Ansari & Johnson, 1975; Snider et al., 1976; Ward et al., 1983;) and sleep disturbances (Comella, 2003; Menza et al., 2010). The most prevalent neuropsychiatric complaints include depression (McDonald et al., 2003; Slaughter et al., 2001; Reijnders et al., 2008), anhedonia (Isella et al., 2003), apathy (Pluck & Brown, 2004) and anxiety (Richard et al., 1995; Stein et al., 1990).

1.2.3 Symptomatic Treatment of Parkinson's Disease

Currently, there is no cure for PD. Dopamine replacement therapy replenishes dopamine in the striatum, alleviating motor and some cognitive impairments. Oral administration of L-3, 4-dihydroxyphenylalanine (levodopa), a precursor to dopamine, remains the primary treatment of choice. Levodopa is decarboxylated after passing through the blood brain barrier, enabling it to act directly on dopamine receptors within the brain. Commonly, levodopa is administered in conjunction with peripheral decarboxylase inhibitors, such as carbidopa, to prevent the decarboxylation of levodopa to dopamine prior to crossing the blood brain barrier.

Despite the known efficacy of levodopa in improving certain motor symptoms, its effects on cognitive functions have proven to be somewhat paradoxical. Increasingly, levodopa has been recognized to improve certain domains, while impairing functioning in others. Such inconsistent findings have been attributed to uneven dopaminergic cell depletion across the SNc and VTA respectively. The SNc, which innervates the dorsal striatum (i.e., bulk of caudate nuclei and putamen), experiences profound dopaminergic neuron loss. In contrast, the VTA, which innervates the ventral striatum (i.e., nucleus accumbens, ventral putamen and ventral caudate), remains relatively spared from such cell death (Fearnley & Lee, 1991; Goto et al., 1989; Hirsch et al., 1988). Therefore, dopamine replacement therapeutics might help restore dopamine levels in depleted neural regions like the dorsal striatum, but might detrimentally 'overdose' less affected neural regions such as the ventral striatum. Accordingly, functions mediated by the dorsal striatum, such as cognitive flexibility and motor control, are thought to improve with dopaminergic therapy (Cools & D'Esposito, 2011; Robbins & Everitt, 1992), whereas certain cognitive tasks, such as probabilistic associative learning and impulsive responding, mediated by VTA-innervated brain regions

are thought to become impaired (Cools et al., 2001; Jahanshahi et al., 2010; MacDonald & Monchi, 2011). That is, overdose effects in PD could be due to exogenous dopamine therapy distributing to relatively dopamine replete brain regions (i.e., those innervated by VTA) as well as to intended regions that are significantly dopamine depleted (i.e., mainly dorsal striatum innervated by SNc). Nevertheless, these findings do not clarify whether these changes in performance are due to a main effect of dopamine medication or if they are due to a PD by medication interaction. To circumvent this ambiguity, the effect of levodopa on performance in healthy controls, who presumably have optimal baseline levels of endogenous dopamine, has been investigated (Cools & Esposito, 2011; Flöel et al., 2005; Rihet et al., 2002; Shellshear et al., 2015; Vo et al., 2015). Such an experimental manipulation allows the effects of dopaminergic medication to be investigated in a way that is unconfounded by PD-related pathology. Moreover, it helps facilitate our understanding surrounding the effects of excessive ventral striatal dopamine.

1.2.4 Online Motor Control in Parkinson's Disease

Although it is well established that PD disrupts certain motor domains, especially those associated with the pre-programming of a movement (Harrington & Haaland, 1991), far less is known about how patients with PD control actions that are underway. To the best of our knowledge, surprisingly few studies have directly examined online motor control in PD. Tunik et al. (2004) developed a postural trunk-perturbation paradigm, in which controls and patients with PD were instructed to touch their finger to their nose while their trunk position was unexpectedly perturbed. Unexpected perturbations in trunk position required the participants to adapt their upper-limb motor plans to smoothly and accurately complete the finger-to-nose action. Here, they found that PD patients were significantly impaired in the

perturbed trunk condition, as revealed by these patients having segmented trajectory paths, increased MDs, and irregular velocity profiles. The authors interpreted these findings as evidence that basal ganglia dysfunction leads to deficits in the flexibility of responses to amended motor states.

Critically, the neural correlates and mechanisms for adjusting to “execution errors” and “target errors” are distinct. Despite both errors inducing similar online corrective responses, they rely on fundamentally different computational strategies (Diedrichsen et al., 2005). As such, one should be hesitant to compare these results to those of online corrections to visual targets, as is assessed using a double-step paradigm. Indeed, in a traditional double-step experiment, PD patients did not demonstrate any deficits in adjusting their hand trajectories in response to subliminal, small target jumps occurring during their initial saccades (Desmurget, 2004). In contrast, in a separate follow up experiment, Desmurget et al. (2004) showed that although PD patients could consciously perceive a target displacement, they failed to adequately modify their ongoing trajectories when that target’s location was largely displaced at hand movement onset. These two findings guided the current interpretation that whereas PD patients are impaired in *consciously-mediated* automatic online motor control, they retain the ability to perform *subconscious* automatic online motor adjustments.

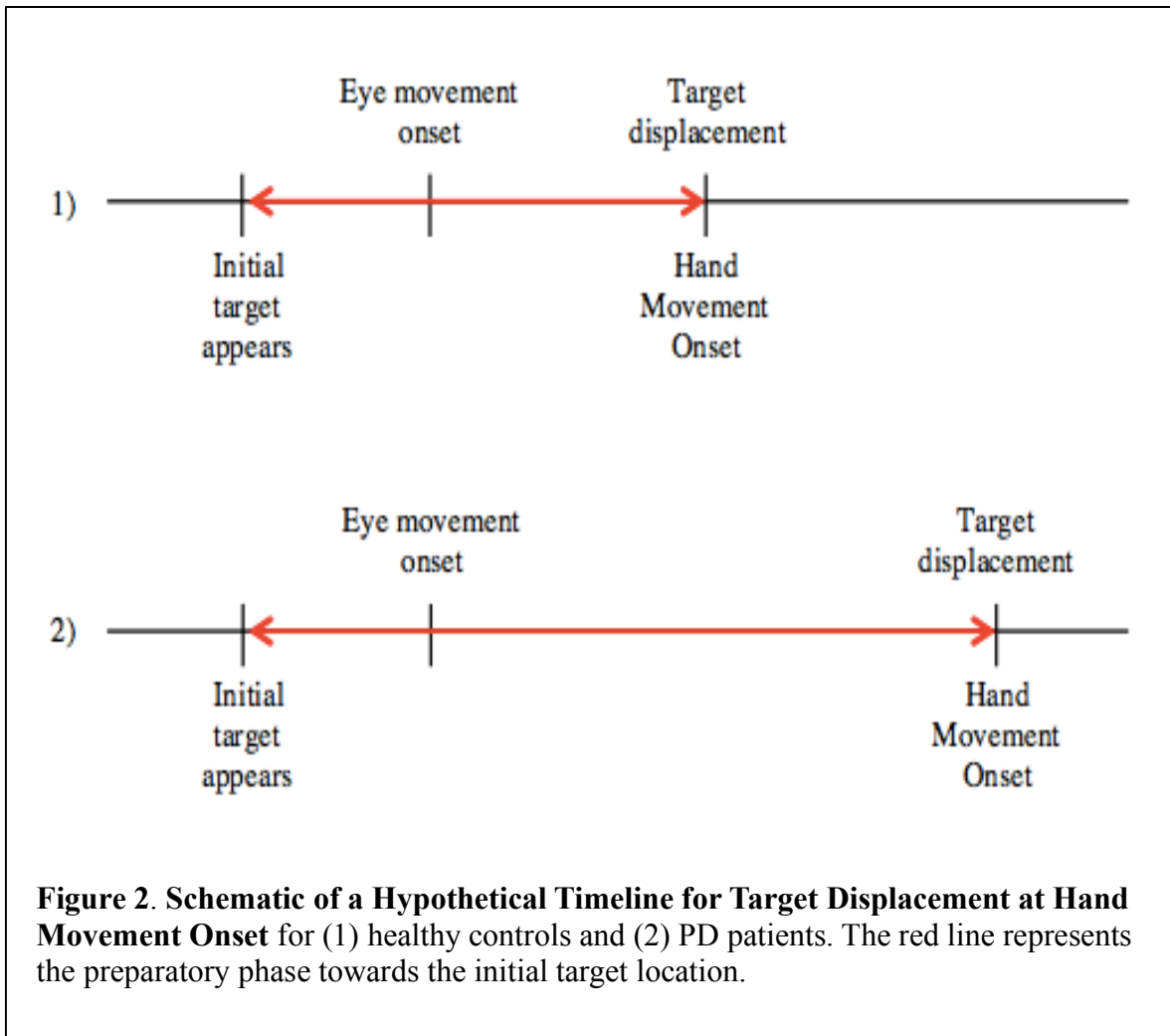
Critically, a finding of impaired automatic online processing in PD directly contradicts the predominant notion that the dorsal striatum is responsible for *suppressing* automatic behavioral responses. That is, the current literature suggests that dysfunction of the dorsal striatum leads to increased interference from salient stimuli and consequently greater automaticity in behavioral responses (Benke et al., 2003; Cameron et al., 2010; Cools et al., 2006; Cools et al., 2010; Rieger et al., 2003; Thoma et al., 2008). During cognitive

assessments, such as the Stroop task, PD patients reveal a greater tendency to perform the automatic response of reading the word rather than the more cognitively controlled response of naming the color (Brown & Marsden, 1988; Dujardin et al., 1999; Henik et al., 1993). Likewise, using a stop-signal paradigm Rieger et al. (2003) showed increased stop signal RTs in patients with striatal lesions relative to their control counterparts, indicating a role of the striatum in the volitional control of an ongoing response. These results are further corroborated by functional magnetic resonance imaging (fMRI) paradigms, which have demonstrated greater dorsal striatal activity in conditions with increased interference (Ali et al., 2010; Liu et al., 2010). For instance, dorsal striatal activity has been shown to increase when participants are required to provide a less-practised or less automatic response, such as naming a picture in their second language relative to their first language (Liu et al., 2010). Moreover, these findings extend to psychophysical paradigms, such as the anti-saccade task, which instructs participants to look in the opposite direction of an appearing visual stimulus. This paradigm requires participants to not only suppress the automatic pro-saccade, elicited by the external visual stimulus, but also generate a volitional saccade via an internal command. Unsurprisingly, PD patients commonly demonstrate robust impairments in this task, as indicated by increased RTs and a greater inability to suppress pro-saccades in the direction of the target (Briand et al., 1999; Kitagawa et al., 2004; Van Koningsbruggen et al., 2009). In contrast, in pro-saccade tasks that instruct participants to look towards the sudden appearing target, participants with PD perform this automatic orienting response normally (Briand et al., 1999;) and in some cases even better than controls (Armstrong et al., 2002; Chan et al., 2005). Although, the effects of consciousness have yet to be directly investigated on automatic action in PD, results from the Stroop task and pro-saccade task indicate that automatic function can in fact rely on consciously perceivable visual cues. Consequently, the

finding that patients with PD are impaired at online automatic motor control when adjustments are conscious is not expected from the literature.

In light of this broader literature, the finding by Desmurget et al. (2004) that PD patients were impaired in automatic online motor corrections, when the need to perform a correction was consciously perceived, was somewhat unforeseen. On further consideration, aspects of Desmurget's experimental setup, unrelated to the consciousness of the corrective action, might have differentially impacted PD patients' performance relative to that of their control counterparts. In particular, in the experiment where the need for a corrective action became consciously perceived, the timing of the target jump was linked to movement onset. Bradykinesia, a cardinal motor symptom, causes PD patients to take longer to initiate actions. Therefore, when target perturbations occurred at movement onset, this target jump and change in the movement trajectory would occur later for PD patients compared to their controls. PD patients would therefore have an increased time to prepare their movement toward the initial target position. That is, PD patients would exhibit an increased preparatory phase to plan their preliminary action before the target is unexpectedly displaced (See Figure 2). This is particularly problematic because it has been shown that longer preparatory phases for an action lead to greater challenges in later modifying or inhibiting that action (Lappin & Eriksen, 1966; Logan, 1981). It is important to note that in contrast to target perturbations at limb movement onset, target jumps elicited during a saccade would not alter the preparatory phases between groups because PD patients and controls have similar pro-saccade onset latencies and durations. Therefore, only in the experiment probing conscious online motor control, where the target displacement was linked to limb movement onset, would the preparatory phases have been increased for the PD patients relative to the healthy controls.

Given this confound, the mechanism underlying impairments in online motor control for PD patients observed by Desmurget in the double-step paradigm remains unclear.



1.3 The Current Study

1.3.1 Rationale for Current Study

In Desmurget et al. (2004), PD patients were impaired in altering their hand-movement trajectories when target displacements occurred at hand-movement onset, but not when target perturbations occurred during the saccade using the classic double-step

paradigm. Traditionally, when target jumps occur at hand-movement onset, they are consciously perceived, in contrast to when they occur during a saccade. Due to disease-associated bradykinesia, however, target jumps that occur at hand-movement onset also produce longer action preparation phases toward the initial reach target in PD patients compared to controls. Indeed movement onset latencies, and hence the preparation of the movement trajectory that ultimately had to be revised, were on average 120 ms longer for PD patients compared to controls. Consequently, the interpretation of Desmurget's pattern of results is confounded. These results could reflect impairments for PD patients for automatic online movement adjustments when the need for this alteration is consciously perceived as Desmurget has argued. Equally possible, however, this pattern of findings could have arisen because PD patients had an increased preparatory phase for the initial target reach trajectory relative to the preparatory phase of controls. It has been shown that longer preparatory phases for actions leads to greater challenges in later modifying or inhibiting those actions (Lappin & Eriksen, 1966; Logan, 1981). This introduced a significant, unintended disadvantage for PD patients that alone could account for their deficient performance. The aim of the current study was to directly contrast automatic online motor corrections that were unconscious versus conscious, eliminating conditions that would disadvantage PD patients owing to their motor symptoms.

1.3.2 Objective

The main objectives of the present study are two-fold. First, we aimed to develop a double-step paradigm that directly dissociated perceptual awareness of a target displacement from potential confounding effects of PD-related bradykinesia. Second, using our adapted paradigm, we aimed to explicitly elucidate the effects of conscious-iterative control on

automatic online motor adjustments in patients with PD and healthy controls. Taken together, we aimed to systematically consider how PD-related bradykinesia might have confounded the previous approaches used to investigate automatic online motor control with and without conscious perception. Furthermore, this research aimed to provide insight into the role of the basal ganglia in online motor control at the behavioral level.

1.3.3 Predictions

An alternative explanation for previously observed PD-related impairments in conscious online corrections lies in the assumption that the preparatory phase timing affects one's ability to perform rapid online motor adjustments. In line with this, we predicted that when confounding effects of bradykinesia are accounted for (i.e. the preparatory phase is equalized between PD patients and healthy controls) that the two groups will perform consciously-perceivable online corrections more similarly. We predicted that corrections made in response to either consciously-perceived or subliminal target jumps will not significantly differ for patients with PD and healthy controls.

Chapter 2: Methods

2.1 Participants

This study included 12 patients with clinically diagnosed idiopathic PD and 12 healthy age-matched controls. All participants provided written and informed consent according to the Declaration of Helsinki (1991) and all procedures were approved by the Health Sciences Research Ethics Board of the University of Western Ontario (London, Ontario, Canada). Participants did not have previous experience with the task, were naïve to the purpose of the experiment and were right-handed. Controls had no history of neurological

illness, major psychiatric disorder, motor deficits or head trauma. Additionally, healthy controls were not taking any cognitive-enhancing medications and had no history of substance abuse. All participants had normal or corrected-to-normal vision. A complete list of inclusion criteria is included in Appendix H. The age of PD patients ($M = 64.83$, $SD = 9.41$) and the age of controls ($M = 65.0$, $SD = 8.62$) did not significantly differ. In addition, controls were matched to PD patients for education. A complete outline of population demographics is included in Table 1.

Patients with PD were all levodopa responsive and were taking dopaminergic medication at the time of testing. The daily levodopa equivalent dose ($M = 673.2$ mg, $SD = 356.67$) was calculated in accordance with Evans et al. (2004): levodopa dose + levodopa x $1/3$ if on entacapone + bromocriptine (mg) x 10 + cabergoline or pramipexole (mg) x 67 + ropinerole (mg) x 20 + pergolide (mg) x 100 + apomorphine (mg) x 8. PD patients did not report any cognitive complaints and were all found to be cognitively unimpaired in accordance with the standard MoCA examination ($M = 27.33$, $SD = 1.37$). Patients and controls were excluded if they scored less than 25/30 on the MoCA. Furthermore, patients had no history of any additional neurological illnesses unrelated to PD, had no suspicion of familial forms of PD, had no history or current treatment with deep brain stimulation and were not taking any cognitive-enhancing medications.

All patients participated in two identical testing sessions on separate days: once while taking their usual dopaminergic therapy as prescribed by their treating neurologist, and once following withdrawal from dopaminergic medication. In the Off dopamine session, patients were instructed to abstain from taking *all* dopaminergic medications including dopamine precursors such as levodopa, aromatic-L-amino-acid decarboxylase inhibitors such as carbidopa, and catechol-O-methyltransferase (COMT) inhibitors such as entacapone for a

minimum of 12 to a maximum of 18 h, and dopamine agonists, such as pramipexole (Mirapex), ropinirole (Requip) or pergolide (Permax), as well as amantadine (Symmetrel), rasagiline (Azilect), and selegiline (Eldepryl or Deprenyl) for 16–20 h prior to testing.

Similarly, all healthy controls participated in two distinct testing sessions, examining the effects of dopamine medication (100 mg levodopa + 25 mg carbidopa, orally) versus placebo (identical cornstarch placebo) on separate days. Healthy participants were thoroughly screened using the Levodopa Safety Screening Questionnaire prior to their participation (Appendix I). Administering levodopa to healthy controls allowed us to directly investigate the effects of this medication independent from any PD pathology on online motor control. All On-Off medication orders were counterbalanced across participants and the On-Off order was identical for each PD patient and his/her age- and education-matched healthy control participant.

The presence and severity of PD symptoms was assessed for each patient, both on and off dopaminergic medication, using the Unified Parkinson's Disease Rating Scale (UPDRS) Motor Subscale. Control participants were also assessed using the UPDRS to screen for any undiagnosed motor or neurological illnesses. All participants completed a series of standardized cognitive and affective screening tests (Appendix C- G). The mean cognitive and affective screening scores and the UPDRS motor subscale scores are included in Table 1.

Table 1. Demographic, clinical information, and screening cognitive and affective measures for participants with PD and controls

Group	Age	Edu	Duration	Levodopa Dose	UPDRS	ANART	BDI-II	BAI	Apathy	MOCA
Day 1										
PD (n=12)	64.83 (2.72)	15.67 (0.99)	6.58 (1.37)	673.21 (102.9)	—	—	10.67 (1.29)	8.92 (1.50)	10.92 (1.15)	—
On (n=6)	62.00 (4.18)	15.17 (1.57)	7.00 (1.89)	632.00 (125.77)	9.20 (1.85)	126.09 (2.30)	9.17 (2.02)	6.50 (2.45)	9.00 (0.82)	27.50 (0.72)
Off (n=6)	67.66 (3.43)	16.17 (1.30)	6.17 (2.15)	714.42 (173.63)	12.42 (2.03)	—	12.17 (1.51)	11.33 (2.39)	12.83 (1.92)	—
Control (n=12)	65.00 (2.48)	15.92 (0.88)	—	—	—	—	2.75 (0.70)	2.75 (0.93)	9.17 (1.02)	—
On (n=6)	65.66 (4.07)	16.83 (1.11)	—	—	0.167 (0.167)	—	3.83 (0.91)	2.17 (0.87)	7.83 (1.60)	—
Off (n=6)	64.50 (3.28)	15.00 (1.36)	—	—	0.00	127.47 (2.08)	1.67 (0.92)	3.33 (1.71)	10.50 (1.15)	28.5 (0.43)
Day 2										
PD (n=12)	64.83 (2.72)	15.67 (0.99)	6.58 (1.37)	673.21 (102.9)	—	—	10.58 (1.59)	7.42 (1.29)	11.42 (1.67)	—
On (n=6)	67.66 (3.43)	16.17 (1.30)	6.17 (2.15)	714.42 (173.63)	10.83 (2.21)	128.65 (1.29)	12.67 (2.72)	8.00 (2.31)	15.17 (2.18)	27.17 (0.40)
Off (n=6)	62.00 (4.18)	15.17 (1.57)	7.00 (1.89)	632.00 (125.77)	12.0 (2.00)	—	8.50 (1.45)	6.83 (1.35)	7.67 (1.38)	—
Control (n=12)	65.00 (2.48)	15.92 (0.88)	—	—	—	—	2.67 (0.49)	2.50 (1.09)	8.75 (1.12)	—
On (n=6)	64.50 (3.28)	15.00 (1.36)	—	—	0.00	—	2.17 (0.65)	3.17 (2.01)	11.17 (1.05)	—
Off (n=6)	65.66 (4.07)	16.83 (1.11)	—	—	0.00	126.42 (1.79)	3.17 (0.75)	1.83 (1.01)	6.33 (1.45)	27.833 (0.65)

Values are presented as group means (SEM). Screening cognitive and affective measures were completed by participants with PD on medication and by healthy controls off medication. All control participants presented with normal neurological exams. Session 1 refers to the first day of testing. Session 2 refers to the second day of testing. Edu, years of education; Duration, years since diagnosis of PD; Levodopa dose, equivalent dose in mg; UPDRS, Unified Parkinson's Disease Rating Scale;

ANART, National Adult Reading Test IQ Estimation; BDI-II, Beck Depression Inventory II score; BAI, Beck Anxiety Inventory I score; Apathy, Apathy Evaluation Scale score; MoCA, Montreal Cognitive Assessment measured for participants with PD and for matched control participants.

2.2 General Design

A modified double-step, pointing paradigm was employed. The premise of the task remained the same: participants were instructed to point to a peripheral visual target, which depending on the trial, either remained stationary or unexpectedly changed locations. To eliminate any confounding effects of bradykinesia, in one condition, we induced online, automatic motor corrections that were consciously perceived in a way that was independent of hand movement initiation compared to another condition in which these perturbations were not consciously noted. To this end, we introduced two sizes of target perturbations: small (3.5 cm) and large (7 cm), both of which occurred during the initial saccade. Given that visually-guided saccades have not previously been shown to be delayed in PD (Armstrong et al., 2002; Briand et al., 1999; Chan et al., 2005), introducing a target displacement during this time would render the initial preparatory phase equivalent for PD patients and healthy controls. Furthermore, by modifying the target jump size, we expected small perturbations to fall below the threshold for conscious perceptual awareness, whereas the larger perturbations would exceed the threshold for awareness (Goodale et al., 1986; Pélisson et al., 1986). To confirm that this method was effective, participants began and ended each session with a two-alternative forced choice task in which we directly assessed their conscious perceptual awareness of the target displacements.

2.3 Apparatus and Stimuli

Participants sat at a table in a darkened room with their head stabilized in a chin-rest. A pressure-sensitive start button was fastened to the table directly in front of the participant

and approximately 10 cm from the edge of the tabletop. The stimuli were presented on a vertically mounted custom-built display board. The board consisted of a horizontal array of red light emitting diodes (LEDs) set below a transparent Plexiglas surface. Each LED was 5 mm in diameter. The board was secured to the table such that the leftmost LED, which functioned as the fixation point, was positioned at the midline 40 cm in front of the subject and aligned with the start button. All other LEDs served as targets and were horizontally aligned at 7 distances to the right of the fixation point: 24.5, 28, 31.5, 35, 38.5, 42, 45.5 cm (See Figure 3). These targets are referred to as T1-T7 respectfully.

Infrared-light emitting diodes (IREDs) were attached to the participant's right index finger and inner wrist with adhesive tape. The experimenter ensured that the pad of the participant's index finger was unobstructed. The diode wires were secured to permit unrestricted arm movements. The 3D positions of the IREDs were recorded with an optoelectronic motion capture system, Optotrak Certus (Northern Digital, Waterloo, ON, Canada) at 200 HZ. Monocular eye position was recorded at 1000 HZ with the Eyelink 1000 table-mount eye-tracking system (SR Research, Mississauga, ON, Canada). The camera lens was positioned approximately 60 cm from the participant's head. The eye tracker was calibrated for every participant, and drift correction was routinely performed according to the manufacturer's guidelines and standards. The synchronization between Optotrak and Eyelink recordings and the stimuli display board was achieved using custom-designed software.

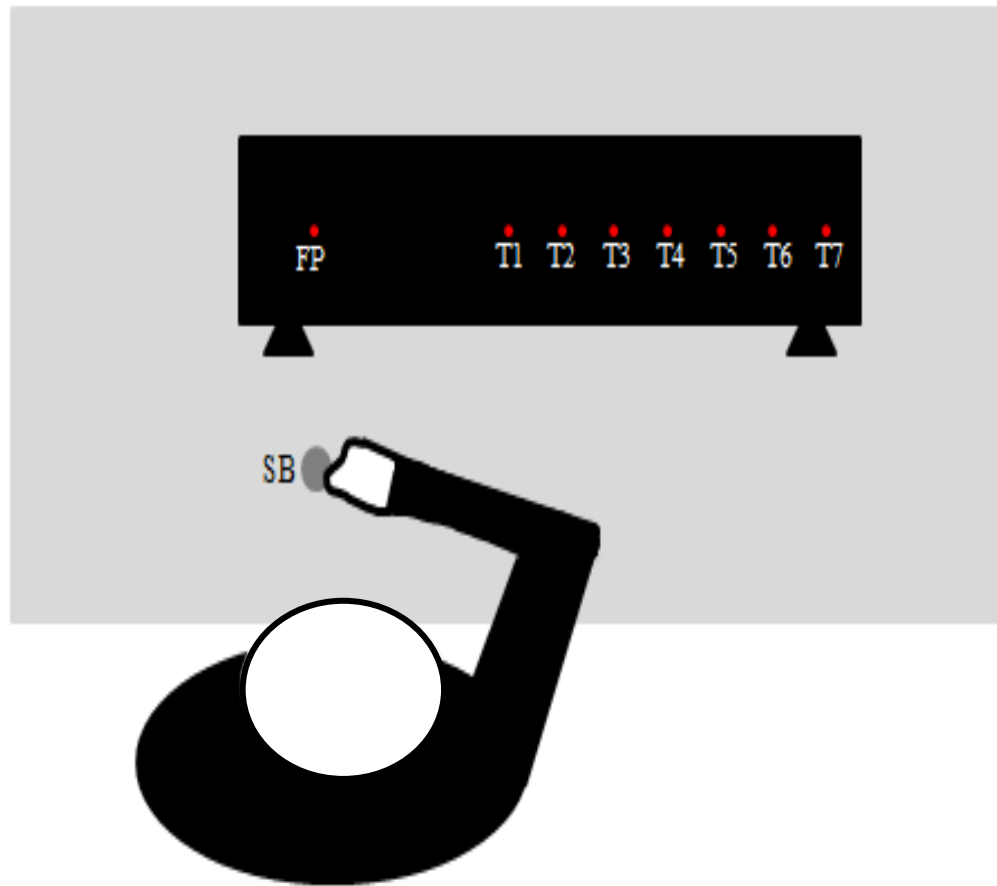


Figure 3. Schematic of Experimental Setup. The fixation point (FP) and the target lights are represented by red circles. Only one red light was illuminated at a time during the actual experimental procedure. The participant began each trial with their right pointer finger depressed on the start button (SB).

2.4 Procedure

Experimental procedures were identical in both Session 1 and Session 2. All participants performed a target displacement judgment task and a pointing task in a darkened room. For both the perceptual judgment and pointing tasks, participants began by staring at a central fixation point. As soon as the fixation point was extinguished, an LED light became illuminated at one of seven peripheral locations (T1-T7) to act as the target. Participants were

instructed to look towards the target as quickly and as accurately as possible. The target would either remain stationary or would be unexpectedly displaced by a distance of 3.5 cm or 7 cm during the participant's initial orienting saccade. Specifically, on jump trials, target displacements were elicited once the saccade reached a velocity threshold of 50 deg/s. Target displacements were only initiated from either T3 or T5 locations and could occur either to the left or to the right of the original target location (See Figure 4). The distance between each target was 3.5 cm, meaning that a small displacement would constitute a jump from T3 to T2, T3 to T4, T5 to T4, or T5 to T6, whereas a large displacement would include those directed from T3 to T1, T3 to T5, T5 to T3, and T5 to T7. Each target jump type specified by size, direction, and starting position, occurred with equal frequency throughout the experiment. A detailed description of each condition type is listed in Table 2. For all statistical comparisons, analyses of variance (ANOVAs) were considered significant when the *p*-value, corrected for multiple comparisons, was $< .05$. The specifics of the target displacement judgment task and pointing task differed as follows.

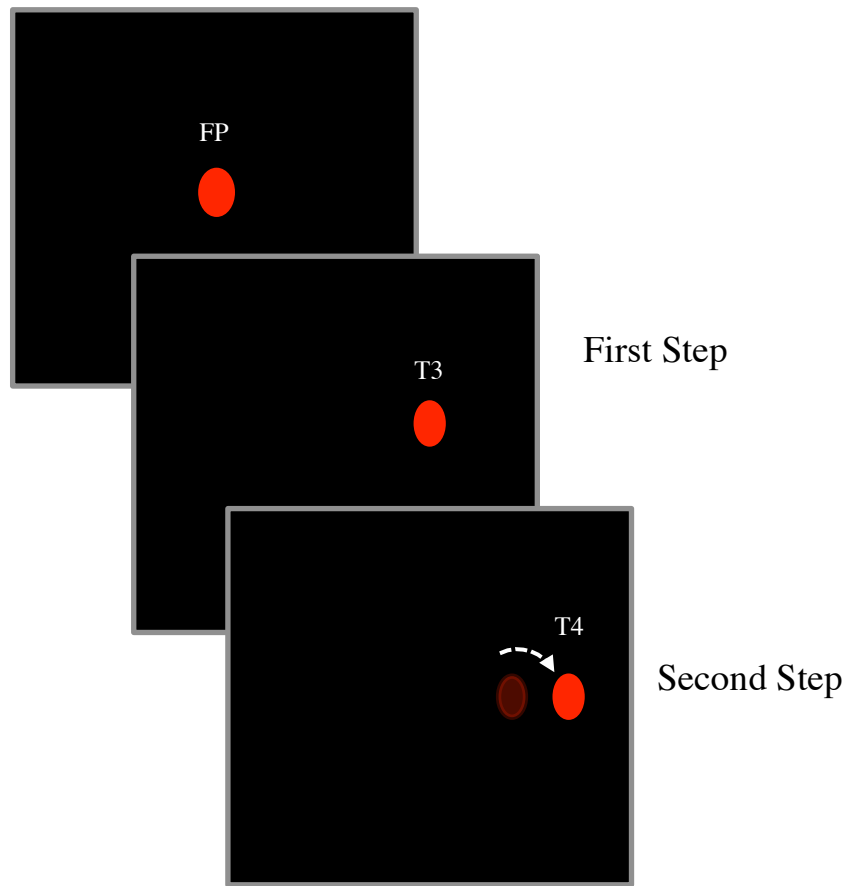


Figure 4. Schematic of Visual Display for an Example Double-Step Trial. The participant begins by staring at the central fixation point. A target will appear in the periphery (T3 shown here) and will either remain stationary (single-step condition) or will be displaced to the left or to the right, a small or a large distance (double-step condition: T3T4 shown here).

Table 2. Detailed description of each condition type

Trial Label	Type	Initial Target Position	Final Target Position	Distance From Fixation Point to Final Target Position (cm)	Size	Direction
T1	Stationary	1	1	24.5	----	----
T2	Stationary	2	2	28	----	----
T3	Stationary	3	3	31.5	----	----
T4	Stationary	4	4	35	----	----
T5	Stationary	5	5	38.5	----	----
T6	Stationary	6	6	42	----	----
T7	Stationary	7	7	45.5	----	----
T3T1	Jump	3	1	24.5	Large	Left
T3T2	Jump	3	2	28	Small	Left
T3T4	Jump	3	4	35	Small	Right
T3T5	Jump	3	5	38.5	Large	Right
T5T3	Jump	5	3	31.5	Large	Left
T5T4	Jump	5	4	35	Small	Left
T5T6	Jump	5	6	42	Small	Right
T5T7	Jump	5	7	45.5	Large	Right

Targets could either remain stationary or could unexpectedly change location during the initial orienting saccade. Initial target position refers to the location of the first LED light illuminated within a trial. Final target position denotes the location of reach endpoint. Large target jumps were 7 cm in size and small target jumps were 3.5 cm. Direction refers to the laterality of the target jump relative to its initial position.

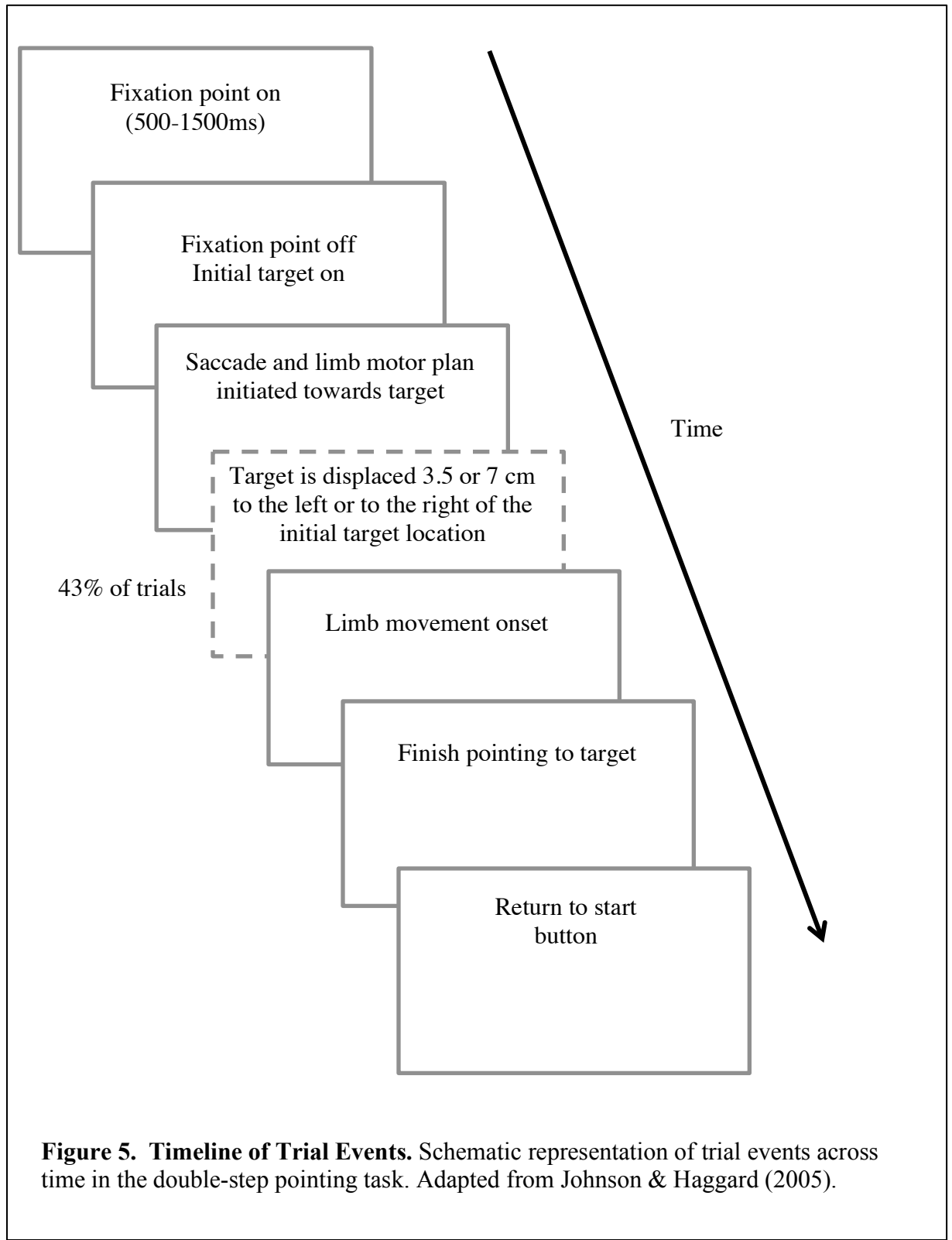
2.4.1 Target Displacement Judgment Task

Each block of the target displacement judgment task consisted of 16 ‘pairs’ of trials. A ‘pair’ of trials was defined as the sequential presentation of a jump and a stationary trial. Each trial type was presented 2 times, for a total of 4 trials per type. The pairing of stationary and jump trials was randomized and the order of presentation was counterbalanced. Following each pair of trials, participants were instructed to verbally report if they thought the target had jumped in either “Trial A” or “Trial B”. The percentage of correct responses were calculated and compared to chance level.

2.4.2 Double-Step Pointing Task

Participants began each trial by depressing a pressure sensitive start button with their right index finger and staring at the fixation point for 500-1500ms. Their left hand rested in their lap. Upon appearance of the peripheral target, participants were instructed to release the start button and point to the final target as quickly and as accurately as possible. The task consisted of 222 trials. To prevent any predictive behavior, the target remained static in 57% of the trials and was displaced in 43% of the trials. Therefore, each stationary condition was presented 18 times, whereas each jump condition was presented 12 times. Jump and stationary trials were randomly interspersed and the trial order was randomized across participants. The target remained visible for the duration of the movement and extinguished when the participant touched it with their pointer finger. Upon touching the target, participants were instructed to return their right pointer finger to the start button to initiate the next trial (See Figure 5).

Prior to experimental trials, participants performed a practice block until they became comfortable with the task



2.5 Data Processing and Analyses

2.5.1 Target Displacement Judgment Task

To assess perceptual awareness of the target jump, the percentages of correct responses for each group and for each jump size were compared to the chance level 50% using separate one-sample t-tests. Further, we ran a $2 \times 2 \times 2$ mixed ANOVA with Group as the between-subject factor (PD vs. Control) and Dopamine Medication Status (On vs. Off) and Target Jump Size (Large vs. Small) as the within-subject factors. The dependent variable was percentage of correct responses.

2.5.2 Double-Step Pointing

Analyses were performed in two steps. First, we analyzed eye and hand movements directed towards stationary targets. Second, we evaluated the effect of target displacement on reach kinematics and trajectories. For both steps, the kinematics of each trial were analyzed offline. To isolate the dependent variables, we restricted the data set to include only points during which the hand was in motion in the forward reach trajectory. Thus, we defined the beginning of the movement as the first of 5 consecutive sample frames in which the wrist IRED exceeded a threshold velocity of 40 mm/s. We defined the end of the movement as the frame with the maximum y-spatial coordinate. If a straight line was drawn between the start button and the array of target lights it would represent increasing depth distance (y-axis). Therefore, the maximum y-spatial coordinate corresponded to the end position when the full reach distance was achieved (i.e. when target was touched).

The specifics of each analysis are described below.

Eye Movements: Stationary Targets

The variable of interest extracted from the eye tracking data was saccade RT. The validity of the experiment was predicated on the premise that saccade RT, and thus timing of target perturbation, did not vary across groups. To confirm this, we ran a 2×2 repeated measures ANOVA with Group as the between-subjects factor (PD vs. Control) and Dopamine Medication Status (On vs. Off) as the within-subject factor.

The saccade of interest was determined as the first saccade greater than 2 degrees that occurred after the initial target light became illuminated.

Kinematic and Reach Trajectories: Stationary Trials

The following dependent variables were extracted from the kinematic data to evaluate performance on stationary trials: hand RT, MD, maximum acceleration, and peak velocity. Hand RT was defined as the time it took to release the start button and to initiate the pointing movement following the illumination of a peripheral target. MD referred to the time from movement onset to reaching the target and therefore movement offset.

Separate 2 (Group: PD vs. Control) \times 2 (Dopamine Medication Status: On vs. Off) mixed ANOVAs, with Group as the between-subject factor and Dopamine Medication Status as the within-subject variable were performed on the four dependent measures.

Kinematic and Reach Trajectories: Jump Trials

The principal dependent measures extracted to assess online corrections were MD difference scores and point of divergence. MD difference scores were calculated with the following equation: Mean MD Jump Target (A) – Mean MD Stationary Target (B) \rightarrow Target (A). This value was calculated individually for each participant and for each jump condition. This concept can best be illustrated with an example. To determine the MD difference score

for when a target first appeared at Position 3 and was subsequently displaced to Position 1 (i.e. T3T1), the mean MD for the stationary T1 condition would be subtracted from the mean MD for the jump T3T1 condition.

A 2 x 2 x 2 mixed ANOVA was performed with the between-subjects factor as Group (PD vs. Control) and the within-subject variables as Dopamine Medication Status (On vs. Off) and Target Jump Size (Small vs. Large). We also computed an additional repeated measures ANOVA including the within-subject factor Direction (Left vs. Right) to confirm that laterality did not have an effect on the dependent variable.

Point of divergence was characterized as the frame at which a reach trajectory on jump trials diverged away from its original hand path to reach the new target location. To determine this point, reach trajectories were first smoothed and normalized in accordance to functional data analysis techniques established by Ramsay and Silverman (2002). In brief, for each participant, on each trial, trajectories were fitted with 6-order b-splines to the x, y, and z spatial coordinates. The data were normalized such that each trajectory was defined at 300 points equally spaced in the y-dimension. As such, the continuously defined data curve constituted a single functional observation, rather than its individual discrete data points (Ramsay & Silverman, 2002; Levitin et al., 2007). We conducted a set of planned mixed functional ANOVAs to contrast each jump type with its corresponding stationary condition (either T3 or T5), across Dopaminergic Medication Status (within-subject: On vs. Off) and Group (between-subject: PD vs. Control). Functional ANOVAs were performed in Matlab 2014 using customized code adapted from <http://www.psych.mcgill.ca/misc/fda/>. Functional ANOVAs extend the uni-variate ANOVA to all points in a trajectory. In this manner, a single functional comparison is performed through the implementation of individual repeated measures ANOVAs at each frame. Critically, these multiple comparisons do not violate

statistical sense as these multiple analyses are only run as a ‘surrogate’ for a single statistical comparison of the entire function (Ramsay & Silverman, 2002). We defined the point of divergence as the point at which greater than 10 consecutive time points for jump trial conditions differed significantly from their respective stationary trial condition at $p < 0.05$, corrected for multiple comparisons.

Chapter 3: Results

First, we empirically evaluated the effects of small (i.e., 3.5cm) and large (i.e., 7cm) intra-saccadic target jumps on conscious perceptual awareness. Second, to isolate any baseline differences between the PD and the control group, we examined ocular and limb kinematics directed towards stationary peripheral targets. Lastly, we assessed online motor performance in response to large, consciously-perceived, and small, subliminal target displacements.

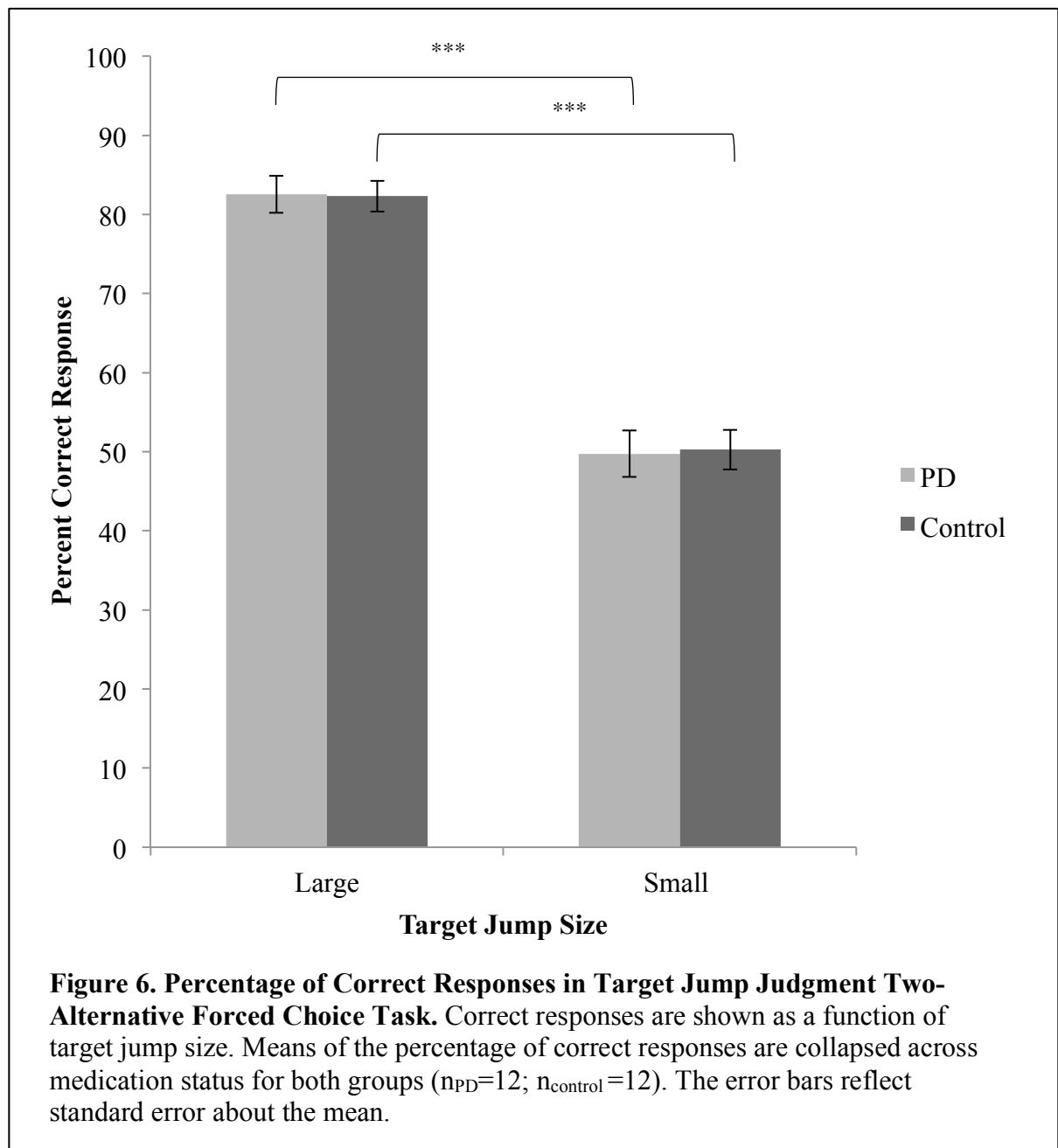
3.1 Target Displacement Judgment Task: Perceptual

Awareness Results

Target jump size had a significant effect on the percentage of correct responses [$F(1, 22) = 221, MSe = 228, p < .001$], with greater accuracy resulting for large relative to small target jumps. This confirmed that the size of the intra-saccadic target jump influenced conscious perceptual awareness (Figure 6). The main effects of Group and Dopaminergic Medication Status, and the Group x Target Jump Size, Group x Dopaminergic Medication Status, Dopaminergic Medication Status x Target Jump Size, and Group x Target Jump Size x Dopaminergic Medication Status interactions were not statistically significant, all $F < 1$.

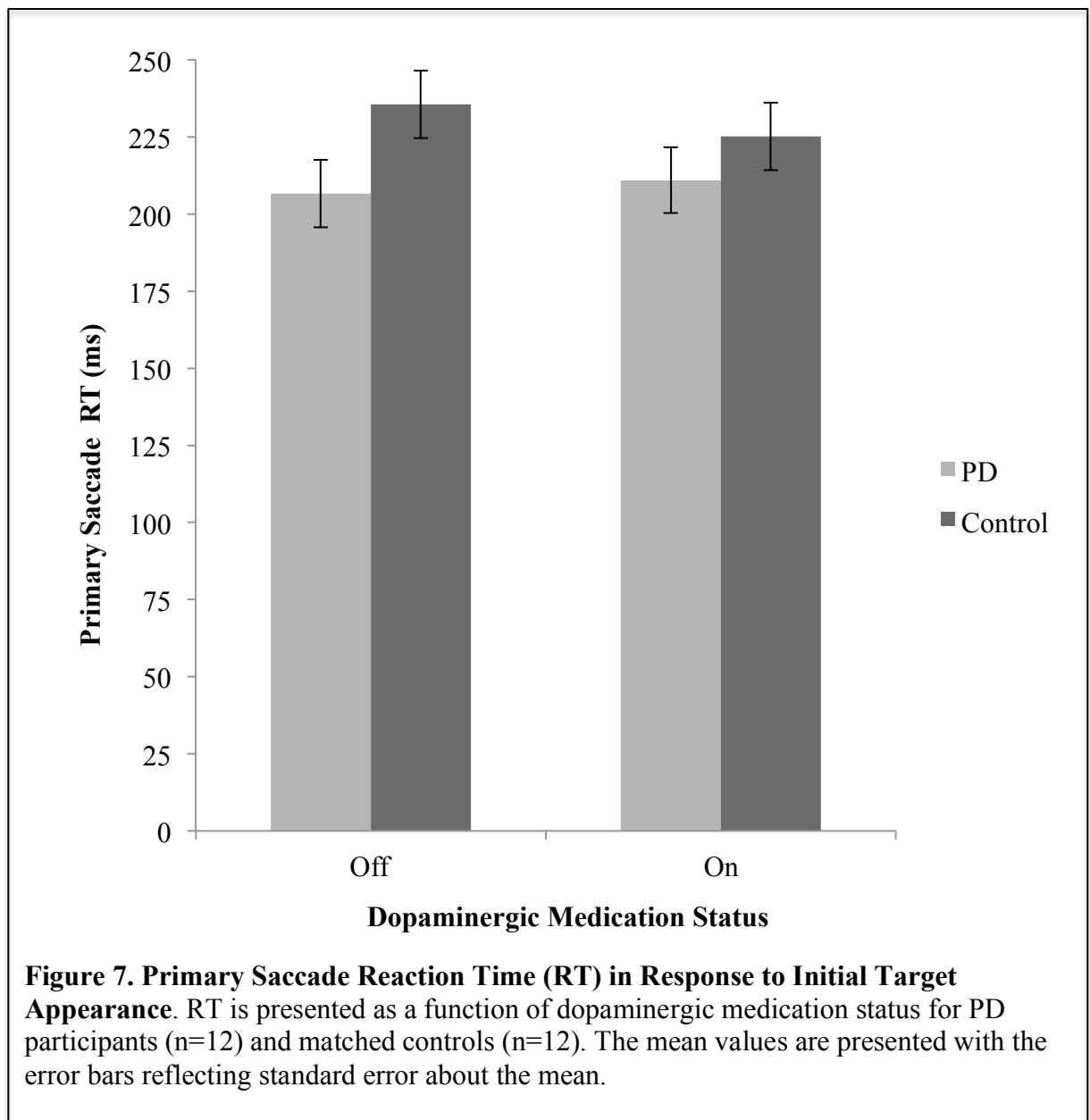
Overall, participants correctly identified 82.4% of the large intra-saccadic target jumps and only 50% of the small intra-saccadic target jumps. One-sample t -tests indicated

that accuracy rates for both groups were significantly greater than the 50% chance level for large intra-saccadic target jumps [$t(11) = 13.827, p < .001$ for PD; $t(11) = 16.679, p < .001$ for controls]. In contrast, accuracy rates for both groups did not significantly differ from 50% chance level for small intra-saccadic target jumps [$t(11) = -0.089, p = 0.534$ for PD; $t(11) = 0.104, p = 0.919$ for controls].



3.2 Saccade RT and Target Jump Timing Results

A 2 x 2 mixed ANOVA revealed no main effect of Group [$F(1,22) = 2.015$, $MSe = 2767$, $p = 0.170$] or Dopaminergic Medication Status [$F(1,22) = 1.497$, $MSe = 71.84$, $p = 0.234$] on saccade RT. The interaction between Medication Status and Group was significant [$F(1,22) = 8.999$, $MSe = 71.84$, $p < .05$, Figure 7] reflecting a slight decrease in saccade RT for controls and a slight increase in saccade RT for PD patients while on dopaminergic medication. To follow up, we directly confirmed that the exact timing of the target jump did not significantly differ between Groups [$F(1,22) = 0.158$, $MSe = 1162$, $p = 0.695$] or across Medication Status [$F(1,22) = 1.96$, $MSe = 137.9$, $p = 0.180$]. Further, these variables did not interact [$F(1,22) = 1.404$, $MSe = 137.9$, $p = 0.249$]. This confirmed that equal preparatory phases occurred for both groups and across all conditions.



3.3 Limb Movement Characteristics: Stationary Trials

Patients with PD exhibited significantly longer hand RTs [$F(1,22) = 4.327$, $MSe = 3.15 \times 10^4$, $p < .05$, Figure 8] and significantly decreased peak velocities compared to healthy controls [$F(1,22) = 4.449$, $MSe = 2.38 \times 10^5$, $p < .05$]. However, there was no significant main effect of group on overall MD [$F(1,22) = 2.331$, $MSe = 2.37 \times 10^5$, $p = 0.141$], nor on

maximum acceleration [$F_{1,22} = 2.374$, $MSe = 5.18 \times 10^7$, $p = 0.138$]. Medication status did not significantly affect any of the dependent variables including hand RT, MD, peak velocity, and maximum acceleration, all $F < 1$. Similarly, Medication Status did not significantly interact with Group for any of these dependent variables [$F(1,22) = 0.580$, $MSe = 2419$, $p = 0.455$ for hand RT; $F(1,22) = 0.054$, $MSe = 5.01 \times 10^4$, $p = 0.819$ for MD; $F(1,22) = 0.234$, $MSe = 1.55 \times 10^4$, $p = 0.633$ for peak velocity; $F(1,22) = 0.461$, $MSe = 1.39 \times 10^7$, $p = 0.504$ for maximum acceleration].

3.4 Limb Movement Characteristics: Jump Trials

A defining trait of automatic online corrections is that they do not increase the overall MD. Our results revealed that patients with PD abide by this trend, both when the online corrections were consciously perceived and when they were subliminal. Separate t -tests indicated that MD difference scores for jump trials minus stationary trials were not significantly different from zero for the PD group across any of the condition types [$t(11) = 1.393$, $p = 0.191$ for PD Off Large; $t(11) = -1.047$, $p = 0.318$ for PD Off Small; $t(11) = 0.409$, $p = 0.690$ for PD On Large; $t(11) = 1.383$, $p = 0.194$ for PD On Small, Figure 9A]. Similar findings were observed in controls, with two notable exceptions. Controls demonstrated MD difference scores significantly greater than zero for large target jumps while off of dopamine medication [$t(11) = 3.071$, $p < .05$] and for small target jumps while on dopamine medication [$t(11) = 3.329$, $p < .01$]. MD Difference scores were not significantly different from zero for the control group for any of the other conditions [$t(11) = 1.687$, $p = 0.120$) for Controls Off Small; $t(11) = 1.749$, $p = 0.108$) for Controls On Large, Figure 9B].

Critically, the mixed ANOVA revealed that MD difference scores were not significantly different between Groups [$F(1,22) = 2.179$, $MSe = 950$, $p = 0.154$], across Dopaminergic Medication Status [$F(1,22) = 0.314$, $MSe = 829.81$, $p = 0.581$] or Target Jump Size [$F(1,22) = 0.513$, $MSe = 2193$, $p = 0.48$]. PD patients and healthy age-matched controls exhibited equivalent changes in MD, regardless of conscious versus unconscious perception of target jumps or medication status. A significant interaction was only demonstrated between Dopaminergic Medication Status and Target Jump Size [$F(1,22) = 4.594$, $MSe = 1045$, $p < .05$], such that participants overall, collapsing across groups, exhibited increased MD difference scores for small/subliminal target displacements on relative to off dopaminergic medication with no effect on larger target jumps.

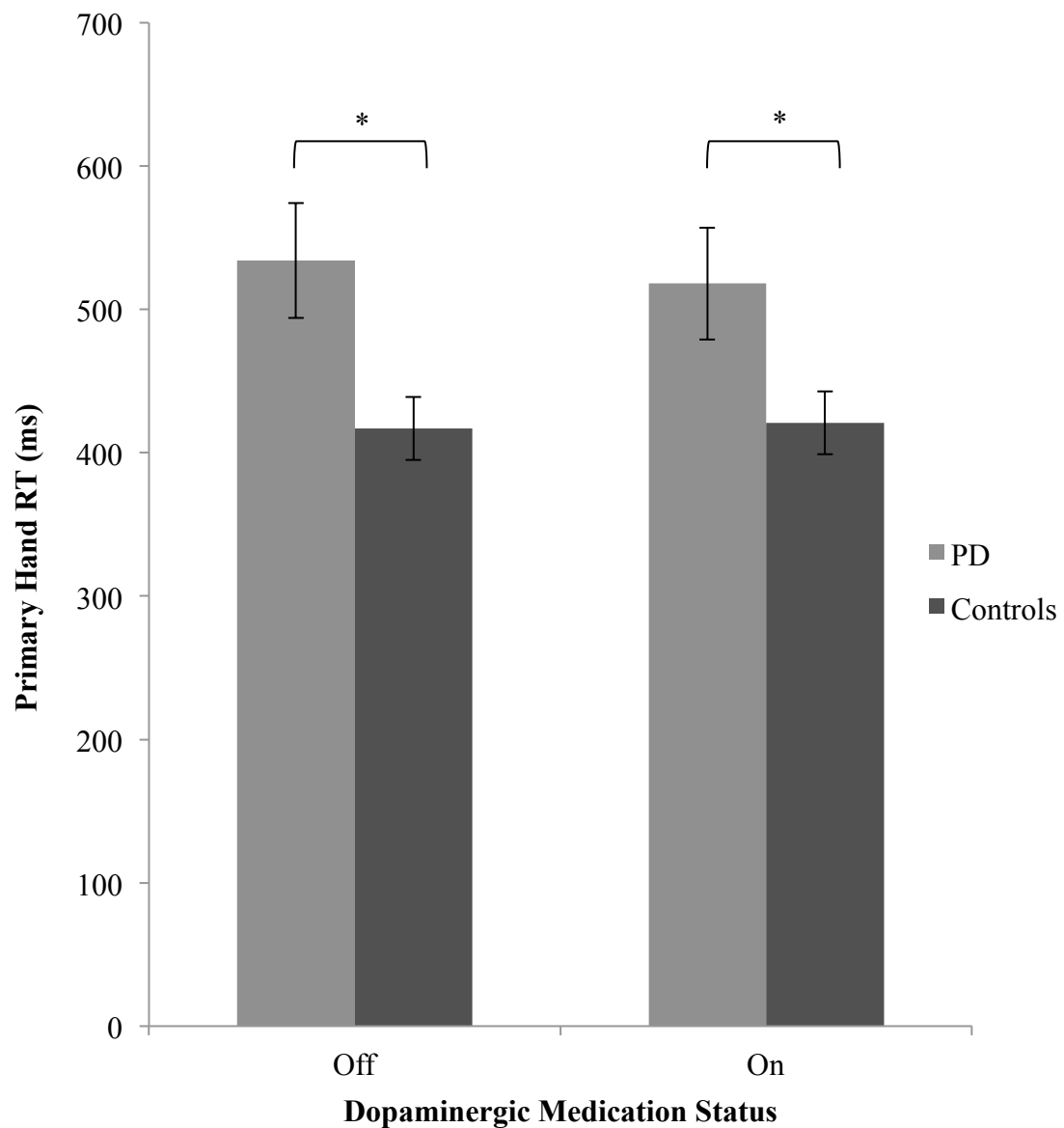
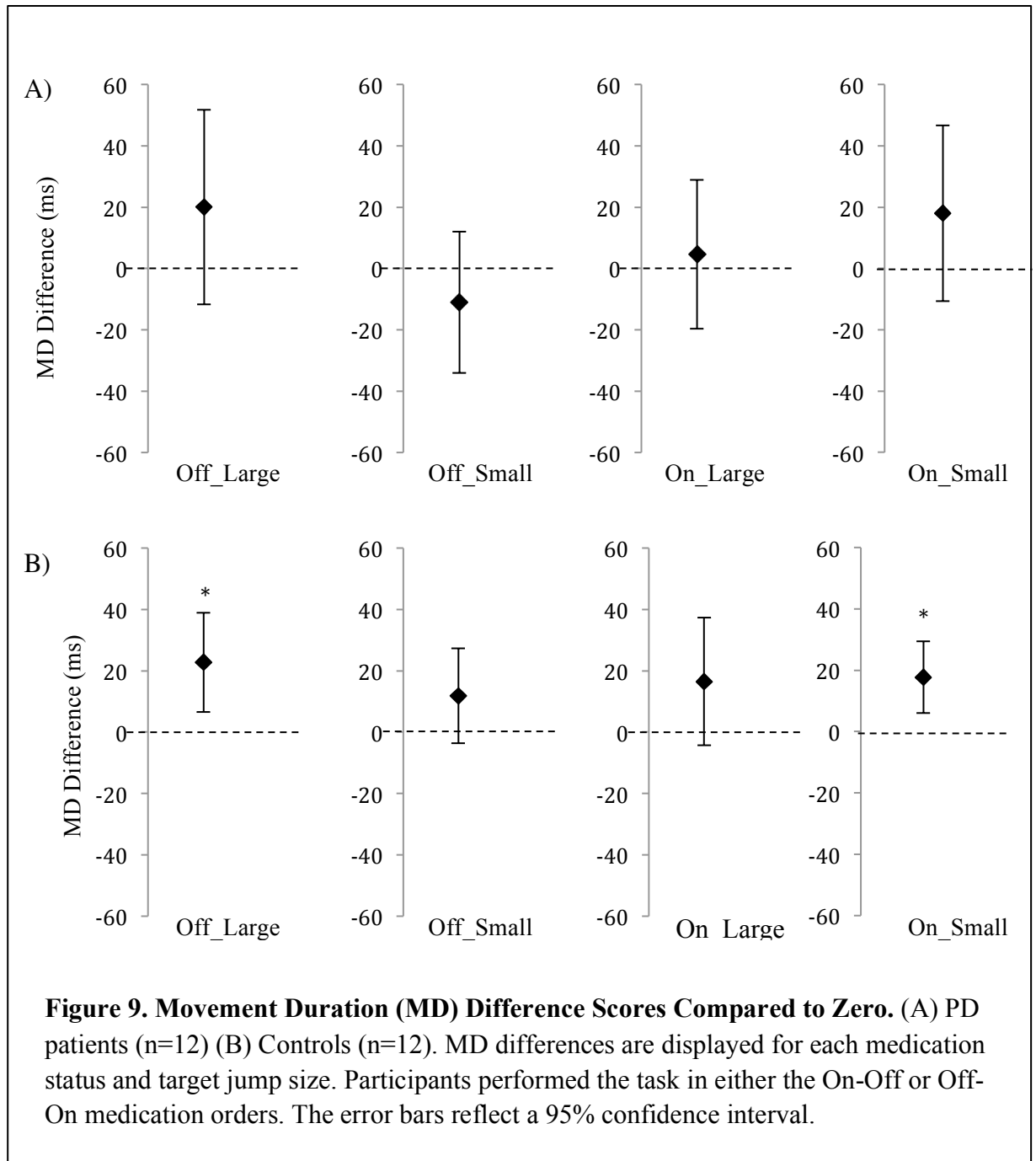
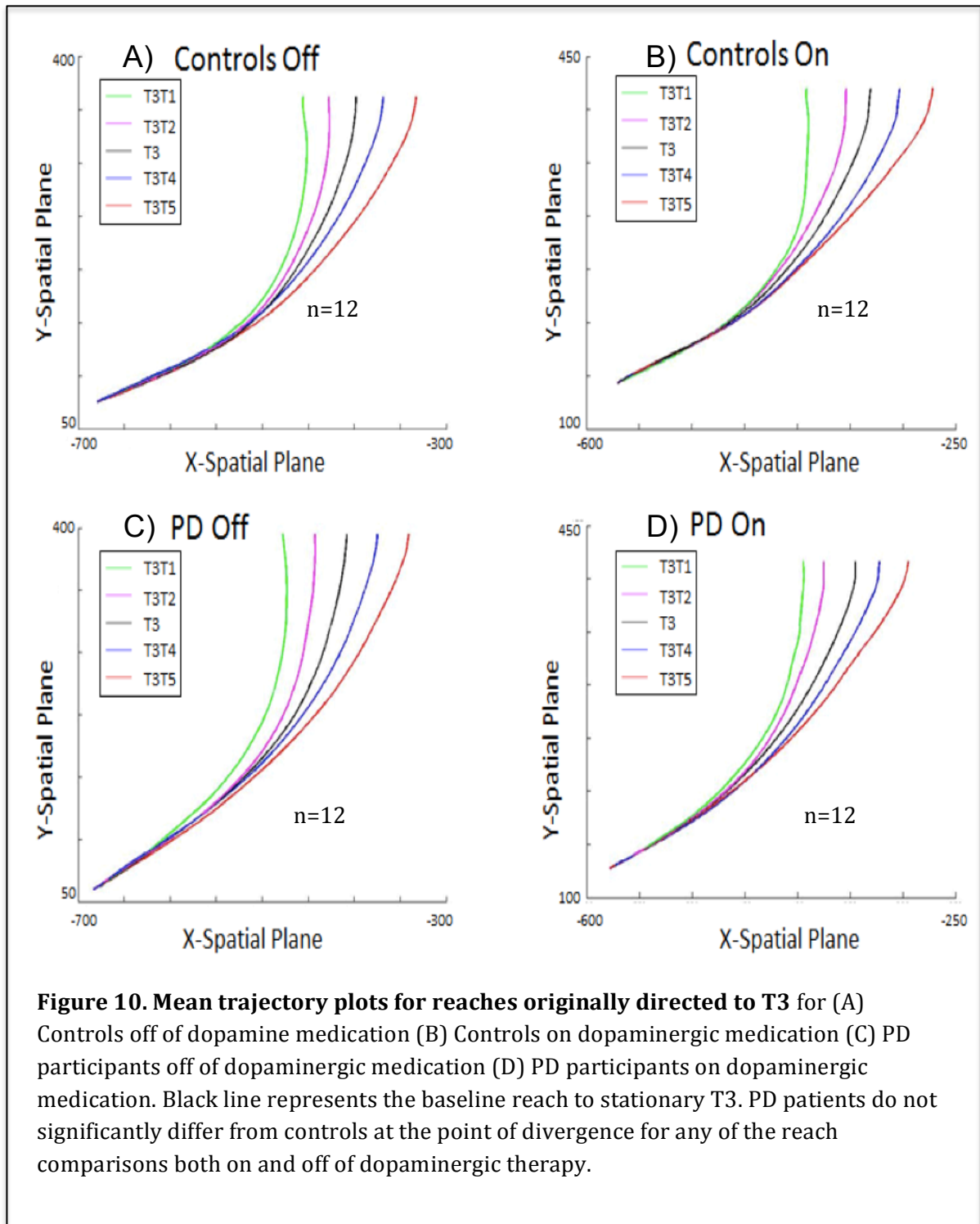


Figure 8. Primary Hand Reaction Time (RT) in Response to Initial Target Appearance. RT is presented as a function of dopaminergic medication status for PD participants (n=12) and matched controls (n=12). The mean values are presented with the error bars reflecting standard error about the mean.





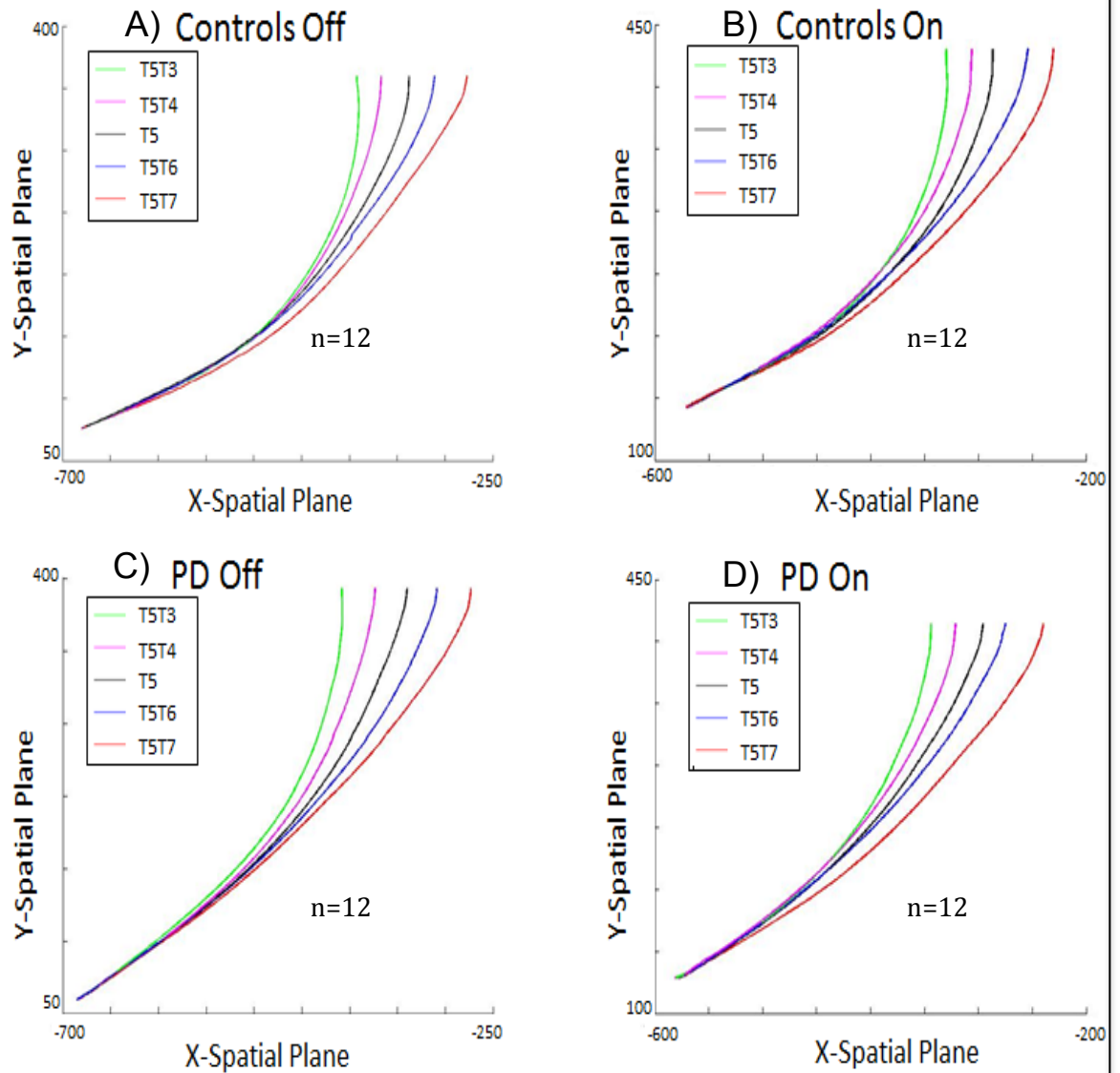


Figure 11. Mean trajectory plots for reaches originally directed to T5 for (A) Controls off of dopamine medication (B) Controls on dopaminergic medication (C) PD participants off of dopaminergic medication (D) PD participants on dopaminergic medication. Black line represents the baseline reach to stationary T5. PD patients do not significantly differ from controls at the point of divergence for any of the reach comparisons both on and off of dopaminergic therapy.

As illustrated in Figures 10 and 11, target end-position had a significant effect on lateral deviation throughout the reach for both healthy controls and PD patients, regardless of medication status. When the target jumped from its original position to the left, a noticeable leftward shift in reach direction occurred relative to the magnitude of the displacement. Similar patterns in online reach adjustments were observed for rightward target displacements. To further investigate this effect, we implemented individual 2 x 2 x 2 mixed measures functional ANOVAs to assess pair-wise comparisons between jump trials and their relative stay trials across the movement trajectories. Group was the between-subject factor (PD vs. Control) whereas Target Condition (Jump vs. Stay) and Dopaminergic Medication Status (On vs. Off) were within-subject variables. A functional main effect of Target Condition (i.e. Jump vs. Stay) revealed the percentage of the trajectory travelled before the two trajectories significantly differed from one another. Furthermore, we examined interactions between Group, Medication Status and Target Condition to investigate whether these factors and variables jointly or differentially impacted reach divergence. There were no significant effects of Group or Dopaminergic Medication Status on divergence scores.

Half of our jump trials were initiated from T3 and half were initiated from T5. We report our divergence analyses relative to this preliminary target position, as divergence was based upon relative deviations from the original target trajectory path. For trajectories initially directed to T3, large target displacements had a relatively early effect on reach trajectories, such that a smooth divergence was noted at 16% and 26% into the total y-movement for T3T1 and T3T5 trials respectively. This divergence from stay trials was maintained for the remainder of the pointing trajectory such that the difference between stay and jump trials was noted for 84% and 74% of the movement for T3T1 and T3T5 trials respectively. Similar results were observed for large displacements for movements initially

directed at T5. T5T3 diverged at 25% and T5T7 diverged at 14% into the total y-movement with differences in trajectory being significant between stay and jump trials for 75% and 86% of the pointing movement respectively. The pair-wise functional comparisons of small target displacements revealed a smooth divergence in reach trajectories at 31%, 30%, 28% and 42% of the total y-movement for T3T2, T3T4, T5T4 and T5T6 conditions respectively. All jump trajectories significantly differed in the x-dimension from their relative stay trial from the identified point of divergence onwards (i.e. until the endpoint of movement). That is, the small target displacements stay and jump trajectories were significantly different for 69%, 70%, 72%, and 58% of the movement for T3T2, T3T4, T3T5 and T5T6 conditions respectively. A significant interaction between condition and group was observed only for T3T4 trials between frames 20 (at 6% of total y-movement) and 46 (at 15% of total y-movement) for a duration of 9% of the trajectory. Group did not interact with condition in any of the other functional pair-wise comparisons, suggesting that disease status did not significantly affect the ability to diverge trajectories online. Similarly, Medication Status significantly interacted with Condition for only the T5T4 pairwise-comparisons between frames 9 (at 3% of total y-movement) and 26 (at 9% of total y-movement), for a duration of 6% of the trajectory. All other functional comparisons did not reveal any significant interactions between Group or Medication Status. This indicates that PD diagnosis and medication status did not significantly influence the point at which movements began to diverge when target location moved relative to when the target position remained invariant. Of importance, there was not a significant 3-way interaction between Group, Medication Status, and Condition (i.e., stay vs. jump) for any of the functional pair-wise comparisons.

Chapter 4: Discussion

4.1 General Summary of Results

In the present study, we investigated the extent to which in-flight reach corrections could be performed automatically in a sample of PD patients, both with and without conscious awareness of the need for reach adjustments. The validity of our methodological design relied on the premise that saccade RT, and thus the target jump timing, did not differ between groups or across medication status. We directly confirmed that orienting saccades were not delayed in PD, and further that medication status did not alter saccade latency. As a control, we directly confirmed that the latency of the target jump was in fact equal between groups and across medication statuses. An alternative forced-choice task was used to empirically confirm that altering the size of intra-saccadic target jumps was an effective method for manipulating conscious perceptual awareness. More specifically, small intra-saccadic target jumps were presented below the threshold for conscious perceptual awareness of change, whereas large intra-saccadic target jumps reached threshold for conscious perceptual awareness. Dopaminergic medication did not significantly affect either group's perceptual threshold. Taken together, we were able to manipulate conscious awareness of target jumps independent of motor demands, rendering all conditions more equivalent in terms of difficulty for PD patients and healthy controls.

To assess baseline differences in hand kinematics, we first assessed performance during stationary target trials. An overall increase in hand RT and decrease in peak velocity was observed for PD patients relative to controls, indicating that the patient group experienced disease-associated bradykinesia. In accordance with our original critique, our results support the notion that triggering a target displacement at hand movement onset, as

per previously applied methodology, would increase the initial preparatory phase for the PD group relative to the healthy controls. Critically, no other movement characteristics differed between groups, allowing for more straightforward assessment of the online motor corrective system in perturbed target trials.

MD difference scores were equivalent between our control and patient groups for all sized target jumps and across all medication statuses. In our PD group, target displacements did not affect the overall MD for both consciously perceived and subliminal online corrections. This is analogous to the pattern observed in healthy young controls. These results stress the similarity in performance of consciously perceived versus subliminal online motor corrections in PD patients. This pattern implies that the degree of consciousness and control over the corrective system is irrelevant for the engagement of the automatic pilot in PD participants.

For our healthy, elderly controls, we did find that in two out of four conditions, MD difference scores were greater than zero (i.e., jump target trajectories took significantly longer than stationary target trials). Despite this increase in MD, smooth, online corrections still occurred early into the movement execution for healthy age-matched controls. Again, these corrections were statistically equal to those of PD patients and were unaffected by dopaminergic therapy.

The most significant findings of this study relate to the intact automatic processing of the corrective system in PD. After controlling for potential confounds, we showed that conscious awareness did not affect the online reach corrections of PD patients. Specifically, we did not find any differences in terms of where trajectories diverged for jump trials relative to stationary trials between PD and control groups for either small, undetected, or large, and hence consciously-perceived, target jumps. Moreover, our kinematic analysis included eight

replications in each of the On and the Off dopamine medication sessions due to numerous different endpoints and initial starting positions. For seven replications, the point of divergence was not affected by dopaminergic medication and for seven replications, it was not affected by group. These results were irrespective of jump size. There was one instance in which Group and one instance in which Dopaminergic Status affected jump trajectory for brief and unsustained periods during the movement trajectories. These differences were observed for PD patients compared to controls during 6-15% of the trajectory period for T3T4 and for dopaminergic therapy during the 3-9% of the trajectory for T3T5. These differences in trajectories occurred before the point of sustained divergence between Jump and Stay trials and their significance is unclear.

4.2 Online Motor Control in Healthy Ageing and in Parkinson's Disease

As mentioned in the General Summary of Results, target displacements were shown to elicit increased MDs for healthy aged-matched controls in two out of four of our jump conditions. Several previous studies have provided evidence for age-induced deficits in online motor control, with older adults taking markedly longer to initiate corrections (Plotnick et al., 1996; Rossit & Harvey, 2008; Sarlegna, 2006). Though delayed corrective mechanisms in older adults might relate closely to general impairments in central planning that naturally accompany ageing, Rossit and Harvey (2008) found that overall smoothness and accuracy for older healthy adults for amended trajectories remained comparable to that of younger adults, as we found here. In their study, Rossit and Harvey (2008) reported MD difference scores of approximately 50 ms longer for elderly participants relative to younger participants, leading them to suggest that the corrections of older adults remained too rapid

for a new motor command to have been completely reprogrammed. Moreover, their data showed that slowness in RTs was not restricted to perturbed double-step trials, but rather older adults also took longer to initiate movements in unperturbed trials. Consequently, it was argued that online corrections were still being performed with a high degree of automaticity; however, general age-related declines in processing speed may have enhanced latencies in their corrective movements. It is unclear whether this trend will persist in our data when an increased number of participants are added.

Interestingly, in contrast, increases in MD were not observed for our PD group in any of the jump conditions. Nonetheless, our data for PD participants appears to be trending in a similar direction as the control results. One possibility for this anomaly between PD patients and controls could relate to the greater within-group variability for our PD data that prevents such trends from reaching significance. Provided that there is high heterogeneity in the phenotypes of PD patients, it might be necessary to increase our power to observe significant differences in MD for jump target trials relative to stay target trials (Foltynie et al., 2002; Lewis et al., 2005). Though less likely, it might be possible that patients with PD are refractory to age-related impairments in online motor control, owing to dorsal striatal dysfunction enhancing automatic behavioural responses and online guidance (Benke et al., 2003; Cameron et al., 2010; Cools et al., 2010; Klockgether et al., 1994; Reed, 1998). In theory, dorsal striatal impairments might lead to motor performance being guided by greater automaticity, yielding enhanced performance by PD patients on tasks such as the automatic double-step paradigm. Alternatively, Reed (1998) posited that patients with PD might experience increased reliance on online motor control as a compensatory mechanism for the initial noise in their motor system during the pre-programming motor phase. Noise and variability in the PD motor system might be attributable to dysregulation of striatal circuits,

and thus inconsistent premotor cortex activation. Though speculative, our current data seems to support the contention that striatal dysfunction might elicit an advanced online monitoring and corrective system in PD to overcome these disruptions. The addition of more participants will help clarify these hypotheses.

The greatest insight into the online corrective system comes from our analyses of the reach divergence points. This functional analysis of online corrections indicated that neither Group nor Medication Status interacted with Condition (i.e. divergence point) across any of the frames for the vast majority of reach comparisons. The consistency in divergence scores suggests that PD patients and healthy controls were able to elicit corrections at approximately the same point in their reach trajectories and that these smooth changes in trajectory were maintained once they occurred, irrespective of Group or Medication Status. However, Group did interact with Condition for T3T4 comparisons between 6% and 15% of the overall movements. We do not believe that this interaction is reflective of significant differences in online corrections between groups. First, this interaction occurred at a non-critical point in the overall reach trajectory. More importantly, there were no significant interactions at relevantly defined points in the trajectory, such as at the point of divergence, which occurred at 42% of the overall reach, or at reach endpoint. Similarly, Dopaminergic Status briefly interacted with Condition at the 3-9% time points in overall movement trajectory for displacements T5T4. Again, this point of interaction occurred well before the point of divergence and reach endpoint. Increased path variability between-subjects may have led to these two potentially spurious interactions earlier on in the reach. Further subjects should be tested to investigate the significance of this finding.

4.3 Conscious Awareness of Online Corrections

The main objective of this study was to elucidate how conscious perceptual awareness of target position change affects PD patients' ability to elicit automatic, online reach corrections. Our results indicate that conscious awareness did not alter the degree to which participants with PD could perform corrections automatically. Corrections in fact started earlier for both PD and controls for the consciously-perceived target perturbations relative to the subliminal perturbations. This was demonstrated by earlier correction times. We attribute this difference to the size of the target displacement that had to be accommodated with a smooth online change. We interpret that divergence appeared earlier for larger (consciously-perceived) jumps because the change in direction is greater relative to the small (subliminal) jumps. The corrective system will aim to make the change smooth and gradual, even after the intention to change end point has been registered. It is therefore likely that both sized jumps start to diverge at the same time, but this smaller change in trajectory takes slightly more time to diverge significantly from the original trajectory, given more similar endpoints for small relative to large jumps.

The results of the present study directly oppose those established by Desmurget et al. (2004), which found PD-related deficits in consciously-perceived target changes, whereas subliminal changes in target locations were performed normally by PD patients. We have identified two potential explanations for our conflicting results. First, Desmurget et al. (2004) applied a between-subject design, using different PD participants in their conscious double-step task than in their subliminal double-step task, making their results less comparable across these different experiments. Further, they included patients in both of their experiments, one in which target changes were consciously perceived ($n=5$) and one in which

they were not ($n=7$), who had atypical ages of PD onset (i.e., $< \text{age } 40$) and with highly variable disease durations. These participant characteristics, as well as the small number of patients, make their results less generalizable and reliable. PD is a highly heterogeneous neurological disorder, often presenting differently among patients. For this reason, we used a within-subject design to help limit any additional sources of variability within our data. Furthermore, we applied strict inclusion and exclusion criteria, restricting our sample of PD participants to ensure all patients had a specific diagnosis of idiopathic PD and presented with typical PD features.

More significantly, as we discussed previously, Desmurget and colleagues (2004) failed to dissociate the conscious perception of the target jump from the temporal aspects of the target jump. Critically, in their study, consciously perceivable target displacements were yoked to the initiation of a participant's pointing movement, whereas subliminal target displacements were yoked to initial pro-saccades. PD-related limb bradykinesia would have led to target perturbation at movement onset, increasing the time PD patients had to plan and prepare their action toward the initial target position. When we equalized the preparatory phase between both groups, we did not find impairments in automatic action control, even with consciously-perceived target displacement in our PD sample. Therefore, our data suggest that the length of time one has to plan and prepare the initial action might influence the overall motor fluidity and flexibility. A similar conclusion can be derived from previous work that has collectively established temporal limitations on online corrections. For example, Liu and Todorov (2007) demonstrated that young healthy adults were unable to fully amend their trajectories in response to late-occurring target perturbations (i.e. 300 ms following movement onset). Likewise, delayed corrections have also been observed when targets are displaced at the time of peak movement velocity (Komilis et al., 1993). As a

movement plan significantly progresses, the visuomotor system might become less efficient at correcting potential errors (Liu & Todorov, 2007; Sarlegna & Mutha, 2014). One theory is that the information surrounding the precise target location might become less relevant in the latter parts of the movement as the motor control system is more heavily focused on endpoint stability (Liu & Todorov, 2007). Undoubtedly, the visuomotor system must take into consideration the costs (i.e. time and stability) and benefits (i.e. precision) before facilitating an online correction. Taken together, we believe that the previously reported PD-related deficits in conscious online motor control might have arisen as a consequence of additional temporal constraints disproportionately affecting the PD group relative to the controls.

4.4 Role of Striatum/Basal Ganglia in Movement Generation and Online Motor Control

Interestingly, we did not find a clear and significant effect of exogenous dopamine on our measured motor variables. However, PD patients had significantly slower hand movement RTs and peak velocities overall. We confirmed that PD participants properly adhered to the medication schedule by performing clinical exams and estimating motor function with the standardized UPDRS during both sessions. UPDRS scores were significantly higher when participants were scheduled to be off of their dopaminergic medication compared to when they were scheduled to be on their dopaminergic medication. This also helped verify that testing did not occur during a “wearing-off” period for the On testing sessions, when patients were taking their usual dopaminergic therapy.

It is worth noting that impairments in PD and correspondingly the magnitude of improvements related to exogenous dopamine seem greater with increasing task complexity (Benecke et al., 1987; Hanna-Pladdy & Heilman, 2010). That is, PD patients are expected to

experience the greatest improvement in functioning with medication during more demanding motor processes, such as when an action has to be initiated and a competing response is inhibited or when complex motor sequences, with multiple, chained action plans are performed (Hood et al., 2007; Shook et al., 2005). It is possible that the relatively simplistic reaching movement that is elicited by a target is less impaired in PD and hence less sensitive to On-Off differences. This interpretation is supported by reports that performance of PD patients in simple behavioral paradigms, such as RT tasks, does not improve under dopaminergic medication (Jahanshahi et al., 1992; Jordan et al., 1992; Müller et al., 2001).

Given that online motor corrections involve the smooth modulation of ongoing responses and do not require complex motor switching, it is not completely unexpected that PD participants performed this automatic function normally compared to age-matched controls and that dopaminergic therapy did not alter performance. Further, the fact that we did not find any between group differences in online corrections questions the role of the dopaminergic system-striatum/basal ganglia in enactment of online motor corrections. In theory, if dopaminergic pathways in the basal ganglia truly mediate the online corrective response, then diminished dopamine supplies associated with PD would hinder functioning in this domain. Similarly, replenishing these dopamine levels should improve performance.

In the literature there are conflicting reports as to the exact role, if any, of the basal ganglia in the online control of action. Reduced capabilities in performing smooth and efficient corrective movements online have been reported in only few experiments investigating patients with HD (Smith et al., 1999) and PD (Desmurget et al., 2004; Tunik et al., 2004). Although some groups have supported these clinical findings by showing increased activity in the Gpi and STN of healthy controls during the error correction (Grafton

& Tunik, 2011; Tunik et al., 2009), other groups have not (Desmurget et al., 2001; Diedrichsen et al., 2005; Jueptner & Weiller, 1998).

Initially, our data appears to be at odds with previous clinical reports. However, we suggest that evidence from HD patients must be interpreted cautiously. Given that atrophy beyond the basal ganglia circuits is common even in the preliminary stages of HD, it is difficult to attribute impairments in online movement guidance strictly to this region (Ciarmiello et al., 2006; Hedreen et al., 1991; Rosas et al., 2008; Walker, 2007). Moreover, in the few other studies reporting a role of the basal ganglia, corrective errors were evoked through viscous mechanical perturbations of the limb or body position, which elicited the additional need for dynamic control of force (Grafton & Tunik, 2011; Tunik et al., 2004; Tunik et al., 2009). We postulate that our double-step design measures a much more simplistic and direct automatic form of online visuomotor corrections. Finally, Desmurget et al. (2004) only reported deficits in the online corrective system when target displacements were evoked at hand movement onset, which posed the possibility for a confounding influence of disease-related bradykinesia on PD performance. In this way, the cause of our apparently discrepant results is clarified.

In contrast, when online feedback and motor control is investigated in the absence of unpredictable effector perturbations and confounding disease pathology, a wide breath of studies support our proposal that the basal ganglia are uninvolved in rapidly controlling ongoing actions. First, using PET, Desmurget et al. (2001) failed to find changes in striatal activity during double-step trials, which evoke automatic online guidance, relative to single-step trials, which do not. Instead, metabolic changes in activity were restricted to the contralateral PPC, contralateral motor cortex and ipsilateral anterior cerebellum during the generation of corrective movements (Desmurget et al., 2001). Likewise, event-related fMRI

designs have investigated the neural substrates involved in the planning and online control of motor sequences and have found increased striatal activity exclusive to when the action is being preprogrammed or internally generated. Notably, no such increases in striatal activity were reported during the online execution of motor sequences or during online sensory feedback processing (Boecker et al., 2008; Elsinger et al., 2006; Ogawa et al., 2006). Congruent with this, overwhelming evidence suggests that PD patients are in fact able to continuously use sensory feedback during reaching or tracking movements (Bloxxham et al., 1984; Day et al., 1984; Flowers et al., 1976; Ghilardi et al., 2000). Pertinent to our findings, Johnson et al. (1994) also reported that exogenous dopamine medication had no effect on the ability for PD patients to control their movements in an online visual tracking task. As first alluded to by Desmurget et al. (2004), if the dorsal striatum is truly responsible for the online processing of actions, then patients with PD should present with deficits in their ability to use visual feedback in these tasks. Furthermore, increasing dopamine supplies to mediate dorsal striatal function should improve performance in this domain. Our data, along with others, contend that this is not the case. PD patients, regardless of dopaminergic medication status, were consistently capable of using online feedback to update their internal representations of goal positions and amend their actions appropriately in-flight. Taken together, the paucity of reports of impaired online control in patients with basal ganglia abnormalities, in contrast with the extensive documentation of other motor and cognitive deficits in PD and patients with BG lesions (Jankovic, 2008; Kudlicka et al., 2011; Moustafa et al., 2016; Park & Stacy, 2009), could further be in support of our findings.

Several alternative roles have been suggested for the dorsal striatum in subserving both motor and cognitive control. Under conditions in which dorsal striatal dopamine is depleted, as prevalent in PD, deficits in decision making, specifically related to action

selection and initiation in ambiguous contexts (Cools et al., 2006; Ell et al., 2006; Thoma et al., 2008; Troyer et al., 2004) and attentional set shifting (Hayes et al., 1998; Hood et al., 2007; Shook et al., 2005) are observed. Additionally, the dorsal striatum has been implicated in reducing the distractibility of highly salient, yet task irrelevant stimuli (Benke et al., 2003; Cools et al., 2006; Cools et al., 2010). For example, patients with PD are more likely to attend to the more salient stimuli among distractors and select the more automatic or well-practiced response. Congruent with these results, the dorsal striatum is well-positioned anatomically to integrate information from multiple modalities and broadly allocate attention in space and time (MacDonald & Monchi, 2011). Consequently, when this region is impaired attention becomes more narrowed and deliberate responses are harder to initiate over responses that are over-learned or automatic. We suggest that because online reach adjustments are highly automatized and can occur without volitional control, such behavioural responses should not rely on intact dorsal striatal functioning.

4.5 Automaticity in Parkinson's Disease

Rapid online reach corrections are an automatic default response that can occur in healthy participants with and without conscious perceptual awareness or control. These corrections provide a naturalistic and well-understood proxy for directly investigating automaticity in an experimental setting. Our results clearly demonstrated that PD participants were neither impaired during consciously perceived corrections nor during subliminally presented automatic corrections, suggesting preservation of motor automaticity in PD.

Our results correspond well with those from oculomotor studies that suggest that PD patients perform with the same, if not greater, automaticity than healthy controls (Chan et al., 2005; Fielding et al., 2005; Praamstra et al., 2001). In addition, studies examining cognitive

control have emphasized similar patterns of highly automated responses in PD participants during assessments such as the Stroop task (Brown & Marsden, 1988; Djamshidian et al., 2011; Dujardin et al., 1999). As discussed earlier, deficits in suppressing automatic response mechanisms have been posited throughout the PD literature (Henik et al., 1993; Obeso et al., 2011; Praamstra et al., 2001). If these trends hold true, we would speculate that PD would also selectively impair higher-level volitional processes, such as inhibiting or countermanding automatic online reach amendments. Such an outcome would further suggest a relatively dominant level of automaticity in PD that mirrors that of healthy controls. Ultimately, the disruption in inhibitory outputs from the basal ganglia would lead to disinhibition of certain reflexive or impulsive orienting systems in PD. In theory this should translate into a double dissociation between impaired volitional control and spared automaticity in PD.

4.6 Limitations and Future Directions

Although our study is able to answer fundamental questions regarding the automatic pilot in PD, we acknowledge that it contains inherent limitations. First, we must recognize that our conclusion of intact online automatic action control in PD and our interpretations that the basal ganglia are not involved in mediating this process rely on a null result. That is, PD patients and controls, both on and off medication, performed statistically equivalent on all of our critical measures. In response to this, we suggest that our results are not simply attributable to a lack of statistical power, nor could features of our paradigm render it insensitive to detect true differences. First, we showed that our experimental paradigm was in fact capable of reliably detecting divergences in trajectories between stay and jump trials. Divergence in reach trajectories became significantly apparent early-on in the action,

suggesting that our functional data techniques were sensitive to slight changes in positioning. Secondly, we used more than double the number of PD patients in our study than were used in Desmurget et al.'s (2004) original design. Given that despite their small sample size, Desmurget et al. (2004) still reported significant differences between healthy controls and PD patients, we have confidence that our experiment was in fact powered significantly. Last and most compelling, we had a total of 8 different replications in both the On medication session and the Off medication session to find differences between PD and healthy controls if they were indeed present. That is, we looked at 8 separate trajectories contrasting Condition (Jump vs. Stay), Group (PD vs. Control) and Medication Status (On vs. Off). Importantly, in all cases, there were no significant differences between PD patients and healthy controls, nor were there significant effects across medication status. Nevertheless, the Condition variable was significant for all comparisons. Further, the divergence started at similar time points for these trials, with the small jumps having slightly later points of divergence and the large jumps having slightly earlier points of divergence, with explanation for this difference provided. Taken together, our high number of replications, larger sample size and sensitive analyses provides us with confidence that our findings are not simply attributable to a Type 2 error.

Additionally, caution must be applied when interpreting our lack of dopaminergic effects on online motor control. Given the absence of drug effects on all of our motor variables our interpretation is limited. Whether our null finding surrounding dopaminergic medication is due to the dopaminergic system itself not being involved in the automatic pilot or because our task was insensitive to capture any On-Off medication differences remains inconclusive. Increasing our power would improve the reliability and generalizability of these results.

Further, our investigation of automaticity in PD was restricted exclusively to online corrections induced through the double-step paradigm. The double-step paradigm elicits automatic corrections by inducing an unexpected spatial error between hand and target position. In contrast, other studies have worked under the loose definition that an action is automatic so long as it can be performed in the absence of cognitive resources (Doyon et al., 1997; Faglioni, et al., 1995; Wylie et al., 2009). In this manner, automaticity can be investigated by ‘over-training’ participants on a complex motor sequence and having the habitually-learned sequence be performed simultaneously with a competing cognitive load. Whether these tasks would encompass the same behaviors as automatic online corrections is uncertain. To our knowledge, no study to date has investigated the similarities and/or differences in the neural correlates and psychomotor demands between these two measures. Presumably, it is critical to distinguish between different forms of automaticity before being able to fully generalize our results.

Finally, we are unable to directly disconfirm the role of the basal ganglia in the automatic corrective system, as this study was performed only at the behavioral level. It would be necessary to integrate functional imaging into our design to investigate the exact neural substrates involved in online corrections in individuals with PD.

4.7 Conclusions

PD is primarily recognized by its cardinal motor symptoms, including tremor, rigidity and bradykinesia. Our results emphasize the importance of isolating the motor symptoms of PD when investigating online motor control. This thesis argues that the previous work examining online motor control was confounded by PD-related bradykinesia and consequently led to the misinterpretation that patients with PD are also impaired in

consciously mediated automatic online corrections. Our results suggest that PD neither affects consciously mediated nor subliminal automaticity, as measured by the double-step paradigm. Equalizing the preparatory phase and thus the task demands between groups allowed PD patients to perform online corrections similar to those without basal ganglia dysfunction. Additionally, we did not find any evidence for a role of the dopaminergic system in the automatic pilot. We suggest that regions beyond the dopamine dependent striatal loops are critical for mediating online motor guidance.

The outcomes from this study have several far-reaching implications. Our results discredit the assumption that there is a dichotomy between conscious and subconscious automatic online processing in PD. To this extent, our findings contribute to an improved understanding of automaticity and online motor control in PD and help clarify previous inconsistencies in the literature. Moreover, our results translate into a better appreciation for the exact motor symptoms of PD and advise for further clarification into the role, if any, of the basal ganglia in the online control of action.

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Appendices

Appendix A: Participant Inclusion/Exclusion Criteria

Healthy Controls	Patients with PD
No diagnosis of a movement disorder	Diagnosis of idiopathic PD from a licensed clinical neurologist
No history of: <ol style="list-style-type: none"> 1. Neurological illness 2. Psychiatric illness 3. Neuro-trauma 4. Psychosis or hallucinations 	No history of the following unrelated to PD: <ol style="list-style-type: none"> 1. Neurological illness 2. Psychiatric illness 3. Neuro-trauma 4. Psychosis or hallucinations
Normal or corrected-to-normal vision	Normal or corrected-to-normal vision
No previous participation in the study	No previous participation in the study
No history of substance abuse (ETOH, prescription medication, illicit drugs)	No history of substance abuse (ETOH, prescription medication, illicit drugs)
Not currently taking cognitive-enhancing medications including: <ol style="list-style-type: none"> 1. Donepezil 2. Galantamine 3. Rivastigimine 4. Memantine 5. Methylphenidate 	Not currently taking cognitive-enhancing medications including: <ol style="list-style-type: none"> 1. Donepezil 2. Galantamine 3. Rivastigimine 4. Memantine 5. Methylphenidate

No clinical diagnosis of dementia or mild cognitive impairment	Responsive to dopaminergic medication
	Currently prescribed and taking dopaminergic medication
	Disease duration < 15 years
	No suspicion of familial form of PD (greater than 2 first degree relatives with PD diagnosis)
	No clinical diagnosis of dementia or mild cognitive impairment
	Must not have unstable or rapidly progressing parkinsonism
	No history of treatment of deep brain stimulation or neurological surgery

Appendix B: Consent Form



PENNY A. MACDONALD, MD, PhD, FRCP(C)
Assistant Professor and Movement Disorder Neurologist
Department of Clinical Neurological Sciences and
The Brain and Mind Institute
University of Western Ontario

LETTER OF INFORMATION AND CONSENT FORM

Study Title

Distinguishing the roles of ventral and dorsal striatum in cognition

Investigators

Penny A. MacDonald MD, PhD, FRCP(C) in Neurology	Adrian Owen PhD
Hooman Ganjavi MD, PhD, FRCP(C) in Psychiatry	Ken Seergobin MSc
Seyed Mirsattari MD, PhD, FRCP(C) in Neurology	Stuart Fogel PhD
Sarah Morrow MD, FRCP(C) in Neurology	Ali Kahn PhD
Jorge Burneo MD, FRCP(C) in Neurology	Robert Bartha PhD
Elizabeth Finger MD, FRCP(C) in Neurology	Ravi Menon PhD
Mary Jenkins MD, FRCP(C) in Neurology	Mel Goodale PhD
Mark Watling MD, FRCP(C) in Psychiatry	Brian Corneil PhD

Sponsoring Agency

The research is funded by a Canada Excellence Research Chair to Dr. Adrian Owen, an Academic Medical Association of Southwestern Ontario Opportunity Fund and Natural Sciences and Engineering Research Council of Canada awarded to Dr. Penny MacDonald.

Purpose

You are being asked to participate in a research project designed to help us understand more about attention, memory, and how people make every day decisions. The study will help show which parts of the brain are involved in these functions. It will also help us to understand whether certain illnesses that affect the brain such as strokes or Parkinson's disease, or obsessive-compulsive disorder change the way people pay attention, remember, and make decisions. Understanding these changes might help us to provide better care for these patients ultimately. We will aim to recruit approximately 200 patients with Parkinson's disease, 200 healthy volunteers, matched in age to PD patients, 200 patients with strokes, 200 patients with neurological or psychiatric disorders that might implicate the striatum (a brain region of interest), and 200 healthy volunteers. The criteria to participate in this study were previously outlined in the recruitment letter that you were given.

1/7

September 18, 2015
Consent Form

initials: _____

339 Windermere Road
London, Ontario, Canada N6A 5A5
Tel: (519) 685-8500 ext. 33631 • Fax: (519) 663-3753

Procedures

If you agree, you will be asked to one or two testing sessions at the Brain and Mind Institute or the Robarts Research Institute at the University of Western Ontario. Each session is expected to last approximately 1.5 hours, but may go as long as 3 hours. The first session will begin with a short clinical interview to evaluate your general health. Your heart rate and blood pressure might also be recorded. A screening neurological examination will be performed. You will also be asked to complete a few standard questionnaires to assess aspects of your mood and temperament. In each session, you will next perform a computerized test that is aimed at testing basic aspects of thinking, memory, or problem solving. Explanations of the paper and pencil tests will be provided orally and detailed written instructions will be given prior to the computerized test on each day. You will have the chance to ask questions and will be encouraged to do so before beginning the tests. Practice trials will also be provided so that you will be comfortable with the computerized test and so that you understand thoroughly what you're asked to do.

Your permission is also requested for Dr. MacDonald to review any CT or MRI scans of the brain that you have previously undergone. This will help us better understand the results of the testing.

Experiments involving functional magnetic resonance imaging

During testing, you might perform tests on a computer that are aimed at testing basic aspects of thinking, memory, or problem solving while you are in a magnetic resonance imaging (MRI) machine. With MRI, we are able to measure blood flow non-invasively in various parts of your brain as a marker of brain activity while you perform specific thinking functions. We will also collect images of your brain in the MRI to measure different brain structures.

Patients with Parkinson's disease

If you are a patient with Parkinson's disease, you will be tested twice, once while you are taking your Parkinson's medication and once after you have abstained from taking your Parkinson's medication for at least 12 hours on two separate days.

Healthy control participants or patients with neurological (e.g. stroke, epilepsy, multiple sclerosis) or psychiatric disorder (e.g. obsessive-compulsive disorder) other than Parkinson's disease

If you are a non-patient volunteer or a patient with a neurological or psychiatric disorder other than Parkinson's disease, you might perform the tasks once or twice. In all testing sessions, you will take all of your regularly prescribed medications.

2/7

September 18, 2015
Consent Form

initials: _____

339 Windermere Road
London, Ontario, Canada N6A 5A5
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Healthy control participants studied while taking dopaminergic therapy

For non-patient volunteers, in some experiments you will perform tasks once while taking a dose of Levocarb or Pramipexole, common medications that are used to treat Parkinson's disease, and once while taking an inactive or *placebo* substance (i.e., cornstarch). The order in which you receive these substances will be randomly determined across participants. You will not be informed of the substance that you are given in either testing session and the experimenter will also be blind to which substance you are given on a particular day. This is done to reduce any effects of expectation that might be induced by knowing that you are receiving active treatment. Levocarb contains 100 mg of levodopa (L-3,4-dihydroxyphenylalanine) and 25 mg of carbidopa. Levodopa is transformed in the brain into dopamine whereas pramipexole mimics dopamine. Dopamine is a neurotransmitter produced naturally in the brain that is involved in regulating movement and some aspects of thinking and memory. Carbidopa is a substance that does not cross into the brain but is given to stop the levodopa from being converted to dopamine before it reaches the brain. Carbidopa reduces side effects that can occur due to dopamine being produced in the body rather than in the brain, such as nausea or lowering of blood pressure.

Experiments involving polysomnographic sleep recordings

You might be asked to undergo polysomnographic sleep recordings during either a 3-h daytime nap or 8-h overnight session. Polysomnography (PSG) is a non-invasive technique that uses surface electrodes applied to the scalp and face to measure brain activity during different sleep-wake cycles.

Benefits

Your participation in this study is of no direct benefit to you.

Risks

If you require treatment for any injuries or illness directly related to procedures implemented during the study, or if you suffer side effects while on study medication, you should contact your study doctor as soon as possible. The necessary medical care will be provided to you at no additional cost to you. You do not waive any legal rights by signing the consent form.

Participants performing computerized tasks

There are no known physical risks associated with performing computerized tasks. You may find some of the tasks dull or tiring.

Experiments involving functional magnetic resonance imaging

The Food & Drug Administration (USA) has indicated that for clinical diagnosis an 'insignificant' risk is associated with human MRI exposure at the intensities used in this project. Current Canadian guidelines follow the USA guidelines. Although very rare, injury and deaths have

3/7

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Consent Form

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occurred in MRI units from unsecured metal objects being drawn at high speeds into the magnet or from internal body metal fragments of which the subject was unaware or had not informed MRI staff. To minimize this latter possibility it is essential that you complete a screening questionnaire. Other remote but potential risks involve tissue burns and temporary hearing loss from the loud noise inside the magnet. The latter can be avoided with ear headphone protection that also allows continuous communication between the subject and staff during the study.

This MRI machine uses a strong magnet and radio waves to make images of the body interior. You will be asked to lie on a long narrow couch for an hour while the machine gathers data. During this time you will be exposed to magnetic fields and radio waves. You will not feel either. You will, however, hear repetitive tapping noises that arise from the magnets that surround you. You will be provided with earplugs or headphones that you will be required to wear to minimize the sound and protect your hearing. The space within the large magnet in which you lie is somewhat confined, although we have taken many steps to relieve the "claustrophobic" feeling. There are no known significant risks with this procedure at this time because the radio waves and magnetic fields, at the strengths used, are thought to be without harm. The exception is if you have a cardiac pacemaker, or a metallic clip in your body (e.g., an aneurysm clip in your brain), have severe heart disease, body piercings, tattoos containing metallic ink or slow release pharmaceutical skin patches.

There is a possibility that you will experience a localized twitching sensation due to the magnetic field changes during the scan. This is not unexpected and should not be painful. However, you can stop the exam at anytime. The magnetism and radio waves do not cause harmful effects at the levels used in the MRI machine. However, because the MR scanner uses a very strong magnet that will attract metal, all metallic objects must be removed from your person before you approach the scanner. In addition, watches and credit cards should also be removed as these could be damaged (these items will be watched for you).

Patients with Parkinson's disease

For Parkinson's patients who are tested off of their Parkinson's medications, you likely will experience an increase in your Parkinson's symptoms. If you do not return to your usual level of function after resuming your medication at the conclusion of the testing session, you are invited to contact Dr. MacDonald to discuss your concerns as well as medication strategies for getting back to your usual self.

Healthy participants taking dopaminergic therapy

If you are a non-patient volunteer taking levodopa or pramipexole, there is a potential risk of developing side effects following drug administration. More serious side effects reported are based on chronic use of these medications in patients, and are not expected to develop in this study given the single, low-dose of drug administered. Less serious side effects are largely

peripheral effects (e.g., nausea) and should be minimized through co-administration of Carbidopa. Any side effects that do occur are temporary and should quickly subside. In the unlikely situation that your symptoms persist, you are invited to contact the experimenter to discuss your concerns.

Less serious side effects include: mild nausea, dry mouth, loss of appetite; heartburn, diarrhea, constipation; headache, dizziness, drowsiness, blurred vision; sneezing, stuffy nose, cough, other cold symptoms; sleep problems (insomnia), strange dreams, muscle pain, numbness/tingly feelings, skin rash/itching. More serious side effects include: severe allergic reactions; restless muscle movements in your eyes, tongue, jaw, or neck; worsening of tremors (uncontrolled shaking); high fever, stiff muscles, sweating, fast or uneven heartbeats, difficulty breathing, feeling like you might pass out; seizure (convulsions); painful or difficult urination; severe nausea, vomiting, or diarrhea; uneven heart rate or fluttering in your chest; confusion, hallucinations, anxiety, agitation, depressed mood, thoughts of suicide or hurting yourself; unusual or intense urges (e.g., gambling, sexual urges); chest pain or heavy feeling, pain spreading to the arm or shoulder.

Experiments involving polysomnographic sleep recording

The only potential risk is for individuals with extremely sensitive skin. These individuals may have a slight skin irritation where the skin has been gently exfoliated during electrode application. When we apply the electrodes to the surface of the skin, we use a gentle, hypoallergenic medical-grade exfoliant, called NuPrep, to clean the skin where the electrodes will be placed. Any mild irritation to the skin normally lasts less than a few hours.

Confidentiality

The investigators will maintain all information collected in this study strictly confidential, shared only with individuals directly involved in this study, except as may be required by court order or by law. To further ensure your confidentiality, information collected from you will be devoid of any unique personal identifier and will be filed under an anonymous subject number. If any publication or presentation results from this research, you will not be referred to by name and no potentially identifying information will be released. The information collected in the course of this study is kept on file in a secure location for no less than 25 years. If you decide you do not want this information to be kept on file, simply advise the research team of your wishes, and your record will be destroyed.

Consent to Use and Disclose Information for Research subjects

Representatives of the University of Western Ontario Health Sciences Research Ethics Board might be granted direct access to your medical records. A representative of the University of Western Ontario Health Sciences Research Ethics Board might contact you or might require access to your study-related records to monitor the conduct of the research. By signing the

5/7

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consent, you also permit the principal investigator to use and disclose health information about yourself for the purposes of this study.

Incidental Findings

The tests you undergo in this study are not intended to diagnose or monitor any medical conditions you may have. Nevertheless, if information that might be relevant to your care is discovered incidentally, this information will be communicated to you, and at your request, to your physician.

Compensation

You will receive \$20 for sessions that involve only behavioural tests and \$50 for sessions that involve an MRI as well, for the time and inconvenience associated with your participation. You will also be reimbursed for parking costs.

Voluntary Participation/Withdrawal from the Study

Your participation in this research is completely voluntary. You may refuse to continue performing the tasks in this study at any time without any consequences. You may refuse to participate, refuse to answer any questions or withdraw from the study at any time with no effect on your future care. You do not waive any of your legal rights by signing the consent form. If the research investigators find it necessary, and/or in your best interest, you will be asked to withdraw from the study. In the event that you withdraw from the study for any reason, you will receive compensation for the sessions that you attended, even if you did not complete the entire session. Your cost of parking will also be reimbursed.

Contact Information

If you have any questions or concerns regarding the study, you may contact the principle investigator. If you wish to speak to a neutral individual who is not involved in the study at all and who will answer any questions about your rights as a research participant or about the conduct of the study, you may contact Dr. David Hill, Scientific Director, Lawson Health Research Institute (519) 667-6649.

Results

If you're interested in obtaining the results of the study, we will gladly provide you with a summary of our findings once the research is complete. Please let the investigator know if you would like a summary of the results mailed or emailed to you.

Consent Form

Distinguishing the roles of ventral and dorsal striatum in cognition

Principle Investigator: Penny A. MacDonald, MD, PhD

I (_____) have read the Letter of Information and Consent form and have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction. I have been provided a copy of the Recruitment/Information Letters and the Consent form. I freely and voluntarily consent to participate in this study.

Signature of participant

Date

Signature of investigator

Date

I have discussed this clinical research study with the participant using a language that is understandable and appropriate. I believe that I have fully informed this participant of the purpose, duration etc. of this research study and its possible benefits and risks and I believe the participant understood this explanation.

Signature of person assisting in consent process

Date

7/7

September 18, 2015
Consent Form

initials: _____

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Appendix C: Starkstein Apathy Scale

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

Starkstein Apathy Scale

Instructions: For each question, indicate as “Not at all”, “Slightly”, “Some”, or “A lot” with an ‘X’ while leaving the other spaces blank.

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

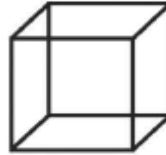
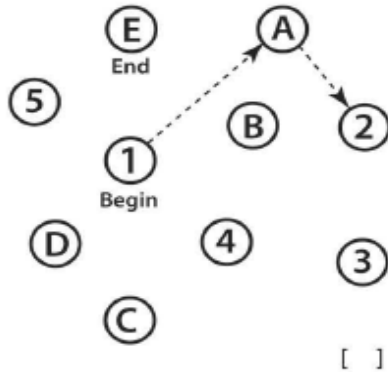
Appendix D: Montreal Cognitive Assessment

MONTREAL COGNITIVE ASSESSMENT (MOCA) Version 7.1 Original Version

NAME :
Education :
Sex :

Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE



Copy
cube

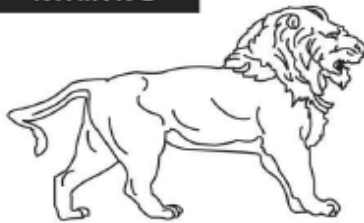
Draw CLOCK (Ten past eleven)
(3 points)

POINTS

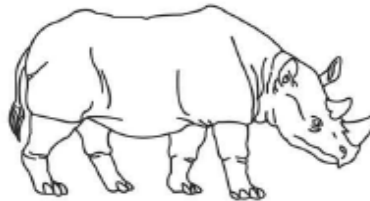
[] [] []
Contour Numbers Hands

___/5

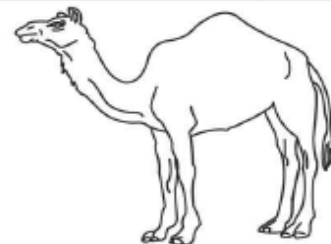
NAMING



[]



[]



[]

___/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No
points

ATTENTION

Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order

[] 2 1 8 5 4

Subject has to repeat them in the backward order

[] 7 4 2

___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

___/1

Serial 7 subtraction starting at 100

[] 93

[] 86

[] 79

[] 72

[] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

___/3

LANGUAGE

Repeat : I only know that John is the one to help today. []

The cat always hid under the couch when dogs were in the room. []

___/2

Fluency / Name maximum number of words in one minute that begin with the letter F

[] _____ (N ≥ 11 words)

___/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit

[] train - bicycle

[] watch - ruler

___/2

DELAYED RECALL

Has to recall words

WITH NO CUE

FACE

[]

VELVET

[]

CHURCH

[]

DAISY

[]

RED

[]

Points for
UNCUED
recall only

___/5

Optional

Category cue

Multiple choice cue

ORIENTATION

[] Date

[] Month

[] Year

[] Day

[] Place

[] City

___/6

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Normal ≥ 26 / 30

TOTAL

___/30

Administered by: _____

Add 1 point if ≤ 12 yr edu

Appendix E: Montreal Cognitive Assessment Evaluation Scale

MoCA Version August 18, 2010 © Z. Nasreddine MD www.mocatest.org 1

Montreal Cognitive Assessment (MoCA)

Administration and Scoring Instructions

The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

1. Alternating Trail Making:

Administration: The examiner instructs the subject: *"Please draw a line, going from a number to a letter in ascending order. Begin here [point to (1)] and draw a line from 1 then to A then to 2 and so on. End here [point to (E)]."*

Scoring: Allocate one point if the subject successfully draws the following pattern:

1 –A- 2- B- 3- C- 4- D- 5- E, without drawing any lines that cross. Any error that is not immediately self-corrected earns a score of 0.

2. Visuoconstructional Skills (Cube):

Administration: The examiner gives the following instructions, pointing to the **cube**: *"Copy this drawing as accurately as you can, in the space below"*.

Scoring: One point is allocated for a correctly executed drawing.

- Drawing must be three-dimensional
 - All lines are drawn
 - No line is added
 - Lines are relatively parallel and their length is similar (rectangular prisms are accepted)
- A point is not assigned if any of the above-criteria are not met.

3. Visuoconstructional Skills (Clock):

Administration: Indicate the right third of the space and give the following instructions: *"Draw a clock. Put in all the numbers and set the time to 10 past 11"*.

Scoring: One point is allocated for each of the following three criteria:

- Contour (1 pt.): the clock face must be a circle with only minor distortion acceptable (e.g., slight imperfection on closing the circle);
- Numbers (1 pt.): all clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour;
- Hands (1 pt.): there must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centred within the clock face with their junction close to the clock centre.

A point is not assigned for a given element if any of the above-criteria are not met.

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4. Naming:

Administration: Beginning on the left, point to each figure and say: *“Tell me the name of this animal”*.

Scoring: One point each is given for the following responses: (1) lion (2) rhinoceros or rhino (3) camel or dromedary.

5. Memory:

Administration: The examiner reads a list of 5 words at a rate of one per second, giving the following instructions: *“This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn’t matter in what order you say them”*.

Mark a check in the allocated space for each word the subject produces on this first trial. When the subject indicates that (s)he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions: *“I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time.”*

Put a check in the allocated space for each word the subject recalls after the second trial. At the end of the second trial, inform the subject that (s)he will be asked to recall these words again by saying, *“I will ask you to recall those words again at the end of the test.”*

Scoring: No points are given for Trials One and Two.

6. Attention: Forward Digit Span:

Administration: Give the following instruction: *“I am going to say some numbers and when I am through, repeat them to me exactly as I said them”*. Read the five number sequence at a rate of one digit per second.

Backward Digit Span:

Administration: Give the following instruction: *“Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order.”* Read the three number sequence at a rate of one digit per second.

Scoring: Allocate one point for each sequence correctly repeated, (N.B.: the correct response for the backwards trial is 2-4-7).

Vigilance:

Administration: The examiner reads the list of letters at a rate of one per second, after giving the following instruction: *“I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand”*.

Scoring: Give one point if there is zero to one errors (an error is a tap on a wrong letter or a failure to tap on letter A).

Serial 7s:

Administration: The examiner gives the following instruction: *“Now, I will ask you to count by subtracting seven from 100, and then, keep subtracting seven from your answer until I tell you to stop.”* Give this instruction twice if necessary.

Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correct subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 100. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond “92 – 85 – 78 – 71 – 64” where the “92” is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3.

7. Sentence Repetition:

Administration: The examiner gives the following instructions: *“I am going to read you a sentence. Repeat it after me, exactly as I say it [pause]: **I only know that John is the one to help today.**”*

Following the response, say: *“Now I am going to read you another sentence. Repeat it after me, exactly as I say it [pause]: **The cat always hid under the couch when dogs were in the room.**”*

Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting “only”, “always”) and substitutions/additions (e.g., “John is the one who helped today;” substituting “hides” for “hid”, altering plurals, etc.).

8. Verbal fluency:

Administration: The examiner gives the following instruction: *“Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will tell you to stop after one minute. Are you ready? [Pause] Now, tell me as many words as you can think of that begin with the letter F. [time for 60 sec]. Stop.”*

Scoring: Allocate one point if the subject generates 11 words or more in 60 sec. Record the subject’s response in the bottom or side margins.

9. Abstraction:

Administration: The examiner asks the subject to explain what each pair of words has in common, starting with the example: *“Tell me how an orange and a banana are alike”*. If the subject answers in a concrete manner, then say only one additional time: *“Tell me another way in which those items are alike”*. If the subject does not give the appropriate response (*fruit*), say, *“Yes, and they are also both fruit.”* Do not give any additional instructions or clarification. After the practice trial, say: *“Now, tell me how a train and a bicycle are alike”*. Following the response, administer the second trial, saying: *“Now tell me how a ruler and a watch are alike”*.

Do not give any additional instructions or prompts.

Scoring: Only the last two item pairs are scored. Give 1 point to each item pair correctly answered. The following responses are acceptable:

Train-bicycle = means of transportation, means of travelling, you take trips in both;

Ruler-watch = measuring instruments, used to measure.

The following responses are **not** acceptable: Train-bicycle = they have wheels; Ruler-watch = they have numbers.

10. Delayed recall:

Administration: The examiner gives the following instruction: *"I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember."* Make a check mark for each of the words correctly recalled spontaneously without any cues, in the allocated space.

Scoring: **Allocate 1 point for each word recalled freely without any cues.**

Optional: Following the delayed free recall trial, prompt the subject with the semantic category cue provided below for any word not recalled. Make a check mark (☒) in the allocated space if the subject remembered the word with the help of a category or multiple-choice cue. Prompt all non-recalled words in this manner. If the subject does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, *"Which of the following words do you think it was, NOSE, FACE, or HAND?"*

Use the following category and/or multiple-choice cues for each word, when appropriate:

FACE: category cue: part of the body multiple choice: nose, face, hand

VELVET: category cue: type of fabric multiple choice: denim, cotton, velvet

CHURCH: category cue: type of building multiple choice: church, school, hospital

DAISY: category cue: type of flower multiple choice: rose, daisy, tulip

RED: category cue: a colour multiple choice: red, blue, green

Scoring: **No points are allocated for words recalled with a cue.** A cue is used for clinical information purposes only and can give the test interpreter additional information about the type of memory disorder. For memory deficits due to retrieval failures, performance can be improved with a cue. For memory deficits due to encoding failures, performance does not improve with a cue.

11. Orientation:

Administration: The examiner gives the following instructions: "Tell me the date today". If the subject does not give a complete answer, then prompt accordingly by saying: *"Tell me the [year, month, exact date, and day of the week]."* Then say: *"Now, tell me the name of this place, and which city it is in."*

Scoring: Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, office). No points are allocated if subject makes an error of one day for the day and date.

TOTAL SCORE: Sum all sub-scores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal.

Appendix F: Bond & Lader Mood Scale

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

Bond & Lader Visual Analogue Mood Scale

ALERT	_____	DROWSY	_____ mm
CALM	_____	EXCITED	_____ mm
STRONG	_____	FEEBLE	_____ mm
MUZZY	_____	CLEAR HEADED	_____ mm
WELL COORDINATED	_____	CLUMSY	_____ mm
LETHARGIC	_____	ENERGETIC	_____ mm
CONTENTED	_____	DISCONTENTED	_____ mm
TROUBLED	_____	TRANQUIL	_____ mm
MENTALLY SLOW	_____	QUICK WITTED	_____ mm
TENSE	_____	RELAXED	_____ mm
ATTENTIVE	_____	DREAMY	_____ mm
INCOMPETENT	_____	PROFICIENT	_____ mm
HAPPY	_____	SAD	_____ mm
ANTAGONISTIC	_____	FRIENDLY	_____ mm
INTERESTED	_____	BORED	_____ mm
WITHDRAWN	<input type="radio"/> _____ <input type="radio"/>	SOCIABLE	_____ mm

Appendix G: ANART



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

Appendix H: Health and Demographic Questionnaire

Please print and fill out this form as accurately as possible and bring it with you to your first appointment session. If you are attending your appointment with another participant, please ensure you both have your own personal copies filled out.

1. Basic Demographic Information

Date of Birth: _____ Age: _____

Weight: _____ Height: _____

Sex: _____ Handedness: _____

First language: _____ Other languages: _____

Level of Education and total years (e.g. 4 years high school, 4 years university, etc.)

Occupation: _____

2. Health-Related Information

A. Smoking History (please circle): Never Smoker Ex-Smoker Current Smoker

If current smoker, indicate how many years and how many cig/day: _____

If ex-smoker, indicate year that you quit; how many years smoking; how many cig/day:

B. Alcohol History

Average number of drinks per week: _____

Has there ever been heavy alcohol consumption? (please circle) Yes No

If yes, when, for how long, and estimate your weekly alcohol consumption during that time:

C. Other Drug History

Have you ever taken street drugs or other drugs that were not prescribed by a physician (please circle)? Yes No

If yes, when, what drugs, how frequently and over what period of time?

D. Eye Glasses (only if applicable)

What is the prescription of your eye glasses? _____

Without the aid of glasses are you able to see near objects well (please circle)? Yes No

Without the aid of glasses are you able to see far objects well (please circle)? Yes No

E. Parkinson's Disease (only if applicable)

What year were you diagnosed with Parkinson's disease? _____

Which side of the body is *more* affected? _____

3. Previous Medical Problems

Have you had any major health problems or do you have any chronic, ongoing medical conditions such as high blood pressure, high cholesterol, diabetes, thyroid problems, multiple sclerosis or epilepsy? Have you had any strokes, heart attacks/ heart surgeries, significant head trauma, or cancer? If you've had cancer, what kind and what treatments did you receive (e.g. chemotherapy)? Have you ever had more than one seizure? Answer in the space below.

4. Family Medical Problems

Is there anyone in your family with a neurological or serious psychiatric illness such as PD, Huntington's, epilepsy, strokes at a young age (< 50 for men and < 60 for women)? Is there anyone who had trouble walking or with balance, needing a wheelchair or a walker at a young age? Any family members with dementia (such as Alzheimer's), schizophrenia, bipolar/manic depression, or severe depression or anxiety requiring hospitalization or close follow up by a psychiatrist? Answer in the space below.

5. Current Medication

Please list any medications you are currently taking, what they are treating for specifically, and the prescribed dosage.

Appendix I: Levodopa Screening Questionnaire

FOR EXPERIMENTER

ID:

Date:

 / /

LEVODOPA SAFETY SCREENING QUESTIONNAIRE

Please answer the following questions as accurately as possible.

1. Do you currently suffer or have you previously suffered from the following:

Yes	No		Yes	No	
<input type="checkbox"/>	<input type="checkbox"/>	Heart or coronary artery disease	<input type="checkbox"/>	<input type="checkbox"/>	Glaucoma
<input type="checkbox"/>	<input type="checkbox"/>	Atrial, nodal, or ventricular arrhythmias (i.e., irregular heart beat)	<input type="checkbox"/>	<input type="checkbox"/>	Asthma, chronic obstructive pulmonary disease (COPD), emphysema
<input type="checkbox"/>	<input type="checkbox"/>	Myocardial infarction (i.e., heart attacks)	<input type="checkbox"/>	<input type="checkbox"/>	Melanoma (skin cancer) or a skin growth that has not been diagnosed
<input type="checkbox"/>	<input type="checkbox"/>	High blood pressure	<input type="checkbox"/>	<input type="checkbox"/>	Phenylketonuria (PKU)
<input type="checkbox"/>	<input type="checkbox"/>	Liver or kidney disease	<input type="checkbox"/>	<input type="checkbox"/>	Endocrine (hormonal) disease
<input type="checkbox"/>	<input type="checkbox"/>	Diabetes	<input type="checkbox"/>	<input type="checkbox"/>	Stomach or intestinal ulcers
<input type="checkbox"/>	<input type="checkbox"/>	Mental illness	<input type="checkbox"/>	<input type="checkbox"/>	Allergies to levodopa (Larodopa)/carbidopa (Lodosyn)

2. Are you currently pregnant, plan to become pregnant, or are breast-feeding? ☐ Yes ☐ No

3. Are you taking any of the following medications (within past two weeks, i.e., 14 days):

Yes	No		Yes	No	
<input type="checkbox"/>	<input type="checkbox"/>	Monoamine oxidase (MAO) inhibitors such as isocarboxazid (Marplan), phenelzine (Nardil), tranylcypromine (Parnate)			
<input type="checkbox"/>	<input type="checkbox"/>	Antidepressants ('mood elevators') such as amitriptyline (Elavil), amoxapine (Asendin), clomipramine (Anafranil), desipramine (Norpramin), doxepin (Adapin, Sinequan), imipramine (Tofranil), nortriptyline (Aventyl, Pamelor), protriptyline (Vivactil), and trimipramine (Surmontil)			
<input type="checkbox"/>	<input type="checkbox"/>	Haloperidol (Haldol)	<input type="checkbox"/>	<input type="checkbox"/>	Metoclopramide (Reglan)
<input type="checkbox"/>	<input type="checkbox"/>	Risperidone (Risperdal)	<input type="checkbox"/>	<input type="checkbox"/>	Papaverine (Pavabid)
<input type="checkbox"/>	<input type="checkbox"/>	Rasagiline (Azilect)	<input type="checkbox"/>	<input type="checkbox"/>	Isoniazid (INH, Nydrazid)
<input type="checkbox"/>	<input type="checkbox"/>	Phenytoin (Dilantin)	<input type="checkbox"/>	<input type="checkbox"/>	Ipratropium (Atrovent)
<input type="checkbox"/>	<input type="checkbox"/>	Antihistamines	<input type="checkbox"/>	<input type="checkbox"/>	Iron pills and vitamins containing iron

Appendix J: UPDRS Protocol

UPDRS Protocol

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

Always start with LESS impaired side

Only model for a few seconds, then stop

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

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

10. Pull test “*Try to maintain your balance and limit yourself to one step backwards*”

Appendix K: Ethics Approval



Western
Research

Research Ethics

Western University Health Science Research Ethics Board HSREB Amendment Approval Notice

Principal Investigator: Dr. Penny MacDonald

Department & Institution: Schulich School of Medicine and Dentistry/Clinical Neurological Sciences, London Health Sciences Centre

Review Type: Full Board

HSREB File Number: 102018

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

Sponsor: Canadian Excellence Research Chair

HSREB Amendment Approval Date: December 18, 2015

HSREB Expiry Date: November 29, 2016

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Amendment	List of changes to ethics protocol and consent form	2015/11/19
Revised Western University Protocol	Marked version of updated ethics protocol	2015/11/19
Instruments	UPPS-P Impulsive Behavior Scale	2015/11/19
Instruments	Domain Specific Risk Taking Scale DOSPERT	2015/11/19
Instruments	Behavioral Inhibition/Approach Scale BIS/BAS Scale	2015/11/19
Revised Letter of Information & Consent		2015/11/19
Revised Western University Protocol		2015/11/19

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the amendment to the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer, on behalf of Dr. Joseph Gilbert, HSREB Chair

Ethics Officer to Contact for Further Information: Erika Baule ☐ Nicole Kanki ☒ Grace Kelly ☐ Mira Méthot ☐ Vicki Tran ☐

This is an official document. Please retain the original in your files.

Curriculum Vitae

University Educational Background

Masters of Science, Physiology/Pharmacology 09/2015 – Ongoing

University of Western Ontario

Master's Thesis: *Is online motor control really impaired in Parkinson's disease?*

Supervisors: Drs. Penny MacDonald and Melvyn Goodale

Bachelor of Sciences, Hons. Spec. Phys/Psych 09/2010 – 04/2015

University of Western Ontario

Undergraduate Thesis: *The role of cognitive supervision in visually-guided action*

Supervisors: Dr. Melvyn Goodale

Research-specific Honours, Scholarships and Awards

Ontario Graduate Scholarship 09/2015 – 08/2016

Western Graduate Research Scholarship 09/2015 – 08/2016

R&D Bio-Techne Travel Grant 10/2015

NSERC Alexander Graham Bell Canadian Graduate Scholarship 09/2014 – 09/2015

Research Interviews

Neuroscience Program Ambassador, University of Western 04/2016

Graduate and Post-doctoral Studies

Research Presentations

Merritt K, Seergobin K, Goodale M & MacDonald P. 07/2016

Automatic online motor control in Parkinson's disease. Brain in

Action, International Research Training Group Research Retreat,
Frankfurt Germany

Merritt K, Seergobin K, Goodale M & MacDonald P. *Is online motor control really impaired in Parkinson's disease?* 05/2016
Neuroscience Research Day, University of Western Ontario,
London, ON

Merritt K, Whitwell R & Goodale M. *Dissociating action and perception using a 3D variant of the Sanders illusion while controlling for visual and haptic feedback.* Inaugural Brain and Mind Institute Symposium, London, ON 09/2015

Merritt K, Seergobin K, Goodale M & MacDonald P. *An alternative explanation for impaired iterative online motor control in Parkinson's disease.* Brain in Action, International Research Training Group Research Retreat, Toronto, ON 07/2015

Merritt K, Whitwell R, Buckingham G, Chouinard, P & Goodale M. *A. Dissociating action and perception using a 3D variant of the Sanders illusion while controlling for visual and haptic feedback.* 05/2014
Vision Sciences Society, St. Pete Beach, United States

Merritt K, Whitwell R, Buckingham G, Chouinard, P & Goodale M. *The debate is over: Dissociating action and perception using a 3D variant of the Sanders parallelogram while controlling for visual and haptic feedback.* Canadian Association for Neuroscience, Montreal, Canada 05/2014

Abstracts

Merritt K, Whitwell R & Goodale MA. *Dissociating action and* 04/2014

perception using a 3D variant of the Sanders illusion while

controlling for visual and haptic feedback. Western

Undergraduate Research Journal: Health and Natural Sciences. 4(1)

Merritt K, Whitwell R, Buckingham G, Chouinard, P & Goodale M 05/2014

A. Dissociating action and perception using a 3D variant of the

Sanders illusion while controlling for visual and haptic feedback,

Journal of Vision 14(10)

Teaching Experience

Graduate Teaching Assistant 09/2015 –12/2015

Department of Psychology, University of Western Ontario

- Taught second-year undergraduate Test and Measurement Course
- Held office hours and exam review sessions

Graduate Teaching Assistant 09/2014 – 04/2015

Department of Psychology, University of Western Ontario

- Taught a second-year undergraduate Statistics for Psychology course
- Planned and taught in-class tutorials
- Evaluated student assignments and exams
- Monitored and responded to an online student forum and held weekly office-hours