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The Effect Of The Dopamine Agonist Pramipexole On Measures Of Impulsivity In Young, Healthy Participants

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Abstract

Patients with Parkinson disease are prescribed dopamine agonists such as pramipexole to improve motor symptoms. Several studies have found that patients taking dopaminergic medication develop impulse control disorders. In contrast, other studies suggest that some behaviors become less impulsive with pramipexole. We evaluated the performance of 20 young, healthy participants who received pramipexole (0.5 mg) and 20 participants who received placebo, on the Go/No-Go, the Stop Signal Task, and the Balloon Analogue Risk Task. We found that the pramipexole group had more timed out Go trials on the Go/No-Go task than the placebo group, suggesting reduced motor impulsivity. There were no differences between the two groups' performance on the other impulsivity tasks. This pattern of results is in line with the theory that impulsivity consists of a motor and a cognitive aspect, and that pramipexole might decrease motor, but not cognitive impulsivity.

Keywords

Parkinson's disease, dopaminergic medication, dopamine agonist, pramipexole, impulsivity, motor inhibition, motor impulsivity, cognitive impulsivity.

Co-Authorship Statement

The thesis was written by myself, with editing provided by Penny A. MacDonald. Ken N. Seergobin programmed the tasks and assisted with some of the analyses. I received help with data collection from Xue Qing Yang and Haley Gallant. Partial results of this thesis have been published in a scientific journal.

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ANART	American national adult reading test
BAI	Beck anxiety inventory
BART	Balloon analogue risk task
BDI	Beck depression inventory
BIS	Barratt impulsiveness scale
BL-VAS	Bond-Lader visual analogue scale
COWAT	Controlled oral word association task
DS	Dorsal striatum
fMRI	Functional magnetic resonance imaging
GPe	Globus pallidus pars externa
GPi	Globus pallidus pars interna
GNG	Go/No-Go
HR	Heart rate
ICD	Impulse control disorder
LID	Levodopa inducted dyskinesia
MOCA	Montreal cognitive assessment
ms	Millisecond
PCA	Principal component analysis
PD	Parkinson's disease
RLS	Restless leg syndrome
RT	Reaction time
SAS	Starkstein apathy scale
SNpc	Substantia nigra pars compacta
SSD	Stop signal delay
SSRT	Stop signal reaction time
SST	Stop signal task
T1	Time 1
T2	Time 2
T3	Time 3
VS	Ventral striatum
VTA	Ventral tegmental area

Chapter 1: Introduction

1.0 Literature review

Parkinson's disease (PD) is a progressive neurodegenerative disorder in which dopamine-producing neurons degenerate in the substantia nigra pars compacta (SNpc), and to a much lesser extent in the neighbouring ventral tegmental area (VTA), leading to motor and cognitive impairments. The hallmark motor symptoms of PD include tremor at rest, rigidity (of limbs and the trunk), and bradykinesia (slowness of movement; Dauer & Przedborski, 2003; Jankovic, 2008). Impairments in cognition, specifically in frontostriatal functions (such as learning, memory, and executive functions) are also recognized as an indisputable feature of PD (Aarsland & Kurz, 2010; Barone et al., 2011). PD is predominantly an age-associated disorder with a sharp increase in prevalence after the age of 60, although there are cases of PD with onset before 50 (de Lau & Breteler, 2006). The estimated prevalence of PD in adults older than 60 is around 1%, with some studies finding rates closer to 2– 3%, making it the second most common age-associated disorder (de Lau & Breteler, 2006). The etiology of PD is not fully understood and there is no cure for the disease. Motor symptoms are well mitigated by medication, whereas non-motor symptoms, which present more varied deficits and do not respond as well to medication, tend to be the major cause of impairments and institutionalization (Aarsland, Larsen, Tandberg, & Laake, 2000; Aarsland, Zaccai, & Brayne, 2005; Dauer & Przedborski, 2003; Halliday, Leverenz, Schneider, & Adler, 2014; Seppi et al., 2011). Non-motor deficits in PD are complex and likely have several causes, including PD pathology, side effects of dopaminergic medication, and adverse interactions between PD pathology and medication effects (Aarsland, Brønnick,

Larsen, Tysnes, & Alves, 2009; Bosboom, Stoffers, & Wolters, 2004; Caballol, Martí, & Tolosa, 2007; Rowe et al., 2008; Seppi et al., 2011).

1.1 Pathophysiology of PD

Physiologically, PD is marked by a selective and rapid degeneration of dopaminergic cells projecting to the striatum from the SNpc. The striatum comprises the caudate nucleus, the putamen, and the nucleus accumbens (Obeso et al., 2008; Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004). The striatum is often described in terms of a ventral and a dorsal portion – the dorsal striatum (DS), and the ventral striatum (VS). Although no clear boundaries exist separating the DS and the VS, the areas tend to be subdivided along relatively consistent demarcations (see **Figure 1**), usually setting the boundary between the dorsal parts of the caudate and putamen (collectively called the DS), and the ventral portion of the putamen as well as the nucleus accumbens (collectively called the VS; Voorn et al., 2004). The division is in large part supported by behavioral and cognitive differences in the functioning of these different areas (Obeso et al., 2008; Voorn et al., 2004). Neuroanatomically, there are also subtle cytoarchitectural changes along different points of the striatum, although there is no clear anatomical difference marking a boundary between the DS and VS (Voorn et al., 2004).

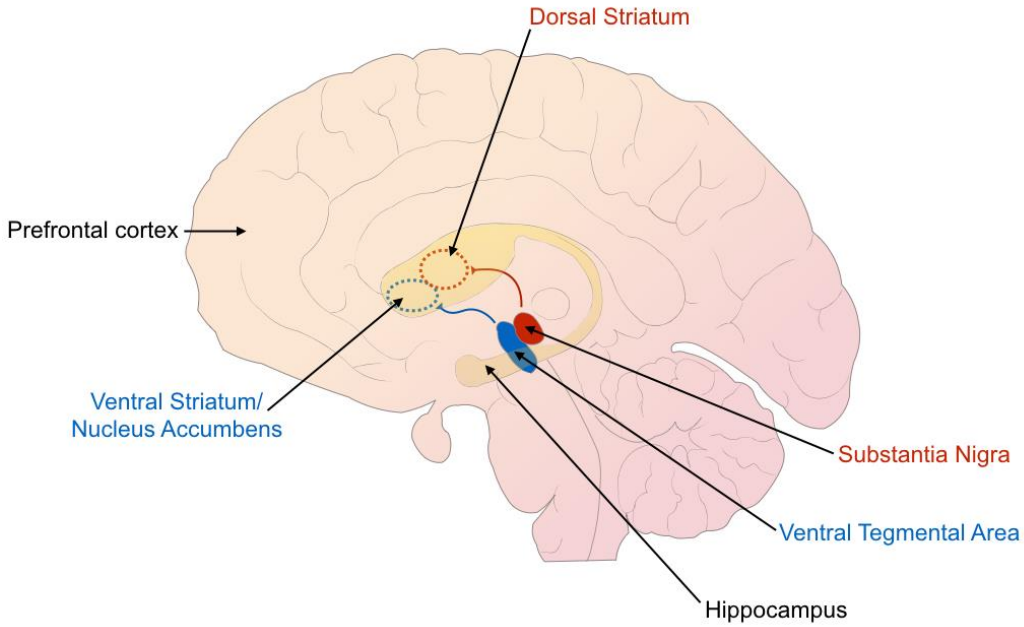

Figure 1: Commonly accepted subdivision of the striatum into the DS and the VS. Adapted from Telzer, 2016.

Cells in the SNpc, which project to the DS, deteriorate much more rapidly than cells in the VTA, which project to the VS (Kish, Shannak, & Hornykiewicz, 1988). This results in a greater overall loss of dopamine in the SNpc and the DS and their afferents, compared to the VTA and the VS. This dopaminergic deficiency in the SNpc-DS pathway produces the cardinal motor symptoms of PD including tremor, rigidity, and bradykinesia (Dauer & Przedborski, 2003; Jankovic, 2008). Rather than being responsible for the execution of motor commands per se, the SNpc-DS system is involved in the selection of actions (Balleine, Delgado, & Hikosaka, 2007). Additionally, the SNpc-DS system is involved in procedural learning and stimulus-response learning, for example, when learning a new motor sequence or a response to a new stimulus (Packard & Knowlton,

2002; White & McDonald, 2002). The DS is also involved in the performance of less habitual and more considered actions (Ali, Green, Kherif, Devlin, & Price, 2009; Benke, Delazer, Bartha, & Auer, 2003; Cameron, Watanabe, Pari, & Munoz, 2010; MacDonald, Seergobin, Tamjeedi, & Owen, 2014; Macdonald & Monchi, 2011; Mestres-Missé, Turner, & Friederici, 2012; Robertson, Hiebert, Seergobin, Owen, & MacDonald, 2015). The medial part of the DS has also been shown to affect inhibitory control of motor actions (Eagle & Robbins, 2003), which is required to stop or prevent an action from being executed.

Similarly, the VTA-VS system can be thought of as a mediator of motor behaviors, but more specifically in the context of reward and reinforcement-based behaviors (Cardinal, Parkinson, Hall, & Everitt, 2002; McBride, Murphy, & Ikemoto, 1999). Reversal learning is mediated by the VTA-VS system, which involves the extinction of previously reinforced behaviors (Cools, Clark, Owen, & Robbins, 2002). Evidence also suggests its involvement in spatial learning (Setlow, 1997). In summary, both the DS and the VS are involved in a range of cognitive functions, thus their dysfunction can contribute to non-motor impairments in PD (Atallah, Lopez-Paniagua, Rudy, & O'Reilly, 2007; Dirnberger & Jahanshahi, 2013; Grahn, Parkinson, & Owen, 2009; Nagano-Saito, Martinu, & Monchi, 2014).

Ultimately, the striatum, which receives inputs from nearly all areas of the cortex, influences actions through its inhibition or disinhibition of the thalamus, which then feeds back into the initial region of the cortex where the signal originated (Obeso et al., 2008). The striatum is predominantly populated by medium spiny neurons, which send inhibitory GABAergic signals along two main pathways known as the direct pathway and the indirect pathway. The direct

pathway functions through the activation of D1 dopaminergic receptors, and begins at the striatum, making inhibitory connections with the globus pallidus pars interna (GPi). The GPi forms inhibitory connections with the thalamus, so inhibition of the GPi actually disinhibits the thalamus. As a result, stimulation of the direct pathway via D1 receptors leads to a disinhibition of the thalamus, which then sends excitatory feedback amplifying the original signal. The indirect pathway contains cells with D2 receptors. The striatum projects inhibitory connections to the globus pallidus pars externa (GPe), which projects inhibitory connections to the subthalamic nucleus. The subthalamic nucleus forms excitatory connections with the GPi, which, as previously discussed, inhibits the thalamus. Thus, stimulation of the indirect pathway inhibits the GPe, which disinhibits the subthalamic nucleus. The subthalamic nucleus then excites the GPi, and the GPi inhibits the thalamus. The net result of stimulation of the indirect pathway is the inhibition of the thalamus, and a dampening of the original signal (Obeso et al., 2008).

1.2 Medication to treat motor symptoms

Although there is no cure for PD, medication sufficiently alleviates the motor symptoms caused by dopamine deficiency in the SNpc, especially in the earlier stages of disease. Medication to treat PD, which primarily acts on dopaminergic cells and receptors, is titrated with the aim of restoring dopamine to the deficient SNpc-DS system. The two most effective drug types used to treat PD are the dopamine precursor L-3,4-dihydroxyphenylalanine (levodopa), and dopamine agonists (such as pramipexole, ropinirole, rotigotine, and apomorphine; Connolly & Lang, 2014). Levodopa is a dopamine precursor that leads to the production of dopamine. In the striatum, it acts presynaptically on dopaminergic cells and is converted to dopamine, making up for the decreased dopamine from the SNpc (Lang & Lees, 2002). In contrast, dopamine agonists act post-

synaptically, by attaching to, and activating dopamine receptors directly (Brooks, 2000; Quinn, 1995). The actions of both types of drugs cause a net increase of activated dopaminergic receptors in the striatum However, the acute dopamine activity caused by the drugs is markedly different from the consistent release of low doses of dopamine that occurs in an unimpaired dopaminergic system (Lang & Lees, 2002). These drugs are currently titrated to treat the motor symptoms of PD resulting from the deficiency in the SNpc-DS system (Connolly & Lang, 2014), with little regard for the effects on more complex behaviors and cognition that are also mediated by the striatum.

Both drug types are associated with the development of behavioral and cognitive complications. Research shows that whereas some functions improve when patients are on medication, others become worse (Cools, Barker, Sahakian, & Robbins, 2001; MacDonald et al., 2011; Macdonald & Monchi, 2011). Continued use of levodopa leads to levodopa-induced dyskinesia (LID), a condition marked by jerky, involuntary and purposeless movements that usually appear at the time levodopa effects are at their peak (Ahlskog & Muenter, 2001; Carta, Carlsson, Kirik, & Bjorklund, 2007). Review studies estimate that over the course of 4-6 years of treatment, around 40% of patients develop LID, and the prevalence increases to between 60-89% by 10 years of treatment (Ahlskog & Muenter, 2001; Fabbrini, Brotchie, Grandas, Nomoto, & Goetz, 2007; Zesiewicz, Sullivan, & Hauser, 2007). To treat LID, patients are commonly given lower doses of levodopa, but this increases the duration of the OFF period (i.e. when the anti-parkinsonian effects of levodopa wear off and motor symptoms worsen) and makes the disease more difficult to manage. Treatment with dopamine agonists leads to fewer instances of dyskinesia than treatment with levodopa (Parkinson Study Group, 2000), so early treatment with dopamine agonists is preferable.

However, the prolonged use of dopamine agonists, such as pramipexole, has been associated with the development of impulse control disorders (ICDs) in patients with PD (Aarsland & Kurz, 2010; Burdick et al., 2014; Pontone, Williams, Bassett, & Marsh, 2006). ICDs are characterized by the occurrence of impulsive actions and behaviors such as gambling, binge eating, hyper-sexuality, and uncontrollable spending. Weintraub and colleagues, (2010) found that patients taking dopamine agonists are at a 2 – 3.5 times greater risk of developing an ICD, but suggested that additional demographic and clinical factors may influence the development of ICDs.

Most studies investigating the effects of dopaminergic medication on cognition and impulsivity have been conducted on PD patients (Macdonald & Monchi, 2011; Poletti & Bonuccelli, 2013), which presents difficulty in interpreting the effects of dopaminergic medication. Typical PD samples vary widely in terms of age, disease duration and time of onset, as well as overall disease severity. To better understand whether the association between dopamine agonists and the development of ICDs is due to the medication, due to an interaction between medication and PD pathology, or due to an interaction with other demographic factors associated with PD, it is necessary to investigate the effects of the medication in isolation from these other confounding variables.

Additionally, the cognitive pathology of PD patients is complex. First, there is strong evidence that some cognitive deficits result from striatal dopamine deficiency (Barone et al., 2011; Bosboom et al., 2004; Caballol et al., 2007). Second, in addition to dopaminergic pathways, dysregulation in cholinergic (Bohnen et al., 2006; Gilman, 2010), serotonergic (Huot, Fox, &

Brotchie, 2011; Ye et al., 2014) and noradrenergic (Del Tredici & Braak, 2013; Vazey & Aston-Jones, 2012; Weintraub, 2010) pathways appears to also contribute to cognitive deficits in PD. Dopamine sensitization following prolonged use of dopaminergic medication (Fenu, Wardas, & Morelli, 2009) could further complicate the relationship between dopamine agonists in PD and the appearance of ICDs. There is also evidence showing that patients with PD have reduced levels of the dopamine transporter DAT, which regulates synaptic dopamine levels, and this decrease could exacerbate the effects of dopamine to pathological levels (Harrington, Augood, Kingsbury, Foster, & Emson, 1996; Kalia & Lang, 2015; Kordower et al., 2013; Voon, 2009). Thus, with many variables potentially affecting cognition in PD, any effects of medication are difficult to interpret.

Dopamine agonists are also increasingly prescribed outside the context of PD, so it is important to understand the effects of this medication in isolation from PD. Individuals with restless leg syndrome (RLS; Comella, 2002; Högl, Paulus, Clarenbach, & Trenkwalder, 2006; Hornyak, Scholz, Kohnen, & Bengel, 2014; Trenkwalder, Hening, Montagna, & Oertel, 2008; Zintzaras, Kitsios, Papathanasiou, & Konitsiotis, 2010) and in some cases dystonia (Cloud & Jinnah, 2010; Jankovic, 2013) are treated with dopamine agonists. Additionally, the use of dopamine agonists is being investigated in the treatment of depression (Goto, Yoshimura, Kakihara, & Shinkai, 2006; Hori & Kunugi, 2012, 2013; Howland, 2012; Papakostas, 2006) , drug addiction (Carroll, Howell, & Kuhar, 1999; Streeter, Hennen, Ke, & Jensen, 2005) and to address withdrawal symptoms (Makhinson & Gomez-Makhinson, 2014; Ohmura, Jutkiewicz, Zhang, & Domino, 2011). Therefore, investigating the effects of dopamine agonists on impulsivity in healthy

controls is necessary to avoid the many factors that might interact with the medication when studied in clinical populations.

1.3 Pramipexole effects on impulsivity

Pramipexole is a nonergot dopamine agonist, which unlike levodopa does not promote the production of dopamine, but directly stimulates dopaminergic receptors. Research in rats (Piercey, Walker, Feldpausch, & Camacho-Ochoa, 1996) and humans (Gerlach et al., 2003) has shown that pramipexole has a high binding affinity to dopaminergic receptors in the striatum. Pramipexole is an agonist on the D2 subfamily of receptors. This includes the D2, D3, and D4 subtypes (Missale, Nash, Robinson, Jaber, & Caron, 1998). It binds primarily to the D2/D3 dopamine receptors and is used to treat PD as well as restless-leg-syndrome (Ferini-Strambi et al., 2008; Montplaisir, Nicolas, Denesle, & Gomez-Mancilla, 1999; Reichmann, Brecht, Koster, Kraus, & Lemke, 2003). Pramipexole's binding of the D2 receptors has been considered responsible for the improvement in motor symptoms in PD, whereas its binding to D3 receptors might be responsible for some improvement in depressive symptoms (Guttman & Jaskolka, 2001).

Studies investigating the effects of pramipexole on impulsivity have yielded results suggesting it increases some aspects of impulsivity and decreases others. Experiments with rats have repeatedly demonstrated that single doses of pramipexole increase impulsive, gambling-like behavior in reward related tasks (Holtz, Tedford, Persons, Grasso, & Napier, 2016; Johnson, Madden, Brewer, Pinkston, & Fowler, 2011; Madden, Johnson, Brewer, Pinkston, & Fowler, 2010). In human studies, experiments have demonstrated that a single dose of pramipexole

affects the reward network. Participants show a preference for riskier rewards and a decrease in brain activity associated with the attainment of a reward (Riba, Krämer, Heldmann, Richter, & Münte, 2008). Another neuroimaging experiment showed that pramipexole increased the connectivity between the nucleus accumbens and the anterior insula, but decreased the connectivity between the nucleus accumbens and the prefrontal cortex **(**Ye, Hammer, Camara, & Münte, 2011). In addition to the studies finding an association between pramipexole and ICDs and impulsivity, these results suggest that pramipexole disrupts reward-related neural pathways, leading to impulsive behavior.

In contrast, Fera and colleagues (2007) found that PD patients were more accurate on the incongruent condition of a Stroop task when they were on dopaminergic medication than when they were off medication, suggesting better cognitive control in the face of ambiguity. Specifically, in the modified Stroop task, patients had to select (via button press) one of four color words (green, blue, red, yellow) describing either the color of a square presented in the centre (Congruent condition) or the color of a color word printed in different ink in the centre of the screen (e.g. the word 'Blue' printed in red ink). In another study, Caillava-Santos and colleagues (2015) found that patients with PD were more quick to respond to incongruent trials of a Stroop task on medication compared to when they were off medication. In an experiment by Hiebert and colleagues (2014) PD patients had to learn stimulus-response associations that were either congruent or incongruent spatially. Patients responded faster to congruent and incongruent trials when they were off medication compared to when they were on medication, which is evidence of attenuated impulsivity by dopaminergic medication. An experiment by van Wouwe and colleagues (2016) elegantly dissociated impulse capture from impulse control in PD patients

on and off medication by employing the Dual Process Activation Suppression framework to examine performance on a Simon task. In the context of the framework, inhibiting an impulse consists of two processes: 1) impulse capture, which is the initial activation and initiation of a response to a stimulus and 2) reactive impulse control, which acts to prevent and inhibit an activated impulsive response. The theory states that in conflicting situations an incorrect impulsive response is initiated through a direct processing route, and that inhibition of this impulse is carried out through a deliberate, goal-oriented processing route (Ridderinkhof, 2002). The framework also provides analytical tools that allow to examine the distribution of responses and separately quantify the strength of impulse capture and of reactive impulse control. In the experiment, which employed the Simon task, participants had to press a button with their right or left hand in response to a colored circle appearing on the left or right side of a screen. A blue circle required a response with the left hand, and a green circle, with the right hand. The task consisted of Congruent trials (e.g. a blue circle, requiring a left-hand response, appearing on the left side) and Noncongruent trials (a blue circle appearing on the right side). The distribution of responses to the Simon task ranges from quick impulsive and incorrect responses (a measure of impulse capture) to slow, deliberate responses (when impulse control processes have built up). The results indicated that PD patients had better impulse control on medication than off, and that impulse capture was not affected by medication. Thus, only the ability to control the execution of an impulsive response was affected by the dopaminergic medication. In summary, it appears that dopaminergic medication slows down or attenuates some impulsive processes in patients with PD, while also exacerbating impulsivity in other, more complex behaviors that are reward-dependent.

An explanation of the seemingly contradictory effects of pramipexole on impulsivity can be offered by looking at impulsivity as a multifaceted phenomenon. Impulsivity is a complex construct entailing many different aspects of thought and behavior. Broadly, impulsivity can be defined as the inability to inhibit premature or pre-potent actions (i.e. actions that have previously been reinforced and become primed), along with a tendency towards risky or less calculated choices (Dalley, Everitt, & Robbins, 2011). Thus, it is clear that impulsivity involves multiple, possibly distinct behaviors.

Impulsivity can be divided into two domains: motor impulsivity and cognitive impulsivity (Antonelli, Ray, & Strafella, 2011). A principal component analysis (PCA) on 11 of the most common questionnaires and tasks used to measure impulsivity, including the Go/No-Go task (GNG), the Stop Signal Task (SST), and the Kirby Temporal Discounting task, supports a division of impulsivity into multiple aspects (Nombela, Rittman, Robbins, & Rowe, 2014). The analysis revealed 4 components, which were classified by the authors as follows: 1) Interference and response conflict in decision making, 2) Motor response inhibition, 3) Delay aversion and time estimation, 4) Temporal discounting. The components were dissociable and correlated with distinct demographic measures.

A larger PCA by Caswell and colleagues (2015) using a sample of healthy young adults further demonstrated that impulsivity is a heterogeneous construct. Specifically, their aim was to test whether impulsivity was composed of different subtypes, including motor-impulsivity, temporal-impulsivity, and reflective-impulsivity. They also aimed to test whether tasks that are used interchangeably to assess subtypes of impulsivity have shared factor loadings and correlations.

The authors tested 160 participants on 10 behavioral and one self-report measure of impulsivity. A PCA revealed four components as well, though the authors did not explicitly classify each component. However, component 1 had a high loading of the SST, which is likely to be the motor-impulsivity component. Curiously, the GNG task, another classic impulsivity measure, did not load on the same component. Component 2 had a high loading of the Information Sampling Task and the Matching Familiar Figures Task, leading the authors to classify it as a reflective-impulsivity component. Component 3 had a high loading of the Immediate Memory Task. Component 4 had a high loading of the Delay Discounting Task and the Monetary Choice Questionnaire, which was classified as the temporal-impulsivity component. The effects of pramipexole on impulsivity therefore are likely a combination of its influence on multiple aspects, cognitive and motor. It appears that pramipexole might increase some aspects of cognitive impulsivity (i.e. risk taking) but decrease other aspects, such as motor impulsivity.

1.4 Measures of impulsivity

Over the years, the complex and multi-faceted construct of impulsivity has been measured by a variety of behavioral tasks (See Figure 2).

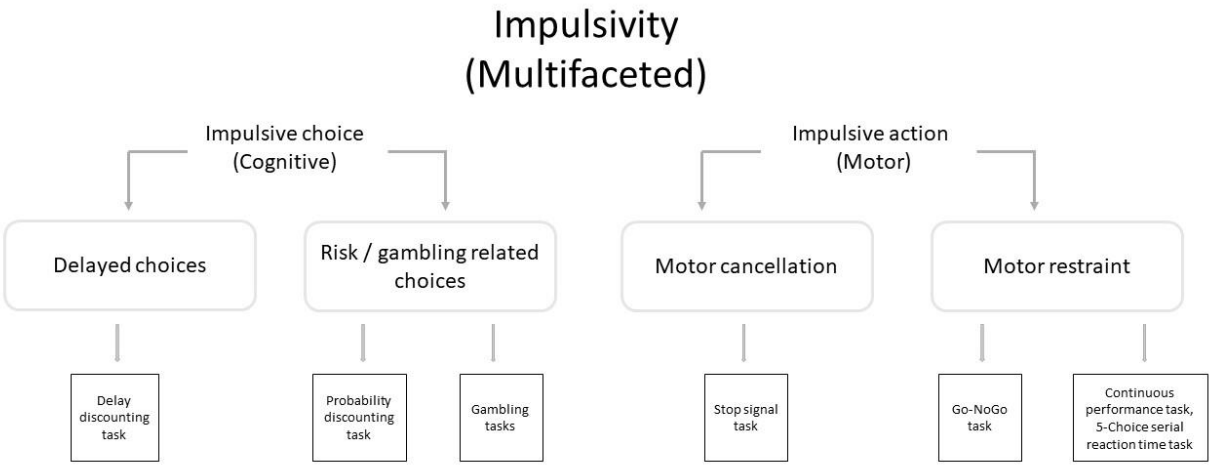

Figure 2: Multiple aspects of impulsivity and commonly used impulsivity tasks. Adapted from Winstanley, Olausson, Taylor, & Jentsch, (2010).

The GNG task is a common measure of impulsivity and motor control, because it requires the inhibition of a highly primed action. In the basic version of a GNG task, participants are told to press a button as quickly as possible when they see a stimulus appear in the centre of the screen. Trials proceed in quick succession such that participants are primed to make a quick button-press. In this way, the action becomes highly primed and pre-potent. On some trials, a different stimulus appears, and participants are told that on these trials no action needs to be taken, that is,

they must withhold the pre-potent impulse to press the button. Behavioral outcome measures on the GNG can be reaction time (RT) and accuracy (omission errors, commission errors, overall accuracy, or a ratio of these measures). The GNG task has been used with healthy participants as well as clinical populations to study impulsivity and differences in cognitive control (Antonelli et al., 2014; Georgiev, Dirnberger, Wilkinson, Limousin, & Jahanshahi, 2016; Hamidovic, Kang, & de Wit, 2008; Reynolds, Ortengren, Richards, & de Wit, 2006; Verbruggen & Logan, 2008; Woltering, Liu, Rokeach, & Tannock, 2013).

We are aware of only one experiment that employed the GNG task in a group of healthy participants to study the effects of pramipexole on impulsivity. Hamidovic and colleagues (2008) administered pramipexole or placebo to healthy participants who then performed a GNG task. They found no effects of pramipexole on any measures of the GNG. However, they employed a GNG task with a 50:50 Go:NoGo ratio, whereas most GNG experiments use higher Go:NoGo ratios to ensure the development of a pre-potent response. Thus, it is unlikely that their GNG task established a pre-potent, impulse-like response in participants.

The SST is a task that also measures impulsivity and the ability to stop a pre-potent action. In the task, participants choose an appropriate response when presented with a stimulus. Participants must respond as soon as the stimulus is presented; these are called Go trials. On Stop trials, the stimulus is followed by a Stop signal. When presented the Stop signal, participants must try to stop their response on that trial. Difficulty is adjusted by changing the delay between the Go stimulus and the Stop signal, known as the Stop Signal Delay (SSD). When the SSD is short (meaning the Stop signal occurs almost simultaneously with the Go stimulus) stopping a

response is easier than when the SSD is longer. The accepted theory behind the SST is that of the 'race model' (Logan, 1994; Logan, Cowan, & Davis, 1984). The model posits that performance on the SST reflects a race between a Go process and a Stop process, and that the two are independent of each other. The two processes compete simultaneously, with each having its own threshold for completion, and the one that reaches its threshold earlier results in a response (or lack thereof). The Go process has its own RT distribution, which is easily observed by presenting participants with stimuli in the absence of Stop-signals. The Stop process is not observable directly, because its successful execution results in no overt response and is, in fact, indicated by the absence of a response or action. Thus, the Stop process must be calculated using the RT distribution of the Go process and the proportion of successfully inhibited Stop trials fitted to that distribution (Logan et al., 1984). We are not aware of any studies in healthy participants that investigated the effects of pramipexole on performance of the SST.

The Balloon Analogue Risk Task (BART; Lejuez et al., 2002) is a task that simulates a risk-taking situation in the form of a game. In the BART, participants inflate a virtual balloon; the more pumps they make to inflate the balloon, the more virtual money they earn. They are presented several balloons, and on each trial they can cash out at any point, or continue inflating the balloon, until at some predetermined, but unknown and varying pump number, the balloon explodes and they lose all potential earnings for that balloon. The task has been used to study impulsivity and risk taking in healthy participants (Chiu et al., 2012; Fukunaga, Brown, & Bogg, 2012; Hamidovic et al., 2008; Rao, Korczykowski, Pluta, Hoang, & Detre, 2008; Reynolds et al., 2006).

Impulsivity can also be measured using questionnaires and self report measures. These measures do not always correlate with results from behavioral tasks, thus it is possible that they capture different aspects of impulsivity, or that self reported impulsivity and behavioral impulsivity are dependent on different processes. Among these, the Barratt Impulsiveness Scale (BIS), and the Sensation Seeking Scale have commonly been used.

Though reports of pramipexole use and the development of impulsivity and ICDs are common in PD, and there is a clear need to study the effects of the drug in healthy controls to disentangle PD pathology from medication effects, we are aware of only one other study that investigated pramipexole's effects on impulsivity tasks in healthy controls. Hamidovic and colleagues (2008) conducted a within-subjects study in young, healthy participants who over three sessions received placebo, 0.25 mg, and 0.5 mg of pramipexole. The participants completed several questionnaires assessing impulsivity, a simple RT and a two-choice RT task, as well as the GNG, the BART, a delayed discounting task, and a card perseveration task. The authors found no effects of pramipexole on any of the impulsivity tasks.

1.5 Aims of the study

In this study, we aimed to explore the effects of a single dose of pramipexole on different aspects of impulsivity in a sample of young healthy controls. We used a between-subjects, double-blinded, placebo-controlled design. Both groups completed the three impulsivity tasks (the GNG, SST, and BART), and measures of impulsivity and impulsivity-related traits using questionnaires (The BIS and the Sensation Seeking Scale), as well as other questionnaires to assess general cognition.

We hypothesized, based on the results appearing in the literature on impulsivity and dopaminergic medication, that pramipexole will decrease motor impulsivity, measured through the GNG and SST tasks. On the GNG, this will be evidenced by slower responding, which might also lead to fewer errors. On the SST, decreased impulsivity might result in a longer SSRT. The effects of dopamine agonists on reward-dependent impulsivity seem to be opposite, in that pramipexole should increase risk-taking on the BART, which is a measure of risk-reward and gambling. This pattern of results would be in line with the theory that pramipexole and dopamine agonists have opposing effects on different aspects of impulsivity.

Chapter 2: Methods

2.0 Participants

This study was approved by the Health Sciences Research Ethics Board (REB #102018) of the University of Western Ontario (See

). Participants were recruited from the University of Western Ontario through word of mouth and advertisements posted around campus. Forty-five young healthy adults were enrolled in the study (28 females, 17 males). Exclusion criteria were: a history of neurological (e.g., stroke, seizures) or psychiatric conditions (including clinical depression, hallucinations), family history of more than one first-degree relative with PD, history of alcohol or drug abuse, any risk factors associated with taking pramipexole (including taking monoamine oxidase inhibitors, history of cardiovascular disease, peptic ulcers). All potential participants were pre-screened during a brief phone interview, and completed an in-person screening form. All participants provided informed

consent before beginning the experiment in accordance with the Declaration of Helsinki (1991). All participants were provided with monetary compensation for their time.

2.1 Materials

2.1.1 Health and Demographics and Safety Screening questionnaires

Copies of the 'Health and Demographics' and the 'Safety Screening' questionnaires are found in Error! Reference source not found. and Error! Reference source not found.. These questionnaires we re administered to collect demographic data and ensure that in addition to the safety screening completed over the phone, there were no contraindications to receiving pramipexole, and that participants did not meet any exclusion criteria.

2.1.2 Pramipexole and placebo capsules

Participants orally ingested an opaque yellow capsule containing either 0.5 mg of pramipexole (tablet form, fitted into the capsule) or cornstarch. Capsules were prepared by the investigator and each capsule was kept inside an individual envelope with a unique code generated by an independent lab associate, ensuring that the investigator remained blind when giving participants the capsule. The chosen dose of pramipexole (0.5 mg) is based on dosages used in other studies in healthy participants (Hamidovic et al., 2008; Pizzagalli et al., 2008; Riba et al., 2008), as this was the dose shown to produce observable behavioral effects with minimal adverse events. This dose is commonly prescribed and falls within the therapeutic range. Pramipexole acts primarily on the D2 family of dopamine receptors, and reaches maximum plasma concentration after approximately two hours, which is when participants completed the impulsivity tasks. It has a terminal half-life of eight hours in young adults and about 12 hours in older adults (Putri et al., 2016; Wright, Sisson, Ichhpurani, & Peters, 1997).

2.1.3 Questionnaires

The Bond-Lader Visual Analogue Scale (BL-VAS; Bond & Lader, 1974) is a 16-item questionnaire assessing subjective feelings associated with alertness (alert—drowsy), calmness (tense—relaxed), and general mood (antagonistic—friendly). We presented participants with combinations of such opposing adjectives and asked them to place a mark with a pencil on a line stretching between the two adjectives corresponding to their current feeling. The distance from each adjective is measured in millimeters and used to calculate a total score for each cluster. See Error! Reference source not found..

The American National Adult Reading Test (ANART; Nelson, 1982) is a quick, commonly used measure of verbal intelligence employed in research in multiple populations. Due to its ease of administration and good overall validity (Bright, Jaldow, & Kopelman, 2002), the ANART was chosen as a measure of verbal intelligence in this experiment. Participants were instructed to read out loud a list of 50 words ranging in difficulty in their irregularity of grapheme-phoneme correspondence (e.g. aisle, hyperbole). They were told to pronounce them correctly, and to make an attempt even if they are not sure. Total number of correctly pronounced words was used as the final score. See Error! Reference source not found..

The Montreal Cognitive Assessment (MOCA; Nasreddine et al., 2005) is a measure used to screen for dementia and mild cognitive impairment. It evaluates basic visuospatial abilities, immediate and delayed recall as well as working memory, executive functioning and attention, language abilities, and time and place orientation. It is scored out of 30 points, with scores 26 and greater

indicating normal cognition. The test is commonly used with older adults. However, it was used in this experiment with young adults to ensure that groups were well-matched in terms of their cognitive functions as well as to parallel the procedures employed with older adults to allow for future between-subject comparisons. See Error! Reference source not found..

The Controlled Oral-Word Association Test (using letters 'F', 'A', 'S'; COWAT FAS; Benton, Hamsher & Silvan, 1994) is a measure of verbal fluency. Participants were asked to generate words out loud that begin with a given letter of the alphabet. They were allowed 60 seconds to do so, with the instructions stating that they should avoid proper nouns (e.g., Bob, Boston) and repetitions of the same word (i.e. perseveration errors) or same word-root with a different ending (e.g., Run, Running, Runners). The COWAT was administered as a control measure for verbal fluency and intelligence. See Error! Reference source not found..

The Barratt Impulsiveness Scale- version 11 (BIS; Patton, Stanford, & Barratt, 1995) is a 30-item questionnaire assessing different aspects of impulsivity. It has been extensively used to study impulsivity in research and clinical settings (Stanford et al., 2009) and consists of measures of attentional, motor, and non-planning impulsivity. It is rated on a Likert scale ranging from 1 = Rarely/Never to 4 = Almost always/Always. The BIS was chosen in this experiment to control for trait impulsivity that might account for differences between participants' impulsivity scores on the behavioral tasks. See **Error! Reference source not found..**

The Sensation Seeking Scale (Zuckerman, Eysenck, & Eysenck, 1978) consists of 40 pairs of statements in which the participant must select the statement that most applies to them and their

beliefs. It is a measure of sensation seeking, composed of scores for Boredom Susceptibility, Disinhibition, Experience Seeking, and Thrill/Adventure Seeking. See Error! Reference source not found..

The Epworth Sleepiness Scale (Johns, 1991) is a measure of fatigue. Participants were asked to rate how likely they are to fall asleep/ doze off (0 = "Would never doze" to 3 = "High chance of dozing") in eight different scenarios (e.g. "Sitting and reading" and "Sitting quietly after a lunch without alcohol"). Total score was used as a final measure of fatigue. We included this measure to be able to control for trait fatigue. See Error! Reference source not found..

The Oxford Happiness questionnaire (Hills & Argyle, 2002) consists of 29 statements which participants rate on a 6-point Likert scale from 1 = strongly disagree, to 6 = strongly agree. The statements assess general well-being (e.g. "I am well satisfied about everything in my life" and "I am not particularly optimistic about the future). The questionnaire was administered to assess participants' trait happiness and well-being to parallel with other experiments and allow for between-subjects comparisons. See Error! Reference source not found.

The Beck Depression Inventory **(**BDI; Beck, Steer, & Brown, 1996) was administered as an additional screening measure for depression. The BDI consists of 21 group of statements about thoughts and feelings experienced in the past two weeks including the day of testing. Participants circled the statement that is closest to their feelings/thoughts and the corresponding number. The total was used as an index of depressive symptoms, with scores of 21 or higher meeting depression criteria. See Error! Reference source not found..

The Beck Anxiety Inventory (BAI; Beck & Steer, 1990) measures general anxiety. It asks participants to rate how much they have been bothered by various common symptoms of anxiety (e.g. “Wobbliness in legs”, “Face flushed”) during the past week, including the day of the testing. Participants put a checkmark under options ranging from “Not at all” to “Severely- it bothered me a lot”, which were then converted to numerical scores and summed. See Error! Reference source n ot found.**.**

The Starkstein Apathy Scale (SAS; Starkstein et al., 1992) presents participants with 16 statements assessing apathy. Participants put a check mark under options ranging from “Not at all” to “A lot” for different statements related to apathy (e.g. “Does anything interest you?” and “Do you need a push to get started on things?”). The answers were then converted to numerical values and used to calculate a total apathy score. See **Error! Reference source not found..**

2.2 Equipment

The computer tasks were performed on a 22.0” monitor (LG Flatron W2242TQ) with a resolution of 1600 x 900 pixels and a desktop (LG model 73821B-10) using the Windows 7 Professional operating system. The screen was placed approximately 50 cm away from the participant. A keyboard (Logitech K120) was used to record participant responses.

2.3 Primary impulsivity measures

2.3.1 Go/No-Go Task

The GNG is a widely-used task measuring motor impulsivity and the ability to inhibit motor responses (Antonelli et al., 2014; Ballanger et al., 2009; Kiehl, Liddle, & Hopfinger, 2000; Petit, Kornreich, Noël, Verbanck, & Campanella, 2012; Rubia et al., 2001; Woltering et al., 2013). The version we used in the current study, the simple two-stimuli GNG, was chosen due to its ability to establish a highly pre-potent response in participants, which must be inhibited on certain trials. During a trial, participants would either see an X, which was the 'Go' stimulus, and then press the spacebar as quickly as possible, or see a K, which was the 'NoGo' stimulus to which any response must be inhibited (i.e. must not press any key). The task consisted of four blocks, each containing 64 trials. Of these trials, 48 were 'Go' trials, and 16 were 'NoGo' trials, constituting a distribution of 75% 'Go' trials to 25% 'NoGo' trials. This distribution was chosen to maximize 'Go' response prepotency, and is consistent with the parameters used in other studies (Boucher et al., 2012; Kiehl et al., 2000; Liddle, Kiehl, & Smith, 2001; Nieuwenhuis, Yeung, Wildenberg, & Ridderinkhof, 2003).

Trials started with a small grey fixation cross presented in the center of a dark background for 500 milliseconds (ms), followed by a stimulus presented in white, either an X or a K for up to 500 ms. If participants made a response before the timeout period, an inter-trial interval of 2000 ms (including the response time) followed, after which the fixation cross for the next trial appeared. These parameters ensured the development of a quick, pre-potent motor response that would require inhibitory control to suppress.

2.3.2 Stop Signal Task

The SST is used to measure control over motor impulsivity, that is, the ability to stop an ongoing action. The task has been widely used to study impulsivity in various populations (Bedard et al., 2002; Eagle, Baunez, et al., 2008; Williams, Ponesse, Schachar, Logan, & Tannock, 1999). In the two-choice version of the task, used in the current experiment, participants were presented one of two stimuli and needed to press one of two corresponding keys as quickly as possible. In our experiment, participants were asked to press the 'Z' key when they saw the letter 'X', and the '/' key when they saw the letter 'O'. Participants were instructed to press these keys as quickly as possible after seeing the stimuli – these were the Go trials. On some trials, referred to as Stop-signal trials, an auditory signal would sound after the presentation of the stimulus, which indicated that participants needed to stop their keypress. The task consisted of 128 trials broken into two blocks of 64 trials. In each block, 25% of the trials were Stop-signal (16 trials) and the remaining 48 trials were Go trials. Inter-trial interval was set at 2000 ms (including response time). Each trial started with the presentation of a grey fixation cross in the centre of the screen for 500 ms, followed by the stimulus which appeared on the screen until a response was recorded or 1250 ms elapsed. The initial SSD was set at 250 ms, with a staircase adjustment method increasing the SSD by 50 ms after successfully inhibited Stop-signal trials, and decreasing SSD by 50 ms after failed Stop-signal trials. This adjustment was used so that that participants successfully inhibited approximately 50% of the Stop-signal trials, which is necessary for analysis of the SST.

Participants were told that on some trials the signal would appear shortly after presentation of the stimulus, which would make stopping their keypress easy, whereas on other trials the signal would

appear after a slight delay, making stopping more difficult. Participants were encouraged to press the associated keys as quickly as they could, and were told that when they hear the signal they should do their best to stop, although on some trials stopping would nearly impossible. That is, they were told that appropriate performance of the task entails being unable to stop on some trials. They were explicitly informed that they should not slow their responding on Go trials to reduce the number of failed stops. This was done in accordance with instructions established previously (e.g. Logan et al., 1984) meant to encourage participants to provide an accurate and proportional number of successful and unsuccessful Stop-signal trials.

2.3.3 Balloon Analogue Risk Task

The BART has been previously used in healthy populations to study risk taking. Developed by Lejuez and colleagues (2002), the BART correlates with multiple established measures of impulsivity (Lejuez et al., 2002), including self-reports of different dimensions of impulsivity (i.e. venturesomeness, risk taking, reward seeking) and self-reports of impulsive behavior (i.e. drug use, alcohol consumption, risky sexual behavior, gambling). Further, the BART accounts for variance in impulsivity that is not captured by any of the above measures, suggesting it taps into an understudied or undetected aspect of impulsivity. This makes the BART a suitable task to capture what is likely a cognitive, reward seeking and risk discounting aspect of impulsivity.

We used a modified version of the original BART task (Lejuez et al., 2002). The version used for this experiment was modified to be shorter due to pilot data indicating that longer sessions were less likely to lead to measurable differences. The balloons were presented one at a time in the

center of the screen, surrounded by a display of the total earned amount, and the current reward in the temporary bank. Each pump increased the reward in the temporary bank by 5 cents. Participants could pump the balloon until they decided to collect their reward from that balloon, or until the balloon exploded. To collect their earnings participants pressed the 'Z' key and saw a smiley face accompanied by sound, indicating a win. Alternatively, if they reached a predetermined point at which the balloon exploded, known as the breakpoint, they saw a sad face and heard a popping sound, indicating they lost their current reward in the temporary bank. Participants were not aware of each balloon's breakpoint. Across all 30 balloons, and across each block of 10 balloons, the average breakpoint was 32 pumps. The range of the number of allowed pumps was between 1 and 64 pumps. For the task in the current study, a single randomly generated list of trial breakpoints, with the constraints noted above, was used for each participant to minimize interactions between different lists and individual differences of participants.

2.4 Physiological measures

Heart rate (HR) and blood pressure readings (i.e. diastolic and systolic) were taken using an automated blood pressure cuff (Omron model BP785N). These readings were taken to monitor participants' well-being and ensure that they did not experience significant physiological side effects from pramipexole, and to account for physiological changes across group or related to medication condition when analyzing behavioral data.

2.5 Procedure

All potential participants were pre-screened during a phone interview before being scheduled for the experiment. During the phone interview, they were provided information about pramipexole

and the testing session. The interviewer also went over a safety screening questionnaire to ensure that potential participants met none of the exclusion criteria for receiving pramipexole.

Upon arrival at the lab, potential participants completed another safety screening questionnaire. They signed the consent form and completed a health and demographics questionnaire. Following this, they completed the BL-VAS and their HR and blood pressure were measured, before they received the capsule. This is referred to as Time 1 (T1). They were provided information about the double blinding process and were reminded that in the less likely event that they should feel any side effects during the session, they should inform the experimenter. A timer set to two hours was started as soon as the participants ingested the capsule. The participants then completed the ANART, the MOCA, the COWAT FAS, the BIS, the Sensation Seeking Scale, the Epworth Sleepiness Scale, and the Oxford Happiness Questionnaire. This was followed by practice trials for each of the computer tasks.

Participants were then given a break with the duration dependent on how much time was left on the timer until the two hours since capsule ingestion elapsed. During the break, participants could do anything as long as they remained in the testing room. The investigator came back every 15 minutes to check on the participants and make sure they were feeling fine and were not experiencing side effects.

After two hours passed since capsule ingestion, when drug concentration was at its peak, HR and blood pressure measures, as well as BL-VAS ratings, were obtained for a second time. This is

referred to as Time 2 (T2). Participants then completed the computerized tasks - the GNG, followed by the BART and the SST.

Task order was the same for all participants to avoid any interactions of task order and differences in the onset of physiological responses to the drug between participants. After completing all tasks, HR and blood pressure measures were recorded for one final time. This is referred to as Time 3 (T3). Participants also completed the BL-VAS one further time, were debriefed about the experiment, and received monetary compensation for their time. An outline of the entire experimental procedure is shown in Figure 3.

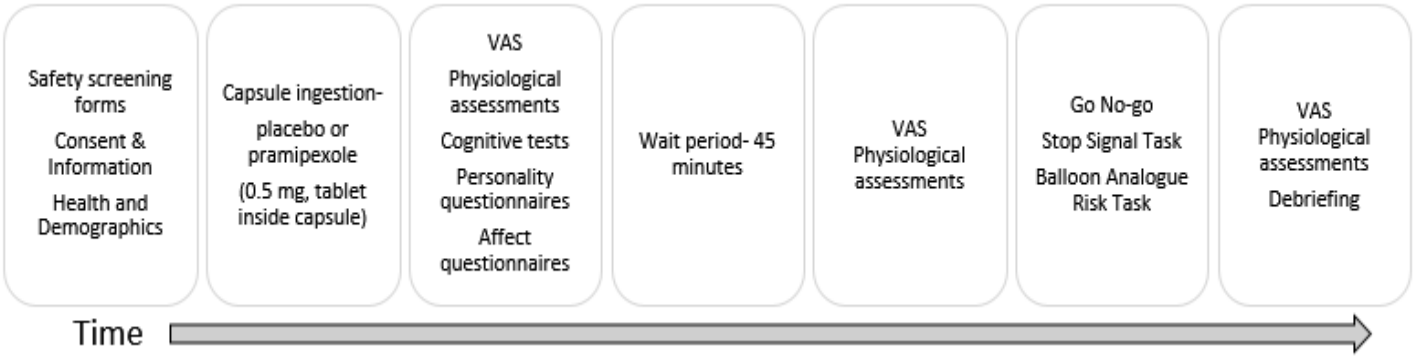

Figure 3*:* Schematic outline of the experiment.

2.6 Analyses

2.6.1 Time effects of pramipexole

To compare the physiological effects of pramipexole and placebo across time in the experiment, separate 2 x 3 mixed ANOVAs with Medication (placebo vs. pramipexole) as the between-subjects variable and Time (T1 vs. T2 vs. T3) as the within-subjects variable were conducted on HR,

diastolic and systolic blood pressure, and on the BL-VAS ratings. T1 measurements were taken right after capsule ingestion; T2 measurements were taken two hours after capsule ingestion; T3 measurements were taken approximately 2 hours and 45 minutes after capsule ingestion (after behavioral tasks).

2.6.2 Go/No-Go Task

A series of independent samples t-tests were conducted on overall GNG accuracy and Go-trial RT. Overall GNG accuracy is commonly used as a measure of cognitive control and inhibition of pre-potent responses. A lower accuracy on the GNG is generally due to higher error rates on NoGo trials, an indicator of increased impulsivity. Average Go-Trial RT was used as a more direct and continuous measure of impulsivity in ms as opposed to a binary correct vs. incorrect measure. A quicker average RT on Go trials would indicate that participants were more predisposed to making a response, whereas a slower RT would mean participants needed more time to generate or execute a response, thus were less impulsive.

2.6.3 Stop Signal Task

Stop-signal RT (SSRT), which is the main outcome measure of the task, was calculated by subtracting the SSD from the average RT (see Logan et al., 1984). An independent samples t-test was used to compare the average SSRT of the pramipexole and the placebo group. SSRT is a measure of the unobservable Stop process involved in inhibiting the Go process once a Stop-signal is heard but a response is still ongoing. In order to calculate the SSRT, two conditions have to be met: 1) The accuracy on Stop trials must be around 50% and 2) mean RT for failed Stop trials must be shorter than the RT for Go trials (Claassen et al., 2015).

2.6.4 Balloon Analogue Risk Task

An independent samples t-test was conducted to compare adjusted average number of pumps between groups. The adjusted average number of pumps is the average number of pumps, excluding trials on which the balloon popped. This is done because popped trials have a fixed limit on the number of pumps for each participant, such that even if some participants were to continue pumping more than others, they would be unable to do so because they were limited by the balloon's breakpoint. There exist other variables that can be compared on the BART such as overall number of pumps, or the number of exploded balloons. To minimize the risk of Type 1 error, analyses on these variables were not performed and the a priori hypothesis was made about the average adjusted number of pumps. This is a procedure similar to that originally used by Lejuez and colleagues, (2002). The adjusted average number of pumps is a measure of risky, reward-dependent impulsivity involved in gambling, as the more pumps a person makes, the greater the reward but the more they risk that the balloon explodes and all earnings for that balloon are lost.

A 2 x 3 mixed ANOVA with Medication as the between-subjects variable and Block (first set of 10 balloons, second 10 balloons, and third 10 balloons) as the within-subjects variable was conducted on the adjusted average number of pumps. This analysis allows examining whether risk-taking behavior changed in later blocks compared to earlier ones (practice trials were not included in this analysis).

Chapter 3: Results

Data from one male and four females were excluded because they were unable to complete the entire testing protocol due to adverse side effects of the medication (nausea, fatigue, and dizziness). The following analyses were all carried out at an alpha level of 0.05, and Bonferroni corrections were used for post-hoc pairwise comparisons.

3.0 Demographics and questionnaires

Demographic data along with trait questionnaire scores and cognitive questionnaire scores are shown in Table 1. The pramipexole and placebo groups did not show significant differences on any of the variables ($p > 0.05$ for all variables; age t (38) = −0.84; education t (38) = −0.49; BDI t (38) = 0.78; BAI t (38) = 0.50; SAS t (38) = 0.23; Happiness t (38) = −0.06; Sleepiness t (38) = 0.42; BIS t (38) = 1.00; Sensation Seeking Scale t (38) = −0.15; ANART t (38) = 0.14; MOCA t (38) = 0.00; COWAT FAS t (38) = 0.46; COWAT Animal t (38) = − 0.14). This rules out any pre-existing differences between the pramipexole and the placebo group on any of these measures which might have affected performance on the impulsivity tasks, including age, cognitive ability, trait impulsivity, and other potentially important variables.

	Placebo	**Pramipexole**
Age	20.5 (1.3)	20.8 (0.9)
Gender	8 M; 12 F	8 M; 12 F
Handedness	18 R; 1 L; 1 Both	17 R; 2 L; 1 Both
Education	15.40 (1.05)	15.5 (0.89)
BDI	9.60 (7.18)	8.05 (5.26)

BAI	8.60 (8.29)	7.45 (6.17)
SAS	11.50 (4.80)	11.20 (3.44)
Happiness	4.45 (0.58)	4.46 (0.64)
Sleepiness	10.05 (2.65)	9.60 (3.94)
BIS	62.05 (10.29)	58.60 (11.41)
Sensation Seeking Scale	19.80 (5.72)	20.05 (4.47)
ANART	118.95 (6.46)	118.71 (4.44)
MOCA	27.80 (1.51)	27.80 (1.94)
COWAT FAS	40.15 (11.00)	38.60 (10.61)
COWAT Animals	24.55 (1.12)	24.80 (1.33)

Table 1: Demographic measures and questionnaire scores of the pramipexole and placebo groups.

3.1 Physiological measures

Heart Rate - A 2 x 3 mixed measures ANOVA (Medication x Time) revealed a main effect of Time [F (2, 74) = 32.40, MSe = 25.12, $p < .001$, $\eta^2 = .47$]. As can be seen in Figure 4, this effect is due to a decrease in HR from T1 to T2, and from T1 to T3 (both $p < .001$). There was also a significant Medication x Time interaction [F (2, 74) = 4.37, MSe = 25.12, p= .016, $\eta^2 = .11$]. The difference in HR between T1 and T2, and T1 and T3 in the placebo group was 9.5 and 11.79, respectively. The difference in HR between T1 and T2, and T1 and T3 in the pramipexole group was 4.5 and 5.4, respectively. Thus, the differences between T1 and both T2 and T3 were larger in the placebo group than in the pramipexole group. The main effect of Medication was not significant [F (1, 36) = 0.084, p = .774], however, meaning that pramipexole had no effect on HR

independently of the passage of time or the time of ingestion. Mauchly's test of sphericity has not been violated.

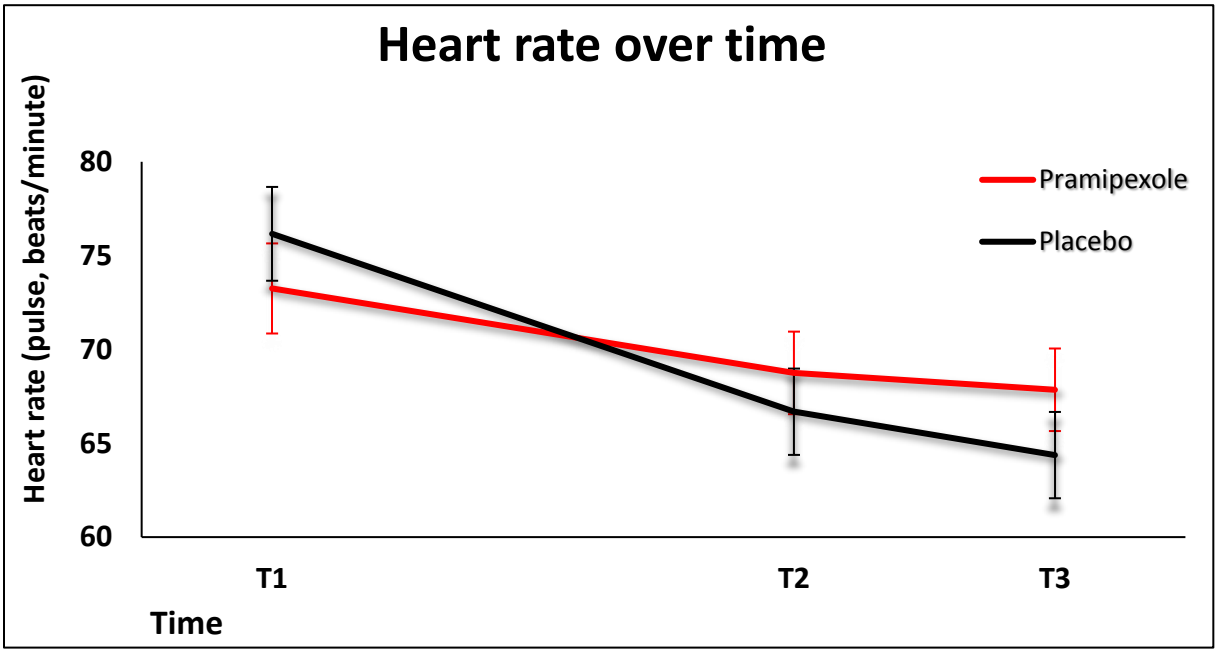

Figure 4: Mean HR over time in the placebo and pramipexole groups. Error bars represent SEM.

Blood pressure- Separate 2 x 3 repeated measures ANOVAs were conducted on diastolic and systolic blood pressure. For diastolic blood pressure, Mauchly's test indicated the assumption of sphericity was not met [X^2 (2) = 9.6, p = .008]. This was due to the variance of differences in both groups in T3 - T2 being lower than in the other comparisons (i.e. T2 - T1 and T3 - T1). After Huynh-Feldt corrections (ε = 0.81), there was a significant main effect of Time [F (1.74, 74) = 6.51, MSe = 28.68, p = .004, η^2 = .123]. Post hoc Bonferroni corrected pairwise comparisons revealed that this was due to diastolic blood pressure decreasing from T1 to T2 (p = .017), and from T1 to T3 (p = .034), in both the pramipexole and the placebo group (see Figure 5). There was

no main effect of Medication [F (1, 37) = 0.180, p = .674], and no Medication x Time interaction [F (1.74, 74) = 0.500, p = 0.583]. These results indicate that participants in the pramipexole and the placebo groups had higher diastolic blood pressure at the beginning of the testing session (T1) than 2 hours later (T2) or at the end of the session (T3). Pramipexole did not change participants' blood pressure readings in comparison to placebo.

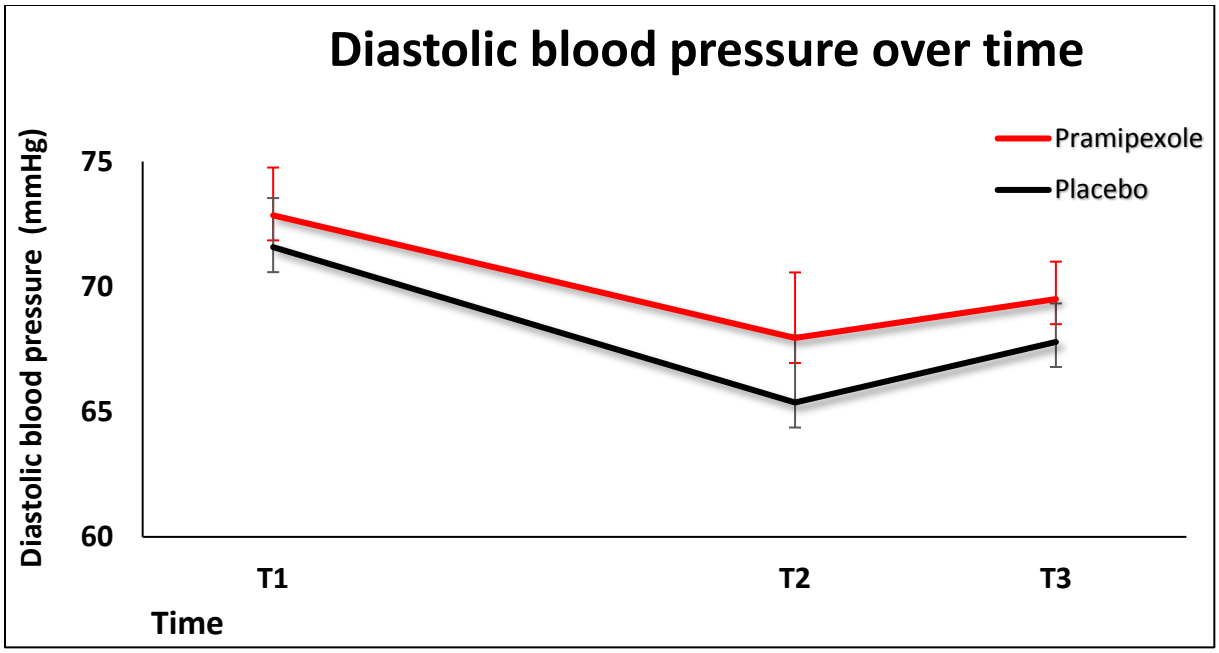

Figure 5: Diastolic blood pressure over time in the placebo and pramipexole groups. Error bars represent SEM.

For systolic blood pressure, Mauchly's test also revealed a violation of the assumption of sphericity due to the variance of differences in both groups in T3 - T2 being lower than in the other comparisons. Due to the lower epsilon (ε = 0.67), and according to Girden (1992), a Greenhouse-Geisser correction was applied and the effect of time was not significant [F (1.35, 74) = 3.54, p =

.054]., The effect of Medication and the Medication x Time interaction were also not significant (see Figure 6**,** all *p*'s > .05).

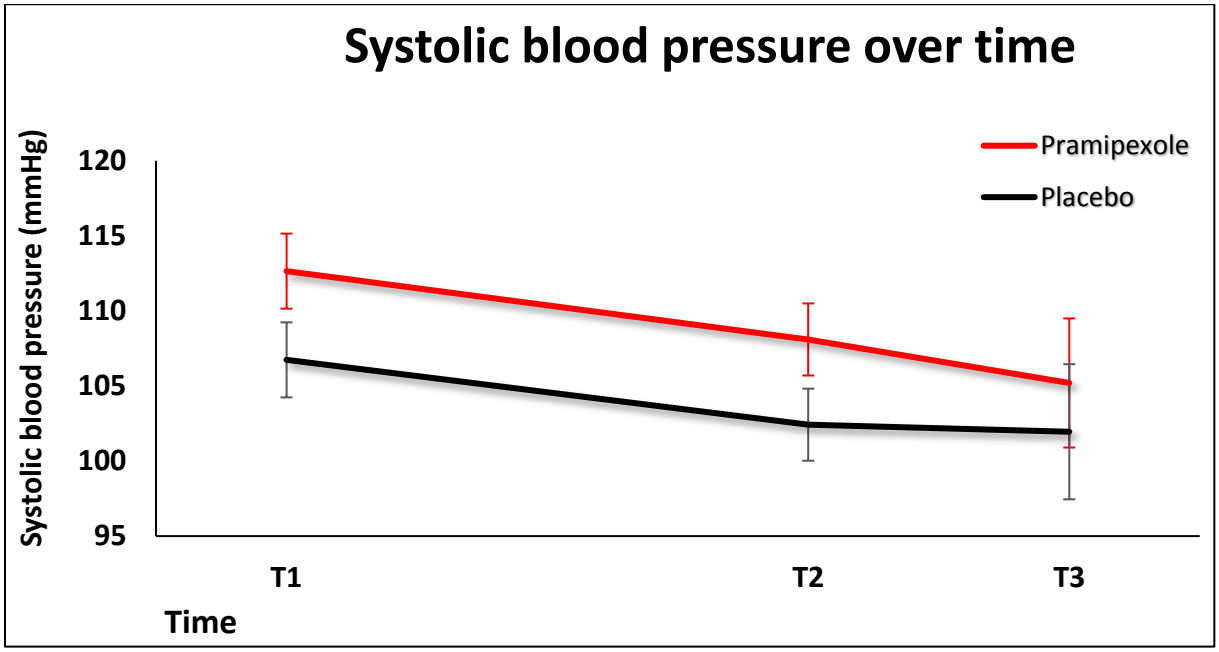

Figure 6: Systolic blood pressure over time in the placebo and pramipexole groups. Error bars represent SEM.

Mood ratings - The BL-VAS ratings across the time points in both groups were compared using a 2 x 3 repeated measures ANOVA. There was a significant effect of Time [F (2, 76) = 13.65, MSe = 1748.37, p < .001, η^2 = .264]. Bonferroni-corrected pairwise comparisons revealed this was due to an overall decrease in alertness ratings from T1 to T2 (p = .001) and T2 to T3 (p < .001; see Figure 7). This main effect was qualified by a Medication x Time interaction [F (2, 76) = 4.11, MSe = 526.62, p = .020, η^2 = 0.098]. This was due to the alertness scores significantly decreasing from T1 to T2 and T1 to T3 in the pramipexole group (p's < .001), but not in the placebo group (p

= .84, and .31, respectively). The main effect of Medication was not significant [F (1, 38) = 2.63, p = .113]. Mauchly's test of sphericity has not been violated.

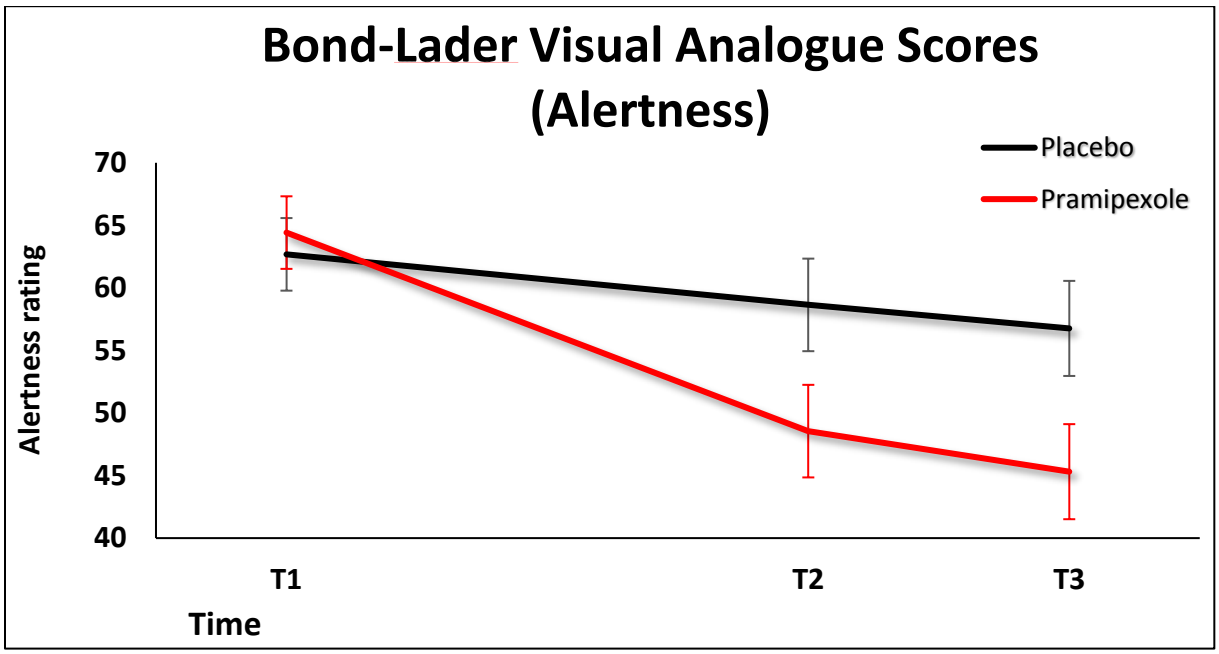

Figure 7: Alertness ratings from the Bond-Lader Visual Analogue Scale over time in the placebo and pramipexole groups. Error bars represent SEM.

3.2 Behavioral measures

3.2.1 Go/No-Go Task

Performance on the GNG for both groups, including accuracy and RT, is shown in Table 2. To compare accuracy on the GNG between the placebo and pramipexole group, an independent samples t-test was used. Levene's test showed that variances were unequal between the groups; a corrected value was used for the t-test, and revealed a significant difference between the groups, t (28.3) = 2.72, p = .011, d = 0.86, with the pramipexole group having a lower accuracy. To further explore whether this difference occurred due to errors on Go or on NoGo trials, separate t-tests

were conducted on both accuracy measures. There was a significant difference in accuracy between the placebo and pramipexole groups on Go trials [t (28.7) = 2.24, p = .033, d = 0.71, corrected for unequal variances], with the pramipexole group having a lower accuracy than the placebo group. The only error that is possible on a Go trial is timing out without making a response, and as seen in **Error! Reference source not found.**, the pramipexole group had twice as many t imed-out Go trials as the placebo group, t (29.1) = 2.26, p = .031, d = 3.22. This is suggesting an inhibition or stunting of a pre-potent and impulsive motor response in the pramipexole group. The accuracy for NoGo trials was not significantly different between the placebo and pramipexole groups, t (38) = 1.30, p = .20. To examine whether there might have been a general cognitive or response slowing on the GNG, Go and NoGo trial RTs were compared between the placebo and pramipexole groups using two tailed independent samples t-tests. There were no significant RT differences between the groups in either Go [t (38) = −0.574, p = 0.569] or NoGo [t (38) = 1.315, p = 0.196] trials. This rules out the explanation that the larger number of timeout Go trials in the group that received pramipexole was due to a general cognitive slowing effect, as the RTs were not significantly longer in the pramipexole group in either Go or NoGo trials. Thus, the inability to respond in time on a Go trial was unique to the pramipexole group only, supporting our hypothesis of decreased motor impulsivity in participants who received pramipexole.

	Placebo	**Pramipexole**
Overall accuracy	0.94 (0.004)	0.91 (0.009)
Go accuracy *	0.96 (0.006)	0.93 (0.01)
Go RT	356.76 (26.23)	361.70 (28.17)
NoGo RT	487.19 (56.19)	470.28 (12.32)

Number of Go timeouts *	6.8 (1.2)	12.5 (2.2)
Number of NoGo errors	8.3 (1.0)	9.3 (1.1)
SSRT	295.54 (32.16)	301.80 (34.32)
BART adjusted pump #	22.2 (2.7)	19.3 (1.1)

Table 2: Performance on the GNG, SST, and BART in the placebo and pramipexole groups. Values are given as mean (SEM), * denotes $p < .05$.

3.2.2 Stop Signal Task

Participants in the placebo group had a successful inhibition rate of 40% (*SD* = 8%), and participants in the pramipexole group had a rate of 39% (*SD*= 14%). An independent samples t-test revealed no significant difference between these rates, t (38) = 0.43, p = .67. The mean RT of failed Stop trials was shorter than the mean RT of Go trials, [Failed Stop trial RT= 412 (118) ms, Go trial RT = 456 (149) ms]. As a main measure of motor impulsivity, the SSRT for each participant was calculated by taking the mean Go RT and subtracting the mean SSD. An independent samples t-test was used to compare the SSRT of the two groups. The average SSRT, which measures the Stop process RT, was compared between the placebo (*M* = 295.54, *SEM* = 32.16) and pramipexole (*M* = 301.80, *SEM* = 34.32) groups, and revealed no significant difference, t (38) = 0.596, p = .555. Thus, the pramipexole and placebo groups did not take a significantly different amount of time to complete the Stop process.

3.2.3 Balloon Analogue Risk Task

The adjusted average number of pumps, which is a measure of the participants' riskiness and tendency to continue pumping a balloon in anticipation of a larger reward, was compared between

the placebo (M = 22.2, SEM = 2.7) and pramipexole (M = 19.3, SEM = 1.1) groups. There was no significant difference between the groups on the adjusted average number of pumps, t (38) = 0.999, p = .324, suggesting that pramipexole did not alter participants' risk-taking in gambling-like situations. The Medication x Block ANOVA on adjusted pumps revealed a main effect of Block, F (2, 74) = 3.99, p = .022, MSe = 53.81 , η^2 = . 098 (see Figure 8). Bonferroni corrected post-hoc analyses revealed that the adjusted average number of pumps in Block 2 was significantly lower than in Block 3. Block 1 did not significantly differ from Block 2 or Block 3. These findings indicate that participants in both groups engaged in more risky-responding on the final block of the task compared to the middle block. This could be a result of fatigue or increased confidence in performance of the task. There was no significant main effect on Medication, or a Medication x Block interaction. Mauchly's test of sphericity has not been violated.

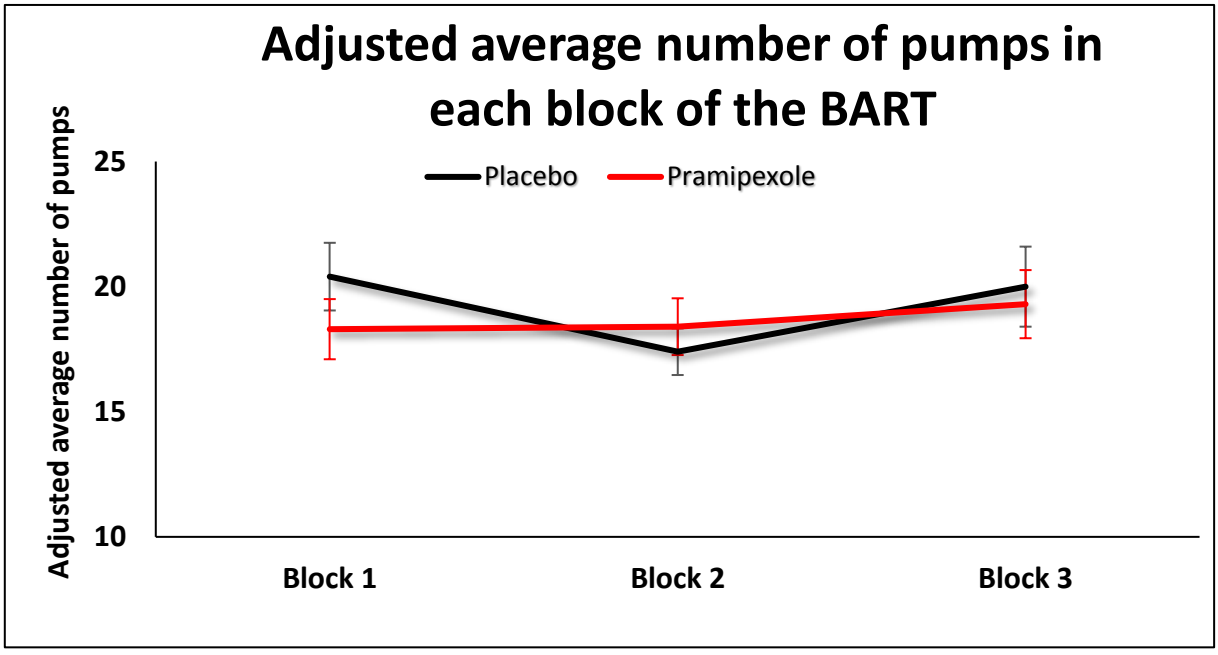

Figure 8: Adjusted average number of pumps in each block of the BART for the placebo and pramipexole groups. Error bars represent SEM.

Chapter 4: Discussion

4.0 Summary of results

In the current study, young healthy participants were given a dose of the dopamine agonist pramipexole, or a placebo, and then completed tasks measuring motor impulsivity and risk-taking. We used three tasks to measure different aspects of impulsivity: the GNG task and the SST to measure motor impulsivity, and the BART to measure risk-taking and gambling. Results indicated that participants who received pramipexole had more timed out Go trials than the participants who received placebo, but there were no RT differences in either Go or NoGo trials. This suggests enhanced motor inhibition, thus evidence of *decreased* motor impulsivity in the pramipexole group, which agrees with our proposed hypothesis and the literature. There was no significant SSRT difference between the groups on the SST. Performance on the BART was also not different between the placebo and the pramipexole groups, indicated by no difference in the adjusted average number of pumps. These results align with the hypothesis that different aspects of impulsivity might not be affected equally by dopamine agonists such as pramipexole.

4.1 Demographic, cognitive, and affective measures

Lack of differences between the groups on any of the demographic, cognitive, or affective measures confirms that the randomization process produced groups similar in these important characteristics. Particularly, there were no differences in pre-existing impulsivity, a factor which has been shown to exacerbate the influence of dopaminergic medication on impulsivity (Claassen et al., 2015; MacDonald et al., 2016). Therefore, because both groups were equivalent

on these measures before drug administration and before the drug had time to take effect, results on the behavioral tasks are not due to any pre-existing differences between the groups.

4.2 Physiological changes

As the experiment progressed, participants showed a decrease in HR and in alertness scores on the BL-VAS. Because there was no main effect of medication on these measures, we interpret these decreases as being a result of participants becoming more comfortable with the experimental setting, and being seated and inactive for nearly 3 hours. The Medication x Time interaction indicates that participants who received pramipexole had greater differences in BL-VAS ratings from T1 to T2 and T3 than those who received placebo. Nevertheless, even at T3, when scores were lowest, the pramipexole participants' average scores on the BL-VAS centered around 'Neutral', indicating they were not feeling particularly tired or sleepy. Additionally, the equivalent RTs between the placebo and pramipexole groups mean that this decrease in alertness did not affect RTs and that our finding of more timed out Go trials in the pramipexole group is not simply due to a decrease in alertness.

4.3 Motor impulsivity

Our findings suggest that pramipexole does not increase motor impulsivity, and might in fact decrease it, in line with other experiments that find either unchanged or decreased motor impulsivity after administration of dopamine agonists (Caillava-Santos et al., 2015; Fera et al., 2007; Hiebert et al., 2014; Müller, Benz, & Börnke, 2001; Müller, Benz, & Przuntek, 2002; Nandam et al., 2013; van Wouwe et al., 2016). It is important to note that participants on pramipexole had more timed out Go trials than those who received placebo, but did not have

longer RTs on the GNG task, or on the other tasks. Thus, it is unlikely that the higher number of timed out trials is simply due to an overall slowing effect or a motor impairment due to pramipexole. Rather, they seemed to have imposed a slightly more conservative criterion for responding in the Go trials (i.e., less motor impulsivity). This pattern suggests that participants on pramipexole were in fact exhibiting a decrease in impulsive behavior.

There was no corresponding difference between the placebo and pramipexole groups in the number of commission errors on NoGo trials, as would have been predicted if pramipexole improves motor impulsivity. It is possible that we did not find fewer commission errors for the pramipexole relative to the placebo group because of our 3:1 ratio of Go:NoGo trials, meaning there were far fewer NoGo trials and therefore less power to detect subtle differences across groups owing to medication in the NoGo condition. Indeed, there were very few NoGo errors overall in either group. We used the chosen ratio to ensure the development of a pre-potent Go response (Boucher et al., 2012; Kiehl et al., 2000; Petit et al., 2012; Rubia et al., 2001) that would engender an impulsive motor action in the NoGo condition. In future studies, more blocks and hence trials overall would be advisable. Alternatively, a different ratio of Go:NoGo trials might be considered though the latter approach could result in a failure to induce the pre-potent motor response.

The experiment by Hamidovic and colleagues (2008) showed that pramipexole did not have an effect on GNG performance in healthy controls, whereas we found more timed out Go trials. This discrepancy may be due to differences between the GNG tasks used. Hamidovic and colleagues employed a more complex GNG task, with four stimuli corresponding to Go

responses and four corresponding to NoGo responses. This complexity and the need to remember stimulus-response associations in addition to executing motor responses or inhibiting them confounds motor impulsivity and working memory, potentially accounting for the differences in their findings. They also used a 1:1 ratio of Go:NoGo trials. In using one Go and one NoGo stimulus in our task, and employing a 3:1 ratio of Go:NoGo trials, we ensured that the task measured motor impulsivity more clearly and promoted the development of a pre-potent motor response. Additionally, due to the small sample size in their study (N=10), they were potentially underpowered to detect subtle medication effects on impulsivity.

Although we could not find any other studies that have investigated the effect of pramipexole on GNG performance in healthy controls, a few similar studies have been conducted with PD patients on and off medication (Antonelli et al., 2014; Farid et al., 2009; Herz et al., 2014). In a small positron emission tomography study (N = 7) of PD patients performing a GNG and a delayed discounting task on and off pramipexole, Antonelli and colleagues (2014) found no influence of pramipexole on RT or errors on the GNG. A functional magnetic resonance imaging (fMRI) study by Farid and colleagues (2009), tested PD patients (N = 9) on and off levodopa in contrast with healthy controls and found that there was no medication effect on GNG performance. Herz and colleagues (2014) also found no medication effects on performance of a more complex GNG task in an fMRI study of 13 PD patients with dyskinesia and 13 without dyskinesia, tested on and off their regular dopaminergic medication. The GNG task consisted of three stimuli, thus it was more complex and less likely to elicit pre-potent responses. The few experiments that investigated the effects of dopaminergic medication on GNG performance in PD patients found no behavioral differences between patients on and off medication. However,

all the studies tested only a small sample of participants, and were very likely underpowered to detect medication effects. Further, the use of complex tasks and less emphasis on inducing a pre-potent motor response could have undermined these studies.

Another task commonly used to measure motor inhibition is the SST (Bedard et al., 2002; Eagle, Baunez, et al., 2008; Williams et al., 1999). We did not find SSRT differences on the SST between the placebo and pramipexole groups. Indeed, results from the SST and the GNG task do not always correspond and a PCA has shown the two tasks load on different factors (Caswell et al., 2015). The tasks, although similar, reflect different inhibitory processes. Schachar and colleagues, (2007) proposed a distinction between 'motor restraint' and 'motor cancellation'. The SSRT measures the time taken to complete a 'stopping' process once an action has already been selected and initiated (Dalley et al., 2011; Winstanley, 2011). In this way, it is measuring 'motor cancellation'. This is different from the motor inhibition process in the GNG, which measures the ability to inhibit the initiation of a response (Dalley et al., 2011; Eagle, Baunez, et al., 2008; Reynolds, Penfold, & Patak, 2008; Winstanley, 2011; Winstanley et al., 2010). This process is therefore one of 'motor restraint'. The two processes elicited by these tasks have also been shown to have distinct neural activation patterns and dissociable pharmacology (Eagle, Bari, & Robbins, 2008; Rubia et al., 2001).

We are aware of only three studies that investigated the effects of dopaminergic medication on SST performance in healthy controls. Farr and colleagues, (2014) gave 25 healthy controls a single dose of the dopamine reuptake inhibitor methylphenidate (45 mg) and asked them to complete the SST while placed in an fMRI scanner. Data from these participants was compared

to a demographically-matched sample of participants who did not receive any drugs but completed the task in a different experiment. Results indicated that methylphenidate did not affect any behavioral measures of performance on the SST. A within-subjects, placebo-controlled study by Costa and colleagues, (2013) tested 54 healthy controls on placebo and on methylphenidate. They found no differences in SST performance between participants whether they received methylphenidate or a placebo. Another within-subjects placebo controlled experiment by Nandam and colleagues (2013) examined the effects of a single dose of the dopamine agonist cabergoline (1.25 mg) on SST performance in healthy controls. Participants showed a faster SSRT on cabergoline compared to placebo, suggesting that cabergoline improved impulse control by speeding up the stopping process of the SST. However, the version of the task employed in this experiment contained a high number of trials (512) in comparison to the task employed in other experiments (e.g. 234 trials in Costa et al., 2013). Thus it is possible that the effects of dopaminergic medication on SST are very small and can only be detected with a very large number of trials. Additionally, cabergoline is a D2 agonist, whereas methylphenidate acts through a different mechanism, by blocking the reuptake of dopamine from the synapse. Based on the findings of these studies, it appears that SST performance is not very sensitive to dopaminergic drugs, which would be in line with the pattern of findings in our study.

Studies of PD patients on and off dopaminergic medication also suggest that there is little influence on SST performance. Obeso, Wilkinson, and Jahanshahi, (2011) tested 17 patients with PD in two sessions, one on and one off levodopa. They found no differences on any measure of SST between on and off sessions. Claassen and colleagues (2015), tested 24 patients with PD on and off dopamine agonists (although half the sample was also on concomitant levodopa

treatment). The PD group was split based on the presence of ICDs (12 PD with ICD, 12 without ICD). The authors found no difference in performance on the SST between sessions on and off dopaminergic medication. From the limited number of studies that have looked at the effects of dopaminergic drugs on performance of the SST, it seems likely that if there is any effect on SSRT and thus impulse control, it is a very small effect that requires a large number of trials to uncover. Thus, one potential explanation for the null results of the SST in our study is that our version of the task did not contain enough trials to detect such a small change.

4.4 Cognitive impulsivity

Cognitive impulsivity, although related to motor impulsivity, is certainly distinct from it. We used the BART to measure cognitive impulsivity, specifically risk-taking and gambling-like behaviour. In our experiment, we found no differences between participants who received pramipexole and those who received placebo on the BART. Claassen and colleagues, (2011) aimed to examine the effects of dopaminergic medication on risk-taking in PD patients with ICDs (N= 22) and without ICDs (N=19). They found that in the PD without ICD group, there was no difference in risk-taking on the BART between the on and off medication testing sessions. However, in the PD with ICD group, there was evidence of increased risk-taking in the session on medication compared to off medication. Thus, dopaminergic medication alone did not increase risk taking. In another study, Simioni, Dagher and Fellows, (2012) tested 23 PD patients on and off dopaminergic medication. They found that although medication had no overall effect on risk-taking on the BART, it did increase risk-taking across the 3 blocks of the BART. That is, PD patients increased the number of pumps from the 1st to the 3rd block of the BART when tested on medication more than they did when tested off medication. These results

suggest that medication effects on risk-taking are more subtle and might require some time before they influence behavior. Finally, a study by MacDonald and colleagues (2016) specifically tested the hypothesis that medication effects on risk-taking are dependent on initial dopamine levels and predisposition for risky behavior using gene polymorphisms in older healthy controls (N=28). Over three testing sessions, participants received ropinirole (0.5 or 1.0 mg) or placebo. Using mixed-model linear regression, they found that controls with a high basal dopamine neurotransmission (measured through gene polymorphisms) exhibited more risk-taking behavior on ropinirole versus placebo, only following negative but not positive reinforcement (i.e. trials on which the balloon popped versus trials they cashed out). The pattern of findings above indicates that dopamine agonists' effects on risk-taking are dependent on initial predisposition to risky behavior and impulsivity (measured either through clinical assessments or gene polymorphisms). Thus, dopaminergic medication alone is not sufficient to lead to more impulsivity and risk-taking.

4.5 Limitations

In this study, conducted with healthy volunteers, participants received a single dose of a dopamine agonist. The dose (0.5 mg) was not as large as the dose prescribed to clinical populations, because dopamine agonist dosage needs to be increased gradually over a longer period of time to avoid side effects. Studies that have found an association between dopamine agonist use and ICDs (Cools, Barker, Sahakian, & Robbins, 2003; Pontone et al., 2006; Weintraub et al., 2010) have all been conducted in clinical populations, with patients who have been treated with dopaminergic medication for a long duration. The current study was not longitudinal so it was impossible to examine any long-term effects of pramipexole. Additionally,

we could not safely administer a higher dose of the drug, and this was the dosage commonly used in other studies that administered pramipexole to healthy participants (Hamidovic et al., 2008; Pizzagalli et al., 2008; Riba et al., 2008). Administering a larger dose would most likely increase the occurrence of adverse effects that lead to participant drop-out. Thus, it is possible that a single (and comparatively low) dose of pramipexole administered to healthy controls does not have enough potency to effect the changes that lead to ICDs and increased risk-reward impulsivity. Pramipexole's effects on impulsive behaviors may need time to build up, and such effects were not investigated in this study.

It is important to note that out of the four participants whose data was discarded, three were females, who had a lower body mass index than the one male. Other studies of healthy controls that administered pramipexole either excluded females (Riba et al., 2008; Samuels, Hou, Langley, Szabadi, & Bradshaw, 2006; Samuels, Hou, Langley, Szabadi, & Bradshaw, 2007; Ye et al., 2011) or excluded participants below a certain body mass index (Hamidovic et al., 2008; Pizzagalli et al., 2008; Santesso et al., 2009). We chose to include all participants in our study to increase generalizability, however, future studies need to weight generalizability versus the chance of participant drop-out.

Additionally, in our study we were not able to analyze results based on our participants' predisposition to, or presence of, impulsive behavior, because all participants scored similarly on the baseline impulsivity measures. Other studies may wish to look at gene polymorphisms in young healthy controls as a moderating variable of the effect of dopaminergic medication on impulsivity.

Finally, it is important to note that participant performance on the SST in this experiment was such that appropriate analysis of the SST was not possible. One of the conditions that needs to be met for a proper interpretation of the SST is that participant accuracy is approximately 50%. In our experiment, the average accuracy was around 40%, suggesting that participants either did not understand the instructions, or that there were not enough trials for participants to develop competency with the task. Thus, it is possible that the results of the SST would be different in our study given more SST trials.

4.6 Conclusion

Dopamine agonists are commonly prescribed to treat the motor symptoms of PD, RLS, as well as some cases of mood disorders, and addiction treatments. Studies have found an association between dopaminergic medication and ICDs in patients with PD, suggesting that dopamine agonists may increase impulsive behavior. At the same time, experiments directly investigating the effects of dopaminergic medication on impulsivity measures found a decrease in impulsivity after dopaminergic medication. The current study hypothesized that dopamine agonists decrease some aspects of impulsivity, particularly motor impulsivity, and may increase other aspects of impulsivity, such as risk-taking and gambling. To test this hypothesis, healthy young adults were given pramipexole, or a placebo pill, and asked to perform tasks measuring impulsivity. The three chosen tasks were the GNG and the SST to measure motor impulsivity, and the BART to measure risk-taking and gambling.

Participants who received pramipexole had more timed-out Go trials on the GNG than those who received placebo. This is supporting the proposed hypothesis that pramipexole decreases motor impulsivity and in fact leads to a delayed response compared to controls who received placebo. There was no difference between the two groups in the SST, which is possibly due to differential effects of pramipexole on motor cancellation (as in the SST) as opposed to motor restraint (as in the GNG), and also due to conditions not being met for appropriate analysis. On the BART, there was also no difference between the pramipexole and the placebo groups. Similar studies have found that dopaminergic medication effects on the BART are moderated by a predisposition to impulsivity as measured by gene polymorphisms. Therefore, it is likely pramipexole decreases some aspects of motor impulsivity such as action restraint, and may also increase other aspects of impulsivity such as risk taking, if there is a predisposition for such behavior.

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Appendix I: Ethics approval form

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 Basile ___ Nicole Kanki ✓ Grace Kelly ___ Mina Mekhail ___ Vikki Tran ___

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

Appendix II: Health and demographics questionnaire

FOR EXPERIMENTER ID: Date: / /

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 completed.

1. Basic Demographic Information

Date of Birth: _____ Age: _____ 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 drugs not prescribed by a physician (please circle)? Yes No

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

_____

D. Vision

Do you wear eye glasses and/or contact lenses? Yes No

Do you have normal colour vision (i.e., no colour blindness)? Yes No

FOR EXPERIMENTER ID: Date: / /

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 III: Pramipexole safety screening questionnaire

FOR EXPERIMENTER ID: Date: / /

PRAMIPEXOLE 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	
☐	☐	Low blood pressure (i.e., feeling dizzy upon sitting or standing too quickly)		☐	☐	High blood pressure (hypertension)
☐	☐	Recurring, uncontrollable sleep episodes during the day		☐	☐	Trouble controlling your muscles (dyskinesia)
☐	☐	Diabetes		☐	☐	Sleeping disorders
☐	☐	Melanoma (skin cancer) or a skin growth that has not been diagnosed		☐	☐	Atrial, nodal, or ventricular arrhythmias (i.e., irregular heart beat)
☐	☐	Myocardial infarction (i.e., heart attacks)		☐	☐	Asthma, chronic obstructive pulmonary disease (COPD), emphysema
☐	☐	Heart or coronary artery disease		☐	☐	Phenylketonuria (PKU)
☐	☐	Liver or kidney disease		☐	☐	Endocrine (hormonal) disease
☐	☐	Glaucoma		☐	☐	Stomach or intestinal ulcers
☐	☐	Mental Illness		☐	☐	Allergies to pramipexole (Mirapex)

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

Yes	No			Yes	No	
☐	☐	**Monoamine oxidase (MAO) inhibitors** such as isocarboxazid (Marplan), phenelzine (Nardil), tranylcypromine (Parnate)				
☐	☐	**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)				
☐	☐	**Neuroleptics** such as phenothiazines, butyrophenones, thioxanthenes				
☐	☐	Antihistamines		☐	☐	Quinidine / Quinine
☐	☐	Ranitidine (DermaSilk, Dermacin)		☐	☐	Cimetidine (Tagamet)
☐	☐	Triamterene (Dyrenium)		☐	☐	Verapamil (Calan)
☐	☐	Haloperidol (Haldol)		☐	☐	Metoclopramide (Reglan)
☐	☐	Risperidone (Risperdal)		☐	☐	Papaverine (Pavabid)
☐	☐	Rasagiline (Azilect)		☐	☐	Isoniazid (INH, Nydrazid)
☐	☐	Phenytoin (Dilantin)		☐	☐	Ipratropium (Atrovent)
☐	☐	Metoclopramide (Metozolv)		☐	☐	Methylphenidate (Ritalin)
☐	☐	Amantadine (Symmetrel)		☐	☐	Thiothixene (Navane)
☐	☐	Diltiazem (Cardizem)		☐	☐	Levodopa

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

Appendix IV: Bond-Lader Visual Analogue Scale

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

Bond & Lader Visual Analogue Mood Scale

Instructions: For each line below, put a vertical mark at the point that represents how you feel at this moment. The ends of each scale are to present the "most" that you have ever felt in your life.

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
INCOMPENTENT	PROFICIENT	_____ mm
HAPPY	SAD	_____ mm
ANTAGONISTIC	FRIENDLY	_____ mm
INTERESTED	BORED	_____ mm
WITHDRAWN	SOCIABLE	_____ mm

Appendix V: American National Adult Reading Test wordlist

1. ache	23. papyrus	45. caprice
2. debt	24. asthma	46. demesne
3. pint	25. hiatus	47. imbroglio
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	

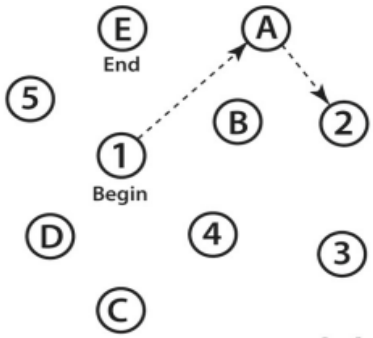
13. gauge
14. naïve
15. thyme
16. courteous
17. algae
18. fetal
19. quadruped
20. epitome
21. superfluous
22. chamois
35. virulent
36. worsted
37. détente
38. anise
39. sieve
40. chassis
41. beatify
42. scion
43. cabal
44. apropos

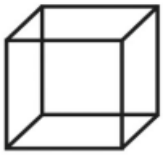
Appendix VI: Montreal Cognitive Assessment

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

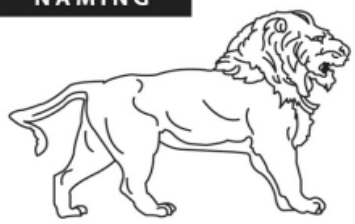




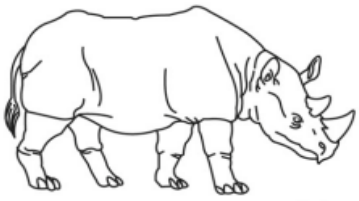
Copy cube [ ] [ ]

Draw CLOCK (Ten past eleven) (3 points) [ ] Contour [ ] Numbers [ ] Hands __/5

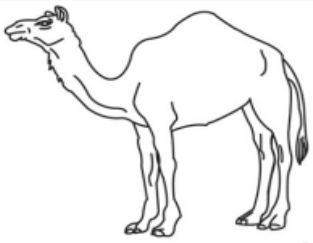
NAMING



[ ]



[ ]



[ ] __/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 [x] 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. [x]
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 [c] _____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __2__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[x]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

© Z.Nasreddine MD **www.mocatest.org** Normal ≥ 26 / 30

TOTAL Text __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

Appendix VII: Controlled Oral Word Association Task

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

Verbal Fluency

Instructions: I will say a letter of the alphabet. Then I want you to give me as many words that begin with that letter as quickly as you can. For instance, if I say "B", you might give me "bad", "battle", or "bed." I do not want you to use words that are proper names such as "Boston" or "Bob." Also, do not use the same word again with a different ending such as "eat" and "eating." Any questions? Begin when I say the letter. The first letter is "F". Go Ahead. *Begin timing immediately. Mark 30 seconds.*

Category Fluency

Instructions: I now want you to name as many animals as you can, as quickly as you can. These can be animals that live in water or on land. Any questions? *Begin timing immediately. Mark 30 seconds. If necessary, give the example that a dolphin lives in water and a dog lives on land.*

F	A	S	Animals

Appendix VIII: Barratt Impulsiveness Scale

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

Barratt Impulsiveness Scale (BIS-11)

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

1	2	3	4
Rarely/Never	Occasionally	Often	Almost Always/Always

1.	I plan tasks carefully.	1 2 3 4
2.	I do things without thinking.	1 2 3 4
3.	I make-up my mind quickly.	1 2 3 4
4.	I am happy-go-lucky.	1 2 3 4
5.	I don't "pay attention."	1 2 3 4
6.	I have "racing" thoughts.	1 2 3 4
7.	I plan trips well ahead of time.	1 2 3 4
8.	I am self-controlled.	1 2 3 4
9.	I concentrate easily.	1 2 3 4
10.	I save regularly.	1 2 3 4
11.	I "squirm" at plays or lectures.	1 2 3 4
12.	I am a careful thinker.	1 2 3 4
13.	I plan for job security.	1 2 3 4
14.	I say things without thinking.	1 2 3 4
15.	I like to think about complex problems.	1 2 3 4
16.	I change jobs.	1 2 3 4
17.	I act "on impulse."	1 2 3 4
18.	I get easily bored when solving thought problems.	1 2 3 4
19.	I act on the spur of the moment.	1 2 3 4
20.	I am a steady thinker.	1 2 3 4
21.	I change residences.	1 2 3 4
22.	I buy things on impulse.	1 2 3 4
23.	I can only think about one thing at a time.	1 2 3 4
24.	I change hobbies.	1 2 3 4
25.	I spend or charge more than I earn.	1 2 3 4
26.	I often have extraneous thoughts when thinking.	1 2 3 4
27.	I am more interested in the present than the future.	1 2 3 4
28.	I am restless at the theatre or lectures.	1 2 3 4
29.	I like puzzles.	1 2 3 4
30.	I am future oriented.	1 2 3 4

Patton, Stanford, Barratt (1995), *J Clin Psy*, vol. 51, pp. 768-774

Appendix IX: Sensation Seeking Scale

1. A. I like "wild" uninhibited parties
   B. I prefer quiet parties with good conversation
2. A. There are some movies I enjoy seeing a second or even a third time
   B. I can't stand watching a movie that I've seen before
3. A. I often wish I could be a mountain climber
   B. I can't understand people who risk their necks climbing mountains
4. A. I dislike all body odors
   B. I like some for the earthly body smells
5. A. I get bored seeing the same old faces
   B. I like to comfortable familiarity of everyday friends
6. A. I like to explore a strange city or section of town by myself, even if it means getting lost
   B. I prefer a guide when I am in a place I don't know well
7. A. I dislike people who do or say things just to shock or upset others
   B. When you can predict almost everything a person will do and say he or she must be a bore
8. A. I usually don't enjoy a movie or play where I can predict what will happen in advance
   B. I don't mind watching a movie or a play where I can predict what will happen in advance
9. A. I have tried marijuana or would like to
   B. I would never smoke marijuana
10. A. I would not like to try any drug which might produce strange and dangerous effects on me
    B. I would like to try some of the new drugs that produce hallucinations
11. A. A sensible person avoids activities that are dangerous
    B. I sometimes like to do things that are a little frightening
12. A. I dislike "swingers" (people who are uninhibited and free about sex)
    B. I enjoy the company of real "swingers"
13. A. I find that stimulants make me uncomfortable
    B. I often like to get high (drinking liquor or smoking marijuana)
14. A. I like to try new foods that I have never tasted before
    B. I order the dishes with which I am familiar, so as to avoid disappointment and unpleasantness
15. A. I enjoy looking at home movies or travel slides
    B. Looking at someone's home movies or travel slides bores me tremendously
16. A. I would like to take up the sport of water skiing
    B. I would not like to take up water skiing
17. A. I would like to try surf boarding
    B. I would not like to try surf boarding
18. A. I would like to take off on a trip with no preplanned or definite routes, or timetable
    B. When I go on a trip I like to plan my route and timetable fairly carefully
19. A. I prefer the "down to earth" kinds of people as friends
    B. I would like to make friends in some of the "far out" groups like artists or "punks"
20. A. I would not like to learn to fly an airplane
    B. I would like to learn to fly an airplane
21. A. I prefer the surface of the water to the depths
    B. I would like to go scuba diving
22. A. I would like to meet some persons who are homosexual (men or women)
    B. I stay away from anyone I suspect of being "gay or lesbian"
23. A. I would like to try parachute jumping
    B. I would never want to try jumping out of a plane with or without a parachute
24. A. I prefer friends who are excitingly unpredictable
    B. I prefer friends who are reliable and predictable
25. A. I am not interested in experience for its own sake
    B. I like to have new and exciting experiences and sensations even if they are a little frightening, unconventional, or illegal
26. A. The essence of good art is in its clarity, symmetry of form and harmony of colors
    B. I often find beauty in the "clashing" colors and irregular forms of modern paintings
27. A. I enjoy spending time in the familiar surroundings of home
    B. I get very restless if I have to stay around home for any length of time
28. A. I like to dive off the high board
    B. I don't like the feeling I get standing on the high board (or I don't go near it at all)
29. A. I like to date members of the opposite sex who are physically exciting
    B. I like to date members of the opposite sex who share my values
30. A. Heavy drinking usually ruins a party because some people get loud and boisterous
    B. Keeping the drinks full is the key to a good party

Appendix X: Epworth Sleepiness Scale

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

Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the situations described below, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:-

0 = would never doze
1 = Slight chance of dozing
2 = Moderate chance of dozing
3 = High chance of dozing

Situation	Chance of dozing
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	
Total	

Score:	
0-10	Normal range
10-12	Borderline
12-24	Abnormal

Appendix XI: Oxford Happiness Questionnaire

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

Oxford Happiness Questionnaire

The Oxford Happiness Questionnaire was developed by psychologists Michael Argyle and Peter Hills at Oxford University.

Instructions

Below are a number of statements about happiness. Please indicate how much you agree or disagree with each by entering a number in the blank after each statement, according to the following scale:

1 = strongly disagree
2 = moderately disagree
3 = slightly disagree
4 = slightly agree
5 = moderately agree
6 = strongly agree

Please read the statements carefully, some of the questions are phrased positively and others negatively. Don't take too long over individual questions; there are no "right" or "wrong" answers (and no trick questions). The first answer that comes into your head is probably the right one for you. If you find some of the questions difficult, please give the answer that is true for you in general or for most of the time.

The Questionnaire

1. I don't feel particularly pleased with the way I am. (R) _____
2. I am intensely interested in other people. _____
3. I feel that life is very rewarding. _____
4. I have very warm feelings towards almost everyone. _____
5. I rarely wake up feeling rested. (R) _____
6. I am not particularly optimistic about the future. (R) _____
7. I find most things amusing. _____
8. I am always committed and involved. _____
9. Life is good. _____
10. I do not think that the world is a good place. (R) _____
11. I laugh a lot. _____
12. I am well satisfied about everything in my life. _____
13. I don't think I look attractive. (R) _____
14. There is a gap between what I would like to do and what I have done. (R) _____
15. I am very happy. _____

1 = strongly disagree
2 = moderately disagree
3 = slightly disagree
4 = slightly agree
5 = moderately agree
6 = strongly agree

16. I find beauty in some things. _____
17. I always have a cheerful effect on others. _____
18. I can fit in (find time for) everything I want to. _____
19. I feel that I am not especially in control of my life. (R) _____
20. I feel able to take anything on. _____
21. I feel fully mentally alert. _____
22. I often experience joy and elation. _____
23. I don't find it easy to make decisions. (R) _____
24. I don't have a particular sense of meaning and purpose in my life. (R) _____
25. I feel I have a great deal of energy. _____
26. I usually have a good influence on events. _____
27. I don't have fun with other people. (R) _____
28. I don't feel particularly healthy. (R) _____
29. I don't have particularly happy memories of the past. (R) _____

Calculate your score

Step 1. Items marked (R) should be scored in reverse:

For example, if you gave yourself a "1," cross it out and change it to a "6."
Change "2" to a "5"
Change "3" to a "4"
Change "4" to a "3"
Change "5" to a "2"
Change "6" to a "1"

Step 2. Add the numbers for all 29 questions. (Use the converted numbers for the 12 items that are reverse scored.)

Step 3. Divide by 29. So your happiness score = the total (from step 2) divided by 29.

Your Happiness Score: _____

Reference:
http://www.meaningandhappiness.com/oxford-happiness-questionnaire/214/

Appendix XII: Beck's Depression Inventory

Beck's Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

1.
- 0 I do not feel sad.
- 1 I feel sad
- 2 I am sad all the time and I can't snap out of it.
- 3 I am so sad and unhappy that I can't stand it.

2.
- 0 I am not particularly discouraged about the future.
- 1 I feel discouraged about the future.
- 2 I feel I have nothing to look forward to.
- 3 I feel the future is hopeless and that things cannot improve.

3.
- 0 I do not feel like a failure.
- 1 I feel I have failed more than the average person.
- 2 As I look back on my life, all I can see is a lot of failures.
- 3 I feel I am a complete failure as a person.

4.
- 0 I get as much satisfaction out of things as I used to.
- 1 I don't enjoy things the way I used to.
- 2 I don't get real satisfaction out of anything anymore.
- 3 I am dissatisfied or bored with everything.

5.
- 0 I don't feel particularly guilty
- 1 I feel guilty a good part of the time.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6.
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7.
- 0 I don't feel disappointed in myself.
- 1 I am disappointed in myself.
- 2 I am disgusted with myself.
- 3 I hate myself.

8.
- 0 I don't feel I am any worse than anybody else.
- 1 I am critical of myself for my weaknesses or mistakes.
- 2 I blame myself all the time for my faults.
- 3 I blame myself for everything bad that happens.

9.
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10.
- 0 I don't cry any more than usual.
- 1 I cry more now than I used to.
- 2 I cry all the time now.
- 3 I used to be able to cry, but now I can't cry even though I want to.

11.

0 I am no more irritated by things than I ever was.
1 I am slightly more irritated now than usual.
2 I am quite annoyed or irritated a good deal of the time.
3 I feel irritated all the time.

12.

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

13.

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions more than I used to.
3 I can't make decisions at all anymore.

14.

0 I don't feel that I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel there are permanent changes in my appearance that make me look unattractive
3 I believe that I look ugly.

15.

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16.

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18.

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19.

0 I haven't lost much weight, if any, lately.
1 I have lost more than five pounds.
2 I have lost more than ten pounds.
3 I have lost more than fifteen pounds.

Appendix XIII: Beck Anxiety Inventory

Beck Anxiety Inventory

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today, by circling the number in the corresponding space in the column next to each symptom.

	Not At All	Mildly but it didn't bother me much.	Moderately - it wasn't pleasant at times	Severely – it bothered me a lot
Numbness or tingling	0	1	2	3
Feeling hot	0	1	2	3
Wobbliness in legs	0	1	2	3
Unable to relax	0	1	2	3
Fear of worst happening	0	1	2	3
Dizzy or lightheaded	0	1	2	3
Heart pounding/racing	0	1	2	3
Unsteady	0	1	2	3
Terrified or afraid	0	1	2	3
Nervous	0	1	2	3
Feeling of choking	0	1	2	3
Hands trembling	0	1	2	3
Shaky / unsteady	0	1	2	3
Fear of losing control	0	1	2	3
Difficulty in breathing	0	1	2	3
Fear of dying	0	1	2	3
Scared	0	1	2	3
Indigestion	0	1	2	3
Faint / lightheaded	0	1	2	3
Face flushed	0	1	2	3
Hot/cold sweats	0	1	2	3
Column Sum				

Scoring **-** Sum each column. Then sum the column totals to achieve a grand score. Write that score here _____ .

Interpretation

A grand sum between **0 – 21** indicates very low anxiety. That is usually a good thing. However, it is possible that you might be unrealistic in either your assessment which would be denial or that you have learned to "mask" the symptoms commonly associated with anxiety. Too little "anxiety" could indicate that you are detached from yourself, others, or your environment.

A grand sum between ***22 – 35*** indicates moderate anxiety. Your body is trying to tell you something. Look for patterns as to when and why you experience the symptoms described above. For example, if it occurs prior to public speaking and your job requires a lot of presentations you may want to find ways to calm yourself before speaking or let others do some of the presentations. You may have some conflict issues that need to be resolved. Clearly, it is not "panic" time but you want to find ways to manage the stress you feel.

A grand sum that **exceeds 36** is a potential cause for concern. Again, look for patterns or times when you tend to feel the symptoms you have circled. Persistent and high anxiety is not a sign of personal weakness or failure. It is, however, something that needs to be proactively treated or there could be significant impacts to you mentally and physically. You may want to consult a physician or counselor if the feelings persist.

Appendix XIV: Starkstein Apathy Scale

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?				

EDUCATION

Master's in Behavioural and Cognitive Neuroscience, Psychology, the University of Western Ontario, 2014- present.
Research thesis: In progress
Supervised by: Dr. Penny A. MacDonald

Honours Bachelor of Science, Psychology, University of Toronto St. George, 2009-2014.
Graduate of the research specialist program.
Honours undergraduate thesis: Age difference in resolving proactive interference.
Supervised by Dr. Lynn Hasher.
Cumulative GPA: 3.87 out of 4.0.

RESEARCH EXPERIENCE

Dr. Penny A. MacDonald Lab, Behavioural and Cognitive Neuroscience Department, Brain and Mind Institute, University of Western Ontario, 2014-present.

- Conducting research aiming to better understand the effects of Parkinson's medication on impulse control and inhibitory functions.

OISE Emotion Regulation Lab, Ontario Institute for Secondary Education, Applied Psychology and Human Development Department, 2010-2014.

- Worked as a paid researcher on a project supervised by Dr. Rosemary Tannock.
- Running experiments with young adults with ADHD using electroencephalography (EEG) and executive function measures.
- Conducting clinical assessment battery.
- Collecting, processing, cleaning & analyzing EEG data and deriving and coding event related potential components.
- Presenting results at lab meetings.

Hasher Aging & Cognition Lab, University of Toronto, 2012-2013.

- Completed a thesis study and an NSERC grant term under the supervision of Dr. Lynn Hasher.
- Collected and analyzed data for a project comparing resolution of proactive interference in younger and older adults on a verbal memory task.
- Presented results at two poster sessions.

Social Cognition and Perception Lab, University of Toronto, 2012.
- Completed two independent study terms supervised by Dr. Nicholas Rule.
- Designed a series of experiments exploring gender judgments from faces of infants.
- Attended regular lab meetings discussing statistical and conceptual research issues, and gave several presentations at these meetings.

Memory and Learning Lab- Course, University of Toronto, 2011.
- Formulated, designed and completed a research project supervised by Dr. Lynn Hasher.
- Conducted a literature review on cross modal interaction between visual and verbal working memory, wrote a formal proposal (approved by the ethics committee) and designed an experiment.
- Collected data, analyzed results, and presented findings in class.

Social Development Lab University of Toronto, 2009-2010.
- Volunteered and then worked as a study manager under Dr. Joan Grusec.
- Helped with a study examining prosocial behaviour and moral development in adolescence.
- Was in charge of training sessions and teaching research assistants study procedures. Had the responsibility of coordinating and scheduling a team of 11 research assistants, monitoring data collection and backup.
- Participated in lab meeting discussions and in data analysis.

TEACHING & LEADERSHIP EXPERIENCE

Teaching Assistant, Psychology- Memory Seminar 3rd year PSY3138, The University of Western Ontario.

The MacDonald Lab- Supervising a 4th year undergraduate student completing their Honour's thesis.

The MacDonald Lab- Training and mentoring a research assistant to help in the lab with testings, data processing, and data analysis.

Teaching Assistant, Psychology-Introduction to Research Methods PSY2800, The University of Western Ontario.

Emotion Regulation Lab, training new recruits in EEG testing procedures and data analysis, 2010-present.

Emotion Regulation Lab, mentoring a student's mini project and poster preparation, 2013.

Social Development Lab, study manager coordinating a team of 11 assistants, 2010.

HONOURS AND AWARDS

CIHR Frederick Banting and Charles Best Award- Canada Graduate Scholar, 2015. ($17,500)
Ontario Graduate Scholarship Award ($15,000 offered, declined)
St. Michael's College Undergraduate Research Forum competition, 2014. ($500)
NSERC Undergraduate Student Research Award, 2013. ($5,624)

Dean's List Award, University of Toronto, 2010-2013.
St. Michael's College In-Course Scholarship, 2013. ($1,500)
St. Michael's College In-Course Scholarship, 2011. ($1,500)
Ontario Scholar Award, Georges Vanier Secondary School, 2009.

PRESENTATIONS & POSTERS

Glizer, D. (January 2016). Cognitive training and aging- can cognition be improved? Windermere on the Mount Retirement Home (part of Retiring with Strong Minds series).

Glizer, D. (2015). Can you train your brain? Computerized cognitive training in Parkinson's disease. Parkinson's Society Canada- Southwestern Ontario Newsletter.

Glizer, D., Kim, S., Liu, Z., Tannock, R., Woltering, S. (February 27, 2014). ADHD and Working Memory: Neural correlates of impaired processing. (Poster- 1st place prize). St. Michael's College Research Forum, University of Toronto.

Fettes, P., **Glizer, D**., & Tannock, R. (June 13, 2013). Executive function performance and self-ratings in post-secondary students with and without ADHD. Harvey Stancer Research Day. 39, 35.

Glizer, D., Ngo, J., & Hasher, L. (May 3, 2013). Age differences in resolving proactive interference (Presentation). The Ontario Psychology Undergraduate Thesis Conference, Guelph-Humber University.

Glizer, D., Ngo, J., & Hasher, L. (April 11, 2013). Conflict resolution and memory in younger and older adults (Poster). Research Specialist Thesis Conference, University of Toronto.

Glizer, D., Kim, S., Liu, Z., Tannock, R., Woltering, S. (October 26, 2012). Impaired neural processing in a visual working memory task during encoding in adults with Attention deficit hyperactivity disorder (Poster). 59th Annual Meeting of the American Academy of Child and Adolescent Psychiatry, San Francisco.

PUBLICATIONS

*Yang, X.Q., ***Glizer, D.,** Vo, A., Seergobin, K., & MacDonald, P. (2016). Pramipexole increases Go timeouts but not No-go errors in healthy volunteers. *Frontiers in Human Neuroscience,* (10), 523.

Glizer, D., MacDonald, A. P. (2016). Cognitive training in Parkinson's disease: A review of studies from 2000- 2014. *Parkinsons Diease,* (2016), http://dx.doi.org/10.1155/2016/9291713.

Liu Z., **Glizer, D.,** Tannock, R., & Woltering, S. (2016). EEG alpha power during maintenance of information in working memory in adults with ADHD and its plasticity due to working memory training: a randomized controlled trial**.** *Clinical Neurophysiology,* (127), 1307-1320.

Kim, S., Liu, Z., **Glizer, D**., Tannock, R., & Woltering, S. (2014). Adult ADHD and working memory: Neural evidence of impaired encoding. *Clinical Neurophysiology,* (125), 1596-1603.