EVALUATION OF A NOVEL TREATMENT FOR DOPAMINE AGONIST-INDUCED IMPULSE CONTROL DISORDERS FOR PARKINSON'S PATIENTS

by

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B.Sc., The University of British Columbia, 2016

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF ARTS

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Psychology)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

August 2019

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Evaluation of a novel treatment for dopamine agonist-induced impulse control disorders for Parkinson's patients

submitted by Brittney Russell in partial fulfillment of the requirements for

the degree of Master of Arts

in Psychology

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Abstract

Selective dopamine $D_{2/3}$ receptor agonists, such as ropinirole (ROP), effectively treat the motor symptoms of Parkinson's Disease (PD), and unlike L-dopa, do not cause problematic dyskinesias after prolonged use. Thus, $D_{2/3}$ agonists can be an attractive alternative to L-dopa for the long-term management of PD. However, $D_{2/3}$ agonists induce impulse control and gambling disorders in a substantial minority of patients, raising concern over the use of these agents. Adjunctive medications that could be safely administered with $D_{2/3}$ agonists and prevent the development of such psychiatric side-effects would therefore be highly desirable. GPR52 is a Gs-coupled g-protein coupled receptor (GPR) enriched in D2 receptor expressing neurons of the striatum. Activation of GPR52 has been demonstrated to attenuate behaviours associated with increased striatal dopamine release without altering basal function. We have previously shown that ROP increases preference for uncertain outcomes on a rodent test of gambling-like decision making known as the rodent betting task (rBT). This task measures preference for certain versus uncertain rewarding outcomes of equal expected value. Although most rats maintain a constant preference for the uncertain outcome regardless of the amount at stake, some rats increase their preference for guaranteed rewards as the wager-size increases, despite the relative expected value of the two options remaining constant. The choice strategy of these wager-sensitive rats may be considered mathematically non-normative, and such irrational decision-making patterns have been linked to the manifestation and severity of problem gambling. The degree of wager-sensitivity has been associated with the density of $D_{2/3}$ receptors in the dorsal striatum. I therefore hypothesized that GPR52 agonists may attenuate the ability of ROP to promote choice of uncertain outcomes in wager-sensitive rats on the rBT. I tested this hypothesis by administering GPR52 agonists BD442618 and S111224 in two cohorts of healthy male rats that were also

implanted with osmotic pumps, delivering either ROP or saline. The rats performed the rBT for 28 days after osmotic pump implantation. A reduction in ROP's ability to increase preference for uncertainty on the rBT would suggest that GPR52 agonists may be a potential treatment for iatrogenic impulse control and gambling disorders.

Lay Summary

This series of experiments used rats to test the effectives of two novel drugs for the treatment of dopamine replacement therapy-induced impulse control disorders in Parkinson's disease patients, who are treated with these medications to manage their motor symptoms. I found that the anti-parkinsonian medication increased preference for uncertainty on a gambling-like task, which is related to the development and severity of Gambling disorder (GD). Both of the novel drugs I tested were able to reduce this increase in preference for uncertainty. In subjects that showed choice patterns thought to mimic those vulnerable to developing GD, the ability of dopamine replacement therapy to increase preference for uncertainty was most pronounced. Although the novel drugs decreased this behaviour, they were not able to block it completely. Both drugs I tested show some promise as effective treatments for medication-induced impulse control disorders, but more testing needs to be conducted before moving them into clinical trials.

Preface

This thesis is submitted to fulfill the requirements for Master of Arts in Psychology at the University of British Columbia. My research supervisor is Dr. Catharine Winstanley. The identification and design of the research program, the writing of the thesis, creation of the figured and tables, and the data analysis has been done solely by the author. Dr. Winstanley acted as project supervisor and assisted with the experimental design and data interpretation. I have done my best to provide references for all research cited in this thesis.

The preparation of the syringes and intraperitoneal injections for all the Latin square experiments conducted in Chapter 2 section 6.1 were done solely by the author. The preparation of the syringes for the chronic experiment in Chapter 2 section 6.2 and injections were performed by the author. For the second chronic experiment in Chapter two section 6.3, the syringes were prepared by Lawrence Ma under the supervision of the author and the injections were done solely by the author.

The osmotic pump preparation and implantation in healthy rats for the first chronic experiment in Chapter 2 section 6.2 were performed by the author and Michael Barrus. The preparation for the osmotic pumps for the second chronic experiment in Chapter 2 section 6.3 was performed by the author and Kelly Hrelja and osmotic pump implantation was performed by the author and Tristan Hynes.

All procedures were in accordance with the Canadian Council on Animal Care and the University of British Columbia Animal Care Committee (ACC) and were covered by the protocol number A17-0022.

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ANOVA	Analysis of variance
BART	Balloon Analogue Risk Task
DRT	Dopamine replacement therapy
DA	Dopamine
DSM	Diagnostic and Statistical Manual of Mental Disorders-5
GD	Gambling disorder
GDT	Game of Dice Task
GPR	G protein-coupled receptor
ICD	Impulse control disorder
IGT	Iowa Gambling Task
L-dopa	Levodopa
PD	Parkinson's disease
rBT	rodent Betting Task
rGT	rodent Gambling Task
SNc	Substantia nigra pars compacta

Acknowledgements

I would first like to acknowledge the endless support and patience provided to me by my supervisor Dr. Catharine Winstanley. Cath, thank you for always believing in me and providing me with the opportunity to be a graduate student in your lab and learn from you. I really don't know if I could have done this without you. You have taught me so much and have always been there for me when I needed your support. I'm excited for the (many) years we have left together and all our future adventures. I've been incredibly grateful to have you, along with Dr. Liisa Galea and Dr. Mariya Cherkasova, as an example of a powerful female scientist and serve as a reminder that you really can do it all. Thank you to all three of you for being great role models and mentors.

Arezoo, I'm so grateful for your friendship. Thank you for always supporting me not only academically, but also encouraging me to take "some" time for self-care. Without you, this program would have been a completely difference experience for me. I'm looking forward to the many memes we will send back and forth over the years and to opening Moderate & Severe in the future. Ariel, you have also provided me with so much support and are the only person I can relate to before presentations. Thank you to the two of you for always being there to calm me down and reassure me that I'm doing ok.

Mel, you taught me all the skills that I used in these experiments in this thesis, and I am so grateful that you spent the little time you had in your final years to ensure that I felt supported. I miss you so much and wish nothing but the best for you. I hope to see you soon. Even if I don't, our rat plushies are always connected.

Tristan (see, I told you that you would make the list), even though we have a “dynamic relationship”, I wouldn’t trade it for anything else. Thank you for always making time to help with my experiments and being there to hold my hand through any difficult procedures. I really am grateful to have your support and friendship.

Kelly, even though we have only known each other for a short period of time, you have been so supportive of me. I’m so grateful for your friendship. Thank you for always looking out for me and being there to listen, help, and eat ice-cream. I’m excited to see all the amazing things you will accomplish over our next five years together.

Chapter 1: Introduction

1.1 Parkinson's Disease

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder that occurs throughout the world, is present in all ethnic groups, and is common in the aging population, affecting 1-2% of adults over the age of 65 with men being 1.5 times more likely to develop PD than women (Alves, Forsaa, Pedersen, Dreetz Gjerstad, & Larsen, 2008; Pavon, Whitson, & Okun, 2010; Zhang & Román, 1993). Based on estimations from 2013-2014, approximately 84,000 Canadians age 40 and older are living with diagnosed PD and this number is only growing (Public Health Agency of Canada, 2018). It is estimated that the number of Canadians with PD will double between 2011 and 2031 (Public Health Agency of Canada, 2014). PD causes not only debilitating functional impairments, but also has significant social implications that further the impact this disease has on the quality of life for these people (De Boer, Wijker, Speelman, & De Haes, 1996). For example, reports from two large Canadian health surveys found that 43% of respondents with PD felt embarrassed by their condition and 29% of respondents felt left out (Wong, Gilmour, & Ramage-Morin, 2014). Unfortunately, there is no cure for PD so symptoms will become increasingly debilitating as the disease progresses. Disease severity related to physical functioning and mobility is thought to be a major contributor to impairments in quality of life (Chapuis, Ouchchane, Metz, Gerbaud, & Durif, 2005).

Although the exact etiology is unknown, the characteristic neuropathology observed in PD is the degeneration of nigrostriatal pathway that is comprised of dopamine (DA) neurons that project from the substantia nigra par compacta (SNc) to the dorsal striatum (Kish, Shannak, & Hornykiewicz, 1988; see Lang & Lozano, 1998 for review). The reduction in DA activity in the striatum caused by the loss of DA neurons in this pathway is thought to produce the hallmark

motor symptoms of PD, such as resting tremors, difficulty initiating movement (bradykinesia), and rigidity (Ehringer & Hornykiewicz, 1998; Hornykiewicz, 1993; Lang & Lozano, 1998). As the disease progresses, other symptoms like depression, anxiety, sleep disturbances, and cognitive dysfunction may also emerge. However, other non-dopaminergic neurotransmitter symptoms appear to be responsible for these non-motor symptoms (Chaudhuri, Healy, & Schapira, 2006). It has been suggested that these non-motor symptoms have a greater negative impact on quality of life than motor symptoms, especially with regards to depression (Schrag, Jahanshahi, & Quinn, 2000; The Global Parkinson's Disease Survey Steering Committee, 2002).

There are medications that can manage the motor and non-motor symptoms of PD patients to restore their quality of life. However, all of the anti-parkinsonian medications have the potential to produce side-effects that may be more debilitating the original symptoms they were intended to treat (see Connolly & Lang, 2014 for review). Furthermore, these medications become increasingly likely to cause side-effects with chronic use. This is clearly problematic, as PD is a chronic disorder with few treatment options. Improved treatment strategies are therefore urgently needed.

1.2 Dopamine replacement therapy

PD motor symptoms are commonly managed with pharmacotherapy. All effective medications compensate for the loss of DA activity in the dorsal striatum, so they are referred to as dopamine replacement therapies (DRTs). DRTs include: Levodopa (L-dopa), a precursor for the synthesis of DA, and DA $D_{2/3}$ receptor agonists such as ropinirole and pramipexole. L-dopa is the first line of treatment for PD. Initial treatment with L-dopa significantly alleviates motor symptoms and substantially increases the quality of life for those with PD (Barbeau, 1969; Yahr, Duvoisin, Schear, Barrett, & Hoehn, 1969). However, there appears to be a limited window of

efficacy for L-dopa. The majority of individuals with PD experience fluctuations in their response to DRT during chronic L-dopa therapy, which is likely produced by the progressive pathology of the disease in combination with the pharmacodynamic and pharmacokinetic factors that occur with chronic use of L-dopa (Fox & Lang, 2008; Obeso, Rodriguez-Oroz, Chana, & Lera, 2000). Initial L-dopa treatment that occurs in early PD has a linear dose and anti-parkinsonian response. As the disease progresses, the dose response changes from a linear to a sigmoid curve with PD patients experiencing a beneficial response at a critical dosage (Mouradian, 1988). Below the critical dose there is no therapeutic effect and above the critical dose prolongs the anti-parkinsonian effect but usually with abnormal involuntary movements that are induced by L-dopa, referred to as dyskinesia (Marsden, 1994). The frequency of these motor complications (i.e., motor fluctuations and dyskinesia) is estimated to be experienced by 40-50% of patients after 4-5 years of L-dopa treatment (Ahlskog & Muenter, 2001). L-dopa-induced dyskinesia is a major concern for PD patients because it affects at least 90% of patients after 10 years of L-dopa treatment and is considered to be just as disabling as the PD motor symptoms the medication was intended to treat (Fabbrini, Brotchie, Grandas, Nomoto, & Goetz, 2007). Furthermore, L-dopa-induced dyskinesia often coincides with the peak antiparkinsonian effect of L-dopa (Obeso et al., 2007).

Fortunately, the risk of developing these motor complications is significantly lower with DA $D_{2/3}$ receptor agonist therapy, even when supplemental L-dopa is given chronically (Hely et al., 1994; Lieberman et al., 1998; Nutt, 1990; Rascol et al., 2000). DA agonists are effective at both the early and late stages of the disease, with DA agonists being used as a monotherapy for early PD and an adjunct therapy to L-dopa for advanced PD (Adler et al., 1997; Lieberman et al., 1998; Matheson & Spencer, 2000; Rascol et al., 1998). Although it is not clear how the early use

of DA agonists, most commonly ropinirole and pramipexole, reduce the risk of developing motor complications, several different factors have been implicated. One theory is that the longer elimination half-life of these compounds provides a more continuous stimulation of the DA receptors rather than a pulsatile stimulation of the DA receptors associated with the short elimination half-life of L-dopa (Chase, 1998). Other factors implicated are a higher dose of L-dopa and greater disease severity (Nutt, 1990). Thus, early use of DA agonists for the management of PD symptoms could prevent the development of debilitating side-effects associated with chronic L-dopa therapy by delaying the use of L-dopa until advanced PD. However, due to the striking prevalence of psychiatric complications in PD patients taking DA agonists, physicians are reluctant to prescribe them as an alternative to L-dopa.

1.2.1 Dopamine replacement therapy induced impulse control disorders

A growing body of literature suggests that aberrant behaviours that are commonly categorized as impulse control and related disorders (ICDs) are more common in PD patients treated with DRTs than in the general population, with ICDs estimated to be present in 6-25% of PD patients (Weintraub, 2009). ICDs that have been observed in PD include hypersexuality, compulsive shopping, compulsive eating, punding, compulsive medication use, and pathological gambling (Voon & Fox, 2007; Zhang et al., 2014). Due to the similar characteristics of the latter two behaviours with substance use disorders, they may be better understood under an addiction framework, which is corroborated by the recent reclassification of pathological gambling, now referred to as gambling disorder (GD), as a behavioural addiction rather than an impulse control disorder in the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5). Regardless of classification, the definition for these behaviours encompasses a maladaptive preoccupation with the behaviour, the inability to control the urges or impulses, engaging in other pathological

behaviours, such as lying or stealing, to allow the individual to act on these urges, and the association with negative consequences (Voon et al., 2009; Voon & Fox, 2007). Although the behaviours may differ in severity, they are considered pathological when they produce significant distress or interference with social, financial, or occupational functioning (Voon et al., 2009). For example, one study reported that the average amount of money lost among ten PD patients due to their GD was US$129,000 (Voon et al., 2006b). Additionally, ICDs are associated with greater functional impairment, poorer quality of life, and higher rates of major depressive disorder (Phu et al., 2014). For the purposes of this thesis, ICDs will still include GD and GD will be used synonymously with pathological gambling to reflect the common nomenclature used in the literature.

The variability in reported prevalence rates is likely due to methodological differences, such as different measures or thresholds being used for categorization (Ceravolo, Frosini, Rossi, & Bonuccelli, 2009). For example, it has been shown that patients with PD do not readily admit to the presence of ICDs and that these behaviours appear to be under-recognized in clinical practice. Therefore, a structured clinical interview is needed to ensure their detection rather than relying on patient self-report (Avila et al., 2011). The shortcomings of patient self-report are also highlighted by the discrepancy between patient self-report and spouse or family member report that reflects either the patient's lack of insight regarding their behaviour or guilt and shame that results in denying that these behaviours are occurring (Weintraub et al., 2009). Additionally, Weintraub et al. (2006) found that clinical charts recorded an ICD in only 27.3% of patients with an active ICD as diagnosed by the Minnesota Impulsive Disorders Interview. Due to the complex symptomology of PD, it is possible that ICDs are being overshadowed by more readily recognizable non-motor symptoms such as anxiety, depression, and cognitive impairments. As

awareness among healthcare professionals increases and diagnostic instruments are further developed, a more precise estimate of prevalence rates will emerge. However, it seems that the current prevalence of ICDs among this patient group is being underestimated. It is likely that a more accurate estimation would be achieved if each ICD was examined independently due to the heterogeneity of behaviours in this category. For example, the most common ICD observed in PD patients, GD, has clear diagnostic criteria and therefore can be estimated more accurately. However, frequency estimations for GD in PD still range from 0.5% to 6.1% (Avanzi et al., 2006; Driver-Dunckley, Samanta, & Stacy, 2003; Molina et al., 2000).

The development of ICDs among PD patients has been associated with the use of DRTs. Several studies have implicated DA agonists, and less commonly L-dopa, as precipitating ICDs in PD patients (Avanzi et al., 2006; Grosset et al., 2006; Voon et al., 2006a). Recently, Sharma et al. (2015) found that ICDs were more frequent in PD patients receiving DA agonist monotherapy than those only exposed to L-dopa, and the most frequent in subjects receiving both L-dopa and a DA agonist. This is consistent with Weintraub et al.'s (2010) findings from their cross-sectional study of over 3000 PD patients. In this study, an ICD was present in 14% of PD patients taking only a DA agonist, 7.2% of those taking only L-dopa, 17.1% of those taking both a DA agonist and L-dopa, and 1.7% of those taking neither a DA agonist nor L-dopa. Additionally, Sharma et al. (2015) also found that DA agonists are the most important predictor of ICDs. Others had similar findings, implicating a larger dose of DA agonist as being a significant predictor of ICD-related behaviours like reward seeking and impulsivity (Ondo & Lai, 2008).

To provide further evidence for the role of DA agonists in the development of ICD, an increased prevalence of ICDs has also been observed in other patient groups that are treated with

DA agonists, such as those with fibromyalgia and restless leg syndrome (Holman, 2009; Ondo & Lai, 2008). However, ICDs are present in these patient groups at a lower frequency, which likely reflects the lower dose of DA agonist being used relative to the dose used to treat PD patients. Interestingly, GD disorder is also one of the most common ICD observed in these patient groups as well. The mechanism that explains the development of ICDs in individuals receiving DRT is unknown. It is possible that the pathology of PD makes individuals more vulnerable to ICDs. However, the increased prevalence in other patient groups suggests that ICDs are a side-effect of DRTs rather than due to PD pathology. There are also some overlapping risk factors between PD and ICDs, such as male sex, that may account for the increased prevalence ICDs among PD patients (Evans, Lawrence, Potts, Appel, & Lees, 2005; Voon et al., 2017; Voon et al., 2007; Weintraub, David, Evans, Grant, & Stacy, 2015). Regarding risk factors associated with the type of DRT being used, ICDs are more prevalent among PD patients taking DA $D_{2/3}$ agonists whereas dopamine dysregulation syndrome is more prevalent among those taking L-dopa (Ceravolo, Frosini, Rossi, & Bonuccelli, 2010; Lawrence, Evans, & Lees, 2003). Additionally, the proportion of PD patients that develop ICDs does not significantly differ depending on the exact DA agonist being used. In Weintraub et al.'s (2010) cross-sectional study of over 3000 PD patients, the proportion of PD patients that developed ICDs was 15.5% and 17.7% following the use of ropinirole or pramipexole respectively. Thus, the difference in prevalence of ICDs among DRTs likely reflects the different underlying mechanism of action of DA $D_{2/3}$ receptor agonists have compared to L-dopa, rather than resulting from a specific DA agonist.

1.3 Mechanism causing ICDs

The mechanism underling the manifestation of idiopathic or iatrogenic ICDs is not well understood. However, the DA system seems to be heavily implicated in the development of these

disorders, especially in PD. This is primarily based on the de novo onset of ICDs after beginning DRT, the overlap between risk factors associated with the development of ICDs and substance use disorders, such as higher scores on novelty seeking, being unmarried, a family history of drug or alcohol use, cigarette smoking, male sex, and younger age, and reports of reduced or reversed ICDs after the withdrawal of the DA agonist (Dodd et al., 2005; Evans et al., 2005; Hassan et al., 2011; Voon et al., 2017; Voon et al., 2007; Weintraub, 2008; Weintraub et al., 2015). Interestingly, PD itself may be a protective factor because it is associated with lower rates of novelty seeking, smoking, and alcohol use compared with the general population prior to the appearance of motor symptoms (Evans et al., 2006). Thus, ICDs may be less likely to develop prior to DRT, again emphasising the association between the DA system and ICDs.

The primary molecular target of DA agonists used to treat PD (i.e., pramipexole, ropinirole, pergolide, rotigotine, apomorphine, and bromocriptine) are the DA G-protein coupled D2 and D3 receptors. The other DA receptors (D1, D4, D5) are not primary targets for DA agonists due to the lower affinity for these receptors compared to D2 and D3. These two receptors can exist in a high affinity or low affinity state for DA or the DA agonists, which is regulated by presence (high affinity) or absence (low affinity) of the G-protein (Seeman, 2007; Seeman et al., 2006). Prolonged stimulation of the high affinity receptor by a DA agonist can produce DA sensitization, which is associated with an increase in the number of high affinity DA receptors as well as repetitive behaviours (Seeman, 2011). Animals with an increased number of high-affinity DA D2 and D3 receptors exhibit hyperactivity, excessive eating, excess repetitive motion, and stereotyped behaviours (Seeman, 2015). These behaviours are similar to the behaviours observed in humans with ICDs. Thus, the D2 and D3 receptor may be implicated in the development of these disorders.

There is a correlation between the proportion of PD patients with ICDs and the selectivity of the DA agonist they're being treated with for D3 receptors compared to D2 receptors (Seeman, 2015). These findings suggest that the action of DA agonists, specifically on the D3 receptor, could be contributing to iatrogenic ICDs in PD patients. This idea is corroborated by the location of D3 receptors. Both D2 and D3 receptors are expressed in caudate nucleus, putamen, and nucleus accumbens, and the substantia nigra (Sokoloff et al., 1992). However, Sokoloff et al. (1992) also found that unlike D2 receptors, D3 receptor were highly expressed in the Islands of Calleja, the olfactory tubercle, the bed nucleus of the stria terminalis, and the mamillary nuclei. These regions form part of the extended limbic system, which has been implicated in many psychiatric disorders including ICDs (Weintraub, 2009), and regulates the expression and evaluation of emotion. Additionally, it appears that the pathway that underlies ICDs may overlap with the reward/addiction pathways, which includes corticolimbic regions (Brewer & Potenza, 2008). The DA D3 receptor is upregulated in the limbic system of animal models of PD in response to L-dopa treatment and at post-mortem in individuals with a substance use disorder (Bordet et al., 1997). The role of D3 upregulation in addiction, including behavioural addictions, is supported by the association between greater D3 receptor binding and gambling severity and impulsivity in individuals with GD (Boileau et al., 2013). However, a recent study did not find greater expression of D2 or D3 receptors in PD patients with ICDs when compared to PD without ICDs (Payer et al., 2015). This could be because endogenous DA is tightly bound to these receptors, making it difficult for radio ligands used for identification to bind to the receptors (Schotte, Janssen, Gommeren, Luyten, & Leysen, 1992). However, it is important to note that there are twice as many D2 than D3 receptors in the striatum, reducing the

likelihood that iatrogenic ICDs are solely produced by D3 receptor stimulation (Booze & Wallace, 1995).

The presence of ICDs among those taking a DA agonist with approximately equal affinities for the D2 and D3 receptor also implicates the D2 receptor in the development of ICDs (Seeman, 2015). The contribution of the D2 receptor to the emergence of these disorders is also supported by the major role of the DA D2 receptor in the reward/addiction pathways that may overlap with the pathways governing ICDs, especially GD as it is now considered a behavioural addiction. For example, low D2 receptor availability in the striatum has been observed in highly impulsive rats and also predicted high rates of intravenous cocaine self-administration in rats and nonhuman primates (Dalley et al., 2007; Nader et al., 2006). Additionally, the *D2A1* allele, which is associated with lower D2 receptor density in the striatum, has been implicated in impulsivity, substance abuse, compulsive eating, and has been found in double the frequency in individuals with GD compared to healthy controls (Blum et al., 1995; Comings et al., 1996; Haile, Kosten, & Kosten, 2007). However, brain imaging studies have yielded inconclusive results. DA D2 receptor levels have been found to be elevated in PD patients with and without an ICD when compared to healthy controls; however, there was no difference in D2 levels between PD patients with and without an ICD (Payer et al., 2015). This finding opposes the theory that low levels of D2 receptors in the striatum dissociate PD patients with GD compared to control PD patients, as observed by Steeves et al. (2009).

A popular proposed mechanism, the dopamine overdose hypothesis, provides an explanation for why all types of DRT may produce ICDs. During early stages of PD, the dorsal striatum is affected while the ventral striatum is mostly intact (Kish et al., 1988). Due to the lack of specificity DRTs have for one area for the striatum over the other, the administration of these

medications may cause overstimulation of the remaining ventral striatal areas while restoring DA neurotransmission in the dorsal striatum (see Vaillancourt, Schonfeld, Kwak, Bohnen, & Seidler, 2013 for review). As postulated by Dagher and Robbins (2009), the effect of low DA in the ventral striatum produced by PD pathology would cause the "parkinsonian personality" that is characterized by mental rigidity, neophobia, introversion, and a slow-tempered nature, whereas the effect of high DA produced by DRT causes an "addictive personality" characterized by impulsivity, novelty-seeking, and impaired reversal learning. Several studies have linked these personality characteristics to substance use disorders and ICDs (Evans et al., 2006; Kim & Grant, 2001). Thus, overstimulation of regions in the limbic system could be causing ICDs to arise in this patient group, especially during the early stages of the disease when the ventral striatum is less affected and patients are considered to be at the highest risk for developing an ICD in response to DRT (Voon et al., 2007).

Additionally, the use of L-dopa may prime the development of ICDs by causing excessive expression of the D3 receptor in the dorsal striatum. There have been several studies demonstrating the association between L-dopa-induced dyskinesia and excessive expression and sensitization of the DA D1 receptors in the nigrostriatal neurons, which produces aberrant excess expression of the D3 receptor in the dorsal striatum (Bézard et al., 2003; Bordet et al., 1997). This association is problematic because PD patients often lower their dose of L-dopa and begin adjunct therapy with a DA agonist to reduce dyskinesia, which could potentially put them at risk of developing an ICDs.

Another prospective mechanism for the development of DRT-induced ICDs is the change in normal patterns of DA release. Phasic DA release occurs when a reward is anticipated and is supressed when an expected reward is not received (Fiorillo, Tobler, & Schultz, 2003). DRTs

tonically stimulate the DA receptors, preventing pauses in DA transmission that would provide negative feedback when experiencing a loss. Eimeren et al. (2009) provided the first empirical evidence for this mechanism, in that tonic DA stimulation with DA agonists in PD patients diminished reward processing by increasing activity in orbitofrontal cortex and ventral striatum during negative errors of reward prediction rather than producing a decrease in activity that would provide negative feedback. Additionally, tonic DA release occurs under uncertainty and the peak of the sustained DA activity occurs at the moment of greatest uncertainty (Fiorillo et al., 2003). Gambling is defined by reward uncertainty; therefore, this uncertainty-induced peak in DA activity could be reinforcing gambling behaviour and may help explain the rewarding properties of gambling, which are not readily explained by monetary gains (Fiorillo et al., 2003). This mechanism is supported by Linnet, Peterson, Doudet, Gjedde, and Møller (2010) who found that individuals with GD have increased DA release in the ventral striatum during periods of losing, but not winning. Furthermore, ICDs are more prevalent in PD patients on DA agonist treatments, which have a longer elimination half-life than L-dopa thereby providing more continuous stimulation of the DA receptors (Chase, 1998). This provides further support for the role of tonic DA stimulation in the development of ICDs among PD patients. More research needs to be conducted to produce conclusive evidence, as research on the association between tonic DA signalling and ICDs other than GD is scarce.

There have also been several studies that have observed blunted activation in the ventral striatum in PD patients on DA agonists with ICDs in response to wins/rewards (Claassen et al., 2011; Riba, Krämer, Heldmann, Richter, & Münte, 2008; Voon et al., 2011a). This effect may be best explained by action of DA agonists on the D2 receptor. The D2 receptor is also located pre-synaptically on neurons in the striatum and serves to regulate neurotransmitter release (Ford,

2014). Therefore, activation of the D2 autoreceptor by the DA $D_{2/3}$ agonists used in PD may cause a decrease in neurotransmitter release, reducing striatal activation, which is consistent with that pattern of activation that is observed in neuroimaging studies. Furthermore, the D3 autoreceptor is located in the midbrain and its activation has been found to inhibit reward-related phasic DA signalling, which is consistent with the decrease activation of the midbrain ventral tegmental area and substantia nigra observed in response to a win in PD patients taking a DA agonist (Riba et al., 2008; Sokoloff et al., 2006).

In sum, there is currently no definitive mechanism by which the DA system causes either idiopathic or DRT-induced ICDs to emerge. There is substantial evidence linking changes in DA transmission and receptor density to ICDs, but the direction these changes occur in is not certain. Furthermore, this section focused exclusively on DA-related mechanisms, as these are believed to play the most prominent role judging by current data, and are the most relevant for this thesis. However, some evidence suggests a potential role for other neurotransmitter systems, like the serotonergic system, which has also been implicated in the underlying pathology of both idiopathic and DRT-induced ICDs (Crockett, Clark, Lieberman, Tabibnia, & Robbins, 2010; Crockett, Clark, & Robbins, 2009; Leeman & Potenza, 2013; Winstanley, Theobald, Dalley, & Robbins, 2005). The manifestation of ICDs likely involves many different neural pathways and neurotransmitter systems. Therefore, research that can contribute conclusive evidence for the role of any one of these factors in urgently needed in order to fully understand these disorders and how to manage them pharmacologically.

1.4 Treatment for iatrogenic ICDs

Treatment of ICDs in PD patients is complex and little is known about optimal management strategies or the long-term outcomes of these patients. ICDs in PD are associated

with other cognitive and psychiatric features like anxiety, affective and obsessive-compulsive symptoms, and impulsivity, which complicates their treatment (Voon et al., 2011b). Also, PD is a chronic and progressive disorder, so DRT is unable to be withdrawn without a significant decline in quality of life due to the debilitating nature of PD motor symptoms. One treatment option would be to try to prevent ICDs from arising by giving PD patients only L-dopa because the proportion of individuals that develop ICDs with this type DRT has been found to be much smaller. However, as noted above, chronic L-dopa produces other debilitating side-effects, such as dyskinesia, at a significant higher rate. Thus, DA agonists should be given to postpone the development of dyskinesia, especially for patients with early-onset PD, which are at an even higher risk of developing these side-effects because they will be treated with DRTs for longer. Additionally, this approach would still leave the few patients that do develop an ICD while on L-dopa without any treatment options. Currently, there are no preventative adjunct therapies for DRT-induced ICDs.

One of the few studies examining the treatment of ICDs in PD patients showed that when PD patients discontinued or significantly decreased the amount of DA $D_{2/3}$ agonist taken and increased their L-dopa intake to compensate, all patients reported experiencing full or partial remission of their ICD symptoms (Mamikonyan et al., 2008). However, this doesn't obviate the risk of L-dopa producing significant side-effects, so patients should have other options beyond taking this medication long-term. Also, ICDs are observed in patients taking L-dopa, although at a lower frequency, so taking L-dopa instead of a DA agonist doesn't provide a solution for all DRT-induced ICDs. Ardouin et al. (2006) found that GD could be resolved in all patients when treatment with DA agonists was replaced with deep brain stimulation of the subthalamic nucleus. However, deep brain stimulation is a novel surgical treatment for PD that is still being evaluated

and has its own significant risks due to its invasive nature. Recent research also indicates that deep brain stimulation of the subthalamic nucleus produced ICDs in PD patients that had significantly reduced or discontinued DA agonist use (Lu, Bharmal, & Suchowersky, 2006). A common problem in the current literature is that most studies evaluating potential treatments for DRT-induced ICDs in PD have very small sample sizes and use inconsistent study methods, such as different inclusion and exclusion criteria, diagnostic criteria, and outcome measures. Therefore, large randomized controlled trials need to be conducted before safe and effective management strategies can be recommended to PD patients (Connolly & Lang, 2014; Ramirez-Zamora, Gee, Boyd, & Biller, 2016).

Adjunctive medications that could be safely administered with DA agonists to prevent the development of ICDs or treat them once they have been diagnosed would be highly desirable for PD patients. However, without knowing the mechanism by which DRTs produce ICDs, a treatment for DRT-induced ICDs is very difficult to develop. There are some case reports that suggest that atypical antipsychotics, antidepressants, mood stabilizers, and a variety of psychosocial interventions may alleviate ICDs in PD patients (Driver-Dunckley et al., 2003; Klos, Bower, Josephs, Matsumoto, & Ahlskog, 2005; Seedat, Kesler, Niehaus, & Stein, 2000; Sevincok, Akoglu, & Akyol, 2007). However, these treatments are often administered alongside changes in DRT, making it difficult to identify if ICD treatment is effective or if the symptoms have been alleviated because the problematic DRT had been withdrawn. The majority of evidence suggests that the change in DRT is producing the effect rather than the other interventions. Thus, the current first-line of management strategy after diagnosis of ICDs is reduction or discontinuation of DA agonists (Ramirez-Zamora et al., 2016). Although discontinuation, tapering, or replacement of DA agonist treatment with other drugs have been

demonstrate to be effective strategies to control ICD symptoms in two long-term follow-up studies, many patients cannot tolerate the adjustment due to the development of off-period dysphoria, DA agonist withdrawal symptoms, or worsening of PD motor symptoms (Mamikonyan et al., 2008; Okai, Samuel, Askey-Jones, David, & Brown, 2011; Ramirez-Zamora et al., 2016; Sohtaoğlu, Demiray, Kenangil, Özekmekçi, & Erginöz, 2010). For these patients, a change in DRT is not a solution. Given the prevalence of ICDs among PD patients, the lack of information on effective treatments for DRT-induced ICDs is alarming. This underscores the need for empirical research on the mechanism underlying DRT-induced ICDs, which will aid the development of treatments for ICDs in these individuals. PD patients resorting to increasing their intake of L-dopa to compensate for a reduction in DA agonist intake to treat their ICDs, when L-dopa has just as debilitating side-effects as DA agonists, is clearly inadequate. Additionally, PD patients with ICDs that do not respond to or cannot tolerate a change in DRT have no viable treatment options.

Although some explanations for DRT-induced ICDs have been proposed, they all seem to lack a targetable mechanism of action because the focus of most etiological studies has been on the role of the DA system in DRT-induced ICDs. For example, the DA overdose hypothesis suggests that DRT replenishes the lost DA in striatum which improves motor symptoms; however, it also causes the mesolimbic reward system to be overwhelmed with DA which causes ICDs to emerge. This hypothesis suggests that a reduction in DA activity in mesolimbic system would ameliorate ICDs. However, it is difficult to reduce DA activity without exacerbating motor symptoms in PD patients because of the extensive overlap of DA D2 and D3 receptor expression in the dorsal and ventral striatum. Therefore, administering a $D_{2/3}$ receptor antagonist may alleviate these non-motor side-effects, but they will also attenuate the therapeutic effect of

the anti-parkinsonian medication. Furthermore, the DA $D_{2/3}$ receptor agonists that are given to PD patients tend to have a higher affinity for D3 receptors than D2 receptor, leading to significant binding outside of the targeted nigrostriatal pathway and instead in limbic regions that have been implicated in ICDs (Potenza, 2008; Reuter et al., 2005). Pharmacologically reducing DA activity only in these regions without impacting motor function in PD patients is challenging. However, it is important to note that the role of D2 and D3 receptors in ICDs still remains unclear. DA $D_{2/3}$ receptor antagonists have produced conflicting results on gambling-related behaviour (Seedat et al., 2000), with Zack and Poulos (2007) findings that a D2 antagonist enhanced the rewarding effect of gambling and increased post-game desire to gamble in those with GD. Moreover, $D_{2/3}$ receptor antagonists have not demonstrated efficacy as a treatment for GD in controlled trials (Potenza, Voon, & Weintraub, 2007).

This overview illustrates the complexity of developing a treatment for ICDs in PD patients when the underlying mechanism that produced idiopathic or iatrogenic ICDs is not well understood, the role of the DA systems in the development of iatrogenic ICDs remains elusive, and DA activity cannot be easily reduced without exacerbating motor symptoms in PD patients. It seems that the most obvious treatment for DRT-induced ICDs, administration of a $D_{2/3}$ antagonist, should be effective, but current research casts doubt on such a conclusion, even if it was feasible to attempt in PD patients. More empirical research on the mechanism by which DRTs produced ICDs is clearly warranted. The therapeutic shortcomings of $D_{2/3}$ antagonists support the investigation of novel treatments that don't exert their action directly on DA receptors.

1.4.1 Agonists for G protein-coupled receptor 52

G protein-coupled receptors are one of the most common therapeutic targets for psychiatric disorders (Komatsu, 2015; Overington, Al-Lazikani, & Hopkins, 2006). Recently an orphan G_s-coupled receptor, GPR52, has been identified (Sawzdargo et al., 1999). At this time, no endogenous ligands have been found for this receptor (Komatsu et al., 2014). GPR52 is predominately expressed in the striatum, where it is nearly completely co-localized with DA D2 receptors but not D1 receptors (Komatsu et al., 2014). Additionally, GPR52 is partially co-localized with D1 receptors in the prefrontal cortex, which is heavily involved in cognitive function (Setoh et al., 2014). Tissue distribution analysis of human, mouse, and rat tissue indicated that GPR52 is highly conserved among vertebrates, especially in the striatum, suggesting that it is involved in common functions across species (Komatsu et al., 2014) . Moreover, the lack of a significant differences in expression across these species adds to the translational value of conducting pre-clinical testing of novel compounds targeting GPR52.

Komatsu et al. (2014) demonstrated that GPR52 is a druggable orphan receptor by eliciting calcium influx with the antipsychotic reserpine. They also found that GPR52 knockout mice that lack the receptor show psychosis related behaviours and transgenic mice that overexpress GPR52 show antipsychotic behaviours, demonstrating that GPR52 agonists could have D2 antagonist-like effects because these behaviours are thought to be mediated via overactive D2 receptor signalling (Ananth, Burgoyne, Gadasalli, & Aquino, 2001). Recently, there have been a few studies investigating the effect of novel GPR52 agonists in rats. The current available data confirm that GPR52 agonists can elicit a D2 antagonist-like effect. Setoh et al. (2014) tested the first GPR52 agonists, finding that oral administration of 3 mg/kg of compound 7m was able to supress methamphetamine-induced hyperactivity but did not impair

basal motor function even at a high dose in mice (100 mg/kg), suggesting that GPR52 agonists have a different downstream function than D2 antagonists thereby reducing the risk of developing motor side-effects, like catalepsy, which are commonly caused by D2 antagonists (Haraguchi, Ito, Kotaki, Sawada, & Iga, 1997). Tokumaru et al. (2017) also suppressed methamphetamine-induced hyperactivity in mice by orally administering 10 mg/kg of 4u, a novel GPR52 agonist. Additionally, other novel GPR52 agonists have demonstrated these D2 receptor antagonist-like effects as well as pro-cognitive effects, like improved performance pre-clinical tasks of cognition (Grottick et al., 2018; Grottick et al., 2017a; Grottick et al., 2017b).

Overall, the research suggests that GPR52 agonists may be able to treat psychiatric disorders that are manifested by aberrant DA activity, especially in the striatum. These novel compounds also seem to elicit a different downstream intracellular mechanism than drugs with similar behavioural effects, like D2 receptor antagonists, significantly reducing the risk of motor complications. Avoiding exacerbating symptoms and further motor impairment is one of the major hurdles when developing a drug that can be safely administer to PD patients. These compounds need to be able to not interfere with motor improvements caused DRT while simultaneously treating ICDs that may be the product of excess DA activity. Thus, agonists for GPR52 may be a potential adjunct therapy for ICDs in PD patients based on their D2 antagonist-like effect in the striatum, pro-cognitive effect in the cortex, and absent effect on movement. However, their effectiveness on ICDs has yet to be tested.

1.5 Decision making in relation to DRT, ICDs, and PD

A potential therapeutic target or measure of treatment effectiveness in ICDs is decision making. There are have been several changes in decision making observed in PD patients with ICDs. However, the majority of studies focus on GD, with only a few examining changes in

decision making in other ICDs. Decision making can be defined as the ability to select an advantageous response from an array of choices. In real life situations, decisions must be made without full knowledge of the probabilities of the consequences of the response (Bechara, Damasio, Tranel, & Anderson, 1998). Evens, Hoefler, Biber, and Lueken (2016) recently conducted a meta-analysis examining all the studies in the past 15 years that have investigated the relationship between PD, DRTs, and performance on the Iowa Gambling Task (IGT), which is the most commonly used task to measure decision-making under uncertainty (Bechara, Damasio, Damasio, & Anderson, 1994). They found that PD patients on dopaminergic medication had significantly impaired performance on the IGT when compared to healthy controls. However, performance on the IGT was not restored during short-term withdrawal of DRT. Patients not on dopaminergic medication still had significantly impaired performance on the IGT compared to healthy controls, and there was no difference in IGT performance between PD patients on and off medication. Interestingly, Evens et al. (2016) excluded studies that included patients with ICDs; therefore, the patient group that is supposed to have the most prominent impairments was not incorporated in the meta-analysis. Thus, the impairments on the IGT observed in PD patients on and off DRT may reflect impairments produced by cortical degeneration that occurs in later stages PD rather than the DRT having no effect on decision making.

As for the relationship between decision making, ICDs and PD, Rossi et al. (2010) found that PD patients with GD had poorer performance when compared to PD patients without a GD on the IGT and in a rating scale of social behaviour, but not on the Game of Dice Task (GDT) and the Investment Task that evaluate decision making under calculable risk and risk aversion respectively (Brand et al., 2005; Shiv, Loewenstein, Bechara, Damasio, & Damasio, 2005). In

this study, PD patients with GD developed the worst strategy on the IGT, selecting disadvantageous alternatives more frequently than the advantageous and did not shift from this preference (Rossi et al., 2010). They also had no impairment on the GDT; however, both PD patients and subjects without PD but with a GD have been shown to have significant deficits on the GDT (Brand et al., 2005; Brand et al., 2004). One shortcoming of Rossi et al.'s (2010) study is that they didn't investigate whether the type of DRT or dosage was related to performance on the IGT or the other tasks they used to evaluate decision making. However, this relationship has been studied by Claassen et al. (2011), finding that DA agonists increased risk taking on the Balloon Analogue Risk Task (BART) in PD patients with an ICD but did not in PD patients without an ICD. This increase in risk taking did not depend on the dose of DA agonists. The PD patients with ICD had a significant increase in risk taking on the BART when compared to their off-medication performance and to PD patients without ICD, even on the lowest dose of DA agonists. A major strength of this study is that it is one of the only that examined decision making in hypersexuality, compulsive shopping, compulsive eating, GD, and punding, capturing DA agonist mediated changes among different ICDs. Voon et al. (2011a) also found that PD patients with ICDs increased their preference for risky gambles compared to PD patients without ICDs, even though the expected value of the safe/sure and risky/uncertain choice were matched. Thus, these patients seem to display a preference for uncertainty even when there is no real risk of losing. This effect was also apparent when comparing the choice preference of PD patients with ICDs on and off their DA agonist (Voon et al., 2011a).

Although the body of literature on decision making, DRTs, and ICDs in PD is growing and is far from conclusive, there still appears to be an increase in preference for risk and uncertainty when PD patients are on DA agonists, with the majority of evidence finding these

changes in PD patients on DA agonists with ICDs. This effect appears across several different tasks, even when the expected value of each choice in matched, suggesting that these patients are displaying a preference for the uncertainty associated with the choice. This is also supported by the riskier options having the highest uncertainty in these decision-making tasks.

1.5.1 Animal models of decision making

Animal models of decision making can help elucidate changes that occur with the administration of DRTs and the mechanism underlying the production of ICDs. The tighter experimental control with animal models is useful for determining whether pre-existing individual differences or risk factors, like baseline differences in preference for risk or impulsivity, contribute to the changes observed with the use of DA agonists. Also, animal models allow for the ethical withdrawal of DRT without having to compensate with an increase in another form of treatment, which permits the confirmation of behavioural changes being caused by DRT administration. Moreover, animal models are invaluable in the pre-clinical testing of novel drug treatments for psychiatric conditions. Thus, an animal model of DA agonist-induced changes in decision making could be used for the pre-clinical testing of adjunct drug treatments that restore healthy decision-making preferences and preserve the therapeutic effect of DRTs on motor symptoms.

Although there are some differences in the neurobiology of rodents, non-human primates, and humans, many structures and patterns of neuronal connectivity appear to be conserved among these vertebrates (Haber & Knutson, 2010; Heilbronner, Rodriguez-Romaguera, Quirk, Groenewegen, & Haber, 2016; Holt, Graybiel, & Saper, 1997). It has also been demonstrated that humans, non-human primates, and rodents are all sensitive to reward size and probability, base decisions on previous outcomes, and display a win-stay/lose-shift decision-making pattern

(Cocker, Dinelle, Kornelson, Sossi, & Winstanley, 2012; Cocker & Winstanley, 2015b; Heilbronner, 2017; Marshall & Kirkpatrick, 2013; Stauffer, Lak, & Schultz, 2014; Stopper & Floresco, 2011; Tremblay, 2017). Similar to humans, rodents are able to learn to choose long-term advantageous options, supporting their validity as a model of decision making (see Heilbronner, 2017 for review). Regarding risky decision making, there are shared modulatory effects, suggesting a common underlying mechanism that is conserved across species. For example, rhesus macaques have been shown to be risk-seeking, preferring a risky/uncertain option over a safe/certain option of equivalent expected value, which is also observed in humans under similar conditions (Hayden, Heilbronner, & Platt, 2010; O'Neill & Schultz, 2010; Stauffer, Lak, Bossaerts, & Schultz, 2015).

The administration of DA agonists to animals engaging in tasks that model human decision making has yielded interesting results. Rokosik and Napier (2012) recently found that chronic administration of the DA $D_{2/3}$ agonists pramipexole induced an increase in preference for the uncertain option of a probability discounting task in both healthy rats and a PD rat model. This effect has also been found with chronic administration of the DA $D_{2/3}$ agonist ropinirole in rats (Tremblay et al., 2017). Similarly, St Onge and Floresco (2008) found that bromocriptine, which has an equal affinity for D2 and D3 receptors, increased preference for the uncertain option on a probability discounting task. These finds are consistent with the human literature, indicating that patients on DA agonists, with or without PD, show an increase preference for the uncertain option regardless of the expected value of the reward (Voon et al., 2011a).

1.5.1.1 The rodent betting task (rBT)

Our lab has developed numerous rodent models that capture different aspects of decision making under risk and uncertainty. These tasks allow us to measure changes in decision making

that are associated with ICDs, especially GD, as well as investigate the underlying neurobiological mechanism that mediates these changes. The rodent Betting Task (rBT) was created to capture preference for uncertainty, which is often referred to as risk in the literature, as well as non-normative decision-making biases that are observed in human decision making under ambiguity (Cocker & Winstanley, 2015a). This task aims to model the escalation of commitment phenomenon that is observed in human gambling. As described in Winstanley and Clark (2016), gamblers will shift their preference towards a guaranteed outcome as the wager size increases even when the odds of winning remain the same. This aversion towards uncertainty when the wager size increases, even though the expectancy is the same in both options, is considered irrational (Tversky & Kahneman, 1974). A similar phenomenon is evident on the rBT; a subset of rats, classified as wager-sensitive, will shift their preference towards a smaller guaranteed reward as the wager size increases, even though the relative reward expectancy is the same (Cocker et al., 2012). Irrational decision-making biases, like the escalation of commitment phenomenon, have been associated with the manifestation and severity of GD (Emond & Marmurek, 2010; Ladouceur & Walker, 1996; Miller & Currie, 2008). Thus, correcting these maladaptive cognitions is a key therapeutic target for both idiopathic and iatrogenic GD (Ladouceur et al., 2001; Sylvain, Ladouceur, & Boisvert, 1997). Interestingly, wager-sensitivity on the rBT is linked to striatal D2 and D3 receptor expression, which has been implicated in the development of DRT-induced GD and other ICDs (Cocker et al., 2012). Furthermore, chronic administration of ropinirole increases preference for the uncertain option on the rBT, which is consistent with the increase in preference for the uncertain option in PD patients with ICDs compared to PD patients without ICDs on an analogous task for humans (Tremblay et al., 2017; Voon et al., 2011a).

Overall, it seems that the rBT is a valid model of decision making under uncertainty that is able to capture changes in responding that may occur with the administration of DA agonists. The rBT also permits the investigation of an irrational decision-making bias that is associated with the development and severity of GD. Both preference for uncertainty and wager-sensitivity may be potential therapeutic targets associated with D2 and D3 receptors that are displayed in both rats and humans. Both behavioural parameters are able to be measured with the rBT, making this task suitable for the pre-clinical testing of novel compounds that aim to reduce them.

1.6 Objectives

The main objective of the present series of experiments is to evaluate the effectiveness of GPR52 agonists for the treatment of DRT-induced ICDs. Specifically, I investigated the effect of three doses of the GPR52 agonist BD442618 on chronic DA agonist ropinirole-induced increase in preference for uncertainty on the rBT in healthy male rats. This ropinirole-induced increase in preference for uncertainty is used as an approximation for GD. Subsequently, I use a different cohort of male rats to investigate the effect of the GPR52 agonist S111224 at the dose that was effective in the first chronic experiment under the assumption that both drugs have a very similar mechanism of action. Given that GPR52 agonists are co-localized with D2 receptors in the striatum and D1 receptor in the cortex, and do not to impair motor function at a high dose, they are valid potential adjunct medications for the treatment of ICDs in PD patients. The D2 antagonist-like effect that occurs without motor impairment shown with GPR52 agonists lends itself extremely well for the treatment of DRT-induced ICDs in PD because these agonists have the potential to reduce ICDs symptoms that are mediated by increase DA activity without reducing the effectiveness of the DRT on motor symptoms. A PD rat model was not used in these experiments because the effect of DRTs on decision making seem to occur independently

of PD pathology (Holtz, Tedford, Persons, Grasso, & Napier, 2016; Rokosik & Napier, 2012; Tremblay et al., 2017).

Based on preliminary data that was collected from a series of screening experiments, I hypothesized that chronic administration of ropinirole will increase preference for uncertainty on the rBT and this effect will be mitigated by chronic adjunct administration of BD442618. I further speculated that the wager-sensitive rats will be more vulnerable to changes caused by both ropinirole and BD442618 because the decision-making bias they display correlates with striatal $D_{2/3}$ receptor density, and has been link to the severity of gambling behaviour in humans. Based on the results from the first chronic experiment, I hypothesized that 3 mg/kg of S111224 would be effective at reducing the ropinirole-induced increase in choice of the uncertain option in wager-sensitive rats.

Chapter 2: Method

2.1 Subjects

I used a total of 120 male Long Evans rats, 56 for the experiment with BD442618 and 64 for the experiment using S111224 (Charles River Laboratories, St. Constant, Canada). All rats were aged around post-natal day 60 and weight between 250-300 grams at the start of the experiment. Males were selected because PD, ICDs, and GD occur more frequently in males (Alves et al., 2008; Mestre, Strafella, Thomsen, Voon, & Miyasaki, 2013; Pavon et al., 2010; Voon et al., 2007). A PD rat model was not used in these initial proof of concept experiments because the DRT-induced ICDs seem to be independent of PD pathology (Holtz et al., 2016; Rokosik & Napier, 2012; Tremblay et al., 2017). All rats were pair-housed from the time of their arrival and kept in a climate-control colony room on a reverse 12 hour light-dark cycle (i.e. lights off at 8:00 a.m.). The rats were free fed standard rat chow for at least a week, during which they were handled daily. They were then food restricted to 85% of their free-feeding weight by giving 14 grams each of standard rat chow per day plus any sugar pellets earned on the task (i.e. ~5 grams per weekday). Water was always available. Behavioural testing began one week following the start of food restriction. Rats were trained between 9:00 a.m. and 4:00 p.m. five days a week and engaged in one behavioural testing session per day. All housing conditions and testing was in accordance with the Canadian Council on Animal care, and the University of British Columbia Animal Care Committee approved all experimental procedures prior to the beginning of the experiment.

2.2 Behavioural apparatus

Behavioural testing took place in 32 standard five-hole operant chambers from Med Associates Inc, Vermont, USA (Figure 1). Each of these chambers was individually housed in a

ventilated and sound-attenuating cabinet. Within each chamber was an array of five response holes on one side, and a food magazine that was positioned in the center of the wall opposite to the response hole array. On each side of the food magazine there was a retractable lever. The food magazine and each of the response holes was equipped with a stimulus light at the back and a horizontal infra-red beam across to detect a nose-poke. The food magazine delivered sucrose pellets (45 milligrams; Bioserv, New Jersey) from a connected pellet dispenser that was mounted on the outside of the chamber. Each chamber also contained a house light to allow for illumination. The chambers were controlled by software written in Med PC by Catharine A. Winstanley that runs on several computers, each controlling multiple chambers at a time.

Figure 1. Standard five-hole operant chamber with two retractable levers

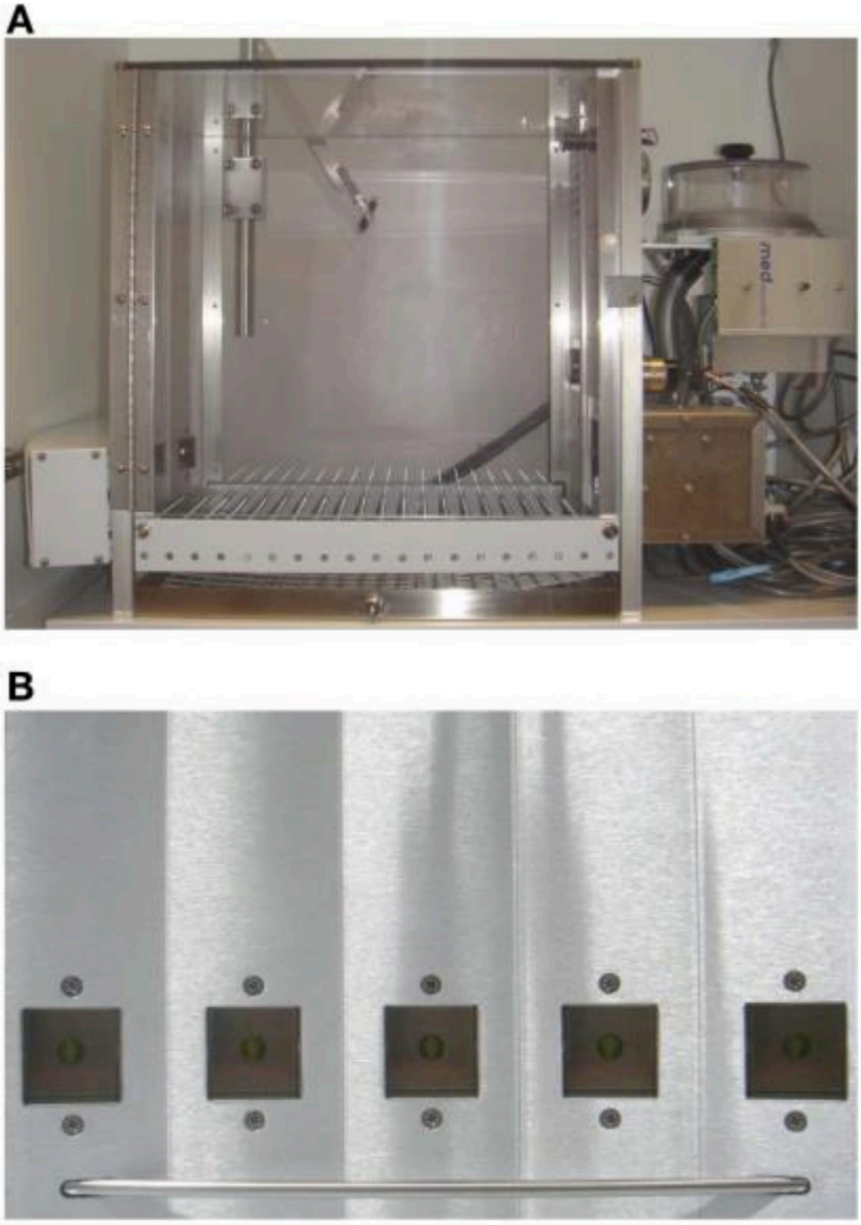

Figure 1. The standard five-hole operant chamber with two retractable levers used for the rBT. Side view of the operant chamber (A) and close-up of the five response holes within the chamber (B).

2.3 Procedure

This section will provide an overview of the procedure used for each experiment (see subsections for more detail). Rats were first trained to perform the rBT, and then the following experiments were conducted.

2.3.1 Experiment 1: Latin square drug challenges

Effect of BD244618 on rBT performance

Once behaviour was stable, an initial exploratory study (n=16) to determine the dose of BD442618 to use in the chronic experiment was conducted. Previous studies with GPR52 agonists indicate that very high doses do not alter basal function and 3 mg/kg of GPR52 agonists produces a therapeutic effect (Setoh et al., 2014; Tokumaru et al., 2017). This initial study was conducted to confirm that none of the potential doses of BD442618 alter basal function. Three doses of BD442618 were administered (0.3, 1, and 3 mg/kg) 30 minutes prior to testing according to a diagram-balanced Latin Square design for three doses and a vehicle: A = vehicle, B = smallest dose, C = medium dose, D = largest dose. BD442618 and vehicle were administered on a three-day schedule that started with a baseline testing day, administration of drug and vehicle for doses A-D: ABCD, BDAC, CADB, DCBA as per Cocker et al. (2012), and a day-off from testing that allowed for washout of the drug. Rats were trained on the rBT for two weeks following this Latin Square to allow for complete washout of the drug and a return to baseline responding on the rBT.

Effect of co-administration of BD442618 with d-amphetamine on rBT performance

A second Latin Square was conducted (n = 16) with a dose chosen from the first Latin Square (0.3 mg/kg) to determine whether this dose would be effective at blocking the effect of *d*-amphetamine on decision making. Cocker et al. (2012) found that *d*-amphetamine increased

choice of the uncertain option in wager-sensitive rats and choice latencies on the rBT. These results used in conjunction with studies that found GPR52 agonists reduce methamphetamine induced hyperactivity, suggest that an effective dose of BD442618 should be able to block the effect of *d*-amphetamine on the rBT. The doses for the Latin Square were the following: A = *d*-amphetamine and BD442618, B = *d*-amphetamine and vehicle, C = saline and BD442618, and D = saline and vehicle. The same three-day schedule as before was followed: baseline, drug and vehicle administration, and washout. BD442618 was administer 30 minutes prior to testing and *d*-amphetamine was administer 10 minutes prior to testing, following Cocker et al. (2012). Again, rats were trained on the rBT for two weeks to allow for complete washout of the drugs and a return to baseline responding prior to any other testing. A third Latin Square was conducted following the same procedure but with a higher dose of BD442618.

2.3.2 Experiment 1: Chronic ropinirole and BD442618

Following the series of Latin Squares and a return to stable baseline responding on the rBT the chronic experiment with ropinirole and BD442618 was conducted (n = 56). Rats were assigned to one of four groups: 1 = ropinirole and BD442618 (n = 16), 2 = ropinirole and vehicle (n = 16), 3 = saline and BD442618 (n = 12), and 4 = saline and vehicle (n = 12). Based on their assignment, osmotic pumps containing either ropinirole or saline were subcutaneously implanted in each of the rats. At the time of implantation, rats also received their assigned injection of either BD442618 or vehicle. This marks experimental day 1. The experimental duration was 28 days due to the limitations of the pumps, with injections being given daily. The rats were given two days to recover from surgery before testing resumed, during this time their recovery was monitored and continued to be monitored for the follow 10 days. After the two recovery days, testing on the free-choice version of the rBT resumed. The rats were tested 5 days per week over

the 28 day duration of the experiment, with injections being given 30 minutes prior to testing. For the first 10 days the rats assigned to the GPR52 agonists group were injected with 0.3 mg/kg of BD442618. For the following 8 days the dose of BD442618 was increased to 1 mg/kg and then 3 mg/kg for the remaining 8 days. At the end of the experiment, the rats were humanly euthanized following our approved protocol for euthanasia via carbon dioxide inhalation. Over the course of the chronic experiment, a total of three rats were euthanized.

2.3.3 Experiment 2: Chronic ropinirole and S111224

Prior to this chronic experiment, no Latin Squares were conducted. Dose selection was based on results from the previous chronic experiment with BD442618 (3 mg/kg). Once rats were trained on the rBT and responding was stable, the chronic ropinirole and S111224 (n = 64) was conducted. Rats were assigned to one of four groups: 1 = ropinirole and S111224, 2 = ropinirole and vehicle, 3 = saline and S111224, and 4 = saline and vehicle. The experimental protocol was identical to chronic dosing with BD442618, only rats assigned to receive the GPR52 agonist were given a dose of 3 mg/kg for the duration of the experiment. One rat did not recover after surgery.

2.4 Behavioural testing

On training days rats were transported form the colony room to the testing room in their home cage prior to being placed in the operant chamber. The rats were tested in the same operant chamber for the duration of the experiment, which is from habituation to the last day of data collection.

2.4.1 Habituation and training

First, the rats were habituated to the operant chambers by allowing them to freely explore the chamber and access sucrose pellets placed in each response hole. There were two of these 30

minute sessions, then animals were trained to poke their nose into illuminated responses holes by using the Five-Choice Serial Reaction Time Task (5CSRT) (Robbins, 2002). In the 5CSRT, a light in one of the five response holes is illuminated pseudorandomly; this signals the beginning of a trial. Rats are rewarded when they poke their nose into the illuminated response hole within 10 seconds. Trials are scored as omissions if the rat fails to respond within 10 seconds. One session of the 5CSRT consists of either 100 trials or 30 minutes. Once their accuracy in responding to the illuminated response hole reached more than 80 percent (i.e. less than 20 percent of trials were omissions), rats were trained to press retractable levers for reward on a fixed ratio 1 schedule. Only one of the two levers in the chamber is presented per session. Once the animal made more than 50 presses per session, training was repeated on the other lever.

2.4.1.1 The rodent Betting Task (rBT)

Training on the rBT began with the forced-choice version of the task, in which only one of the levers is extended per trial pseudorandomly. Before the session begins, each lever was permanently designated as safe or uncertain and counterbalanced across rats. Each session consisted of 12 blocks of 10 trials. The wager size remained constant within each block but varied between blocks in a pseudorandom pattern that ensureed 4 blocks of each wager size within a session, and no more than 2 consecutive blocks of the same wager size. To indicate the wager size in play, either 1, 2, or 3 lights was illuminated in response holes 2, 3, and 4; 1 light indicated a wager size of one sucrose pellet, 2 lights indicated a wager size of two sucrose pellets, and 3 lights indicated a wager size of three sucrose pellets. A nose-poke in each of the response holes, in any order, was necessary to extinguish the light. Once the rat turned off the lights, a lever was inserted into the chamber; pressing the safe lever guaranteed delivery of the number of sugar pellets indicated by the number of response holes illuminated whereas pressing

the uncertain lever resulted in twice the number of sugar pellets or nothing on a 50:50 basis. The expected value of both options was always equal in each block of trials. The sugar pellets were dispensed into the food tray on rewarded trials. The food tray was illuminated after a response has been made on the lever, regardless of whether reward was delivered. If the rat failed to make the appropriate response within 10 seconds when the response holes are illuminated or when the lever is extended, the trial is scored as a hole omission or choice omission respectively. Both types of omissions were punished by a 5 second time-out period. During this period, the house-light was illuminated and no rewarded could be earned because no trials could be initiated. Once the time-out period ended, the food tray light was illuminated, indicating that the rat could begin another trial.

Rats were trained on this forced-choice version of the rBT for 10 sessions, then progressed to the free-choice version of the task. Sessions on both versions of the rBT lasted until all 120 trials are completed or until 30 minutes had elapsed. The free-choice version of the rBT is identical to the forced-choice version, expect that both levers extend, allowing the rat to freely choose either the safe or the uncertain lever by pressing on the lever of its choice. Additionally, to ensure that the rats were familiar with the contingencies, the first 4 trials of each block were always forced choice, so only the safe lever (2 trials) or uncertain lever (2 trials) was presented in random order. Rats were trained 5 times per week on the free-choice version of the rBT until their pattern of choice is stable over 5 sessions; this is determined by a non-significant effect of session and session x wager size in a repeated measures analysis of variance (ANOVA) across all variables. The rBT training procedure has been previously outlined by Cocker et al. (2012) and Tremblay (2017).

2.5 Osmotic pump implantation

Following the procedure outlined by Tremblay (2017), rats were subcutaneously implanted with a model 2ML4 osmotic pump (Alzet, DURECT Corporation, Cupertino, CA) delivering either 5 milligrams/kilogram/day of ropinirole hydrochloride (Tocis, R&D Systems, Minneapolis, USA) or 0.9% saline solution for 28 days. The osmotic pump allowed for chronic drug delivery over 28 days, and its use has been validated across multiple experiments (Kapur, VanderSpek, Brownlee, & Nobrega, 2003; Kemmerer, Desmond, Albin, Kilbourn, & Frey, 2003; Kippin, Kapur, & van der Kooy, 2005; Tremblay, 2017; Tremblay et al., 2017; Vernon et al., 2012). The dose of ropinirole used in these experiments is similar to the single daily dose of the prolonged released formulae of ropinirole used in human patients (Nashatizadeh, Lyons, & Pahwa, 2009). Additionally, our lab has previously shown that this dose reliably produces an increase in preference for uncertain choice in healthy rats (Tremblay, 2017; Tremblay et al., 2017).

Osmotic pumps were sterilely filled with a solution based on the rat's weight a day prior to implantations. Following the instructions provide by Alzet, these filled pumps were kept overnight in a sterile 50 milliliter falcon tubes filled with 0.9% saline solution; this allows the pores on the pump to open, allowing the solution to flow out of the pump. These pumps were implanted subcutaneously into each animal while they were anesthetized with isoflurane. Rats remained in their home cage for two days following surgery before testing resumed. All animals' recovery was monitored for a minimum of 10 days. Once the pump was implanted, the experimental phase had begun (i.e. experimental day 1). The osmotic pumps can only be implanted in the rats for 28 days, limiting the duration of these experiments to 28 days after implantation.

2.6 Intraperitoneal injections

The rats received an intraperitoneal injection of either GPR52 agonist or vehicle. The first injection was administered immediately after osmotic pump implantation. Injections occurred every day thereafter for 28 days. All rats received the injection 30 minutes prior to testing as advised by Beacon Laboratories, allowing for the drug to become fully active. On days that the animals were not tested, they still received an injection at a similar time to test day. All solutions, both drug and vehicle, were made fresh each day no more than 2 hours prior to testing.

2.6.1 Preparation of BD442618 injectable solution

BD442618 was dissolved in the following solvent: 97.2% 0.9% saline, 2.4% Dimethyl Sulfoxide, and 0.4% Tween 20. This solution was too acidic to inject into live animals (~pH 2), so the pH of this solution was adjusted by adding less than 10 microliters of 10M sodium hydroxide until it reached an acceptable range for injection (i.e. ~ pH 7-7.5). The animals received an injection volume of 5 milliliters/kilogram of BD442618 or vehicle.

2.6.2 Preparation of S111224 injectable solution

S111224 was dissolved at a volume of 1 mg/ml. First, 10 µl/ml of 2N Hydrochloric Acid was added, the solution vortexed, then 20% β-cyclodextrin was added, leaving volume for pH adjustment. The solution was then sonicated. Again, this solution was too acidic to inject into live animals (~pH 1), so the pH of the solution was adjusted with 10M sodium hydroxide until it reaches an acceptable range for injection (i.e. ~ pH 7-7.5). Finally, the desired volume was achieved by adding 20% β-cyclodextrin.

2.7 Data analysis

2.7.1 Power analysis

A power analysis was conducted using G*Power (University of Dusseldorf, Germany). The following values were used. The total sample size for the experiment was 56 or 64, both with 4 groups. The number of measurements that will be analyzed is 5. I assumed that the correlation among repeated measures would be 0.6 because the drugs will be administered consistently over 28 days; therefore, behavior may be changing but it should be relatively gradually. The conventional alpha of 0.05 was used for this power analysis. The effect size and non-sphericity correction epsilon was chosen based on previously collected data from Tremblay (2017). Thus, a medium effect size (partial η^2 of 0.06) was used. On G*Power I selected ANOVA: Repeated measures, between factors and Post hoc: Compute achieved power – given alpha, sample size, and effect size. The resulting achieved power of 0.42 and 0.48 depending for a sample size of 56 and 64 respectively. When the power analysis was conducted for within factors and with-between interaction, with a sample size of either 56 or 64, the achieved power was larger than 0.95. An a priori power analysis was conducted to inform sample size selection, G*Power indicated that a total sample size of 124 was needed to achieve power of 0.8 to be powered to look between factors and a sample size of 32 rats was needed to be powered for within factors and between-within interactions. A sample size of 56 and 64 was used to attempt to ensure a sufficient number of wager-sensitive and wager-insensitive animals would be in each group, and so the sample size was manageable given the time constraints and availability equipment and other resources. For example, testing a sample size of 124 would require the available operant chambers to be occupied by this experiment for 5 hours. The sample sizes that were chosen are considered large for behavioural research with animals.

2.7.2 Baseline data analysis

All analyses were conducted with SPSS (version 24, SPSS/IBM corp, Chicago, USA). An arcsine transformation was performed prior to statistical analysis of variables expressed as percentages in order to limit the effect of an artificially imposed ceiling. All data was subjected to a within-subjects repeated measures ANOVA. Violations of the sphericity assumption indicated by Mauchly's test were corrected using the Greenhouse-Geisser correction. The data was analyzed in weekly groups of 5 sessions with session as a within-subjects factor (5 levels; session 1-5). The most critical dependent variable, percent choice of the uncertain lever, was analyzed as a within-subjects factor across wager size (3 levels; wager size of 1-3 sugar pellets). Rats were considered to be behaviourally stable when there was a statistically nonsignificant effect ($p > 0.05$) of session and session x wager size on each variable being measured.

2.7.3 Determination of wager sensitivity

As previously outlined by both Cocker et al. (2012) and Tremblay (2017), rats were classified as either wager-sensitive or wager-insensitive based on their choice of the uncertain lever across all three wager sizes on the rBT over five stable baseline sessions. The choice of the uncertain lever at each wager size was averaged over 5 sessions and plotted in order to generate the slope using the linear equation: $y = mx + b$ in which m indicates the slope of the line. The slope is considered the degree to which the choice of the uncertain option changed as a function of increasing wager size. Rats are classified as wager-sensitive if this value falls more than one standard deviation below a theoretical zero. This classification was used as a between subjects factor (wager-sensitivity: 2 levels) in the following data analyses.

2.7.4 Latin square data analysis

For the first Latin square conducted with the different doses of BD442618, the data were analysed via within-subjects repeated measure ANOVA, with dose as a within-subjects factor (4 levels: vehicle, 0.3, 1, 3 mg/kg). All dependent variables: percent choice of the uncertain lever, uncertain lever and safe lever choice latency, reward collection latency after choosing the safe and uncertain lever, hole omissions, and choice omissions, were analyzed as a within-subjects factor across wager sizes (3 levels: wager size 1-3 sugar pellets). Wager-sensitivity was included as a between-subjects factor (2 levels). For the two Latin Squares with both BD442618 (2 levels; BD442618 vs. vehicle) and *d*-amphetamine (2 levels; *d*-amphetamine vs. saline), both drugs were included as within-subjects factors in a 2x2 design.

2.7.5 Chronic ropinirole and BD442618 or S111224 data analysis

All data were subjected to a within-subjects repeated measure ANOVA. The data was analyzed in weekly groups of 5 sessions with session as a within-subjects factor (5 levels; session 1-5). The last 5 sessions of data for each dose was used in the analyses. For the most critical dependent variable, namely percent choice of the uncertaint lever, the wager-sensitive and wager-insensitive groups were analyzed independently based on the findings from the Latin square challenges indicating that wager-sensitive and wager-insensitive rats react differently to amphetamine plus BD442618, in addition to the significant difference in choice preference demonstrated at baseline. All analyses included wager size (3 levels; wager size of 1-3 sugar pellets) as a within subjects factor. Ropinirole treatment (2 levels; ropinirole vs. saline) and BD442618 treatment (2 levels; BD442618 vs. vehicle) were included as between subjects factors. Our power analysis indicated I was underpowered for between subjects analyses. I therefore also compared data from each week of drug treatment to that obtained either the

preceding week, or at baseline (pre drug-treatment) as appropriate. For these analyses, timepoint (2 levels; week 1, week 2) was included as a within subjects factor. For all other dependent variables, wager-sensitivity was also included as a between-subjects factor (2 levels; wager-sensitive and wager-insensitive). The same structure was used for analyzing data from the chronic experiment with ropinirole and S1112244 instead of BD442618.

Chapter 3: Results

3.1 BD442618 Latin Square

Choice behaviour: The wager-insensitive rats (n = 8) chose between both levers fairly equally regardless of the wager size at play (wager size: $F(2,14) = 0.013$, $p = 0.988$, NS). However, the wager-sensitive rats (n = 7) decreased their preference for the uncertain lever as the wager size increased (wager size: $F(2,12) = 21.999$, $p < 0.001$). BD442618 did not affect choice behaviour at any dose, regardless of baseline preference for the uncertain option (Dose: $F(3,39) = 0.723$, $p = 0.544$, NS; dose x wager-sensitivity: $F(3,39) = 2.747$, $p = 0.056$, NS; dose x wager size: $F(6,26) = 1.296$, $p = 0.269$, NS). All choice data is provided in table 1.

Non-choice variables: BD442618 also did not affect any other task parameters, regardless of baseline preference for uncertain option or wager-sensitivity (lever choice latency for the safe and uncertain lever, collection latency after the safe and uncertain lever, choice omissions, and hole omissions; dose, dose x wager-sensitivity, dose x wager size: all Fs < 2.035 all ps > 0.070, NS). See table 2 for data from these non-choice measurements.

Trials: The highest dose of BD442618 reduced the number of trials performed, irrespective of wager sensitivity (dose: $F(1.737,24.324) = 7.019$, $p = 0.005$; (3 mg/kg of BD442618 vs. vehicle: $t(18.394) = 2.444$, $p = 0.025$), whereas the lower doses had no effect on this behavioural measure (dose of BD442618 vs saline: 1 mg/kg : $t(21.529) = 1.605$, $p = 0.123$, NS; 0.3 mg/kg: $t(30) = -0.143$, $p = 0.888$, NS). See table 2 for trial data.

3.2 BD442618 Latin square – *d*-amphetamine vs. 0.3 mg/kg of BD442618

Choice behaviour: As reported previously (Cocker et al. 2012), the effect of *d*-amphetamine depended on wager sensitivity (Figure 2A. *d*-amphetamine x wager-sensitivity: $F(1,14) = 3.926$, $p = 0.068$; *d*-amphetamine: $F(1,14) = 0.847$, $p = 0.373$, NS). The output from

the omnibus ANOVA suggested that *d*-amphetamine increased preference for the uncertain lever across all wager sizes in wager-sensitive rats, regardless of the administration of 0.3 mg/kg BD442618 (Figure 2 B; *d*-amphetamine: $F(1,6) = 6.754$, $p = 0.041$; BD442618 x *d*-amphetamine: $F(1, 6) = 2.994$, $p = 0.134$, NS; *d*-amphetamine x wager size: $F(2,12) = 0.018$, $p = 0.982$, NS). In order to confirm this finding via a series of planned comparisons, the effects of vehicle-saline injections to vehicle-amphetamine in wager-sensitive rats was compared, which resulted in a significant difference (Figure 2B. wager-sensitive – vehicle-*d*-amphetamine vs. vehicle-saline: $F(1,6) = 7.822$, $p = 0.031$; *d*-amphetamine x wager size: $F(2,12) = 0.554$, $p = 0.589$, NS). If the effect of *d*-amphetamine was as robust when combined with BD442618, a similar significant difference between vehicle-saline and BD442618-*d*-amphetamine in wager-sensitive animals would be expected. However, these two datasets did not differ significantly from each other (Figure 2B. wager-sensitive – BD442618-*d*-amphetamine vs. vehicle-saline: $F(1,6) = 1.037$, $p = 0.348$, NS; *d*-amphetamine x wager size: $F(2,12) = 0.401$, $p = 0.678$, NS). This implies that BD442618 at least partially attenuated the effects *d*-amphetamine on choice. When the effects of vehicle-*d*-amphetamine were compared to BD442618-*d*-amphetamine, there was also no statistical difference (Figure 2B. wager-sensitive –BD442618- *d*-amphetamine vs. vehicle-*d*-amphetamine: $F(1,6) = 3.498$, $p = 0.111$, NS; BD442618 x wager size: $F(2,24) = .401$, $p = 0.678$, NS), again suggesting that the blockade of amphetamine's effects by BD442618 in wager-sensitive rats was not complete.

d-amphetamine did not alter choice behavior in wager-insensitive rats, regardless of wager size (Figure 2C. wager-insensitive – *d*-amphetamine: $F(1,8) = 0.337$, $p = 0.577$, NS; *d*-amphetamine x wager size: $F(2,16) = 0.990$, $p = 0.393$, NS).

Non-choice variables: All data are provided in Table 3. *d*-amphetamine increased the latency to choose both the uncertain and certain lever, regardless of wager-sensitivity, presence of BD442618, or wager size at play (uncertain lever choice latency: *d*-amphetamine: $F(1,10) = 14.501$, $p = 0.003$; *d*-amphetamine x wager-sensitivity: $F(1,10) = 3.890$, $p = 0.077$, NS; *d*-amphetamine x BD442618: $F(1,10) = 0.057$, $p = 0.816$, NS; *d*-amphetamine x wager size: $F(2,20) = 1.022$, $p = 0.378$, NS; safe lever choice latency- *d*-amphetamine: $F(1,9) = 5.556$, $p = 0.043$; *d*-amphetamine x wager-sensitivity: $F(1,9)=2.914$, $p = 0.122$, NS; BD442618 x *d*-amphetamine: $F(1,9) = 0.890$, $p = 0.652$, NS; BD442618 x *d*-amphetamine x wager-sensitivity = $F(1,9)=0.217$, $p = 0.652$, NS; *d*-amphetamine x wager size: $F(2,18) = 0.374$, $p = 0.693$, NS). In contrast, *d*-amphetamine reduced the latency to collect the larger, uncertain rewards across all wager sizes, regardless of wager-sensitivity (*d*-amphetamine: $F(1,9) = 5.436$, $p = 0.045$; amphetamine x wager-sensitivity: $F(1,9) = 1.180$, $p = 0.306$, NS; *d*-amphetamine x wager size: $F(2,20) = 1.227$, $p = 0.314$, NS). A similar effect was observed following administration of BD442618 (BD442618: $F(1.10) = 7.668$, $p = 0.020$; BD442618 x wager-sensitivity: $F(1,10) = 0.502$, $p = 0.495$, NS), and co-administration of the two drugs resulted in further speeding of reward collection across all rats and wager sizes (BD442618 x *d*-amphetamine: $F(1,9) = 5.566$, $p = 0.043$; *d*-amphetamine x wager size: $F(2,22) = 0.694$, $p = 0.510$, NS; BD442618 x *d*-amphetamine x sensitivity: $F(1,9) = 0.350$, $p = 0.565$, NS). The time taken to collect reward as a result of pressing the safe lever was unaffected by drug condition (all Fs < 3.051, all ps > 0.100, NS). *d*-amphetamine increased choice omissions regardless of wager-sensitivity or wager size at play (*d*-amphetamine: $F(1,14) = 7.342$, $p = 0.017$; amphetamine x wager-sensitivity: $F(1,14) = 1.964$, $p = 0.183$, NS; *d*-amphetamine x wager size: $F(2,28) = 2.182$, $p = 0.132$, NS). This effect was attenuated at higher wager sizes by co-administration of BD442618 (BD442618 x

amphetamine x wager size: $F(2,28) = 3.954$, $p = 0.031$, NS). There were no changes in hole omissions (All Fs < 1.752 and all ps > 0.205, NS).

3.3 BD442618 Latin square – *d*-amphetamine vs. 3 mg/kg of BD442618

Choice behaviour: Similar to the first Latin square challenge, the omnibus ANOVA suggested that *d*-amphetamine increased responding on the uncertain lever in wager-sensitive rats as the wager size at play increased, regardless of administration of 3 mg/kg of BD442618 (Figure 2D. *d*-amphetamine x wager-sensitivity: $F(1,15) = 4.951$, $p = 0.042$,; *d*-amphetamine x wager-sensitivity x wager size: $F(2, 30) = 5.865$, $p = 0.007$; *d*-amphetamine x BD442618: $F(1,15) = 4.086$, $p = 0.061$, NS; *d*-amphetamine x BD442618 x wager-sensitivity: $F(1,15) = 0.162$, $p = 0.693$, NS). As before, a series of planned comparisons were conducted to try and confirm these observations. When comparing administration of vehicle-*d*-amphetamine to vehicle-saline, there was a significant increase in responding on the uncertain lever in wager-sensitive rats (Figure 2E. *d*-amphetamine x wager size: $F(2,22) = 5.361$, $p = 0.013$). Again, however, comparison of vehicle-saline and BD442618-*d*-amphetamine did not result in a significant difference, implying BD442618 may have attenuated the effect of *d*-amphetamine (Figure 2E. injection x wager-size: $F(2, 22) = 0.156$, $p = 0.857$, NS). Administration of 3 mg/kg BD442618 did not alter choice behaviour when compared to animals receiving control injections (Figure 2D. BD442618-saline vs. vehicle-saline: $F(1,11) = 2.318$, $p = 0.159$, NS). When the effects of vehicle-*d*-amphetamine were compared to BD442618-*d*-amphetamine, there was also no statistical difference (wager-sensitive –BD442618- *d*-amphetamine vs. vehicle-amphetamine: $F(1,11) = 3.475$, $p = 0.089$, NS; BD442618 x wager size: $F(2,22) = 1.211$, $p = 0.317$, NS), again suggesting that the blockade of *d*-amphetamine's effects by BD442618 in wager-sensitive rats was not complete.

There was no effect of *d*-amphetamine on choice of the uncertain lever in wager-insensitive rats, irrespective of administration of BD442618 or wager size (Figure 2F. *d*-amphetamine: $F(1,23) = 0.269$, $p = 0.609$, NS; *d*-amphetamine x BD442618: $F(1,10) = 3.468$, $p = 0.092$, NS). This was also apparent when comparing the *d*-amphetamine only group to the control group (Figure 2F. *d*-amphetamine-vehicle vs saline-vehicle: $F(1,23) = 2.412$, $p = 0.134$, NS; *d*-amphetamine x wager size: $F(2,46) = 0.756$, $p = 0.475$, NS).

Non-choice variables: As per the previous Latin square challenge, *d*-amphetamine increased latency to choose both the uncertain and safe lever across all wager sizes, regardless of wager-sensitivity or the presence of BD442618 (lever choice latency- uncertain: *d*-amphetamine: $F(1,10) = 34.842$, $p < 0.001$; *d*-amphetamine x wager size: $F(2,20) = 0.703$, $p = 0.5007$, NS; *d*-amphetamine x wager-sensitivity: $F(1,10) = 1.360$, $p = 0.271$, NS; *d*-amphetamine x BD442618: $F(1,10) = 4.601$, $p = 0.058$, NS; safe: *d*-amphetamine: $F(1,8) = 14.751$, $p = 0.005$; *d*-amphetamine x wager size: $F(2,16) = 0.692$, $p = 0.515$, NS *d*-amphetamine x wager-sensitivity: $F(1,8) = 0.030$, $p = 0.867$, NS; *d*-amphetamine x BD442618: $F(1,8) = 1.565$, $p = 0.246$, NS). *d*-amphetamine also increased latency to collect pellets after choosing the uncertain lever across all wager sizes, regardless of wager-sensitivity or presence of BD442618 (*d*-amphetamine: $F(1,8) = 9.396$, $p = 0.015$, *d*-amphetamine x wager-sensitivity = $F(1,8) = 1.681$, $p = 0.231$, NS; BD442618 x *d*-amphetamine: $F(1,8) = 0.807$, $p = 0.395$, NS; *d*-amphetamine x wager size: $F(2,16) = 0.503$, $p = 0.614$, NS). Neither *d*-amphetamine or BD442618 had an effect on the time taken to collect reward after choosing the safe lever in either wager-sensitive or insensitive rats (*d*-amphetamine: $F(1,8) = 0.306$, $p = 0.565$, NS; BD442618: $F(1,8) = 0.753$, $p = 0.411$, NS; BD442618 x *d*-amphetamine: $F(1,8) = 0.426$, $p = 0.532$, NS; *d*-amphetamine x wager-sensitivity: $F(1,8) = 0.481$, $p = 0.508$, NS). *d*-amphetamine increased choice omissions regardless of wager-

sensitivity (*d*-amphetamine: $F(1,22) = 28.365$, $p < 0.001$, *d*-amphetamine x wager-sensitivity: $F(1,22) = 0.556$, $p = 0.464$, NS). BD442618 did not reduce this effect (BD442618 x *d*-amphetamine: $F(1,22) = 0.104$, $p = 0.705$, NS). Both BD442618 and *d*-amphetamine increased hole omissions, regardless of wager-sensitivity (*d*-amphetamine: $F(1,22) = 19.938$, $p < 0.001$; *d*-amphetamine x wager-sensitivity = $F(1,22) = 0.524$, $p = 0.477$, NS; BD442618: $F(1,22) = 6.377$, $p = 0.019$; BD442618 x wager-sensitivity: $F(1,22) = 0.081$, $p = 0.778$). Overall, hole omissions increased depending on the wager size at play (wager size = $F(2,44) = 4.660$, $p = 0.015$). This effect was also independent of wager-sensitivity (wager size x wager-sensitivity = $F(2,44) = 0.490$, $p = 0.616$, NS). However, the magnitude of the change was minimal. See table 4 for data collected on non-choice variables from this Latin square.

Table 1. The effect of the low to high dose of BD442618 on choice behaviour

	Wager size	Vehicle	0.3 mg/kg	1 mg/kg	3 mg/kg
All rats	1	55.83 ± 5.41	55.59 ± 5.46	58.98 ± 5.72	53.13 ± 5.08
	2	45.38 ± 7.07	48.03 ± 6.30	46.89 ± 6.54	47.12 ± 6.31
	3	39.73 ± 6.93	35.19 ± 7.08	37.62 ± 6.45	37.99 ± 7.34
Wager-sensitive	1	59.48 ± 6.84	52.75 ± 8.86	58.69 ± 6.90	57.03 ± 5.68
	2	33.79 ± 9.88	38.95 ± 9.45	39.86 ± 9.24	40.64 ± 9.69
	3	20.35 ± 6.81	13.63 ± 5.97	22.52 ± 6.06	22.69 ± 9.04
Wager-insensitive	1	52.99 ± 8.25	57.80 ± 7.23	59.20 ± 9.01	49.71 ± 8.32
	2	54.39 ± 9.31	55.08 ± 8.13	52.36 ± 9.18	52.79 ± 8.30
	3	54.81 ± 8.24	51.90 ± 8.15	49.36 ± 8.83	51.38 ± 9.25

Table 2. The effect of the low to high dose of BD442618 on other measurements

	Trials	Wager size	Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Vehicle All rats	114.31 ± 2.67	1	1.78 ± 0.09	1.74 ± 0.09	0.45 ± 0.04	0.41 ± 0.05	2.73 ± 0.97	0.00 ± 0.00
		2	1.76 ± 0.08	1.77 ± 0.08	0.37 ± 0.05	0.39 ± 0.03	1.87 ± 0.75	0.00 ± 0.00
		3	1.70 ± 0.07	1.73 ± 0.07	0.34 ± 0.06	0.39 ± 0.03	3.27 ± 0.75	0.00 ± 0.00
0.3 mg/kg BD442618 All rats	114.94 ± 3.47	1	1.78 ± 0.10	1.85 ± 0.12	0.49 ± 0.04	0.42 ± 0.04	2.13 ± 0.80	0.06 ± 0.06
		2	1.74 ± 0.07	1.84 ± 0.10	0.39 ± 0.04	0.39 ± 0.03	1.56 ± 0.52	0.00 ± 0.00
		3	1.72 ± 0.08	1.71 ± 0.07	0.33 ± 0.05	0.39 ± 0.04	3.38 ± 0.60	0.00 ± 0.00
1 mg/kg BD442618 All rats	104.38 ± 5.59	1	1.91 ± 0.10	1.89 ± 0.10	0.44 ± 0.04	0.40 ± 0.05	3.50 ± 0.96	0.00 ± 0.00
		2	1.86 ± 0.08	1.87 ± 0.07	0.39 ± 0.04	0.39 ± 0.03	2.19 ± 0.66	0.00 ± 0.00
		3	1.84 ± 0.09	1.72 ± 0.05	0.39 ± 0.04	0.38 ± 0.03	3.94 ± 0.58	0.06 ± 0.06
3 mg/kg BD442618 All rats	93.94 ± 7.90	1	1.91 ± 0.13	2.01 ± 0.12	0.44 ± 0.05	0.40 ± 0.05	3.00 ± 0.92	0.00 ± 0.00
		2	1.81 ± 0.10	1.88 ± 0.07	0.39 ± 0.04	0.40 ± 0.03	2.00 ± 0.42	0.00 ± 0.00
		3	1.84 ± 0.08	1.66 ± 0.05	0.33 ± 0.06	0.37 ± 0.03	3.38 ± 0.60	0.00 ± 0.00

	Trials	Wager size	Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Vehicle Wager-sensitive	114.86 ± 5.14	1	1.61 ± 0.14	1.78 ± 0.15	0.45 ± 0.06	0.44 ± 0.02	1.83 ± 0.79	0.00 ± 0.00
		2	1.70 ± 0.12	1.81 ± 0.13	0.29 ± 0.08	0.44 ± 0.02	2.67 ± 1.71	0.00 ± 0.00
		3	1.65 ± 0.13	1.78 ± 0.10	0.22 ± 0.08	0.45 ± 0.03	2.67 ± 0.67	0.00 ± 0.00
0.3 mg/kg BD442618 Wager-sensitive	120.00 ± 0.00	1	1.58 ± 0.12	2.05 ± 0.22	0.52 ± 0.06	0.45 ± 0.03	1.29 ± 0.42	0.00 ± 0.00
		2	1.64 ± 0.09	1.99 ± 0.17	0.33 ± 0.06	0.42 ± 0.02	1.86 ± 0.99	0.00 ± 0.00
		3	1.69 ± 0.13	1.76 ± 0.12	0.20 ± 0.07	0.45 ± 0.04	3.29 ± 0.92	0.00 ± 0.00
1 mg/kg BD442618 Wager-sensitive	113.71 ± 5.08	1	1.77 ± 0.14	1.97 ± 0.17	0.43 ± 0.04	0.47 ± 0.04	3.29 ± 1.29	0.00 ± 0.00
		2	1.78 ± 0.13	1.95 ± 0.12	0.32 ± 0.06	0.43 ± 0.02	2.00 ± 0.85	0.00 ± 0.00
		3	1.74 ± 0.15	1.73 ± 0.08	0.33 ± 0.06	0.43 ± 0.02	3.86 ± 0.55	0.00 ± 0.00
3 mg/kg BD442618 Wager-sensitive	104.43 ± 8.94	1	1.59 ± 0.10	2.00 ± 0.22	0.47 ± 0.06	0.44 ± 0.02	3.00 ± 1.15	0.00 ± 0.00
		2	1.55 ± 0.06	1.82 ± 0.10	0.33 ± 0.06	0.43 ± 0.02	1.14 ± 0.40	0.00 ± 0.00
		3	1.70 ± 0.11	1.65 ± 0.09	0.16 ± 0.08	0.41 ± 0.01	0.93 ± 0.93	0.00 ± 0.00

	Trials	Wager size	Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Vehicle Wager-insensitive	113.89 ± 2.89	1	1.91 ± 0.10	1.71 ± 0.10	0.45 ± 0.06	0.40 ± 0.08	3.33 ± 1.54	0.00 ± 0.00
		2	1.80 ± 0.12	1.73 ± 0.09	0.43 ± 0.06	0.35 ± 0.08	1.33 ± 0.58	0.00 ± 0.00
		3	1.72 ± 0.08	1.70 ± 0.10	0.43 ± 0.06	0.34 ± 0.05	3.67 ± 1.18	0.00 ± 0.00
0.3 mg/kg BD442618 Wager-insensitive	111.00 ± 5.98	1	1.94 ± 0.13	1.68 ± 0.11	0.47 ± 0.06	0.40 ± 0.07	2.78 ± 1.38	0.11 ± 0.11
		2	1.80 ± 0.09	1.71 ± 0.12	0.44 ± 0.06	0.36 ± 0.05	1.33 ± 0.55	0.00 ± 0.00
		3	1.73 ± 0.11	1.67 ± 0.09	0.43 ± 0.06	0.35 ± 0.05	3.44 ± 0.84	0.00 ± 0.00
1 mg/kg BD442618 Wager-insensitive	97.11 ± 8.60	1	2.02 ± 0.14	1.80 ± 0.12	0.45 ± 0.07	0.37 ± 0.09	3.67 ± 1.44	0.00 ± 0.00
		2	1.91 ± 0.10	1.79 ± 0.06	0.44 ± 0.06	0.38 ± 0.04	2.33 ± 1.01	0.00 ± 0.00
		3	1.90 ± 0.11	1.70 ± 0.07	0.44 ± 0.06	0.34 ± 0.05	4.00 ± 0.97	0.11 ± 0.11
3 mg/kg of BD442618 Wager-insensitive	85.78 ± 11.93	1	2.19 ± 0.19	2.02 ± 0.13	0.42 ± 0.08	0.37 ± 0.09	3.00 ± 1.42	0.00 ± 0.00
		2	1.98 ± 0.13	1.93 ± 0.11	0.44 ± 0.06	0.38 ± 0.04	2.67 ± 0.60	0.00 ± 0.00
		3	1.90 ± 0.10	1.67 ± 0.06	0.45 ± 0.07	0.34 ± 0.05	3.67 ± 0.83	0.00 ± 0.00

Figure 2. The effect of BD442618 on amphetamine-induced choice behaviour

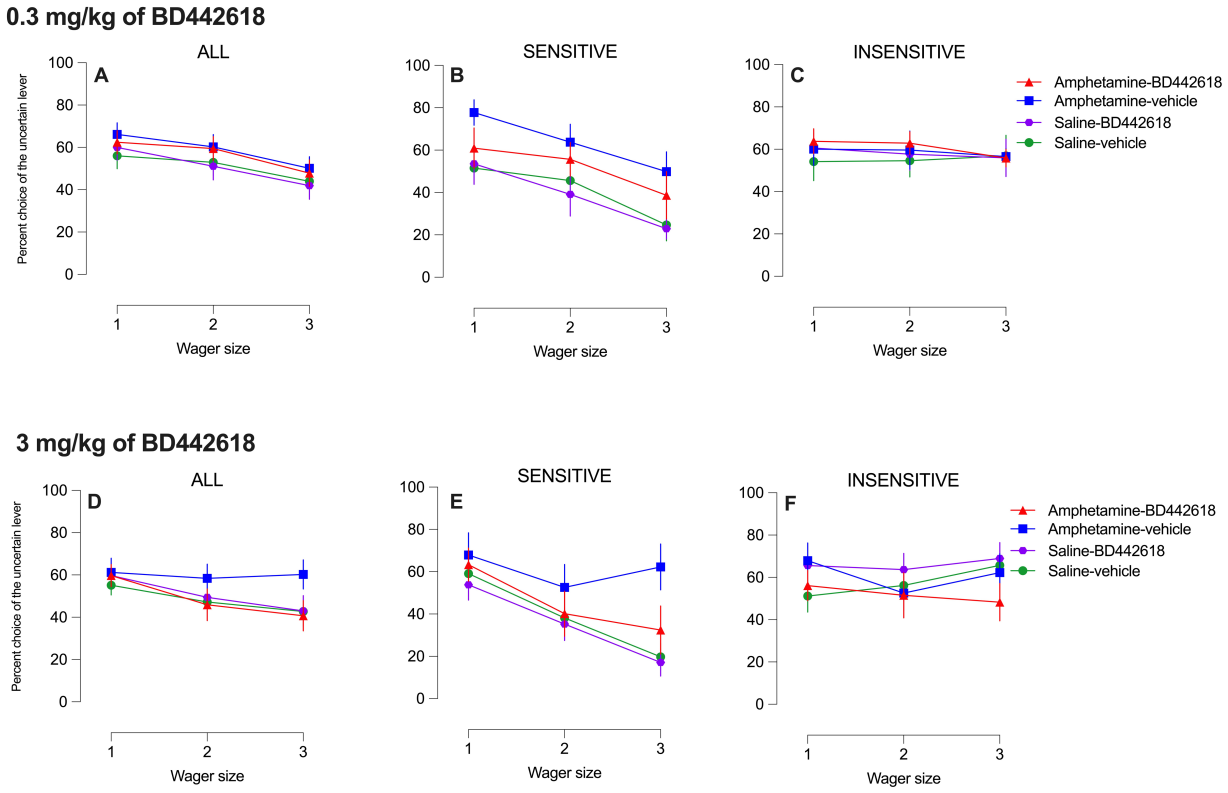

Figure 2. Amphetamine increased choice of the uncertain option as the wager size increased in wager-sensitive rats (B, D) but not wager-insensitive rats (C, F). This effect of amphetamine on choice behaviour was attenuated by the administration of both 0.3 mg/kg and 3 mg/kg of BD442618. Data shown when evaluating the effect of 0.3 mg/kg of BD442618 (A-C) and 3 mg/kg of BD442618 (D-F) across all rats (A, D), wager-sensitive rats (B, E), and wager-insensitive rats (D, F).

Table 3. Other measurements for 0.3 mg/kg of BD442618 and amphetamine

	Wager size	Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Saline-vehicle All rats	1	1.67 ± 0.10	1.68 ± 0.08	0.58 ± 0.13	0.56 ± 0.11	3.25 ± 0.78	0.00 ± 0.00
	2	1.62 ± 0.06	1.71 ± 0.09	0.70 ± 0.29	0.50 ± 0.06	1.06 ± 0.25	0.00 ± 0.00
	3	1.65 ± 0.10	1.58 ± 0.06	0.75 ± 0.36	0.43 ± 0.04	3.56 ± 0.96	0.00 ± 0.00
Saline-BD442618 All rats	1	1.66 ± 0.08	1.76 ± 0.09	0.44 ± 0.03	0.47 ± 0.05	2.19 ± 0.74	0.06 ± 0.06
	2	1.69 ± 0.09	1.78 ± 0.07	0.44 ± 0.04	0.48 ± 0.07	1.38 ± 0.57	0.00 ± 0.00
	3	1.61 ± 0.07	1.67 ± 0.06	0.42 ± 0.03	0.42 ± 0.04	2.75 ± 0.56	0.00 ± 0.00
Amphetamine-vehicle All rats	1	2.56 ± 0.36	2.81 ± 0.51	0.51 ± 0.01	0.41 ± 0.04	5.13 ± 2.15	0.13 ± 0.09
	2	2.55 ± 0.42	2.73 ± 0.50	0.40 ± 0.03	0.41 ± 0.03	5.06 ± 2.10	0.63 ± 0.33
	3	2.34 ± 0.32	2.48 ± 0.29	0.45 ± 0.04	0.38 ± 0.02	4.19 ± 1.51	0.88 ± 0.44
Amphetamine-BD442618 All rats	1	2.31 ± 0.26	2.41 ± 0.39	0.43 ± 0.04	0.38 ± 0.01	4.94 ± 2.14	0.25 ± 0.11
	2	2.34 ± 0.27	2.28 ± 0.31	0.41 ± 0.04	0.38 ± 0.02	4.69 ± 2.13	0.00 ± 0.00
	3	2.23 ± 0.26	2.33 ± 0.26	0.40 ± 0.04	0.37 ± 0.01	4.13 ± 1.66	0.13 ± 0.09

	Wager size	Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Saline-vehicle Wager-sensitive	1	1.58 ± 0.14	1.76 ± 0.13	0.72 ± 0.28	0.44 ± 0.04	4.00 ± 1.11	0.00 ± 0.00
	2	1.55 ± 0.10	1.70 ± 0.11	1.05 ± 0.65	0.41± 0.02	1.14 ± 0.46	0.00 ± 0.00
	3	1.63 ± 0.18	1.58 ± 0.08	1.24 ± 0.91	0.39 ± 0.01	4.29 ± 1.66	0.00 ± 0.00
Saline-BD442618 Wager-sensitive	1	1.55 ± 0.10	1.88 ± 0.12	0.43 ± 0.03	0.44 ± 0.02	2.29 ± 1.23	0.14 ± 0.14
	2	1.61 ± 0.13	1.88 ± 0.10	0.41 ± 0.04	0.42 ± 0.02	1.29 ± 0.97	0.00 ± 0.00
	3	1.55 ± 0.11	1.70 ± 0.08	0.38 ± 0.03	0.50 ± 0.09	3.29 ± 0.87	0.00 ± 0.00
Amphetamine-vehicle Wager-sensitive	1	2.40 ± 0.55	3.34 ± 1.41	0.61 ± 0.22	0.40 ± 0.01	2.57 ± 1.15	0.14 ± 0.14
	2	2.56 ± 0.37	3.30 ± 1.01	0.39 ± 0.03	0.43 ± 0.04	1.57 ± 0.84	1.29 ± 0.68
	3	2.81 ± 0.61	2.62 ± 0.53	0.40 ± 0.03	0.38 ± 0.03	1.57 ± 0.57	1.57 ± 0.92
Amphetamine-BD442618 Wager-sensitive	1	2.76 ± 0.56	2.39 ± 0.29	0.41 ± 0.05	0.39 ± 0.01	0.71 ± 0.29	0.29 ± 0.18
	2	2.53 ± 0.45	2.47 ± 0.49	0.39 ± 0.03	0.38 ± 0.01	0.86 ± 0.70	0.00 ± 0.00
	3	2.57 ± 0.60	2.38 ± 0.42	0.33 ± 0.02	0.38 ± 0.01	1.71 ± 1.08	0.00 ± 0.00

Wager size		Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Saline-vehicle Wager-insensitive	1	1.75 ± 0.15	1.58 ± 0.10	0.45 ± 0.06	0.65 ± 0.19	2.67 ± 1.09	0.00 ± 0.00
	2	1.67 ± 0.07	1.72 ± 0.15	0.43 ± 0.05	0.56 ± 0.09	1.00 ± 0.53	0.00 ± 0.00
	3	1.67 ± 0.12	1.59 ± 0.09	0.42 ± 0.06	0.46 ± 0.07	3.00 ± 1.17	0.00 ± 0.00
Saline-BD442618 Wager-insensitive	1	1.75 ± 0.11	1.64 ± 0.12	0.45 ± 0.05	0.52 ± 0.12	2.11 ± 0.96	0.00 ± 0.00
	2	1.74 ± 0.13	1.69 ± 0.11	0.45 ± 0.05	0.44 ± 0.07	1.44 ± 0.73	0.00 ± 0.00
	3	1.65 ± 0.10	1.65 ± 0.09	0.44 ± 0.05	0.34 ± 0.05	2.33 ± 0.75	0.00 ± 0.00
Amphetamine-vehicle Wager-insensitive	1	2.69 ± 0.50	2.52 ± 0.28	0.42 ± 0.04	0.43 ± 0.07	7.44 ± 3.64	0.11 ± 0.11
	2	2.54 ± 0.75	2.35 ± 0.50	0.40 ± 0.05	0.40 ± 0.04	7.78 ± 3.50	0.11 ± 0.11
	3	1.93 ± 0.21	2.38 ± 0.35	0.48 ± 0.07	0.38 ± 0.03	6.22 ± 2.49	0.33 ± 0.24
Amphetamine-BD442618 Wager-insensitive	1	1.96 ± 0.12	2.43 ± 0.72	0.45 ± 0.07	0.37 ± 0.02	8.22 ± 3.48	0.22 ± 0.15
	2	2.17 ± 0.34	2.14 ± 0.41	0.44 ± 0.06	0.38 ± 0.03	7.67 ± 3.50	0.00 ± 0.00
	3	2.03 ± 0.21	2.30 ± 0.34	0.44 ± 0.06	0.35 ± 0.02	6.00 ± 2.73	0.22 ± 0.15

Table 4. Other measurements for 3 mg/kg of BD442618 and amphetamine

	Wager size	Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Saline-vehicle All rats	1	1.62 ± 0.11	1.81 ± 0.10	0.37 ± 0.02	0.38 ± 0.01	3.00 ± 0.49	0.04 ± 0.04
	2	1.62 ± 0.09	1.77 ± 0.12	0.36 ± 0.02	0.37 ± 0.02	2.00 ± 0.43	0.00 ± 0.00
	3	1.66 ± 0.09	1.66 ± 0.09	0.36 ± 0.02	0.36 ± 0.01	3.46 ± 0.56	0.00 ± 0.00
Saline-BD442618 All rats	1	1.60 ± 0.07	1.97 ± 0.17	0.40 ± 0.02	0.40 ± 0.02	4.88 ± 0.84	0.00 ± 0.00
	2	1.66 ± 0.08	1.85 ± 0.08	0.37 ± 0.02	0.38 ± 0.01	2.75 ± 0.53	0.00 ± 0.00
	3	1.62 ± 0.08	1.68 ± 0.07	0.37 ± 0.02	0.35 ± 0.01	4.50 ± 0.85	0.00 ± 0.00
Amphetamine-vehicle All rats	1	2.98 ± 0.31	3.38 ± 0.46	0.39 ± 0.02	0.63 ± 0.16	8.21 ± 1.47	0.88 ± 0.28
	2	3.02 ± 0.31	2.82 ± 0.23	0.42 ± 0.03	0.52 ± 0.10	7.79 ± 1.37	0.42 ± 0.22
	3	2.80 ± 0.27	3.17 ± 0.41	0.39 ± 0.02	0.43 ± 0.07	8.50 ± 1.42	0.71 ± 0.29
Amphetamine-BD442618 All rats	1	2.80 ± 0.23	3.52 ± 0.38	0.39 ± 0.02	0.73 ± 0.22	10.25 ± 1.61	0.92 ± 0.28
	2	2.58 ± 0.20	3.52 ± 0.49	0.37 ± 0.02	1.38 ± 0.66	10.00 ± 1.90	0.54 ± 0.20
	3	2.91 ± 0.31	3.15 ± 0.29	0.36 ± 0.02	1.21 ± 0.85	10.54± 1.88	0.75 ± 0.27

	Wager size	Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Saline-vehicle Wager-sensitive	1	1.44 ± 0.07	1.74 ± 0.16	0.34 ± 0.01	0.38 ± 0.01	2.33 ± 0.36	0.00 ± 0.00
	2	1.52 ± 0.09	1.65 ± 0.12	0.34 ± 0.01	0.37 ± 0.02	2.17 ± 0.63	0.00 ± 0.00
	3	1.57 ± 0.10	1.55 ± 0.09	0.33 ± 0.01	0.37 ± 0.01	3.50 ± 0.78	0.00 ± 0.00
Saline-BD442618 Wager-sensitive	1	1.52 ± 0.10	2.13 ± 0.29	0.39 ± 0.03	0.39 ± 0.02	4.08 ± 1.01	0.00 ± 0.00
	2	1.54 ± 0.11	1.77 ± 0.11	0.33 ± 0.01	0.38 ± 0.02	3.25± 0.91	0.00 ± 0.00
	3	1.51 ± 0.09	1.68 ± 0.10	0.34 ± 0.02	0.37 ± 0.01	3.42 ± 0.60	0.00 ± 0.00
Amphetamine-vehicle Wager-sensitive	1	3.11 ± 0.45	3.00 ± 0.73	0.41 ± 0.04	0.37 ± 0.03	9.25 ± 1.82	1.00 ± 0.52
	2	3.14 ± 0.43	2.91 ± 0.34	0.40 ± 0.03	0.40 ± 0.02	7.83 ± 1.72	0.50 ± 0.42
	3	3.29 ± 0.42	3.11 ± 0.89	0.38 ± 0.03	0.35 ± 0.02	9.42 ± 1.79	0.75 ± 0.35
Amphetamine-BD442618 Wager-sensitive	1	2.92 ± 0.37	3.71 ± 0.59	0.37 ± 0.02	0.35 ± 0.02	10.75 ± 2.14	0.75 ± 0.25
	2	2.45 ± 0.29	3.04 ± 0.53	0.36 ± 0.02	0.33 ± 0.02	10.83 ± 3.03	0.25 ± 0.13
	3	2.54 ± 0.26	2.85 ± 0.27	0.32 ± 0.02	0.36 ± 0.03	11.00 ± 2.95	0.33 ± 0.14

Wager size		Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Saline-vehicle Wager-insensitive	1	1.82 ± 0.20	1.89 ± 0.13	0.40 ± 0.04	0.37 ± 0.03	3.67 ± 0.89	0.08 ± 0.08
	2	1.74 ± 0.16	1.90 ± 0.22	0.38 ± 0.04	0.37 ± 0.02	1.83 ± 0.60	0.00 ± 0.00
	3	1.73 ± 0.14	1.81 ± 0.17	0.38 ± 0.04	0.35 ± 0.02	3.42 ± 0.84	0.00 ± 0.00
Saline-BD442618 Wager-insensitive	1	1.68 ± 0.10	1.78 ± 0.15	0.41 ± 0.04	0.40 ± 0.04	5.67 ± 1.34	0.00 ± 0.00
	2	1.77 ± 0.11	1.93 ± 0.12	0.39 ± 0.04	0.37 ± 0.02	5.25 ± 0.54	0.00 ± 0.00
	3	1.69 ± 0.11	1.68 ± 0.11	0.38 ± 0.04	0.33 ± 0.02	5.58 ± 1.57	0.00 ± 0.00
Amphetamine-vehicle Wager-insensitive	1	2.86 ± 0.44	3.64 ± 0.62	0.37 ± 0.02	0.82 ± 0.26	7.17 ± 2.35	0.75 ± 0.22
	2	2.91 ± 0.47	2.74 ± 0.34	0.43 ± 0.05	0.62 ± 0.19	7.75 ± 2.20	0.33 ± 0.19
	3	2.39 ± 0.30	3.21 ± 0.35	0.39 ± 0.03	0.50 ± 0.12	7.58 ± 2.25	0.67 ± 0.47
Amphetamine-BD442618 Wager-insensitive	1	2.68 ± 0.27	3.33 ± 0.50	0.41 ± 0.02	1.10 ± 0.41	9.75 ± 2.50	1.08 ± 0.51
	2	2.70 ± 0.29	3.95 ± 0.80	0.38 ± 0.03	2.33 ± 1.20	9.17 ± 2.41	0.83 ± 0.37
	3	3.17 ± 0.49	3.40 ± 0.48	0.38 ± 0.03	1.91 ± 1.55	10.08 ± 2.45	1.17 ± 0.51

3.4 Chronic ropinirole and BD442618

Wager-sensitive rats (n = 25) decreased their responding on the uncertain lever as the wager size at play increased (wager size: $F(2,48) = 195.549$, $p < 0.001$), whereas the wager-insensitive rats responded relatively equally on each lever for each wager size (wager size: $F(2,58) = 0.235$, $p = 0.791$, NS). Given the substantial baseline differences in choice patterns between wager-sensitive and wager-insensitive rats, and our hypothesis that the effects of ropinirole and BD442618 will be more pronounced in wager-sensitive animals based on the results of the *d*-amphetamine Latin square challenge, I will therefore conduct separate ANOVAs in wager-sensitive and wager-insensitive animals when analysing the effects of ropinirole with and without co-administration of BD422618 on choice.

3.4.1 0.3 mg/kg of BD442618

Choice behaviour:

Wager-sensitive rats: After 10 days of chronic ropinirole, there was an increase in choice of the uncertain lever as the wager size increased, regardless of the presence of 0.3 mg/kg BD442618 (Figure 3C. ropinirole: $F(1,20) = 7.748$, $p = 0.011$; ropinirole x BD442618: $F(1,20) = 0.411$, $p = 0.529$, NS). Choice patterns across this timepoint were stable (session: $F(4, 80) = 1.292$, $p = 0.280$) and co-administration of BD442618 did not appear to be altering behaviour over time (session x BD442618: $F(4, 80) = 1.703$, $p = 0.158$) The effect of ropinirole can also be seen when conducting a within-subjects analysis, comparing baseline data to the first week of drug treatment (timepoint x ropinirole: $F(1, 20) = 30.944$, $p < 0.001$; timepoint x BD442618: $F(1,20) = 0.416$, $p = 0.526$, NS).

Wager-insensitive rats: Comparing data across groups, ropinirole had no effect on choice in wager-insensitive rats, regardless of co-administration of BD442618 (Figure 3D. ropinirole:

$F(1,25) = 1.216$, $p = 0.281$, NS; ropinirole x BD442618: $F(1,25) = 0.04$, $p = 0.952$, NS). Choice patterns did appear to be fluctuating over time, but this was unaffected by either drug treatment group BD442618 (session: $F(4, 100) = 3.080$, $p = 0.019$; session x BD442618: $F(4, 100) = 0.572$, $p = 0.684$; session x ropinirole: $F(4, 100) = 0.401$, $p = 0.807$). Comparing animals' baseline data to that recorded during drug treatment, however, revealed a subtle ropinirole-induced shift in choice (timepoint x ropinirole: $F(1,26)= 14.799$, $p = 0.001$), but no effect of BD442618 (timepoint x BD442618: $F(1, 20) = 0.416$, $p = 0.526$, NS). Further analysis confirmed this timepoint effect was driven by changes in choice patterns of ropinirole-treated rats, independent of BD442618 treatment (ropinirole-treated: timepoint: $F(1,16) = 5.601$, $p = 0.031$; timepoint x BD442618: $F(1, 16) = 0.110$, $p = 0.744$, NS).

Non-choice variables: The latency to choose the uncertain lever was unaffected by drug treatment (all Fs < 2.906 and ps > 0.097). Rats treated with BD442618 and ropinirole were slightly slower to choose the safe lever, but this effect was small in size, and unlikely to be biologically significant (ropinirole x BD442618: $F(1,39) = 4.977$, $p = 0.032$; all other factors Fs < 1.037, ps > 0.315, NS). Ropinirole also significantly increased hole omissions (ropinirole: $F(1,45) = 15.246$, $p < 0.001$; all other Fs < 1.952 and ps > 0.169, NS), but again, levels remained very low (<5 per session). Ropinirole slightly increased the latency to collect rewards following a response on the uncertain lever, particularly in wager-sensitive rats, but this effect was nominal in magnitude despite being statistically significant (ropinirole x wager-sensitivity: $F(1,35) = 6.481$, p = 0.015; wager-sensitive rats – ropinirole: $F(1,12) = 7.024$, $p = 0.021$; wager-insensitive rats – ropinirole: $F(1,23) = 0.366$, $p = 0.551$, NS). There was no effect of ropinirole or BD442618 on collection latency after choosing the safe lever or choice omissions (All Fs < 3.326 and all ps > 0.075, NS). See table 5 for data collected on non-choice measurements.

3.4.2 1 mg/kg of BD442618

Choice behaviour:

Wager-sensitive rats: Analysing the last five out of eight days that BD442618 was administered at 1 mg/kg, ropinirole continued to potentiate choice of the uncertain lever, (Figure 3E. ropinirole: $F(1,20) = 8.81$, $p = 0.008$). Choice patterns did not appear to be shifting over time, or depend on co-administration of BD442618 (session: $F(4,80 = 1.416$, $p = 0.236$; session x BD442618: $F(4, 80) = 0.389$. $p = 0.816$). When compared to data from the previous week, ropinirole-treated rats did not show any further increase in choice of the uncertain option, and this was not altered by co-administration of BD442618 (timepoint: $F(1, 10) = 1.239$, $p = 0.292$, NS; timepoint x BD442618: $F(1.10) = 1.184$, $p = 0.302$, NS)

Wager-insensitive rats: Between-subjects analysis of choice patterns did not indicate that ropinirole had significantly altered preference for the uncertain option, and co-treatment with BD442681 did not appear to be altering behaviour (Figure 3F. ropinirole: $F(1, 25) = 1.48$, $p = 0.235$, NS; session: $F(4, 100) = 0.438$, $p = 0.781$, NS; session x BD442618: $F(4, 100) = 0.811$, $p = 0.521$, NS). However, when compared to data from the previous week, ropinirole treated rats exhibited a significant increase in choice of the uncertain option (timepoint (1, 15): $F = 9.236$, $p = 0.008$), but this was not altered by co-treatment with BD422618 (timepoint x BD442618: $F(1, 15) = 0.335$, $p = 0.571$, NS).

Non-choice variables: There was no effect of drug treatment on latency to choose the uncertain lever (All Fs < 3.906, ps > 0.110, NS). Latency to choose the safe lever was again significantly affected by drug treatment, with co-administration of BD442618 blocking the decrease in choice latency caused by ropinirole (ropinirole x BD442618: $F(1,36) = 9.119$, $p = 0.005$; all other Fs < 2.112 and ps > 0.155). Ropinirole treatment continued to increase hole

omissions (ropinirole: $F(1,44) = 39.431$, $p < 0.001$; all other Fs < 3.812 and ps > 0.057, NS). Collection latency was unaffected by drug administration (All Fs < 3.082 and ps > 0.088, NS). While there was a interaction between BD442618 and ropinirole on choice omissions, this reflects an increase from zero to in one omission per session, and is therefore of little consequence (ropinirole x BD442618: $F(1,44) = 4.316$, $p = 0.044$, all other Fs < 2.358 and ps > 0.132, NS). See table 6 for data from non-choice measurements.

3.4.3 3 mg/kg of BD442618

Choice behaviour:

Wager-sensitive rats: Over the final 5 days of treatment, choice of the uncertain lever continued to pull apart in animals treated with ropinirole (Figure 3G. ropinirole: $F(1,18) = 9.985$, $p = 0.005$), but there was some indication that treatment with BD442618 was altering choice over time (session: $F(4, 72 = 2.793$, p = 0.032; session x BD442618: $F(4, 72 = 2.405$. p = 0.057). In saline-treated rats, treatment with the GPR52 agonist appeared to have no effect on choice: (Figure 3G. BD442618: $F(1,8) = 0.057$, $p = 0.817$, NS; session x BD442618: $F(4, 32) = 1.492$, $p = 0.228$, NS). However, in ropinirole-treated animals, choice of the uncertain lever was significantly lower in those co-treated with BD442618 (Figure 3G. BD442618: $F(1,10) = 5.569$, $p = 0.040$). To probe the potential validity of this effect further, data from this timepoint were compared to data from the prior week, in order to ascertain whether the higher dose of BD442618 had impacted the steady rise in choice of the uncertain option caused by ropinirole. As expected, choice of the uncertain option continued to escalate over time in animals treated with ropinirole, but this effect was blocked by co-treatment with 3 mg/kg BD442618 (timepoint x BD442618 = $F(1, 18) = 6.768$, p = 0.018; timepoint- ropinirole + vehicle group: $F(1.5) = 7.882$, p = 0.038; timepoint- ropinirole + BD442618 group: $F(1.5) = 2.277$, $p = 0.192$, NS).

Wager-insensitive rats: In the final week of treatment, between-subjects analyses indicated that choice behaviour was still not significantly different in animals treated with ropinirole; this seemed stable across sessions, and did not interact with BD442618 co-treatment (Figure 3H. ropinirole: $F(1, 25) = 1.017$, $p = 0.311$, NS; session: $F(4, 100) = 1.978$, $p = 0.104$, NS; session x BD442618: $F(4, 100) = 0.630$, $p = 0.642$, NS; session x ropinirole: $F(4, 100) = 0.659$, $p = 0.622$, NS). To be sure there was no effect of ropinirole, and to match the analyses done with wager-sensitive rats, data from this timepoint were compared to data obtained from the previous week. There was no shift in choice, regardless of the presence of BD442618 (timepoint: $F(1, 15) = 0.01$, $p = 0.923$; timepoint x BD442618: $F(1,15) = 0.411$, $p = 0.531$, NS).

Non-choice variables: There was no effect of drug treatment on the latency to choose the uncertain lever, regardless of wager-sensitivity or wager size at play (all Fs < 2.838 and ps > 0.101). Similar to findings with administration of 1 mg/kg of BD442618, animals that received ropinirole plus vehicle were faster to respond on the safe lever, whereas animals that received 3 mg/kg of BD442618 and ropinirole, had a latency similar to the control group (ropinirole x BD442618: $F(1,36) = 7.740$, $p = 0.009$; all other Fs < 1.978 and ps > 0.168, NS). Ropinirole decreased hole omissions on the rBT across all wager sizes, regardless of wager-sensitivity (ropinirole: $F(1,45) = 22.094$, $p < 0.001$; wager size x ropinirole: $F(2,90) = 2.237$, $p = 0.113$, NS; all other Fs < 2.404 and ps > 0.128, NS). There was a significant effect of ropinirole on collection latency after choosing the uncertain lever across all wager sizes, depending on wager-sensitivity (ropinirole x wager-sensitivity: $F(1,35) = 5.947$, $p = 0.020$, all other Fs < 0.451 and ps > 0.506, NS). However, when the wager-sensitive and wager-insensitive rats were analyzed separately, the effect of ropinirole was no longer significant (All Fs < 4.4487 and ps > 0.053). There was no effect of drug treatment on collection latency after choosing the safe lever,

regardless of wager-sensitivity or wager size (All Fs < 3.018 and ps > 0.091, NS). There was also a significant effect of ropinirole dependent on wager-sensitivity on choice omissions (ropinirole x wager-sensitivity: $F(1,45) = 5.884$, $p = 0.019$; ropinirole: $F(1,45) = 0.368$, $p = 0.547$, NS; all other Fs < 1.471 and ps > 0.232, NS). However, when wager-sensitive and wager-insensitive rats are analyzed separately, no significant effect of ropinirole is evident, suggesting a small effect size (all Fs < 3.811 and ps > 0.062, NS). See table 7 for data collected on non-choice variables.

Figure 3. Chronic ropinirole with BD442618 at different doses

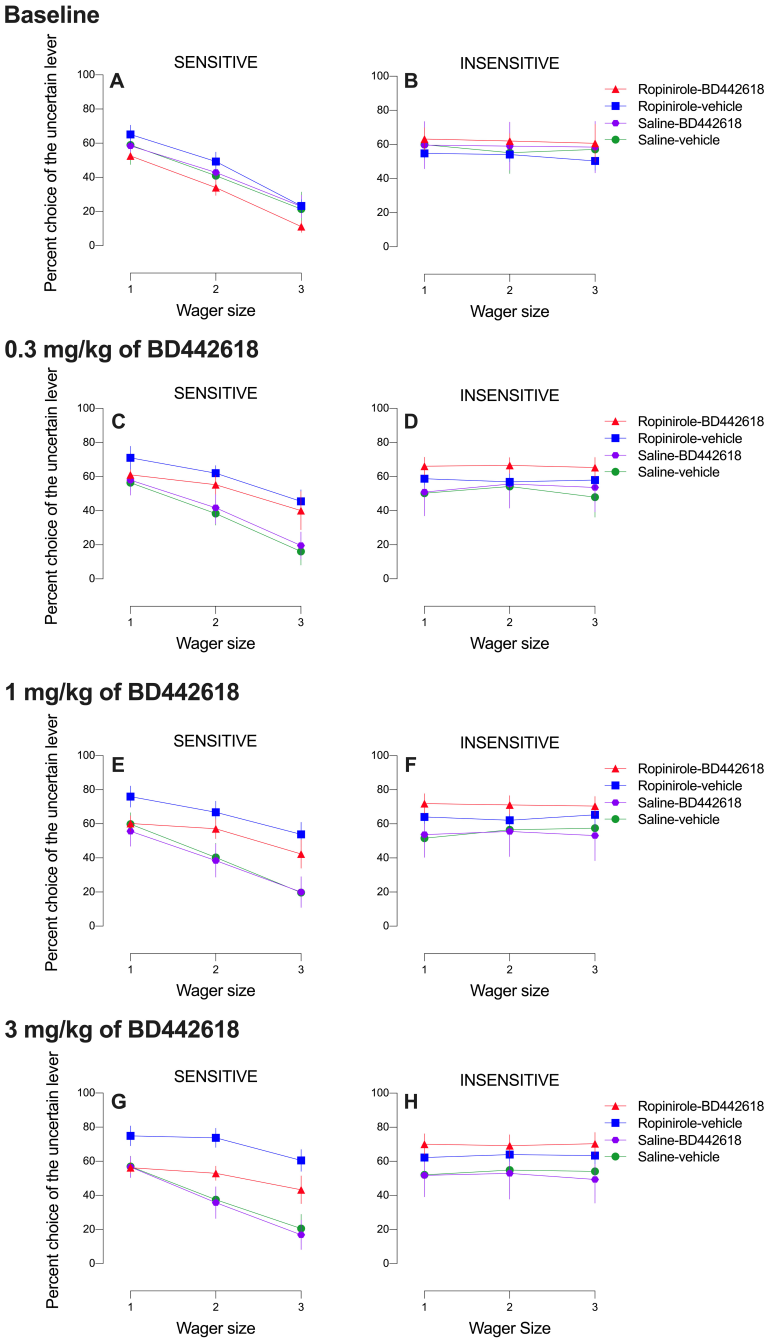

Figure 3. Chronic ropinirole increased choice of the uncertain lever on the rBT in wager-sensitive rats at all timepoints (C, E, G) but not in wager-insensitive rats (D, F, H). Data is shown at baseline and during the chronic administration of ropinirole across the different doses of BD442618 (0.3, 1, 3 mg/kg). The co-administration of neither the low or medium dose of BD442618 was able to reduce the effect of ropinirole (C,E). However, wager-sensitive rats co-administer ropinirole and 3 mg/kg of BD442618 had a significantly lower preference for the uncertain option compared to wager-sensitive rats that only received ropinirole (G).

Table 5. The effect of ropinirole and 0.3 mg/kg BD442618 on other measurements

	Wager size	Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency – safe	Hole omissions	Choice omissions
Saline-vehicle All rats	1	1.92 ± 0.29	2.10 ± 0.17	0.40 ± 0.03	0.43 ± 0.04	3.13 ± 0.60	0.03 ± 0.02
	2	1.72 ± 0.10	1.99 ± 0.11	0.40 ± 0.03	0.41 ± 0.04	1.85 ± 0.27	0.05 ± 0.03
	3	1.65 ± 0.10	1.84 ± 0.12	0.38 ± 0.03	0.39 ± 0.03	3.42 ± 0.50	0.02 ± 0.02
Saline-BD442618 All rats	1	1.59 ± 0.05	1.87 ± 0.11	0.39 ± 0.03	1.20 ± 0.81	4.07 ± 0.62	0.02 ± 0.02
	2	1.60 ± 0.06	1.69 ± 0.07	0.38 ± 0.03	0.37 ± 0.02	2.27 ± 0.27	0.00 ± 0.00
	3	1.57 ± 0.06	1.72 ± 0.14	0.36 ± 0.03	0.35 ± 0.01	4.03 ± 0.41	0.00 ± 0.00
Ropinirole-vehicle All rats	1	1.71 ± 0.10	1.67 ± 0.08	0.43 ± 0.02	0.49 ± 0.05	1.81 ± 0.42	0.04 ± 0.02
	2	1.69 ± 0.10	1.73 ± 0.07	0.42 ± 0.02	0.43 ± 0.02	0.88 ± 0.23	0.01 ± 0.01
	3	1.66 ± 0.09	1.63 ± 0.07	0.42 ± 0.02	0.42 ± 0.02	2.03 ± 0.40	0.03 ± 0.03
Ropinirole-BD442618 All rats	1	1.79 ± 0.11	1.90 ± 0.12	0.44 ± 0.02	0.41 ± 0.02	2.25 ± 0.51	0.01 ± 0.01
	2	1.75 ± 0.10	1.85 ± 0.09	0.42 ± 0.02	0.39 ± 0.02	1.11 ± 0.25	0.00 ± 0.00
	3	1.68 ± 0.08	1.75 ± 0.07	0.41 ± 0.02	0.39 ± 0.02	2.72 ± 0.51	0.00 ± 0.00

	Wager size	Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Saline-vehicle	1	1.50 ± 0.11	1.95 ± 0.14	0.35 ± 0.02	0.42 ± 0.04	2.90 ± 0.73	0.03 ± 0.03
Wager-sensitive	2	1.55 ± 0.07	1.88 ± 0.11	0.34 ± 0.02	0.38 ± 0.03	1.96 ± 0.48	0.03 ± 0.03
	3	1.52 ± 0.10	1.70 ± 0.08	0.35 ± 0.02	0.38 ± 0.03	3.46 ± 0.91	0.03 ± 0.03
Saline-BD442618	1	1.63 ± 0.07	1.79 ± 0.10	0.41 ± 0.02	2.04 ± 1.62	3.57 ± 0.48	0.00 ± 0.00
Wager-sensitive	2	1.64 ± 0.07	1.73 ± 0.11	0.40 ± 0.04	0.40 ± 0.01	2.17 ± 0.29	0.00 ± 0.00
	3	1.65 ± 0.10	1.59 ± 0.09	0.33 ± 0.01	0.39 ± 0.01	4.23 ± 0.47	0.00 ± 0.00
Ropinirole-vehicle	1	1.48 ± 0.13	1.62 ± 0.11	0.48 ± 0.07	0.42 ± 0.01	2.03 ± 0.98	0.04 ± 0.04
Wager-sensitive	2	1.50 ± 0.10	1.62 ± 0.08	0.47 ± 0.07	0.42 ± 0.01	0.83 ± 0.47	0.00 ± 0.00
	3	1.55 ± 0.10	1.47 ± 0.05	0.46 ± 0.07	0.40 ± 0.01	1.63 ± 0.29	0.00 ± 0.00
Ropinirole-BD442618	1	1.69 ± 0.21	1.85 ± 0.24	0.47 ± 0.04	0.44 ± 0.02	3.03 ± 1.11	0.00± 0.00
Wager-sensitive	2	1.65 ± 0.18	1.83 ± 0.15	0.44 ± 0.03	0.41 ± 0.02	0.83 ± 0.32	0.00 ± 0.00
	3	1.69 ± 0.17	1.70 ± 0.13	0.44 ± 0.03	0.41 ± 0.02	1.77 ± 0.57	0.00 ± 0.00

Wager size		Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Saline-vehicle Wager-insensitive	1	2.35 ± 0.52	2.24 ± 0.33	0.45 ± 0.06	0.43 ± 0.06	3.36 ± 1.02	0.03 ± 0.03
	2	1.90 ± 0.17	2.10 ± 0.19	0.45 ± 0.06	0.43 ± 0.08	1.73 ± 0.31	0.07 ± 0.04
	3	1.78 ± 0.15	1.97 ± 0.21	0.40 ± 0.05	0.40 ± 0.06	3.38 ± 0.54	0.00 ± 0.00
Saline-BD442618 Wager-insensitive	1	1.56 ± 0.08	1.95 ± 0.21	0.38 ± 0.06	0.35 ± 0.02	4.57 ± 1.17	0.03 ± 0.03
	2	1.56 ± 0.09	1.65 ± 0.11	0.37 ± 0.05	0.33 ± 0.02	2.37 ± 0.48	0.00 ± 0.00
	3	1.50 ± 0.06	1.84 ± 0.26	0.39 ± 0.06	0.32 ± 0.01	3.83 ± 0.71	0.00 ± 0.00
Ropinirole-vehicle Wager-insensitive	1	1.85 ± 0.13	1.71 ± 0.11	0.40 ± 0.01	0.54 ± 0.09	1.67 ± 0.45	0.04 ± 0.03
	2	1.81 ± 0.12	1.81 ± 0.10	0.39 ± 0.01	0.44 ± 0.04	0.91 ± 0.29	0.02 ± 0.02
	3	1.73 ± 0.12	1.74 ± 0.10	0.39 ± 0.01	0.43 ± 0.03	2.29 ± 0.64	0.04 ± 0.04
Ropinirole-BD442618 Wager-insensitive	1	1.85 ± 0.12	1.93 ± 0.12	0.42 ± 0.03	0.40 ± 0.02	1.73 ± 0.41	0.02 ± 0.02
	2	1.82 ± 0.13	1.86 ± 0.12	0.40 ± 0.03	0.38 ± 0.02	1.29 ± 0.37	0.00 ± 0.00
	3	1.69 ± 0.08	1.79 ± 0.07	0.39 ± 0.02	0.37 ± 0.02	3.36 ± 0.71	0.00 ± 0.00

Table 6. The effect of ropinirole and 1 mg/kg BD442618 on other measurements

	Wager size	Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Saline-vehicle All rats	1	1.81 ± 0.19	2.02 ± 0.13	0.46 ± 0.07	0.43 ± 0.03	3.62 ± 0.52	0.00 ± 0.00
	2	1.73 ± 0.16	1.92 ± 0.13	0.38 ± 0.03	0.39 ± 0.03	1.71 ± 0.34	0.00 ± 0.00
	3	1.67 ± 0.13	1.89 ± 0.19	0.37 ± 0.03	0.38 ± 0.03	3.38 ± 0.46	0.00 ± 0.00
Saline-BD442618 All rats	1	1.60 ± 0.05	1.83 ± 0.09	0.40 ± 0.03	0.39 ± 0.02	4.64 ± 0.74	0.02 ± 0.02
	2	1.58 ± 0.05	1.68 ± 0.07	0.49 ± 0.03	0.37 ± 0.02	2.65 ± 0.43	0.05 ± 0.03
	3	1.53 ± 0.05	1.57 ± 0.06	0.35 ± 0.03	0.36 ± 0.02	3.59 ± 0.54	0.00 ± 0.00
Ropinirole-vehicle All rats	1	1.58 ± 0.10	1.59 ± 0.08	0.42 ± 0.02	0.42 ± 0.01	1.00 ± 0.19	0.04 ± 0.02
	2	1.58 ± 0.10	1.52 ± 0.05	0.41 ± 0.02	0.41 ± 0.01	0.33 ± 0.12	0.00 ± 0.00
	3	1.53 ± 0.08	1.54 ± 0.05	0.40 ± 0.02	0.40 ± 0.01	1.26 ± 0.41	0.00 ± 0.00
Ropinirole-BD442618 All rats	1	1.75 ± 0.11	1.81 ± 0.12	0.42 ± 0.02	0.43 ± 0.03	1.84 ± 0.31	0.01 ± 0.01
	2	1.75 ± 0.11	1.82 ± 0.10	0.40 ± 0.02	0.40 ± 0.02	0.75 ± 0.17	0.00 ± 0.00
	3	1.66 ± 0.10	1.68 ± 0.08	0.40 ± 0.02	0.39 ± 0.02	2.35 ± 0.52	0.00 ± 0.00

	Wager size	Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Saline-vehicle Wager-sensitive	1	1.47 ± 0.07	1.96 ± 0.13	0.35 ± 0.01	0.43 ± 0.04	2.93 ± 0.61	0.00 ± 0.00
	2	1.45 ± 0.08	1.86 ± 0.13	0.33 ± 0.02	0.38 ± 0.03	1.93 ± 0.59	0.00 ± 0.00
	3	1.45 ± 0.07	1.65 ± 0.07	0.32 ± 0.02	0.37 ± 0.03	3.40 ± 0.76	0.00 ± 0.00
Saline-BD442618 Wager-sensitive	1	1.53 ± 0.05	1.84 ± 0.14	0.40 ± 0.03	0.42 ± 0.02	3.60 ± 0.55	0.00 ± 0.00
	2	1.53 ± 0.08	1.66 ± 0.07	0.41 ± 0.03	0.40 ± 0.01	2.70 ± 0.58	0.03 ± 0.03
	3	1.55 ± 0.03	1.52 ± 0.04	0.34 ± 0.02	0.30 ± 0.01	3.00 ± 0.50	0.00 ± 0.00
Ropinirole-vehicle Wager-sensitive	1	1.41 ± 0.10	1.64 ± 0.18	0.45 ± 0.05	0.42 ± 0.02	1.03 ± 0.26	0.04 ± 0.04
	2	1.41 ± 0.10	1.47 ± 0.08	0.44 ± 0.04	0.41 ± 0.02	0.37 ± 0.21	0.00 ± 0.00
	3	1.43 ± 0.11	1.44 ± 0.06	0.44 ± 0.05	0.40 ± 0.02	0.63 ± 0.16	0.00 ± 0.00
Ropinirole-BD442618 Wager-sensitive	1	1.72 ± 0.23	1.86 ± 0.27	0.45 ± 0.02	0.49 ± 0.07	1.83 ± 0.51	0.03 ± 0.03
	2	1.69 ± 0.21	1.78 ± 0.19	0.43 ± 0.02	0.43 ± 0.03	0.80 ± 0.35	0.00 ± 0.00
	3	1.73 ± 0.21	1.75 ± 0.16	0.43 ± 0.02	0.43 ± 0.02	1.33 ± 0.57	0.00 ± 0.00

Wager size		Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Saline-vehicle Wager-insensitive	1	2.15 ± 0.33	2.08 ± 0.23	0.56 ± 0.12	0.42 ± 0.05	4.30 ± 0.80	0.00 ± 0.00
	2	2.01 ± 0.27	1.98 ± 0.25	0.43 ± 0.06	0.41 ± 0.05	1.50 ± 0.39	0.00 ± 0.00
	3	1.90 ± 0.22	2.12 ± 0.36	0.41 ± 0.05	0.39 ± 0.05	4.30 ± 0.59	0.00 ± 0.00
Saline-BD442618 Wager-insensitive	1	1.70 ± 0.05	1.82 ± 0.13	0.40 ± 0.05	0.36 ± 0.03	5.68 ± 1.29	0.03 ± 0.03
	2	1.62 ± 0.06	1.71 ± 0.14	0.38 ± 0.05	0.34 ± 0.02	2.59 ± 0.67	0.07 ± 0.04
	3	1.51 ± 0.08	1.63 ± 0.14	0.35 ± 0.05	0.32 ± 0.02	4.18 ± 0.95	0.00 ± 0.00
Ropinirole-vehicle Wager-insensitive	1	1.71 ± 0.14	1.55 ± 0.06	0.39 ± 0.02	0.42 ± 0.02	0.98 ± 0.29	0.03 ± 0.03
	2	1.71 ± 0.14	1.56 ± 0.07	0.38 ± 0.02	0.41 ± 0.02	0.30 ± 0.14	0.00 ± 0.00
	3	1.61 ± 0.12	1.62 ± 0.07	0.37 ± 0.02	0.40 ± 0.02	1.73 ± 0.68	0.00 ± 0.00
Ropinirole-BD442618 Wager-insensitive	1	1.77 ± 0.10	1.77 ± 0.10	0.40 ± 0.03	0.40 ± 0.03	1.84 ± 0.42	0.00 ± 0.00
	2	1.78 ± 0.13	1.86 ± 0.10	0.38 ± 0.02	0.38 ± 0.03	0.71 ± 0.19	0.00 ± 0.00
	3	1.62 ± 0.09	1.62 ± 0.08	0.38 ± 0.02	0.37 ± 0.03	3.02 ± 0.72	0.00 ± 0.00

Table 7. The effect of ropinirole and 3 mg/kg BD442618 on other measurements

Wager size		Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Saline-vehicle All rats	1	1.90 ± 0.32	2.03 ± 0.18	0.38 ± 0.03	0.42 ± 0.03	3.37± 0.47	0.03 ± 0.02
	2	1.69 ± 0.08	1.97 ± 0.17	0.37 ± 0.03	0.39 ± 0.02	1.61 ± 0.30	0.00 ± 0.00
	3	1.65 ± 0.07	1.81 ± 0.13	0.38 ± 0.04	0.37 ± 0.02	3.88 ± 0.74	0.00 ± 0.00
Saline-BD442618 All rats	1	1.66 ± 0.07	1.80 ± 0.09	0.40 ± 0.03	0.39 ± 0.02	3.62 ± 0.50	0.03 ± 0.02
	2	1.61 ± 0.07	1.76 ± 0.08	0.37 ± 0.03	0.37 ± 0.02	2.65 ± 0.44	0.00 ± 0.00
	3	1.67 ± 0.09	1.57 ± 0.05	0.36 ± 0.04	0.36 ± 0.02	3.87 ± 0.53	0.00 ± 0.00
Ropinirole-vehicle All rats	1	1.60 ± 0.11	1.60 ± 0.09	0.42 ± 0.03	0.43 ± 0.02	1.29 ± 0.49	0.00 ± 0.00
	2	1.60 ± 0.09	1.62 ± 0.06	0.41 ± 0.02	0.41 ± 0.02	0.54 ± 0.16	0.00 ± 0.00
	3	1.58 ± 0.09	1.58 ± 0.08	0.40 ± 0.03	0.41 ± 0.01	1.50 ± 0.41	0.00 ± 0.00
Ropinirole-BD442618 All rats	1	1.85 ± 0.12	1.94 ± 0.19	0.41 ± 0.02	0.44 ± 0.02	1.64 ± 0.28	0.03 ± 0.02
	2	1.83 ± 0.12	1.86 ± 0.13	0.39 ± 0.02	0.41 ± 0.02	1.04 ± 0.27	0.00 ± 0.00
	3	1.78 ± 0.11	1.77 ± 0.11	0.40 ± 0.02	0.39 ± 0.02	2.53 ± 0.35	0.01 ± 0.01

	Wager size	Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Saline-vehicle Wager-sensitive	1	1.43 ± 0.06	1.87 ± 0.15	0.34 ± 0.01	0.41 ± 0.03	3.12 ± 0.76	0.00 ± 0.00
	2	1.53 ± 0.05	1.92 ± 0.13	0.34 ± 0.02	0.38 ± 0.03	1.78 ± 0.52	0.00 ± 0.00
	3	1.58 ± 0.09	1.76 ± 0.08	0.33 ± 0.03	0.37 ± 0.02	3.78 ± 0.93	0.00 ± 0.00
Saline-BD442618 Wager-sensitive	1	1.68 ± 0.12	1.74 ± 0.12	0.40 ± 0.02	0.42 ± 0.01	4.17 ± 0.84	0.00 ± 0.00
	2	1.61 ± 0.11	1.72 ± 0.08	0.37 ± 0.02	0.41 ± 0.02	2.43 ± 0.52	0.00 ± 0.00
	3	1.78 ± 0.09	1.61 ± 0.05	0.33 ± 0.02	0.39 ± 0.01	3.48 ± 0.52	0.00 ± 0.00
Ropinirole-vehicle Wager-sensitive	1	1.48 ± 0.16	1.67 ± 0.20	0.46 ± 0.06	0.42 ± 0.01	1.43 ± 0.53	0.00 ± 0.00
	2	1.46 ± 0.12	1.62 ± 0.11	0.44 ± 0.05	0.41 ± 0.02	0.63 ± 0.30	0.00 ± 0.00
	3	1.50 ± 0.13	1.59 ± 0.13	0.43 ± 0.06	0.41 ± 0.02	1.23 ± 0.47	0.00 ± 0.00
Ropinirole-BD442618 Wager-sensitive	1	1.90 ± 0.26	2.09 ± 0.44	0.45 ± 0.02	0.50 ± 0.06	1.70 ± 0.48	0.07 ± 0.04
	2	1.90 ± 0.24	1.98 ± 0.26	0.42 ± 0.02	0.44 ± 0.03	1.27 ± 0.59	0.00 ± 0.00
	3	1.94 ± 0.25	1.88 ± 0.23	0.43 ± 0.04	0.42 ± 0.02	2.27 ± 0.55	0.00 ± 0.00

Wager size		Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Saline-vehicle Wager-insensitive	1	2.37 ± 0.60	2.20 ± 0.33	0.42 ± 0.06	0.44 ± 0.05	3.62 ± 0.63	0.07 ± 0.04
	2	1.85 ± 0.12	2.03 ± 0.33	0.40 ± 0.05	0.40 ± 0.03	1.45 ± 0.32	0.00 ± 0.00
	3	1.73 ± 0.11	1.88 ± 0.29	0.43 ± 0.06	0.37 ± 0.03	3.98 ± 1.26	0.00 ± 0.00
Saline-BD442618 Wager-insensitive	1	1.64 ± 0.09	1.86 ± 0.15	0.39 ± 0.06	0.36 ± 0.02	3.07 ± 0.54	0.07 ± 0.04
	2	1.60 ± 0.11	1.79 ± 0.14	0.38 ± 0.06	0.32 ± 0.02	2.87 ± 0.76	0.00 ± 0.00
	3	1.58 ± 0.14	1.53 ± 0.10	0.38 ± 0.06	0.31 ± 0.02	4.20 ± 0.90	0.00 ± 0.00
Ropinirole-vehicle Wager-insensitive	1	1.69 ± 0.15	1.54 ± 0.05	0.40 ± 0.02	0.45 ± 0.03	1.18 ± 0.79	0.00 ± 0.00
	2	1.70 ± 0.12	1.62 ± 0.06	0.38 ± 0.02	0.41 ± 0.02	0.48 ± 0.19	0.00 ± 0.00
	3	1.65 ± 0.13	1.57 ± 0.09	0.37 ± 0.02	0.40 ± 0.02	1.70 ± 0.64	0.00 ± 0.00
Ropinirole-BD442618 Wager-insensitive	1	1.82 ± 0.13	1.82 ± 0.10	0.39 ± 0.02	0.40 ± 0.03	1.60 ± 0.36	0.00 ± 0.00
	2	1.77 ± 0.12	1.76 ± 0.09	0.38 ± 0.02	0.39 ± 0.03	0.89 ± 0.25	0.00 ± 0.00
	3	1.67 ± 0.09	1.67 ± 0.06	0.37 ± 0.02	0.37 ± 0.03	2.71 ± 0.46	0.02 ± 0.02

3.5 Chronic administration of ropinirole and 3 mg/kg of S111224

In this experiment, the wager-sensitive rats that were randomly assigned to the control condition had unusually low responses on the uncertain lever (figure 4B). This did not occur because of the implantation of the saline osmotic pump or vehicle injections, as there was no difference between responding at baseline and during the experiment (control group - baseline vs. experiment: $F(1,3) = 2.745$, $p = 0.196$, NS). However, to prevent false positives in the results, the control group from the first chronic experiment with BD442618 was used for the current data analysis. These animals received identical treatments (saline-vehicle) but show a more typical pattern of choice on the rBT. This will be further discussed in the limitations section.

Wager-insensitive rats (n = 40) sampled equally from each wager size (wager size: $F(2,78) = 0.080$, $p = 0.923$, NS), whereas wager-sensitive rats (n = 23) decreased their preference for the uncertain lever as wager size increased (wager size: $F(2,44) = 84.012$, $p < 0.001$). For simplicity, the analysis will focus on data from week 4, at which point the effect of ropinirole should be maximal, and both between subjects analyses to compare responding under the different drug conditions, as well as within-subjects analyses, comparing choice at week 4 of drug treatment to pre-treatment baseline will be conducted.

3.5.1 Week 4

Choice behaviour:

Wager-sensitive rats: Comparing choice patterns across groups at week 4, ropinirole treatment increased choice of the uncertain option (Figure 4B. ropinirole: $F(1,19) = 6.364$, $p = 0.021$). Although this effect was visibly smaller in rats co-treated with S111224, this difference was not sufficient to drive significance in the omnibus ANOVA (Figure 4B. ropinirole x S111224: $F(1,19) = 0.294$, $p = 0.594$, NS). When analysing each individual's response to drug as

compared to their pre-treatment baseline, there was a significant interaction between the time-point and ropinirole treatment (timepoint x ropinirole: $F(1,19) = 10.958$, $p = 0.004$) in addition to a strong trend interaction between time-point and S111224 administration (timepoint x S111224: $F(1,19) = 4.116$, $p = 0.057$, NS). When considering rats that were administered ropinirole, there was a highly significant effect of timepoint, indicating a robust increase in choice of the uncertain option (timepoint: $F(1.13) = 11.268$, $p = 0.005$). However, there was a trend for treatment with S111224 to marginally alter this response (timepoint x S111224: $F(1,13)= 3.169$, $p = 0.098$, NS). Based on my a priori hypotheses that S111224 may affect the response to ropinirole, vehicle treated and S111224 treated animals were analyzed separately. While ropinirole-vehicle rats showed a significant increase in choice of the uncertain option (Figure 5A. timepoint: $F(1,7) = 9.149$, $p = 0.019$, timepoint x wager size: $F(2,14) = 17.926$, $p < 0.001$), this effect is reduced to a trend in rats co-treated with S111224 (Figure 5B. timepoint: $F(1,6) = 4.145$, $p = 0.088$, NS; timepoint x wager size: $F(2,12) = 8.119$, p = 0.006).

Wager-insensitive rats: When choice patterns were compared between subjects at week 4, the effect of ropinirole was far less apparent in wager-insensitive rats (Figure 4A. ropinirole: $F(1,36) = 2.913$, $p = 0.094$, NS; ropinirole x S111224: $F(1,36) = 0.293$, $p = 0.591$, NS). When comparing choice patterns within subjects to the pre-treatment timepoint, however, there was a significant shift in choice, depending on ropinirole administration (timepoint x ropinirole: $F(1,36) = 10.795$, $p = 0.002$). When ropinirole-treated animals were analysed independently, it appeared that S111224 was altering choice patterns over time (timepoint x session x S111224: $F(4, 56) = 4.508$, $p = 0.003$). In the absence of S111224, ropinirole treatment resulted in a highly significant increase in choice of the uncertain option (Figure 5C. timepoint: $F(1,7) = 9.396$, $p = 0.018$). In contrast, animals co-administered S111224 and ropinirole did not show any change in

choice (Figure 5D. timepoint: $F(1,7) = 0.005$, $p = 0.946$, NS). This suggests that the effect of ropinirole was attenuated by chronic administration of 3mg/kg of S111224 in wager-insensitive animals (Figure 5C-D).

Non-choice variables: Data are provided in table 8. Drug administration did not alter the latency to choose either lever, regardless of wager-sensitivity or wager size at play (all Fs < 3.650 and ps > 0.063). Ropinirole significantly decreased, whereas S111224 increased, hole omissions, regardless of wager size or wager sensitivity (ropinirole: $F(1,55) = 8.214$, $p = 0.006$; ropinirole x wager-sensitivity: $F(1,55) = 0.412$, $p = 0.524$, NS; wager size x ropinirole: $F(2,110) = 0.322$, $p = 0.725$, NS; S111224: $F(1,55) = 4.505$, $p = 0.038$; S111224 x wager-sensitivity: $F(1,55) = 2.656$, $p = 0.109$, NS; wager size x S111224: $F(2,110) = 1.264$, $p = 0.287$, NS; all other Fs < 0.655 and ps> 0.422, NS). No other variable was affected (all Fs < 3.715 and ps > 0.059, NS).

Figure 4. Choice of the uncertain lever at week four of ropinirole and S111224

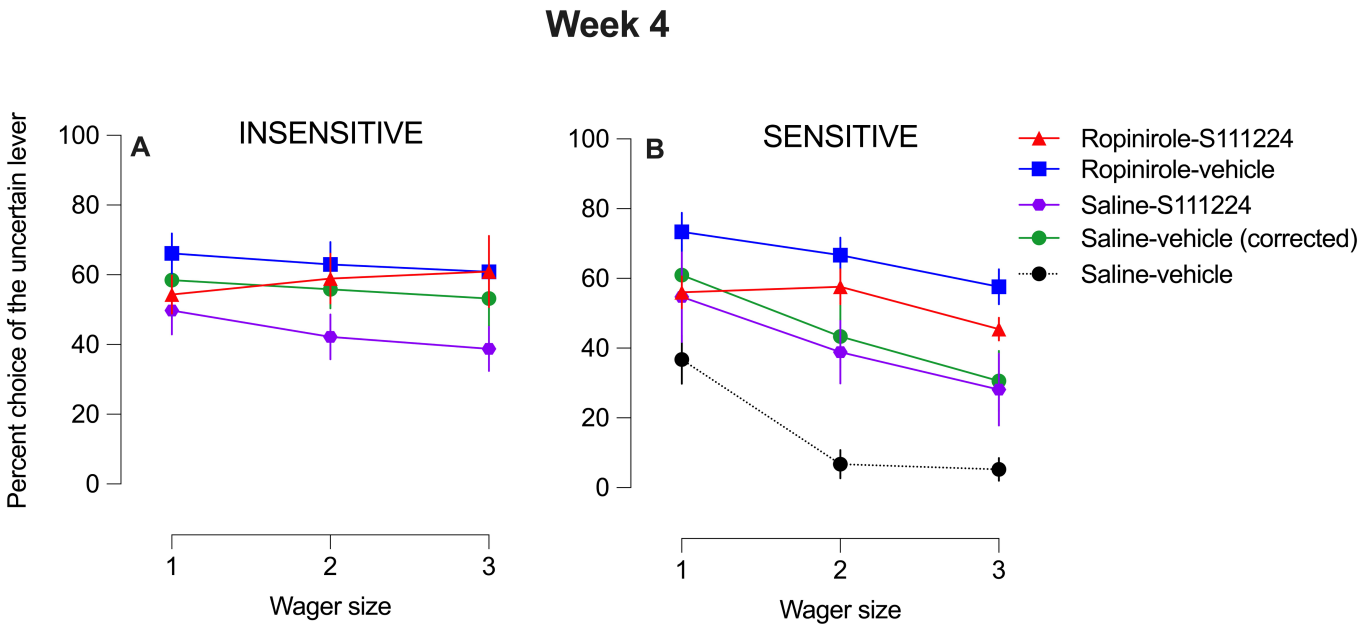

Figure 4. Chronic ropinirole increase preference for the uncertain lever across wager sizes in wager-sensitive rats at week 4 (B). The effect of ropinirole was not significant in wager-insensitive rats (A). 3 mg/kg of BD442618 did not block the effect of ropinirole when compared to the other treatment groups at this timepoint (A-B).

Figure 5. Effect of S111224 on ropinirole-induced changes at week four compared to baseline

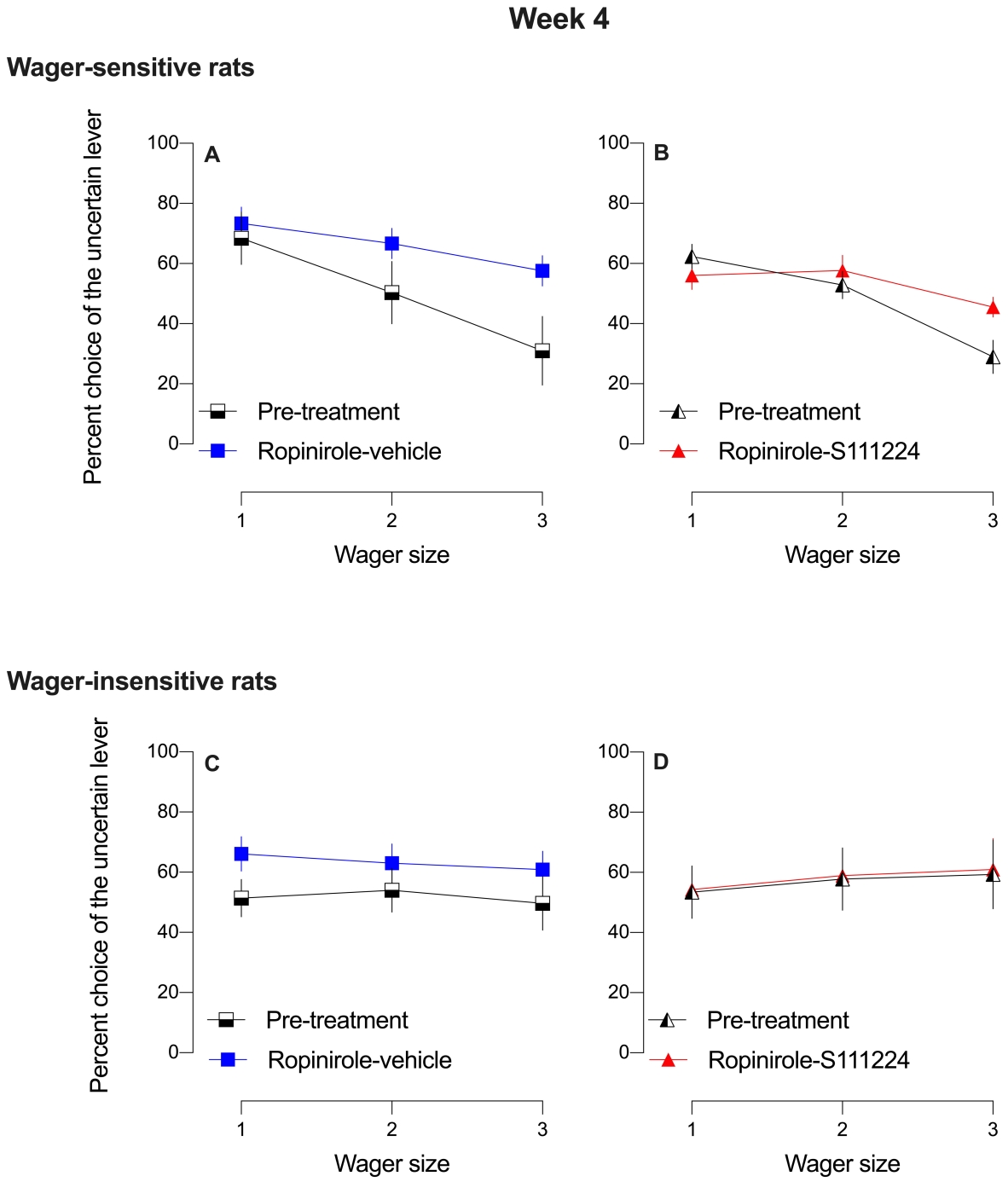

Figure 5. Ropinirole increased choice of the uncertain lever at week 4 in both wager-sensitive and wager-insensitive rats when compared to baseline choice data (A, C). This increase in responding on the uncertain lever was not observed in ropinirole receiving wager-insensitive rats treated with S111224 (D). However, S111224 was not able to significantly reduce the effect of ropinirole at week 4 in wager-sensitive rats (B).

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Table 8. The effect of ropinirole and S111224 on non-choice measurements at week 4

	Wager size	Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Saline-vehicle All rats	1	1.89 ± 0.10	1.89 ± 0.09	0.41 ± 0.02	0.46 ± 0.06	3.15 ± 0.53	0.06 ± 0.03
	2	1.97 ± 0.14	1.77 ± 0.07	0.36 ± 0.01	0.41 ± 0.03	1.79 ± 0.29	0.03 ± 0.02
	3	1.86 ± 0.24	1.78 ± 0.10	0.42 ± 0.05	0.39 ± 0.03	3.26 ± 0.52	0.03 ± 0.03
Saline-S111224 All rats	1	1.98 ± 0.10	1.97 ± 0.12	0.42 ± 0.02	0.41 ± 0.02	4.01 ± 0.58	0.03 ± 0.02
	2	1.84 ± 0.06	1.85 ± 0.09	0.40 ± 0.02	0.39 ± 0.02	3.76 ± 0.54	0.00 ± 0.00
	3	1.68 ± 0.06	1.70 ± 0.06	0.38 ± 0.02	0.38 ± 0.01	5.11 ± 0.74	0.01 ± 0.01
Ropinirole-vehicle All rats	1	1.54 ± 0.10	1.80 ± 0.12	0.39 ± 0.02	0.49 ± 0.09	1.80 ± 0.48	0.09 ± 0.05
	2	1.57 ± 0.09	1.93 ± 0.19	0.38 ± 0.02	0.48 ± 0.06	1.23 ± 0.41	0.05 ± 0.03
	3	1.57 ± 0.08	1.93 ± 0.24	0.40 ± 0.04	0.40 ± 0.04	2.65 ± 0.62	0.01 ± 0.01
Ropinirole-S111224 All rats	1	1.88 ± 0.11	1.96 ± 0.13	0.43 ± 0.04	0.47 ± 0.05	2.32 ± 0.50	0.01 ± 0.01
	2	1.86 ± 0.10	2.02 ± 0.12	0.40 ± 0.02	0.41 ± 0.02	1.21 ± 0.25	0.00 ± 0.00
	3	1.77 ± 0.10	1.94 ± 0.13	0.40 ± 0.02	0.40 ± 0.02	2.92 ± 0.75	0.01 ± 0.01

	Wager size	Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Saline-vehicle Wager-sensitive	1	1.91 ± 0.21	2.03 ± 0.20	0.46 ± 0.09	0.62 ± 0.23	3.25 ± 1.20	0.00 ± 0.00
	2	2.37 ± 0.76	1.79 ± 0.23	0.35 ± 0.02	0.50 ± 0.12	1.55 ± 0.80	0.00 ± 0.00
	3	3.23 ± 1.60	1.86 ± 0.29	0.35 ± 0.02	0.48 ± 0.10	1.55 ± 0.61	0.10 ± 0.10
Saline-S111224 Wager-sensitive	1	1.79 ± 0.26	2.22 ± 0.28	0.40 ± 0.00	0.40 ± 0.03	4.10 ± 1.29	0.00 ± 0.00
	2	1.66 ± 0.11	1.84 ± 0.15	0.38 ± 0.01	0.37 ± 0.02	4.40 ± 1.14	0.00 ± 0.00
	3	1.51 ± 0.07	1.71 ± 0.12	0.38 ± 0.02	0.37 ± 0.02	5.85 ± 1.52	0.05 ± 0.05
Ropinirole-vehicle Wager-sensitive	1	1.59 ± 0.19	1.91 ± 0.18	0.41 ± 0.02	0.39 ± 0.02	0.85 ± 0.30	0.13 ± 0.10
	2	1.61 ± 0.17	1.92 ± 0.24	0.39 ± 0.03	0.50 ± 0.11	0.63 ± 0.38	0.00 ± 0.00
	3	1.63 ± 0.14	1.74 ± 0.21	0.46 ± 0.07	0.38 ± 0.02	2.23 ± 0.90	0.03 ± 0.03
Ropinirole-S111224 Wager-sensitive	1	1.71 ± 0.08	1.93 ± 0.17	0.37 ± 0.02	0.40 ± 0.02	2.74 ± 0.85	0.00 ± 0.00
	2	1.79 ± 0.13	1.97 ± 0.19	0.36 ± 0.02	0.39 ± 0.02	1.23 ± 0.33	0.00 ± 0.00
	3	1.77 ± 0.14	1.80 ± 0.13	0.35 ± 0.02	0.39 ± 0.02	2.20 ± 0.88	0.03 ± 0.03

Wager size		Choice latency-uncertain	Choice latency-safe	Collection latency - uncertain	Collection latency - safe	Hole omissions	Choice omissions
Saline-vehicle Wager-insensitive	1	1.88 ± 0.12	1.84 ± 0.10	0.39 ± 0.02	0.41 ± 0.02	3.12 ± 0.61	0.08 ± 0.04
	2	1.90 ± 0.12	1.77 ± 0.08	0.37 ± 0.01	0.39 ± 0.02	1.87 ± 0.51	0.03 ± 0.02
	3	1.63 ± 0.09	1.76 ± 0.11	0.43 ± 0.06	0.36 ± 0.02	3.83 ± 0.58	0.00 ± 0.00
Saline-S111224 Wager-insensitive	1	2.05 ± 0.11	1.88 ± 0.12	0.43 ± 0.03	0.42 ± 0.02	3.98 ± 0.68	0.03 ± 0.02
	2	1.90 ± 0.07	1.85 ± 0.11	0.40 ± 0.03	0.40 ± 0.02	3.55 ± 0.63	0.00 ± 0.00
	3	1.74 ± 0.06	1.69 ± 0.08	0.39 ± 0.03	0.39 ± 0.02	4.87 ± 0.87	0.00 ± 0.00
Ropinirole-vehicle Wager-insensitive	1	1.49 ± 0.10	1.70 ± 0.15	0.37 ± 0.02	0.59 ± 0.18	2.75 ± 0.79	0.05 ± 0.05
	2	1.54 ± 0.08	1.95 ± 0.31	0.38 ± 0.02	0.45 ± 0.06	1.83 ± 0.69	0.10 ± 0.05
	3	1.51 ± 0.07	2.11 ± 0.43	0.36 ± 0.02	0.42 ± 0.08	3.08 ± 0.89	0.00 ± 0.00
Ropinirole-S111224 Wager-insensitive	1	2.03 ± 0.19	1.98 ± 0.20	0.48 ± 0.06	0.54 ± 0.08	1.95 ± 0.61	0.03 ± 0.03
	2	1.93 ± 0.16	2.06 ± 0.17	0.44 ± 0.03	0.42 ± 0.04	1.20 ± 0.39	0.00 ± 0.00
	3	1.78 ± 0.15	2.07 ± 0.21	0.44 ± 0.04	0.41 ± 0.03	3.55 ± 1.20	0.00 ± 0.00

Chapter 4: Discussion

The current series of experiments investigated the effectiveness of two novel GPR52 agonists for the treatment of DRT-induced ICDs. In these experiments, ropinirole-induced increases in uncertain choice on the rBT were used as a proxy for GD (Cocker et al., 2012). First, a dose of GPR52 agonist was decided upon based on a series of Latin squares in which the effects of 0-3 mg/kg BD442618 were assessed on performance of the rBT. Although none of the doses tested affected preference for the uncertain lever, our primary dependent variable, the higher dose slightly decreased trials completed. Based on this data and in-house data from Beacon Pharmaceuticals that indicated potential locomotor sedating effects at this high dose, I then tested whether the lowest and highest dose of compound could block the ability of *d*-amphetamine to promote choice of the uncertain option. I found that both 0.3 mg/kg and 3 mg/kg BD442618 were able to attenuate, but not completely block, *d*-amphetamine's effects on choice behaviour. Given that 3 mg/kg did not seem superior to 0.3 mg/kg at minimising *d*-amphetamine's effects, I therefore opted to try and block the effects of ropinirole with the lower dose of 0.3 mg/kg BD442618 initially, and stepped up the dose over 28 days until signs of a significant attenuation of ropinirole's effects was observed at 3 mg/kg BD442618. This effect was only observed in wager-sensitive rats, which are considered to exhibit a mathematically-irrational decision-making bias similar to the escalation of commitment phenomenon in human gamblers that is associated with the manifestation and severity of GD (Cocker et al., 2012; Cocker & Winstanley, 2015a; Winstanley & Clark, 2016). In a subsequent experiment, I then tested whether chronic dosing with 3 mg/kg S111224, another GPR52 agonist with similar pharmacokinetics to BD442618, was able to attenuate the ability of chronic ropinirole to bias choice on the rBT in favour of uncertain outcomes. S111224 significantly attenuated the ability

of ropinirole to increase choice of uncertain rewards. This was observed in both wager-sensitive and wager-insensitive rats. This is the first time that these compounds have been shown to be effective at reducing impairments in decision making associated with hyperdopaminergic states. Chronic administration of neither GPR52 agonist had lasting effects on basal function. The data in this thesis also demonstrate the robust nature of the increase in preference for the uncertain outcomes caused by ropinirole on the rBT, demonstrating once more that this is a reliable and reproducible effect.

4.1 Selecting a Dose of BD442618

The objective in this initial series of experiments was to select a dose of BD442618 that did not alter basal function, with specific interest in locomotor activity because the patient group that the compound is intended for, PD patients, have substantial motor impairments. Thus, I wanted to select a dose of BD442618 that did not reduce motor activity or cause any other changes from baseline. The latter is important because the compound should be only reducing aberrant DA activity produced by the DA agonist. If the drug is altering functioning at baseline, it may be impacting a healthy system. Therefore, it could reduce the effect of ropinirole by producing a counteracting effect in a system that is not impacted by the DA agonist rather than correcting the pathology introduced by the DA agonist. In the first Latin square, which tested a low, medium, and high dose, BD442618 did not alter any of the choice and non-choice variables on the rBT at any dose, but it did significantly reduce trials at the high dose (3 mg/kg). It is possible that the medium and high dose may be reducing locomotor activity, so the rats are not able to make complete as many trials. However, without directly measured motor activity in response to different doses of BD442618, it is not clear why the drug had this effect on trials. Motor impairment is a potential side-effect of this medication because it had been shown to have

a D2 antagonist-like effect and traditional D2 antagonist have known motor side-effects like catalepsy and bradykinesia (Haraguchi et al., 1997). However, previous research has shown that although GPR52 agonists produce D2 antagonist-like effects, they do not reduce basal motor function, even at 100 mg/kg, which is substantially higher than the dose used in these experiments (Setoh et al., 2014; Tokumaru et al., 2017). It is important to note that for this particular GPR52 agonist, in-house data from Beacon Pharmaceuticals suggested that doses of 3 mg/kg BD442618 or higher may slow motor responding. Based on the potential effect on basal motor function, 0.3 mg/kg of BD442618 was selected as the initial dose of interest.

To test the therapeutic potential of 0.3 mg/kg on choice behaviour, another Latin square was conducted with 0.3 mg/kg and *d*-amphetamine. Acute administration of *d*-amphetamine has been shown to increase preference for the uncertain option on the rBT in wager-sensitive rats (Cocker et al., 2012). Therefore, it reproduces the effects of chronic ropinirole to some degree. Although it has yet to be conclusively determined that this effect of *d*-amphetamine stems from potentiation of DA signalling, the ability of this psychostimulant to precipitate impulsive responding and drive preference for uncertainty are thought to be at least partly dopaminergic. I therefore opted to use this as an initial screen for BD442618's therapeutic effectiveness. If the GPR52 agonist was capable of attenuating *d*-amphetamine's effects on choice, I would be more confident it could block the effects of chronic ropinirole.

I first replicated the effect observed in Cocker et al. (2012), namely that *d*-amphetamine increased responding on the uncertain lever in wager-sensitive rats. As previously mentioned, this subgroup of animals are considered analogous to humans predisposed to develop GD due to the cognitive bias they display (Cocker et al., 2012; Cocker & Winstanley, 2015a; Winstanley & Clark, 2016). This effect in wager-sensitive animals was significantly reduced when 0.3 mg/kg

of BD442618 was co-administered. Furthermore, BD442618 did not alter choice when administered without *d*-amphetamine. This finding suggests that BD442618 does not alter basal function. Instead, it mitigates aberrant DA levels that may produce problematic responding patterns on gambling-like tasks in vulnerable individuals. To provide further support for this idea, *d*-amphetamine did not increase preference for the uncertain option in wager-insensitive rats, replicating findings from Cocker et al. (2012). Also, *d*-amphetamine has been shown to prime the desire to gambling in humans with GD but not healthy controls, which could be considered analogous to the current findings (Zack & Poulos, 2004). This appears to be the first evidence of the effect of GPR52 agonists on gambling-like behaviour. I subsequently conducted another Latin square with highest dose of interest of BD442618 (3 mg/kg) and *d*-amphetamine. Again, *d*-amphetamine increased preference for the uncertain option in wager-sensitive rats, replicating the effect of *d*-amphetamine previously observed in Cocker et al. (2012) and the Latin square I conducted prior with 0.3 mg/kg of BD442618 and *d*-amphetamine. The effect of *d*-amphetamine in wager-sensitive rats was reduced when 3 mg/kg of BD442618 was co-administered, mirroring the effect of BD442618 that was observed in the previous Latin square with 0.3 mg/kg of BD442618. Furthermore, 3 mg/kg of BD442618 did not alter choice when administered without *d*-amphetamine, suggesting that this dose of BD442618 does not cause meaningful alterations to basal function.

Overall, the results from this series of Latin squares indicate that BD442618 does have the ability to mitigate the effect of excessive DA signalling on preference for the uncertain option at a dose of either 0.3 mg/kg or 3 mg/kg. A similar increase in preference for uncertain options is also found in PD patients on DRTs that have an ICD (Voon et al., 2011a). Based on these results, GPR52 agonists have the potential to reduce the effect of DRTs on preference for

uncertainty that may be perpetuating gambling behaviour in those with GD and making individuals prone to developing a GD, without interfering with motor function. However, these experiments were conducted with *d*-amphetamine, not a DRT, and DRTs are usually administered chronically whereas the administration of *d*-amphetamine was done only once prior to testing.

4.2 Chronic Ropinirole and BD442618

Subsequently a 28-day experiment was conducted to investigate the effect of chronic ropinirole and the ability of BD442618 to attenuate its effect on preference for the uncertain option. In support of my first hypothesis, ropinirole increased preference for the uncertain option in wager-sensitive rats and 3 mg/kg BD442618 was able to reduce the effect of ropinirole in these rats. However, when comparing their responding during the experiment to their choice at baseline, there was still a significant increase in preference for the uncertain lever depending on the wager size at play.

The effect of ropinirole, and the ability of BD442618 to ameliorate it, was maximal in wager-sensitive rats. The precise mechanism underlying this individual difference in choice behaviour, and theoretically in response to both ropinirole and BD442618, are currently unknown. On the rBT, wager-sensitivity correlates with lower striatal D2 and D3 receptors (Cocker et al., 2012). It is possible that chronic DA agonist administration causes changes to D2 or D3 receptor density, producing a lasting increase in choice on the uncertain lever. This explanation is supported by the association between greater D3 receptor binding and gambling severity and impulsivity in individuals with GD (Boileau et al., 2013). However, changes in receptor density during chronic ropinirole administration would need to be measured in order to

make a cogent argument for this explanation. Also, the literature is not conclusive on the role of DA D2 or D3 receptor in idiopathic or DRT-induced ICDs.

4.3 Chronic Ropinirole and S111224

Based on the findings from the previous chronic experiment with BD442618, another chronic experiment was conducted using the dose that was most effective at attenuating ropinirole-induced choice behaviour, 3 mg/kg, but with a different GPR52 agonist. The data analyses suggest that S111224 is able to at least partially attenuate the effects of ropinirole, without causing any changes in choice when given in isolation. Unexpectedly, S111224 was most effective in wager-insensitive rats, which are not considered are vulnerable group. Furthermore, ropinirole increased preference for uncertainty in the wager-insensitive rats, which was not observed in the previous chronic experiment but has been demonstrated by Tremblay et al. (2017). However, the effect of ropinirole on decision making appeared to be smaller in magnitude in the wager-insensitive group than the wager-sensitive group, suggesting that it was a smaller ropinirole-induced effect to be block. Just an in humans, it is difficult to categorize how much of an increase in preference for uncertainty would be considered pathological. Here, any departures from baseline preference or changes compared to the control group are considered problematic, but whether they are a true representation of GD in humans is not certain. What is certain is that that these changes in decision making are observed in patients on DA agonists with ICDs and can therefore be used to model problematic gambling behaviour induced by DA agonists in rats (Voon et al., 2011a). Therefore, the blockade of ropinirole's effect in wager-insensitive rats should still be considered to be of clinical significance.

Another unexpected finding was that 3 mg/kg of S111224 increased hole omissions. This may indicate possible motor impairment because nose-poking in the five-hole array after lever

pressing requires the rat to turn around and move to the back of the operant chamber to poke its nose. However, other similar non-choice variables were not altered, like lever choice latency and collection latency, which measure speed to reach the lever and food tray respectively, but none of these variables require the rat re-orientate themselves completely. Also, the distance between each lever and between the lever and the food tray is significantly smaller than the distance between the front of the box, where the lever and food tray are located, and the five-hole array. To further address this potential impairment in movement, locomotor activity in response to a 3 mg/kg of S111224 or vehicle injection should be measured in future research.

4.4 Strengths and Limitations

This series of experiments are the first demonstration that GPR52 agonists might have potential as a medication for iatrogenic GD and other ICDs mediated by the preference for uncertainty and decision-making distortions. Understandably, the changes in decision making that occur in psychiatric disorders are difficult to model. However, the DA agonist ropinirole reliably induced an increase in preference for uncertainty on the rBT, allowing for this change in preference to be used as an approximation for GD. By using rats to model GD, social and environmental factors are able to be tightly controls and standardized across animals. Therefore, the effect that these drugs have on behaviour is considered to be causal rather than correlational.

A limitation of these experiments is the number of animals. Specifically, the number of wager-sensitive animals was small per cohort. If wager-sensitive rats are considered the vulnerable group that shows the largest response to ropinirole, it would be ideal to have as many of these animals as possible. However, wager-sensitivity can only be determined once the rats are trained and have a stable responding pattern on the task. Based on previous experiments in our lab, anywhere between 20-40% of the rats are classified as wager-sensitive (Cocker et al.,

2012; Tremblay et al., 2017). This becomes problematic when they need to be dispersed equally between the experimental groups. In the chronic experiment with S111224, there were only 4 to 6 wager-sensitive rats in each group, making wager-insensitive rats the majority. Due to individual difference in responding, it is hard to make firm conclusions about the responses of the wager-sensitive animals when there is only a few in each group. This was evident with the wager-sensitive rats that were assigned to the control condition in the second chronic experiment. These rats demonstrated a preference for uncertain that was atypically low; therefore, the control group from the previous chronic experiment had to serve as a comparison. However, this could have potentially been mitigated by ensuring that the wager-sensitive and wager-insensitive groups are better balanced before experimentation.

Another potential limitation is the route of administration of both the GPR52 agonists and ropinirole. PD patients administering DA agonists orally have a higher prevalence of ICDs compared to patients that received their DA agonist transdermally, suggesting that "slow release" formulations are less effective at triggering an ICD than more pulsatile release (Garcia-Ruiz et al., 2014). However, both mechanisms of DA agonist administration can invoke ICD-related behaviour in rats, validating the use of osmotic pumps for the administration of ropinirole (Holtz et al., 2016; Rokosik & Napier, 2012; Tremblay et al., 2017). Furthermore, the increased prevalence of ICD with DA agonists compared to L-dopa is thought to be caused by the longer lasting tonic stimulation that occurs with DA agonists compared to L-dopa because of the longer elimination half-life (Chase, 1998). This argument would oppose the idea that prevalence rates differ between PD patients administered DA agonists orally due to the pulsatile action of the drug compared to the tonic action of transdermal DA agonist. However, more research needs to be conducted on the underlying mechanism of DRT-induced ICDs and their prevalence among

PD patients to be certain. As for the administration of GPR52 agonists via intraperitoneal injection, this is not an ideal route of administration for any novel compound because it will likely be administered orally in humans. However, oral administration is technically very challenging in Long Evans rats. These experiments serve as a preliminary proof of concept that this drug class might be efficacious, and further testing can be done with effective oral formulations. For the purposes of this experiment, administering the compound via injection allowed the drug to be active in each rat at approximately the same time during testing. A limitation that impacts all of the common routes of administration, is the inability to measure the amount of active compound in the blood without full pharmacokinetic/pharmacodynamics analyses. We our working with our industry partners on obtaining these data for Long Evans rats, but this was unavailable at the time this thesis was submitted. Such analyses are not trivial to conduct, and our lab does not have the required equipment in house.

In these experiments, a PD model wasn't used, potentially limiting the translational value of the research. However, DA agonists have been shown to produce ICDs in other patient groups with substantially different pathology than PD patients (Holman, 2009; Ondo & Lai, 2008). Also, DA agonists have been shown to induce the same changes in decision making in a PD rat model and healthy rats (Holtz et al., 2016; Rokosik & Napier, 2012; Tremblay et al., 2017). Overall, these findings add to a growing body of literature suggesting that DA agonist-ICDs occur independent of PD pathology. Therefore, at this stage in testing, a PD rat model is not needed. Although to ensure that neither of these GPR52 agonists do not exacerbate PD motor symptoms or interfere with ropinirole's anti-parkinsonian effects, they will eventually need to be tested in a PD rat model. Currently, the results demonstrate that GPR52 agonists have the potential to be effective not only for PD patients, but also for other individuals taking DA

agonists, but there are several steps in pre-clinical testing that need to be conducted prior to drawing any firm conclusions in this regard.

4.5 Implications

This research has several different clinical implications. First, it contributes to the growing body of research implicating DA agonists in the development of ICDs, especially GD. In both chronic experiments conducted with ropinirole, there was a significant increase in preference for uncertainty, which is a known decision-making bias observed in humans with GD (Voon et al., 2011a). Although this was a chronic experiment in terms of the experimental duration, this effect occurred relatively quickly. In the first chronic experiment, the effect of ropinirole on decision making was present after 10 days of administration and was substantially larger by the fourth week. Thus, DA agonists have the potential to alter decision making quickly. This research also demonstrates that the effect of DA agonists can occur in healthy individuals because these rats don't have any prior history of problematic gambling behaviour or substance use. In humans, these factors may make individuals more susceptible to effects of DA agonists but don't appear to be necessary for the development of DRT-induced ICDs, which is supported by the findings here (Evans et al., 2006). However, the effect of ropinirole is more prominent in rats with a pre-existing decision-making bias. These biases can easily be tested in humans prior to prescription of DA agonists and used to inform the patient. Although this is not a solution for DRT-induced ICDs, it may lower the prevalence rate and at least patients can be warned that this is a side-effect that they are at an increased risk of developing. Also, these at-risk patients on DA agonists could then be monitored for the development of ICDs, which may help the identification and subsequent treatment of these disorders occur sooner. Being able to catch DRT-induced ICDs early is important because the effects of these medications may increase over time, which

was demonstrated in these experiments. Therefore, if the development of an ICD is suspected, the patient can change their medication before the severity increases. It is important to note that this application applies more to GD than other ICDs because they may not be mediated by changes in decision making that can be readily tested using decision-making tasks like the IGT.

This research also provides further support for DRT-induced ICDs being caused by changes in DA signalling. It was clearly demonstrated that changes in preference for uncertainty were caused by the administration of ropinirole, even though it was delivered via a "slow release" mechanism. This provides evidence against the argument that DRT-induced ICDs are produced due to pulsatile stimulation of DA receptors and provides support for the hypothesis that implicates tonic DA receptor stimulation in the manifestation of these disorders (Eimeren et al., 2009). Moreover, GPR52 receptors are exclusively localized on the D2-expressing neurons in the striatum, suggesting that ropinirole is causes this effect via D2 rather than D3 receptors (Komatsu et al., 2014; Sawzdargo et al., 1999). It is also possible that ropinirole is effecting decision making via the D1 receptors in the cortex, which are also co-expressed with GPR52 receptors (Komatsu et al., 2014). This provides support for the further investigation of cortical regions that may be impacted by DA agonists. Moreover, the current research opposes the striatal overdose hypothesis that implicates the excessive DA activity in the ventral but not dorsal striatum in the development of DRT-induced ICDs due to the lack of PD-related neuronal degeneration in the rats used in these experiments (Vaillancourt et al., 2013).

So far, applications for novel GPR52 agonists have focused on the treatment of schizophrenia due to the motor side-effects produced by D2 antagonists (Grottick et al., 2018; Grottick et al., 2017a; Grottick et al., 2017b; Tokumaru et al., 2017). In the current experiments, GPR52 agonists demonstrated a pro-cognitive effect without significantly interfering with basal

or motor function, which is consistent with previously findings with other novel GPR52 agonists. However, there were some indications that both of the novel compounds tested may interfere with motor activity at a higher dose, but this was not directly measured and was not consistent among related indirect measurements. The results overall indicate that these compounds are viable as a potential treatment for not only DRT-induced ICDs, but also idiopathic ICDs, substance use disorders, and schizophrenia because aberrant DA signalling is implicated as the underlying cause of all these disorders (Franken, Booij, & van den Brink, 2005; Howes & Nour, 2016; Weintraub, 2008). The current research focuses on GD and iatrogenic ICDs, leaving the effectiveness of GPR52 agonists to reduce symptoms of idiopathic ICDs and substance use disorders to still be evaluated.

4.6 Future Directions

As much as this research takes a step towards further understanding DRT-induced ICDs and medications that may be able to manage their corresponding symptoms, there is still a lot of work to be done. The current research demonstrates that ropinirole can produce changes to decision making but it doesn't investigate why. To aid in the understanding of the mechanism underlying these changes, imaging techniques can be used to measure D2 and D3 receptor density in rats during chronic administration of ropinirole. This is especially relevant for the wager-sensitive rats because they have a pre-existing decision-making bias as well as altered D2 and D3 receptor density, and they show the most substantial change in behaviour with chronic ropinirole administration. This would help not only elucidate potential neurobiological mechanism underlying ICDs in humans, but also has potential clinical applications. For examples, if decreased D2 and D3 receptor density contributes to the development of DRT-

induced GD, then patients can be screened for this pre-existing vulnerability, be informed of the implications, and DRTs can be administered accordingly.

Another future experiment that would be useful is the administration of chronic ropinirole during the acquisition of the rodent Gambling Task (rGT), which is the rat analog to the IGT (Zeeb, Robbins, & Winstanley, 2009). During acquisition of the task, the rat is considered to be exploring different contingencies (Zeeb, Floresco, & Winstanley, 2010; Zeeb et al., 2009). This time period is especially relevant for the development of DRT-induced GD because they seem to appear without previous history of gambling. Thus, introduction to gambling games while on a DA agonist may put individuals at risk of developing GD and is a risk factor that could be monitored. By administered ropinirole during acquisition on the rGT, whether choice strategies are altered by ropinirole while acquiring the task rather than after they have formed can be investigated. This could also be done in the rBT to see if ropinirole administration during acquisition produces more wager-sensitive animals. Additionally, the effect of a pulsatile route of ropinirole administration could also be investigated to ensure there is no difference between tonic and pulsatile action of DA agonists on the rBT.

Lastly, future research should investigate the effect of GPR52 agonists on locomotor activity at a range of doses, both in healthy animals, and in a rat model of PD to ensure that these compounds don't interfere with motor function or ropinirole's anti-parkinsonian effect. Further, the compounds effectiveness via oral administrations should also be examined because that is the common administration route in humans. It would also be interesting to investigate whether GPR52 agonists administered during acquisition of the rBT prevent wager-sensitivity from developing due to their D2 antagonist-like effect and the correlation of wager-sensitivity with striatal D2 and D3 receptor density (Cocker et al., 2012).

4.7 Conclusion

This research demonstrated that GPR52 agonists have to potential to be not only an adjunct therapy for DRT-induced ICDs in both PD patients and other affected patient groups, but also a monotherapy for idiopathic GD and other disorders that are characterized by impairments in decision making. Regarding the safety of administered these compounds to patients with PD, further testing needs to be completed to ensure there is no impairment of motor function. This further testing should be conducted in PD rat model and with the GPR52 agonist being administered orally. This research also further confirmed that DA agonists are capable of significantly altering decision making in the absence of PD pathology, opposing the DA overdose hypothesis. Additionally, this effect was attenuated by GPR52 agonists, which exert a D2 antagonist-like effect in the striatum, suggesting that the D2 rather than the D3 receptor is involved in the emergence of these disorders. Overall, these findings highlight the role of DA agonists in iatrogenic ICDs, demonstrate the effectiveness of a potential pharmacological solution, and underscore the need for a better understanding of the neurobiological mechanisms underlying the development of DRT-induced ICDs.

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