IMPACTS OF REWARD SCHEDULES AND A DOPAMINE AGONIST ON DOPAMINE RECEPTOR EXPRESSION IN AN ANIMAL MODEL OF GAMBLING ADDICTION

CATHERINE LASKOWSKI
Master of Science, University of Lethbridge, 2022

A thesis submitted
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

NEUROSCIENCE

Department of Neuroscience
University of Lethbridge
LETHBRIDGE, ALBERTA, CANADA

IMPACTS OF REWARD SCHEDULES AND A DOPAMINE AGONIST ON DOPAMINE RECEPTOR EXPRESSION IN AN ANIMAL MODEL OF GAMBLING ADDICTION

CATHERINE LASKOWSKI

Date of Defence: December 20, 2022

Dr. D. Euston Thesis Supervisor	Associate Professor	Ph.D.
Dr. A. Gruber Thesis Examination Committee Member	Associate Professor	Ph.D.
Dr. D. Christensen Thesis Examination Committee Member	Associate Professor	Ph.D.
Dr. J. B. Leca Internal External Examiner Department of Psychology Faculty of Arts and Science	Associate Professor	Ph.D.
Dr. L. Clark External Examiner The University of British Columbia Vancouver, British Columbia	Professor	Ph.D.
Dr. A. Luczak Chair, Thesis Examination Committee	Professor	Ph.D.

DEDICATION

To my grandmother, who inspired me as a woman and let me stay up late to watch science fiction movies. You encouraged my love of science and I wish you were here today.

ABSTRACT

The unpredictable payouts of random-ratio schedules are highly motivating. This is likely due to the relationship between unexpected rewards and dopamine neurons, which release dopamine in response to unexpected reward. Dopaminergic activity can also be increased by certain types of drugs, many of which are used to treat Parkinson's disease. These medications have been linked to gambling addiction. This research explored the relationship between gambling schedules and dopamine and had three goals. First, we wished to test whether extended exposure to gambling-like reward schedules would induce addiction-like behaviour in rats, thus serving as a model of gambling addiction. Second, we sought to test whether any addictive properties of gambling-like reward schedules would be enhanced by chronic administration of a dopamine agonist, pramipexole, implicated in gambling addiction. Third, we sought to examine whether changes in dopamine receptor density in any reward-related brain regions predicted compulsive behaviour. In a series of experiments, rats were assessed for addiction-like behaviours after working for food reward on either a random or fixed ratio schedule of reinforcement. This was repeated in follow-up experiments with the addition of a dopamine agonist, pramipexole. Rats that were trained on the random ratio schedule were highly motivated but did not exhibit other signs of addiction. When pramipexole was added, rats displayed additional addiction-like symptoms. Finally, the brains of these animals were assessed for changes in dopamine receptor expression. Both reward schedule and pramipexole affected dopamine receptor expression in certain brain regions and, in some cases, receptor density correlated with addiction-like behaviours.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
BOLD	Blood-oxygen-level-dependent
CG	Cingulate gyrus
CNR	Cued no-reward
COMT	Catechol-O-methyltransferase
DA	Dopamine agonist
DDS	Dopamine dysregulation syndrome
DLPFC	Dorsolateral prefrontal cortex
DRA	Dopamine releasing agent
DRI	Dopamine reuptake inhibitor
DRT	Dopamine replacement therapy
fMRI	Functional magnetic resonance imaging
FR	Fixed ratio
GD	Gambling Disorder
ICD	Impulse Control Disorder
ICJ	Islands of Calleja
IGT	Iowa Gambling Task
INS	Insular cortex
MAOI	Monoamine oxidase inhibitor
MFC	Medial prefrontal cortex
MS	Medial septum
NAC	Nucleus accumbens
OFC	Orbitofrontal cortex
MS	Medial septum
PA	Progressive aversion
PAG	Periaqueductal grey
PET	Positron emission tomography
PFC	Prefrontal cortex
PD	Parkinson's disease
PPX	Pramipexole dihydrochloride
PR	Progressive ratio
PRP	Post reinforcement pause
RN	Dorsal raphe nucleus
RR	Random ratio
SCR	Skin conductance response
SN	Substantia nigra
SPECT	Single photon emission computed tomography
STR	Striatum
VP	Ventral pallidum
VR	Variable ratio
VTA	Ventral tegmental area

Chapter 1: Introduction and Background

1.1 Overview of Gambling Disorder

Gambling Disorder (GD) is classified as a mental illness whereby individuals will persist in gambling behaviours despite accumulating costs, often involving the inability to maintain healthy relationships, stable work or finances and in extreme cases, involves criminal behaviours such as theft to pay back debts to maintain gambling habits. As of 2018, more than 65% of the Canadian population had engaged in some form of gambling in the previous year, with lottery and raffle tickets being the most popular form of gambling (Williams et al., 2021). Overall, the rates of GD have decreased in Canada since 2002, mirroring a decrease in EGM/slot machine gambling as well as bingo, however, rates of online gambling have increased, particularly in the most recent years (Shaw et al., 2022). Continuous forms of gambling such as EGMs, slots, and table games (e.g., poker, blackjack, roulette) remain the highest-risk forms of gambling and are associated with the highest rates of GD (Binde et al., 2017). These games are characterized by rapid play, frequent reward and positive events, instantaneous rewards, and small bet sizes (Harrigan et al., 2010; Walker et al., 2012; Dixon et al., 2014a). The experiments in this document were designed to investigate the addictive nature of this continuous form of gambling and the effects that it has on reward-seeking behaviour and neurobiology in a rodent model.

Previously, GD was termed pathological gambling in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR; American Psychiatric Association, 2000) and classified as an impulse control disorder (ICD) rather than as an addiction. However, due to the considerable overlap in personality traits and etiological, genetic, and neurobiological factors, pathological gambling has recently been recategorized in the DSM-5 (American Psychiatric Association, 2013) as a behavioural addiction. In line with this recent recognition, in the

following pages, I will refer to GD as an addiction. Currently, GD is the only behavioural addiction recognized by the American Psychiatric Association. That said, other behavioural disorders that fall under the umbrella of ICDs, such as sex addiction/hypersexuality, binge eating, compulsive buying, as well as internet and gaming addiction share much in common with GD (Pinna et al., 2015), and so within the academic literature, these other disorders are often grouped with GD in a category called behavioural addictions. The problems experienced by people with behavioural addictions closely resemble many of the same problems experienced by individuals suffering from substance addiction.

The following document will explore the neurophysiological and neurochemical underpinnings known to be associated with gambling and other behavioural addictions. Chapter 1 will begin with one of the most prominent theories of GD, the Pathways Model by Blaszczynski and Nower (2002) and the role of random ratio (RR), and fixed ratio (FR) schedules of reinforcement on behaviour. This will lead to a discussion on the role of dopamine, dopamine receptors, and dopamine agonists (DA) in reinforcement, learning, motivation, and addiction. Then I overview genetic, demographic, psychological and clinical factors that confer an increased risk of developing a behavioural addiction. Following this, I overview findings from studies investigating GD and other behavioural addictions focusing on investigations into neuroanatomical and neurochemical correlates with a particular emphasis on the role of DAs. Finally, the chapter will close with questions derived from the literature and the experimental predictions that led to the series of experiments conducted to address these questions. Chapter 2 details the first two behavioural experiments conducted which examine whether prolonged exposure to RR schedules of reinforcement is sufficient to cause rats to exhibit behaviours consistent with addiction. In Chapter 3, I present data from another two experiments designed to

assess whether the administration of a dopamine D3 receptor-preferring agonist, pramipexole dihydrochloride (PPX), would elicit additional addiction-like behaviours in rats trained to respond for food reward on a RR schedule (as well as an FR schedule in Exp. 4) of reinforcement. Finally, in Chapter 4, I will overview the main findings from the experiments and discuss their relevance to the study of gambling addiction. Limitations of the interpretation of the findings will be considered. Lastly, I will relate the findings back to the initial experimental questions, consider whether the results of the studies support current theories of gambling addiction, and what future questions should be addressed.

An important note about the focus and content contained in this thesis is that although many other neurotransmitters are certainly integral to the development and maintenance of addiction; this thesis will focus primarily on the role of dopamine, dopamine precursors, dopamine agonists and related cellular infrastructure including dopamine receptors, transporters, and enzymes. Additionally, the literature review below focuses primarily on GD and ICDs. While the research into substance use disorders has been critical to our current understanding of the neurobiology of addiction, a full review of that literature is beyond the scope of this thesis.

1.2 The Pathways Model of Gambling Addiction

GD is a multifaceted disorder that affects a wide variety of people, each with their own particular emotional/motivational needs, and gambling preferences. Prevalence, epidemiological, and clinical studies have noted several different dimensional manifestations among this group primarily related to personality, reasons for gambling, preferred game type, psychiatric comorbidities, and biological/genetic vulnerabilities (Blaszczynski, 2000; Christensen et al., 2019).

Perhaps the most widely known theory of GD to address this multidimensionality is 'the Pathways Model' by Blaszcynski and Nower (2002). In this manuscript, the authors outline a theoretical framework to explain several different etiological pathways, incorporating biological, psychological, and ecological variables that contribute to the development of GD. In their model, they propose three distinct subgroups of gamblers, namely; (1) behaviourally conditioned, (2) emotionally vulnerable, and (3) antisocial, impulsivist disordered gamblers. According to this theory, the first and primary pathway requires that gamblers experience the reinforcing effects of gambling games; that is repeated pairings of gambling behaviour with monetary reinforcement, associated stimuli (lights and sounds) and physiological arousal (feelings of excitement). Theoretically, the addictive nature of the gambling game revolves around the uncertainty or unpredictability of the reward, which both animals and humans find highly motivating (this will be discussed in more depth below). This group is characterized by a lack of premorbid psychopathology and gambling is introduced and reinforced by family and friends or sometimes just by chance. The two other pathways derive from the first in that all gamblers that go on to develop GD must necessarily experience behavioural conditioning. However, the other two groups exhibit additional premorbid psychiatric vulnerabilities. Specifically, the emotionally vulnerable group has a history of anxiety and/or depression, traumatic life events, and poor coping and problem-solving skills. The antisocial, impulsivist type, on the other hand, is characterized by substance abuse, low tolerance for boredom, irritability, poor interpersonal relationships, and criminality. So central to this theory of GD is the nature of the games themselves in that regardless of which pathway a person takes toward gambling addiction, all must be exposed to the addictive nature of the games themselves, which then act upon certain psychological, environmental, or social vulnerabilities.

The most obvious factor that distinguishes gambling from other sorts of activities is the unpredictable nature of the rewards, also known as the reward schedule. Unpredictable reinforcement has long been recognized as a particularly powerful mechanism of behavioural conditioning (Skinner, 1953) and it is well known that unpredictable outcomes drive dopamine release (Mirenowicz and Schultz, 1994; Schultz, 1997), which is important because all drugs of abuse, directly or indirectly overdrive the dopamine system (Volkow and Morales, 2015). While there is a general recognition of the importance of reward schedules, little is known about why they are so attractive or whether they alone are powerful enough to generate addiction. The first aim of this research is to test the theory that simple repeated exposure to unpredictable schedules of reinforcement can produce addiction-like behaviours in healthy rats via the mechanisms of operant and classical conditioning, similar to the first pathway in Blaszcynski and Nower's model. However, one of the core features of the behavioural conditioning theory is that the exposure must be repetitive and prolonged – addiction does not happen overnight. There must be many pairings between action and outcome often over the course of weeks to months. This of course makes it very difficult to do experimentally with humans.

While animal models cannot capture all aspects of the gambling experience or the addiction processes - after all, it is difficult to get rats to care about money or how the time they spend in the casino is affecting their marriage - there are many aspects of gambling addiction that can be studied using animal models. Animal models also provide certain advantages over human studies: experimental conditions can be rigorously controlled, neurotransmitters monitored and manipulated, tissue extracted, and gene expression can be manipulated. Of particular relevance to this thesis is the study of behavioural and neurobiological changes in response to unpredictable schedules of reinforcement. Using a rodent model, I will explore whether

prolonged exposure to unpredictable RR schedules of reinforcement will cause rats to develop gambling addiction-like behaviours. I will also investigate the effect of chronic DA administration on the development of gambling addiction in rats using the same behavioural task. DAs have been linked to substantial increases in the prevalence of GD and other ICDs, particularly in the Parkinson's disease (PD) patient population. Prolonged DA administration alters the dopamine system and is thought to shift behaviour and cognition toward increased impulsivity and compulsivity, constituting a vulnerability to addiction. However, many of the neurobiological changes that happen as a result of this process remain unclear. So, I also aim to clarify some of these changes, specifically how dopamine D2 and D3 receptor expression is modified in several brain regions as a consequence of both PPX exposure and the schedule of reinforcement.

1.3 Animal Models of Gambling Disorder and Schedules of Reinforcement

Several attempts have been made to capture aspects of GD in animal models. Gambling addiction can be conceptualized as a disorder in decision-making where individuals trade valuable resources (their time and money) for the chance to win money. In line with the idea that people with GD have impaired decision-making abilities, most of the animal models of GD that have been developed previously focus on risky decision-making (Cocker and Winstanley, 2015). In these models, animals typically choose between several response options that differ in the probability of food reward payout or a time-out punishment. The animals learn the risks of each response option over time and the risk-preferring rats will usually prefer the option associated with high amounts of food reward paired with large time-outs, whereas less risk-preferring animals will maximize the food reward over time by choosing options with lower trial-by-trial food rewards, but much shorter time-outs (Zeeb et al., 2009). One of these tasks, the "rodent

gambling task", was modelled after the Iowa Gambling Task (IGT). The IGT was designed by Bechara et al. (1997) to measure decision-making deficits that they observed in patients with medial prefrontal cortex (MFC) lesions. In this task, human subjects choose between decks of cards that differ in the amount and probability of monetary gain and loss (Bechara et al., 1994). The high-reward/high-risk decks are initially appealing but ultimately result in a net loss. Healthy humans quickly learn to avoid these decks whereas people with MFC lesions, people with GD, and other groups of people with high levels of impulsivity and risk-taking are drawn to them (Goudriaan et al., 2005). In the rodent analogue, the cognitive impairments seen in risky option-preferring rats are thought to mirror the decision-making impairments seen in those with GD (Winstanley and Clark, 2016).

Other animal studies have used probability discounting paradigms to explore risk preference. In these tasks, a fixed, low-value reward is offered against a high-value reward which decreases in probability over time (St Onge and Floresco, 2009; McKerchar and Renda, 2012). The slower an animal or human is to switch away from the probabilistic high-value reward, the higher their risk tolerance - a trait found in GD (Madden et al., 2009). Another prominent task is the 'rodent betting task', in which a rat must decide between collecting a definite reward or 'doubling down' and opting for a 50% chance of receiving double the reward or nothing. Although the expected value of both the safe and risky options is equivalent across trials, some animals will prefer the risky option more often while others are risk averse (Cocker et al., 2012; Cocker et al., 2017). Given that risk-seeking and risky decision-making are correlated with gambling involvement and are a predictor for GD in humans (Mishra et al., 2010), these animal models offer insights into one of the central traits associated with GD.

Another approach, and the one explored in this thesis, is to focus on the gambling payout schedule. Slot machines employ a RR schedule of reinforcement, where the number of bets between rewards is random. It has been recognized for more than half a century that animals respond faster and longer when reward is unpredictable (Skinner, 1953; Ferster and Skinner, 1957). This phenomenon has been documented in both humans (Repp and Deitz, 1975; Williams et al., 2011) and animals (Mazur, 1983, 1986), both of which have a strong preference for these types of schedules over FR schedules, where the number of responses required to earn reward is fixed and thus predictable. The main theory as to why the RR schedule is so compelling derives from investigations into dopamine. Briefly, it is known that every major addictive substance either directly or indirectly increases dopamine action in the brain (Bonci et al., 2003) and dopamine neurons are known to respond most vigorously to unexpected rewards (Mirenowicz and Schultz, 1994; Shizgal and Arvanitogiannis, 2003). Additionally, there is evidence from both positron emission tomography (PET) imaging (Zald et al., 2004) and at least one microdialysis study (Mascia et al., 2019) that dopamine is released at higher levels when humans or animals respond on variable ratio (VR) schedules (which are similar to RR schedules) compared to FR schedules of reinforcement (cf. Sokolowski et al., 1998). So, it is not a great leap to theorize that gambling activities, defined by uncertain rewards, may drive dopamine neurons in a way that resembles drugs of abuse, thus creating an environment favourable to addiction pathogenesis.

Although each of the animal models discussed above captures some aspects of GD, none addresses the development of addiction or the shift from voluntary engagement to compulsion. Animal models of drug addiction have largely taken the same route, focusing on a single dimension of addiction, such as conditioned place preference, relapse/reinstatement of drug-seeking, self-administration/drug escalation, drug-seeking under second-order schedules of

reinforcement, or pairing drug reinforcement with punishment. One animal model of drug addiction developed in the early 2000s attempts to combine these features to produce a multidimensional assessment tool for drug addiction (Belin-Rauscent and Belin, 2012b). The 'three criteria model' by Deroche-Gamonet et al. (2004) assess animals using three criteria which are derived from the diagnostic criteria used to diagnose addiction in humans. The criteria are: **(1)** The animal should have difficulty refraining from drug seeking which is modelled after a persistent desire or repeated unsuccessful attempts to control, cut back or stop substance use, **(2)** the animal should have a high motivation to obtain the drug which taps into the DSM IV criteria of spending a great deal of time in activities necessary to obtain, use or recover from the effects of substance use, and **(3) t**he animal will maintain drug use despite negative consequences which mirror the continuation of substance use despite knowledge of having a persistent physical or psychological problem that is likely caused or exacerbated by continued use. The experiments detailed in Chapters 2 and 3 use a very similar task but are adapted for gambling addiction. The largest change to the paradigm was substituting cocaine self-administration with sucrose reinforcement on a RR schedule. These tasks are discussed in greater depth in section 2.3.

1.4 Dopamine Agonists and Behavioural Addictions

Parkinson's disease (PD) is a progressive neuropsychiatric disorder characterized by motor and non-motor symptoms. The former result from nigrostriatal dopaminergic neuronal loss and the latter include dysfunction within a wide range of neural structures involved in reinforcement learning, motivation, decision-making, inhibition, and cognition among others (Cilia et al., 2014). As of this time, there is no cure for PD, and the current therapies that are used primarily treat the symptoms of the disease. This involves replacing or substituting the deficit in dopamine transmission that is associated with disease pathology. Replacement therapy generally

includes the dopamine precursor (levodopa) which promotes dopamine synthesis and release and/or DAs which act directly on dopamine receptors and bypass the requirement for functioning presynaptic terminals.

Beginning in the early 2000s, clinicians treating patients with PD started reporting incidences of *de novo* GD in their patients (see Table 1.1). In these reports, clinicians noted that GD presented within 8 months (usually after 1-2 months) after the initiation of DA treatment or an increase in DA or levodopa dosage (Klos et al., 2005). It is important to note that it typically takes at least 6–8 weeks to escalate an agonist into the therapeutic range. Moreover, the problematic behaviours often resolve after either DA cessation or a reduction in dosage (Gschwandtner et al., 2001; Jiménez-Jiménez et al., 2002; Klos et al., 2005; Drapier et al., 2006; Imamura et al., 2006; Quickfall and Suchowersky, 2007; Mamikonyan et al., 2008; Bostwick et al., 2009; Fernández and González, 2009; Munhoz et al., 2009), however, there is evidence that if the problematic gambling behaviours were present before PD onset, then reduction of dopaminergic medication has little benefit (Kurlan, 2004). Many of these PD patients had little gambling experience and the minority that did gamble prior to PD onset reported significant increases in preoccupation with gambling and a heightened feeling of euphoria while gambling followed by distress and dysphoria at the end of a gambling session (Imamura et al., 2006). Of note, some of these reports indicate that the patients in their studies preferred slots to other forms of gambling (Molina et al., 2000), but this association has not been reviewed systematically. While this association between PD and GD appeared to be an emerging phenomenon, it falls in line with reports of other disorders that had been noted in a minority of PD patients since at least the 1980s, most of which were known to be rare consequences of dopamine replacement therapy (DRT). DRT is the standard treatment for the motor symptoms of PD, however, due to the

Reference	Case	ICD	Dopamine Agonist*	Dose	Dopamine Replacement	Dose
Avanzi et al. (2004)	1	GD	ropinirole entacapone	15 mg/day 400 mg/day	levodopa	525 mg/day
	2	GD	cabergoline entacapone	4 mg/day 800 mg/day	levodopa	425 mg/day
Dodd et al. (2005)	1	GD	pramipexole	4.5 mg/day	levodopa	600 mg/day
	2	GD	pramipexole	4.5 mg/day	levodopa	1000 mg/day
	3	GD	pramipexole amantadine	4.5 mg/day 200 mg/day		
	4	GD	pramipexole	4.5 mg/day	levodopa	1000 mg/day
	5	GD, HS, CS	pramipexole	4.5 mg/day	levodopa	300 mg/day
	6	GD, HS, BE	pramipexole	13.5 mg/day	levodopa	600 mg/day
	7	GD	pramipexole	7.5 mg/day		
	8	GD, HS	pramipexole	4.5 mg/day	levodopa	600 mg/day
	9	GD	pramipexole amantadine entacapone	8 mg/day 200 mg/day 1000 mg/day	levodopa	1000 mg/day
	1011	GD, HS, SA	ropinirole	21 mg/day		
		GD	ropinirole	15 mg/day	levodopa	1500 mg/day
Drapier et al. (2006)	1	GD	ropinirole	15 mg/day	levodopa	300 mg/day
	2	GD	pergolide	5 mg/day	levodopa	500 mg/day
	3	GD	pergolide	6 mg/day	levodopa	1800 mg/day
	4	GD	bromocriptine	12.5 mg/day	levodopa	950 mg/day
	5	GD	bromocriptine	40 mg/day	levodopa	900 mg/day
	6	GD	selegiline	10 mg/day	levodopa	500 mg/day
Fernández and González (2009)	1	GD, HS	ropinirole selegiline amantadine	20 mg/day 10 mg/day 300 mg/day	levodopa	400 mg/day
Gschwandtner et al. (2001)	1	GD	pergolide	3.5 mg/day	levodopa	800 mg/day
	2	GD	ropinirole	6 mg/day	levodopa	400 mg/day

Imamura et al. (2006)	1	GD	pramipexole	6 mg/day	levodopa	600 mg/day
	2	GD, HS	pramipexole	3 mg/day	levodopa	300 mg/day
	3	GD	pramipexole	4.5 mg/day	levodopa	300 mg/day
	4	GD	pramipexole	3 mg/day		
	5	GD	ropinirole	4.5 mg/day	levodopa	1000 mg/day
	6	GD	cabergoline	n.r.		
Jiménez-Jiménez et al. (2002)	1	HS	bromocriptine	15 mg/day	levodopa	750 mg/day
Klos et al. (2005)	1	GD, HS, BE,	pramipexole	13.5 mg/day		
	2	SA	pramipexole	4.5 mg/day	levodopa	1750 mg/day
		HS, CS, WA	selegiline	n.r.		
			tolcapone	n.r.		
	3		pramipexole	4.5 mg/day		
	4	HS, BE	pramipexole	3 mg/day	levodopa	1000 mg/day
		HS, SA	dextroamphetamine	n.r.		
			selegiline	n.r.		
	5		pramipexole	4.5 mg/day	levodopa	1000 mg/day
	6	GD, HS, WA	pramipexole	6 mg/day	levodopa	1200 mg/day
	7	HS	pramipexole	6 mg/day		
	8	HS	ropinirole	21 mg/day		
	9	GD, HS, BE,	ropinirole	20 mg/day	levodopa	600 mg/day
		SA	amantadine	n.r.		
		HS	tolcapone	n.r.		
	10		ropinirole	32 mg/day	levodopa	1000 mg/day
	11		ropinirole	24 mg/day	levodopa	1500 mg/day
	12	HS	pergolide	1.5 mg/day	levodopa	1875 mg/day
		HS	selegiline	n.r.		
	13	GD, HS	pergolide	3 mg/day	levodopa	1000 mg/day
			tolcapone	n.r.		
	14	HS	pergolide	3 mg/day	levodopa	700 mg/day
			amantadine	n.r.		
		HS	selegiline	n.r.		
	15				levodopa	600 mg/day

		HS				
Kurlan (2004)	1	GD	pramipexole	3 mg/day	levodopa/ carbidopa	900 mg/day
	2	GD	pramipexole	1.5 mg/day	levodopa/ carbidopa	750 mg/day
	3**	RCB			levodopa/ carbidopa	1000 mg/day
	4**	RCB			levodopa/ carbidopa	1800 mg/day
	5**	RCB	tolcapone	50 mg/day	levodopa/ carbidopa	800 mg/day
	6**	RCB	entacapone	400 mg/day	levodopa/ carbidopa	1200 mg/day
Molina et al. (2000)	1	GD	n.r.	n.r.	levodopa	n.r.
	2	GD, RCB	n.r.	n.r.	levodopa	n.r.
	3	GD, RCB	n.r.	n.r.	levodopa	n.r.
	4	GD	n.r.	n.r.	levodopa	n.r.
	5	GD, BE	n.r.	n.r.	levodopa	n.r.
	6	GD, SA	n.r.	n.r.	levodopa	n.r.
	7	GD, RCB	n.r.	n.r.	levodopa	n.r.
	8	GD	n.r.	n.r.	levodopa	n.r.
	9	GD	n.r.	n.r.	levodopa	n.r.
	10	GD	n.r.	n.r.	levodopa	n.r.
	11	GD	n.r.	n.r.	levodopa	n.r.
	12	GD	n.r.	n.r.	levodopa	n.r.
Montastruc et al. (2003)	1	GD	bromocriptine	n.r.	levodopa	n.r.
Munhoz et al. (2009)	1	HS	pramipexole	4.5 mg/day	levodopa/ carbidopa	400 mg/day
Pignatti et al. (2012)	1	GD	pramipexole cabergoline	n.r.	levodopa	n.r.

Pontone et al. (2006)	1	GD	pramipexole amantadine	3 mg/day 300 mg/day	levodopa	400 mg/day
	2	GD	pramipexole	6 mg/day	levodopa	800 mg/day
	3	HS	pramipexole entacapone selegiline	2.75 mg/day 600 mg/day 10 mg/day	levodopa	300 mg/day
	4	HS	pramipexole	1.5 mg/day	levodopa	300 mg/day
	5	HS, CS	pramipexole entacapone	5 mg/day 800 mg/day	levodopa	1000 mg/day
	6	CS	pramipexole	1.5 mg/day	levodopa	700 mg/day
	7	GD	pramipexole ropinirole	6 mg/day 5 mg/day		
	8	GD	ropinirole entacapone	6 mg/day 900 mg/day	levodopa	300 mg/day
	9	HS, CS	ropinirole amantadine	4 mg/day 300 mg/day	levodopa	600 mg/day
Seedat et al. (2000)	1	GD	pergolide selegiline	n.r. n.r.	levodopa/ carbidopa	n.r.

Table 1.1. Case reports. Not reported (n.r.). Doses reported are those prescribed at the onset of GD/ICD. Many of these patients reported increasing doses of both levodopa and DAs well beyond these levels without the knowledge of their physicians. Gambling disorder (GD), hypersexuality (HS), compulsive shopping (CS), binge eating (BE), substance abuse including nicotine (SA), walkabout (WA), repetitive compulsive behaviours (RCB).

*Note: Although the majority are DAs, this column also includes the MAOI, selegiline, the COMT inhibitors, entacapone and tolcapone, and the dopamine releasing agent/reuptake inhibitor, amantadine.

**Note: These patients developed obsessive-compulsive-like behaviours (repetitive ordering/cleaning) rather than impulsive/addictive behaviours.

progressive nature of the neurodegenerative disease, increasing doses of levodopa and other antiparkinsonian medications such as DAs are needed to control the worsening motor symptoms. Consequently, a minority of patients that are chronically treated with these drugs may develop cognitive and behavioural disturbances that mirror that of drug addiction, a condition called dopamine dysregulation syndrome (DDS). Most of the earliest case reports reveal that a portion (3-4%) of PD patients, of their own volition, increased their levodopa medication to levels far above what was needed to control their motor symptoms. These patients often reported feeling that they needed the larger doses to control their motor behaviours and to combat low mood and may develop mood disorders, hypomania, or manic psychosis (manifesting usually as paranoia) as a result of this excessive consumption (Giovannoni et al., 2000; Cilia et al., 2014). This has also been reported in two patients who tried to switch from PPX immediate release to extended-release. These patients refused the switch in medication and both began to increase their levodopa and PPX immediate-release medications to maintain the elevated mood state (Solla et al., 2013). Although levodopa is the most commonly abused parkinsonian medication, some patients abuse other medications with or without concurrent levodopa misuse. Cilia et al. (2014) conducted a retrospective case-control study with 35 PD patients with DDS, 70 PD-matched controls, and 1281 unmatched PD subjects and reported that although most of the medication abuse was focused on levodopa, a minority of patients (9%) preferentially abused their DA medication. The increased consumption of levodopa seen in DDS carries several potential side effects including unpleasant “off” motor and non-motor side effects which further reinforce drug taking through negative reinforcement mechanisms, precipitation or worsening of mood disorders, frontostriatal dysfunction, and motor sensitization. Most of these effects are also risk factors for DDS along with certain environmental (such as being unmarried or having a poor

level of care/oversight) and genetic vulnerabilities (Lawrence et al., 2003; Katzenschlager, 2011; Solla et al., 2013).

The other major behavioural side effect noted early on was hypersexuality in mostly male PD patients. For example, Vogel and Schiffter (1983) reported the case of a male PD patient treated with levodopa and bromocriptine. This patient admitted to abusing his medication and developed hypersexuality along with paranoid-hallucinatory psychosis. Prevalence studies of this phenomenon found that about 1% of PD patients would experience hypersexuality as a complication of levodopa treatment (Goodwin, 1971; Munhoz et al., 2009). Later, other forms of dopaminergic treatment, particularly DAs, were connected to several pathological sexual behaviours, particularly hypersexuality, exhibitionism, sexual jealousy, and paraphilias, sometimes causing legal problems for these patients (Fernandez and Durso, 1998; Jiménez-Jiménez et al., 2002; Riley, 2002; Berger et al., 2003; Klos et al., 2005; Cannas et al., 2006).

These syndromes have a few names in the literature. As mentioned previously, the most established is DDS, which generally refers to the pattern of excessive medication consumption. Other DRT-related disorders such as hypersexuality, walkabout (which is defined as a restlessness that manifests in a strong urge to walk or travel (Leeman and Potenza, 2011), and compulsive shopping were categorized under the term hedonistic homeostatic dysregulation (Giovannoni et al., 2000; Avanzi et al., 2004), and are collectively still referred to by that name in some of the literature, but most researchers, clinicians, and scholars now refer to these disorders as impulse control disorders (ICDs). ICDs and DDS share much in common including personality, neurobiological, genetic and environmental risk factors (Pontone et al., 2006; Smeding et al., 2007), however, there are some differences (Napier et al., 2015) that will be discussed below (see section 1.7).

Following these initial case reports, researchers began to collate this data, conducted larger controlled prevalence studies and noted markedly higher prevalence rates of GD in patients with PD (.48%-5.7%) compared to the general population (Becona, 1997; Shaffer et al., 1999; 0.25-2.3%; Avanzi et al., 2006; Voon et al., 2006; Giladi et al., 2007; Crockford et al., 2008; Bostwick et al., 2009; Barns Neurauter et al., 2010; Williams et al., 2012). They also noted that the risk of developing GD jumps substantially when considering only those patients treated with a DA (0.7-14.1%). When including all ICDs (Voon and Fox, 2007), the effects are even more dramatic (see Table 1.2). The largest of these studies, the DOMINION study, found 13.6%

Reference	Screening Target	Sample Size	Overall Prevalence	DA Prevalence
Bostwick et al. (2009)	GD and HS	267	2.6%	13.2%
Callesen et al. (2013a)	ICD	490	35.9% life 14.9% cur	n.r.
Corvol et al. (2018)*	ICD	411	46.1%	51.5%
Crockford et al. (2008)	GD	140	5.7%	14.1%
Driver-Dunckley et al. (2003)	GD	1884	0.48%	0.7%
Garcia-Ruiz et al. (2014)	ICD	233	n.r.	39.1%
Grosset et al. (2006)	GD	388	4.4%	8%
Hassan et al. (2011)	ICD	321	n.r.	24%
Isaias et al. (2008)	ICD	100	n.r.	28%
Lee et al. (2010)	ICD	1167	10.1%	10.8%
Lu et al. (2006)	GD	~200	n.r.	7%
Pontone et al. (2006)	ICD	100	9%	13.8%
Ribacoba et al. (2010)	GD	106	2.8%	n.r.
Singh et al. (2007)	ICD	300	n.r.	19.3%
Vela et al. (2016)**	ICD	87	58.3%	66.2%
Voon et al. (2006)	GD	297	3.4%	7.2%
Weintraub et al. (2006b)	ICD	272	6.6%	n.r.
Weintraub et al. (2010)	ICD	3090	13.6%	17.1%

Table 1.2. Prevalence studies of GD and ICDs in PD patients. Not reported (n.r.).
*Note: This longitudinal study used a 5-year cumulative incidence rate.
**Note: This prevalence study reported on early-onset PD patients only and included hobbyism in the screening.

of PD patients from US and Canadian treatment centres had a concurrent ICD. Of the 3090 patient screens, 5% were positive for GD, 3.5% for hypersexuality, 5.7% for compulsive buying, and 4.3% for binge-eating disorder. The authors also found that 3.9% had more than one ICD (Weintraub et al., 2010). A similar study with 1167 South Korean participants found 10.1% ICD point prevalence in their PD patients. When examining particular kinds of disorders, they found relatively high rates of punding (4.2%; punding is a term that refers to repetitive, stereotyped motor patterns); compulsive eating (3.4%); hypersexuality (2.8%); compulsive buying (2.5%), gambling (1.3%), while 28.8% of this group had 2 or more ICDs (Lee et al., 2010). Lastly, Moore et al. (2014) identified 1580 people with ICDs and comorbid PD, restless legs syndrome, or hyperprolactinemia from a public database of 2.7 million reported adverse events related to drug use. Of these individuals, 44.9% were prescribed DAs, while 55.1% were prescribed other dopaminergic medications. GD was the most frequently reported adverse event (39.7%), followed by hypersexuality, compulsive shopping, and walkabout. Considering the emergence of GD in a relatively large number of PD patients exposed to DAs, investigations into how DA affects neurophysiology may provide a model of the pathophysiology of GD/ICDs in the general population.

It is important to note that studies intended to analyze the prevalence of GD and ICDs in the context of antiparkinsonian medication are particularly difficult to conduct for several reasons. First, many patients fail to report even serious side effects to their physician (Perez-Lloret et al., 2012). This may be compounded in GD/ICDs due to embarrassment or fears of judgment by the attending physician or family members (Weintraub et al., 2009). Many patients have to be asked directly and only reveal behavioural problems after initial denials indicating that the true incidence is likely larger than reported (Quickfall and Suchowersky, 2007; Hassan

et al., 2011). Another related phenomenon noted by clinicians is the low level of insight that some of these patients appear to have into their behaviour. Illustrating this, Munhoz et al. (2009) reported a case of a male PD patient who was encouraged to come to an appointment by his wife. She told the neurologist that her husband had been exhibiting hypersexuality which included practices that they had never engaged in as a couple prior to his PD diagnosis. At first the, patient denied any abnormalities, but went on to explain that although these were new to his experience with his wife, he assumed these were practices that he secretly desired when he was younger but never felt comfortable enough to open up to her. He said that he simply felt less ashamed to put his desires into practice. This patient appears to have withheld telling the physician about these changes in behaviour because he simply did not see them as being outside of the normal range of his behaviour and could not understand why his wife should have a problem with it. His symptoms subsided after discontinuation of his PPX treatment. Adding to the issue of low levels of disclosure, several aspects of ICDs such as compulsive shopping and excessive hobbyism (i.e., excessive engagement in hobbies such as internet use, fishing, driving, etc.) are not considered abnormal behaviours for many patients or their caregivers (Garcia-Ruiz et al., 2014). Lastly, many patients with PD are, over the course of the disease progression, switched from one medication to another, including withdrawing and adding different DAs and sometimes combinations of different DAs, MAOIs, DRA, and DRI are used, making the link between individual medications and GD/ICD difficult to establish (Garcia-Ruiz et al., 2014). All of this combines to make it particularly difficult to determine the true prevalence of GD/ICDs in patients treated with dopaminergic medications. Generally, those studies that used self-report or reviews of patient files find lower over rates of GD/ICDs whereas those that used structured face

to face clinical interviews and corroborated testimony with family members/caregivers find significantly higher rates.

One particularly strong factor that is noted in these prevalence studies is the dopamine replacement therapy that the patients were prescribed, particularly the DA medication. A plurality of the prevalence studies agree on a higher incidence of GD and ICDs in patients treated with DAs (2-3.5-fold increased odds; Weintraub et al., 2010) compared with levodopa/ carbidopa monotherapy (Pontone et al., 2006; Voon et al., 2006; Lee et al., 2010). There are also reports of individuals developing these disorders on DA monotherapy (Klos et al., 2005; Avanzi et al., 2006; Vela et al., 2016) and monoamine oxidase inhibitory monotherapy (Fernandez and Chen, 2007; Weintraub and Mamikonyan, 2019), therefore no medication is necessary for these disorders to present. That said, the large majority of patients treated with a DA were also treated with levodopa/carbidopa, so teasing apart the relative contributions of each are difficult.

There also appears to be an association between GD/ICDs and DRT dose, specifically

Pharmacological Agent	Pharmacological Target	Maximum Recommended Dosage		
		Parkinson's Disease	Restless Leg Syndrome	Hyperprolactinemia
levodopa/carbidopa	dopamine precursor	420 mg/day	n.t.	n.t.
pramipexole	D3>D2	4.5 mg/day	.5 mg/day	n.t.
ropinirole	D3>D2	8 mg/day	4 mg/day	n.t.
pergolide	5-HT_{1A}>D3>D2	3-5 mg/day	n.t.	0.1 mg/day
cabergoline	D2=D3>5-HT	3 mg/day	n.t.	1 mg/biw
selegiline	MAO-B inhibitor	10 mg/day	n.t.	n.t.
bromocriptine	α_1>D2=D3	100 mg/day	n.t.	15 mg/day
amantadine	DRI and DRA	322 mg/day	n.t.	n.t.
entacapone	COMT inhibitor	1600 mg/day	n.t.	n.t.
tolcapone	COMT inhibitor	300 mg/day	n.t.	n.t.

Table 1.3. Pharmacological Agents. Not an indicated treatment (n.t.). Maximum dosage information was collected from the Mayo Clinic (n.d.) website. Monoamine oxidase inhibitor (MAOI), Dopamine reuptake inhibitor (DRI), dopamine releasing agent (DRA), catechol-O-methyltransferase (COMT).

higher doses of levodopa and DAs (Driver-Dunckley et al., 2003). However not all higher doses of levodopa and DAs (Driver-Dunckley et al., 2003). However not all studies have found this association (Weintraub et al., 2010; Callesen et al., 2013a) and these disorders have been seen even in individuals with relatively low doses (Grosset et al., 2006). While it does appear that most individuals that develop GD/ICDs while taking DAs are prescribed doses at the high end of (or significantly over) the recommended maximum daily amount (see Table 1.3), regardless if they are prescribed the medication for PD or for other disorders (this is discussed in more depth in section 4.2), several research groups reported a lack of a DA dose relationship with GD/ICDs which suggests that the medications interact with an underlying vulnerability (Voon et al., 2007b; van Eimeren et al., 2009). In this context, the emergence of GD/ICDs in response to high doses of DAs and other dopaminergic medications could be seen as a pharmacological challenge, which may serve to unmask various neurobiological, genetic, and/or physiological vulnerabilities that are latent in the general population (Steeves et al., 2009).

One possible neurobiological explanation for the association between DAs and GD/ICDs centers around dopamine-receptor binding profiles. D1 and D2 receptors are both found abundantly in the dorsal striatum (Gurevich and Joyce, 1999; Bentivoglio and Morelli, 2005). These receptors are thought to mediate most of the motor effects of DRT, whereas D3 receptors are most abundant in the ventral striatum (Sokoloff et al., 1990; Murray et al., 1994), a region of the brain heavily implicated in both behavioural (Holden, 2001) and substance addictions (Brewer and Potenza, 2008). This is important because the most commonly prescribed DAs, PPX and ropinirole, have particularly high binding affinity for D3 receptors. Furthermore, studies into drug addition have consistently found dopaminergic dysregulation in the ventral striatum. So, this places DA medications such as ropinirole and PPX in a unique position, via their ability to

preferentially activate D3 receptors, to affect ventral striatal dopaminergic signalling. Data from many reports have supported the link between DAs that have high affinity for D3 receptors and incidence of GD/ICDs (Zand, 2008; Garcia-Ruiz et al., 2014; Seeman, 2015), while others found no difference between DAs with different binding affinities for D3 compared to D2 receptors (Singh et al., 2007; Voon et al., 2007b). Seeman (2015) in particular conducted an in-depth analysis of the types of DA medications used and proposed that not only are DAs that target D3 receptors more likely to induce GD/ICDs in PD patients, but that the proportion of ICDs are related to the selectivity for D3 over D2 receptors, with PPX having the highest incidence of ICDs associated with its use. In his review of the literature, he found that the percentage of PD patients reporting ICDs was 32% for PPX, 25% for ropinirole, 16% for pergolide, 22% for rotigotine, 10% for apomorphine, and 6.8% for bromocriptine. That said, many early studies reporting the high levels of GD/ICDs with PPX and ropinirole, failed to take into account the overall prescribing patterns. In North America and also in many European countries, PPX is the most used DA. It may simply be the case that more patients are exposed to PPX compared with the other agonists and likely lead to more reports of GD/ICDs that were associated with it (Constantinescu, 2008). Nevertheless, the ability of DAs to stimulate D3 receptors in the ventral striatum remains an intriguing avenue of investigation into addiction pathogenesis.

1.5 The Dopamine D3 Receptor

There are five dopamine receptors, split into two families, the D1 family consists of D1 and D5 receptors, while the D2 family is comprised of D2, D3, and D4 receptors. All dopamine receptors are metabotropic G-protein coupled receptors that either activate (D1 family) or suppress (D2 family) adenylyl cyclase-cyclic AMP-dependent protein kinase signalling (Missale

et al., 1998). Among these five receptors, the D3 receptor in particular exhibits distinct features suggesting its involvement in addiction (Sokoloff et al., 1990). It has been proposed that GD/ICDs in PD develop when dopaminergic treatment overstimulates the ventral striatum, including the nucleus accumbens (NAC). Molecular imaging studies demonstrate that D3 receptors are found in homologous locations in both human and rodent brains, and that these receptors are activated by D2/D3 receptor agonists in vivo. For example, [^{11}C]-PHNO, a selective D2/D3 radiotracer used in PET imaging has a higher affinity for D3 receptors, exhibits a dorsal to ventral gradient of D2/D3 receptors in the striatum of healthy humans, with the ventral striatum showing higher levels of D3 receptor binding (Graff-Guerrero et al., 2008; Graff-Guerrero et al., 2010). Although most of the focus on D3 receptors is due to the their prominent expressed in the NAC, there are also high levels of D3 expression in the ventral pallidum (VP), Islands of Calleja (ICJ) and olfactory tubercles as well as moderate levels of expression in the ventral tegmental area (VTA), amygdala, hippocampus, and several other regions.

Although D2 and D3 receptors have similar mechanisms of action, they differ in their respective distribution patterns in the brain and so may be differentially impacted by region-specific changes that occur in response to pathology. Sokoloff and Le Foll (2017) in particular have noted these different expression patterns and have hypothesized that upregulation and sensitization D3 receptor are linked to addiction, which differs greatly with overall picture of D2 receptors. Studies of drug addiction have consistently reported decreases in D2 receptors in both animals (Morgan et al., 2002; Nader et al., 2006; Dalley et al., 2007) and humans (Volkow et al., 2001; Martinez et al., 2005; Martinez et al., 2007; Lee et al., 2009a). In contrast, results from animal studies investigating D3 expression following exposure to cocaine, nicotine, alcohol,

PPX, and food indicate an upregulation of D3 receptor expression (Maj et al., 2000; Le Foll et al., 2002; Le Foll et al., 2003; Neisewander et al., 2004; Jeanblanc et al., 2006; Vengeliene et al., 2006; Dardou et al., 2014). Furthermore, PET imaging studies using [11C]-(+)-PHNO, a D3-preffering radiotracer, also report increased D3 receptors in cocaine and methamphetamine abusers (Boileau et al., 2012; Boileau et al., 2013), as well as those with GD (Boileau et al., 2013). Finally, post-mortem studies looking at the brains of cocaine overdose fatalities have also reported higher levels of D3 receptors (Staley and Mash, 1996; Mash, 1997b, a; Segal et al., 1997). All of these studies support an upregulation of D3 receptors in response to addiction rather than a decrease.

There is additional support for sensitization and upregulation of D3 receptors in response to DRT that comes from the PD literature. In the treatment of PD, prolonged administration of levodopa eventually induces debilitating dyskinesias, likely resulting from basal ganglia motor sensitization processes. Specifically, repeated exposure to levodopa causes a D1 and BDNF-mediated ectopic expression of D3 receptors in the dorsal striatum, sensitization to levodopa in rats (Bordet et al., 1997), and an upregulation of D3 receptors in monkeys (Guillin et al., 2001; Bézard et al., 2003). This contrasts both with rodent (Lévesque et al., 1995) and primate (Bézard et al., 2003) models of PD as well as drug-naïve PD patients where D3 receptors are downregulated after dopaminergic lesions (Boileau et al., 2009).

This evidence supports a role of D3 receptors in both substance abuse and GD/ICDs. In contrast to the down regulation of D2 receptors often reported in addiction literature, D3 receptors exhibit patterns of increased expression in the brains of individuals with both substance or behavioural addictions.

1.6 Pramipexole Dihydrochloride

As discussed earlier, PPX is commonly prescribed to PD patients to help manage the symptoms of the disease. However, its use has been linked to very high rates of GD/ICDs in this patient population. The following section will provide an overview of the pharmacological characteristics of this drug and provide a background for its use in PD.

PPX and other non-ergolinic DAs have been promoted as effective pharmacotherapies to treat PD without some of the more serious health complications associated with levodopa or older ergolinic based DAs. PPX, ropinirole, and rotigotine, are all DAs of the non-ergoline class of dopaminergic medications and are full agonists of the D2 receptor family. PPX in particular has 7-30 times higher affinity for the D3 receptor than for D2 and can act on both pre- and postsynaptic receptors (Dooley and Markham, 1998; Collins et al., 2007; Eisenreich et al., 2010; Antonini and Calandrella, 2011). These relatively new medications were designed to replace the older ergolinic agonist medications that carried serious risks of cardiovalvular fibrosis and were subsequently withdrawn from many markets (Antonini and Poewe, 2007; Rasmussen et al., 2008; Steffensen et al., 2014). PPX in particular was designed as an adjunct therapy to levodopa or as a monotherapy to treat PD. Although levodopa is the gold standard for PD treatment of motor symptoms (Olanow et al., 2004), long-term use is associated with the development of several motor complications, including response oscillations and dyskinesias which affect approximately 30% of patients within a few years of levodopa therapy initiation (Holloway et al., 2004). While the precise mechanisms underlying these motor complications are not completely understood, it is believed that one of the main reasons is that the pulsatile stimulation of the dopamine-receptors by levodopa causes maladaptive neuroplastic changes in basal ganglia

circuitry (Gerfen et al., 1990; Herrero et al., 1995; Jolkkonen et al., 1995; Gerfen and Surmeier, 2011; Hametner et al., 2012). DAs on the other hand, act directly on striatal (and other) dopamine receptors, bypassing the need for intrinsic dopamine stimulation and have considerably longer half-lives than levodopa, reducing the amount of pulsatile stimulation on postsynaptic neurons (Antonini et al., 2009). In clinical trials, treatment of PD with non-ergolinic DA monotherapy was associated with significantly reduced risk of those motor complications seen when PD patients are treated with levodopa and so were recommended as first-line therapies – particularly for patients with early onset PD (Parkinson Study Group, 2000; Rascol et al., 2000; Hametner et al., 2012).

Although PPX reduces the risk of several of the more serious complications from prolonged use of levodopa, carbidopa, as well as the ergolinic DAs, there are still many known side effects of this medication. The most commonly reported adverse events by patients treated with PPX are nausea, dizziness, constipation, dry mouth, urinary frequency, weakness or lack of energy, somnolence, orthostatic hypotension, dyskinesias, extrapyramidal syndrome, accidental injury, dystonia, gait abnormality, hypertonia, amnesia, dream abnormalities, insomnia, confusion, and hallucinations, (Dooley and Markham, 1998). Many of these adverse effects subside when tolerance develops after repeated exposures (Richtand et al., 2001a; Richtand et al., 2001b; Napier et al., 2020).

1.7 Dopamine Agonists and Levodopa

One question that arises when looking at the evidence from the PD literature is, how much of the effect on the development of GD and other ICDs in PD depends on levodopa and how much on DAs? It appears that both are important, but that they contribute in different ways. Accumulating evidence supports a dissociation between the types of behaviours that are linked to

levodopa dose versus those linked to DAs. Higher doses of levodopa medication are associated with repetitive, stereotyped motor patterns that are not compulsive/distressing in nature (collectively referred to as punding; Lee et al., 2010), increases in consumption of dopaminergic medication (i.e., DDS) and in some studies, obsessive compulsive behaviours such as ordering, cleaning, and rearranging - which are distressing (Molina et al., 2000; Kurlan, 2004; Smeding et al., 2007). Stereotyped behaviours are a well-known side effect of drugs that increase dopaminergic activity in the brain and have been observed in both humans and animals (Costall and Naylor, 1975; Ridley, 1994). These behaviours include excessing grooming, repetitive orofacial movements, and repetitive locomotor activity such as jumping up and down or running in circles. Punding behaviours are related but tend to be more elaborate, for example, repeatedly dismantling medical equipment. Patients also do not report distress when performing these rituals.

These behaviours may be related to the activation of both the D1 and D2 receptor families by levodopa (Evans et al., 2004; Fasano and Petrovic, 2010), whereas the DAs typically used to treat PD have low affinities for the D1 family. A related theory that addresses this dissociation is that stereotypical repetitive behaviours may be related to the overactivity of the dorsal striatal circuitry compared to the overactivity of the ventral striatal circuitry implicated in GD and other ICDs. Stereotypy appears to manifest as a consequence of sensitization processes caused by the pulsatile stimulation of dorsostriatal pyramidal neurons by short-acting dopaminergic drugs (Lee et al., 2010). Compared to DAs, levodopa has a significantly shorter half-life and so must be ingested several times a day (in immediate release formulas). This leads to large increases and decreases in dopamine availability throughout the day and may induce secondary plastic changes related to pulsatile stimulation of the relatively intact dorsal striatal

dopaminergic receptors (Wolters et al., 2008; Lee et al., 2010; Perez Lloret and Rascol, 2010). And as discussed earlier, D1 and D2 receptors are heavily expressed in the dorsal striatum, while D3 receptors are located largely in the ventral striatum.

Related to the theory of motor sensitization is the concept of incentive sensitization, a theory with high impact in the field of addiction. The idea is that, similar to how levodopa induces sensitization in the motor areas of the striatum, sensitization by DAs and other addictive drugs also occurs in the limbic regions of the striatum, particularly the ventral striatum (Berke and Hyman, 2000; Evans et al., 2006; Berridge, 2007). However, rather than sensitizing motor patterns, there is a sensitization of motivation and attention toward highly rewarding stimuli. So, the different modes of action of levodopa and DAs (i.e., whether they are short or long acting and in which brain regions they primarily act) may induce different changes in the dopaminergic system. In regard to drugs of abuse, it is well known that drugs with shorter half-lives carry higher risk of addiction (Farre and Cami, 1991) and there is some evidence that sensitization is enhanced by intermittent access to addictive drugs where drug levels in the blood of animals increase rapidly and then are allowed to wash out compared to long access procedures where the levels of the drug present in the blood is more stable (Kawa et al., 2016). Consistent with this hypothesis, the short acting nature of standard immediate release levodopa may explain why this antiparkinsonian medication has been associated with DDS whereas there is less evidence for a relationship between DDS and longer acting DAs or controlled release forms of levodopa (Kulisevsky et al., 2007; Goole and Amighi, 2009; Solla et al., 2013; Beaulieu-Boire and Lang, 2015).

DAs targeting D2/D3 receptors have different observed effects on dopamine neurons compared to levodopa and stimulant drugs such as amphetamines. Levodopa increases dopamine

neuron population activity whereas administration of a D2 preferring agonist like quinpirole decreases post-synaptic burst firing in neurons receiving dopamine input (Sesia et al., 2013). However, both of these effects are correlated with observations of increased compulsive behaviours. This may be because both direct agonism by DAs and the increased dopamine release by levodopa/amphetamines ends up saturating D2 autoreceptors, prompting a downregulation of these autoreceptors over time (Harden and Grace, 1995; Henry et al., 1998). Theoretically this would not increase the postsynaptic action of dopamine if there was also a coincident decrease in postsynaptic dopamine receptors and dendritic contacts. However, the exact opposite appears to happen, with increased dopaminergic activity being associated with increases in dendritic elaboration and spine density, which are believed to underly the process of sensitization in the basal ganglia (Robinson and Kolb, 1997, 2004). So, it is possible that these processes are at least partially responsible for the addictive and compulsive behaviours associated with chronic DRT.

1.8 Genetic Associations with Gambling Disorder and Impulse Control Disorders

As mentioned earlier, both GD and ICDs are complex disorders and there is substantial evidence that supports underlying biological vulnerabilities. Family, adoption, and twin studies have estimated that underlying genetic factors contribute around 33-54% of the overall variance for the development of GD (Eisen et al., 1998; Eisen et al., 2001; da Silva Lobo and Kennedy, 2006; Slutske et al., 2010). Moreover, 45-63% of people with GD have a comorbid alcohol or substance use disorder (Black and Moyer, 1998).

Several genes that impact brain neurotransmitter systems have been implicated in GD and ICDs, particularly the monoamines: dopamine, serotonin, and norepinephrine (Comings et al., 2001). Studies investigating the genetics of GD/ICDs have found linkages with polymorphisms

of dopamine D1 (Comings et al., 1997), D2 (Comings et al., 1996; Comings et al., 2001; da Silva Lobo et al., 2010), D3 (Liu et al., 2009; da Silva Lobo et al., 2015; Castro-Martínez et al., 2018), and D4 (Pérez de Castro et al., 1997; Comings et al., 1999; Comings et al., 2001) receptors, the dopamine transporter protein (Comings et al., 2001), the 5-HT_{2A} receptor (Lee et al., 2012; Kraemmer et al., 2016), the 5-HT transporter protein (Pérez de Castro et al., 1999), the tryptophan hydroxylase and dioxygenase enzymes (the latter of which is responsible for the enzymatic conversion of tryptophan to kynurenine and is an important factor in immune responses; Comings et al., 2001), the noradrenergic α_{2A} receptor, the MAO-A (Ibanez et al., 2000; Pérez de Castro et al., 2002) and COMT enzymes (Grant et al., 2015), the aromatic acid decarboxylase enzyme (Kraemmer et al., 2016), the NMDA glutamate receptor (Comings et al., 2001; Lee et al., 2009b), the κ opioid receptor (Kraemmer et al., 2016), the presenilin-1 gene (involved in the manufacture of amyloid beta) (Comings et al., 2001), and the $CAMK_2D$ enzyme (da Silva Lobo et al., 2015). However, each of these genes only explain a small amount of the variance attributable to genetic inheritance of this biological vulnerability to GD/ICDs (Napier et al., 2015). One genome-wide association study by Lind et al. (2013) analyzed 1312 people from 894 families and found no single single-nucleotide polymorphisms that reached genome-wide significance. Surprisingly, the three single-nucleotide polymorphisms that came closest to significance had little association with monoamine functioning, rather they were linked to processes such as neuronal migration, synaptic plasticity, regulation of gene expression, and neuroprotection from oxidative stress.

When specifically looking at D3 receptor, a few polymorphisms have been associated with increased risk of GD/ICD. Castro-Martínez et al. (2018) found that the rs6280 dopamine D3 single nucleotide variation gene was associated with ICD in early onset PD patients which

interacted with PPX and ropinirole treatment. This variant consists of a thymine/cytosine change that produces a Ser9-to-Gly substitution at the D3 receptor which produces an autoreceptor with a higher binding affinity with dopamine (Jeanneteau et al., 2006). Liu et al. (2009) directly investigated the interaction of PPX and the dopamine D3 receptor Ser9Gly allele in PD patients. They found that the Ser/Ser group had higher response rates (60%) as measured by more than a 20% improvement in PD symptoms, compared to the Ser9Gly group (13%). This suggests that decreased length of dopaminergic action on postsynaptic neurons due to highly sensitive D3 autoreceptors may contribute to the development of GD/ICDs. These and likely other yet to be discovered genetic factors have a major impact on the likelihood that someone will develop GD/ICD and set the stage for other factors, such as environment, to interact with this underlying biological vulnerability.

1.9 Demographic, Psychological, and Clinical Factors

The etiology of GD/ICDs remains unclear, but likely involves complex interactions among neurobiological, psychological and environmental risk factors (Blaszczynski, 2000; Shaffer et al., 2004; Richmond-Rakerd et al., 2014). Overall, most studies have agreed on several demographic, psychological, and clinical factors that characterize patients with GD/ICDs in both the general population and in those patients with comorbid PD (Blaszczynski et al., 1997). Both prospective and retrospective studies indicate that individuals with GD/ICDs exhibit high levels of novelty-seeking and impulsivity traits in their personalities (Steel and Blaszczynski, 1998; Alessi and Petry, 2003; Forbush et al., 2008; Michalczuk et al., 2011). In otherwise healthy individuals, high levels of novelty seeking are positively correlated with GD and is characterized by exploratory approach behaviours, feelings of excitement in novel situations, impulsivity, and rapid decision making (Slutske et al., 2005; Voon et al., 2007b).

Patients with PD and comorbid GD/ICDs tend to be younger in age, unmarried, and have a personal or family history of GD/ICDs, substance abuse, and other psychiatric disorders (Molina et al., 2000; Pontone et al., 2006; Giladi et al., 2007; Ondo and Lai, 2007; Singh et al., 2007; Voon et al., 2007b; Constantinescu, 2008; Weintraub et al., 2010; Poletti and Bonuccelli, 2012; Cilia et al., 2014). Many of these demographic similarities are also factors in the general GD population (Shaffer and Martin, 2011). Individuals who are diagnosed with GD/ICD, both with and without comorbid PD, are more likely to have either a personal or family history of alcohol addiction (Molina et al., 2000; Voon et al., 2007b). Slutske et al. (2000) found that 12-20% of the genetic risk for GD was explained by alcohol dependence. Some early studies found an association with sex (i.e. increased incidence with males; Imamura et al., 2006); however, larger, more carefully controlled studies have found an equal likelihood males and females developing an ICD (Barns Neurauter et al., 2010; Cilia et al., 2014). That being said, there are some sex/gender differences within the umbrella of ICDs with men more likely to report PG and hypersexuality and women more likely to report compulsive shopping/buying and binge eating (Gallagher et al., 2007; Weintraub et al., 2010; Ramirez-Zamora et al., 2016; Weintraub and Claassen, 2017; Weintraub and Mamikonyan, 2019). This mirrors the pattern seen in the general population (Striegel-Moore and Franko, 2003; Koran et al., 2006; Black, 2007; Kuzma and Black, 2008; Schreiber et al., 2011; Erskine and Whiteford, 2018). These findings are consistent with the idea that there are shared neurobiological, genetic, and/or environmental contributions in all individuals that are more likely to develop a behavioural addiction, not just those with PD (Comings et al., 1999; da Silva Lobo et al., 2007; da Silva Lobo and Kennedy, 2009; Slutske et al., 2010; da Silva Lobo et al., 2011).

1.10 Effects of Dopamine Pharmacotherapy on Risk Preference and Impulsivity

When it comes to personality traits that predict the development of GD/ICDs increased impulsivity is the largest and more consistent finding in both the PD patient population and in those without PD. While some studies have found increases in motor impulsivity (which relates to difficulty withholding motor responses or controlling motor actions that have been initiated) in tasks such as the stop-signal reaction time task and the Go/No-Go task (Chowdhury et al., 2017), there is more general consensus that other forms of impulsivity that more closely relate to decision-making and other cognitive processes (i.e., choice, waiting, and reflection impulsivity) play a larger role in GD/ICD. As a group, people with high impulsivity demonstrate a strong preference for the small immediate rewards (Voon et al., 2010) and evidence suggests that there is greater subjective devaluation of the large-delayed reward perhaps compounded by impairments in the ability to wait for the delayed reward (Housden et al., 2010; Napier et al., 2015). It is important to note that while PD patients both with and without GD/ICDs exhibit impairments in motor inhibition and other forms of impulsivity (Obeso et al., 2011; Nombela et al., 2014), at least some of this impairment depends on whether the patient is in an DRT induced 'on' or 'off' state with the 'on' state being associated with significantly higher levels of impulsivity. For example, PD patients exhibit delay aversion and temporal distortions, but only during the 'on' state.

There is also evidence that DAs increase preference for risky options in PD patients with and without ICDs (Cools et al., 2006; Bódi et al., 2009; Voon et al., 2011). Kobayashi et al. (2019) examined the influence of dopamine on risk preference (reward probabilities were indicated) in PD patients and found that levodopa increased the subjective value of the risky rewards and prolonged decision time. The authors suggested that the increase in decision time

was due to an increase in the subjective value of rewards. Both PD patients and healthy individuals exhibit increased decision-making latencies as the magnitude of potential rewards increase. This increase in subjective value appears to bring PD participants' risk preferences in line with those of healthy controls—when in an unmedicated state, PD patients tend to be risk averse. All patients in the study were more risk averse when they were off levodopa medication, but that decrease was attenuated in those patients that had an ICD while patients with high apathy score exhibited increased levels of risk aversion. One could theorize that administration of a DA to PD patients with or at risk of developing an ICD would further increase the subjective value of rewards beyond that of healthy controls. In a similar vein, Rossi et al. (2010) compared the performance 7 PD patients with GD to 13 matched PD controls on several risky decision-making, cognitive, and social behaviour tasks. The PD patients with GD had impaired performance on the IGT and were rated as having issues conforming to normal social behaviours (i.e., rated by first degree relatives as being less cooperative, having difficulty making and maintaining close relationships, and doing whatever they wanted while not caring about other's opinions), both consistent with MFC impairments, which are seen in non-Parkinsonian individuals with GD (Reuter et al., 2005). Furthermore, this PD group with GD did not differ from controls in other tests of decision-making or cognitive tasks; also consistent with the findings from a large retrospective study of PD patients with DDS (Cilia et al., 2014) and from the non-parkinsonian GD literature (Ledgerwood et al., 2012). It is important to note that this study included two other risky decision-making tasks called the Game of Dice Task and the Investment Task. These two tasks differ from the IGT in that the probabilities are known or calculable, whereas the IGT simulates real-life decision-making under ambiguity where the outcome probabilities are unknown. Generally, people with GD show more impairment in latter

compared to the former (Brevers et al., 2012). In line with the findings from other studies assessing the performance of people with GD on the IGT, PD patients with comorbid GD developed a disadvantageous strategy by selecting more frequently from the disadvantageous decks compared to the advantageous ones throughout the entire session, whereas healthy controls typically switch to the advantageous decks in the later half of the task (Bechara, 1997). As mentioned in section 1.3, during the IGT subjects choose between four decks of cards (decks A, B, C, or D) that differ in the amount and probability of monetary gain and loss. It appears that individuals with addiction are particularly attracted to the deck B option as this deck is associated with the highest per trial gains, although the losses associated with this deck are the most extreme, resulting in a net loss over time. This disadvantageous strategy could be explained by a hypersensitivity to rewards amongst patients with GD combined with failure to adequately process aversive outcomes (Bechara et al., 2000; Bechara, 2005).

A predominant theory of the role of dopamine in reinforcement learning and particularly those changes in reward vs. punishment learning seen in PD was put forward by Frank, Seeberger, and O'Reilly in the paper 'By Carrot or by Stick: Cognitive Reinforcement Learning in Parkinsonism" (2004). They proposed that PD patients off dopaminergic medication are better at learning to avoid choices that lead to negative outcomes while those on medication are better at learning from positive outcomes. The idea is that when dopaminergic medications used to treat Parkinson's disease tonically bind to D2 receptors this produces an effect where dips in phasic dopamine bursts from negative feedback reinforcement are reduced and therefore impair the ability of these patients to learn from negative outcomes. This is in contrast to positive reinforcement where large increases in dopamine efflux are needed to stimulate D1 receptors because endogenous dopamine has a lower affinity for D1-like receptors compared to the D2-

like family. So, tonic stimulation of dopamine receptors by dopaminergic medication therefore could enhance D1-mediated positive reinforcement and at the same time prevent pauses in D2 signaling impairing learning from negative feedback. This theory is further supported by evidence from a follow-up study by the same group (Frank et al., 2007) as well as a study by van Eimeren et al. (2009). In the latter study, the authors tested the hypothesis that tonic stimulation of dopamine receptors by DAs desensitizes the dopamine reinforcement learning system by preventing decreases in phasic dopamine signals after negative feedback. Using a probabilistic discounting task, they were able to measure BOLD signal changes in various regions of interest in the brains of eight PD patients after PPX administration. These patients were scanned in three conditions; (1) off medication, (2) after levodopa treatment, and (3) after an equivalent dose of PPX. They found that PPX specifically altered activity in the orbitofrontal cortex (OFC). Activations related to outcomes were generally larger in the PPX condition and caused a decreased trial by trial correlation with reward prediction errors mainly due to impaired deactivation of the region in response to negative outcomes. The authors posit that is due to the prevention of phasic dopamine pauses caused by the tonic activation of dopamine receptors by PPX. Importantly, this effect was not seen in the levodopa condition.

Of particular significance, are the findings that D2 receptors in particular are downregulated in people with substance use disorders (Volkow et al., 2001). That is, if there are less D2 receptors for dopamine to bind to and D2 receptors are primarily responsible for signalling negative outcomes, individuals with addiction may be less likely to be able to learn from negative outcomes related to repeated drug use. Furthermore, according to Michael Frank and his colleagues, the addition of DAs or levodopa could exacerbate this problem.

The effects of DAs on reinforcement learning may interact with PD pathology, in that degeneration of the nigrostriatal dopaminergic pathway causes in imbalance in the relative contribution of that pathway and the relatively spared mesocorticolimbic pathway (Kish et al., 1988). Administration of a DA would shift the nigrostriatal functioning back up toward a normal level of functioning, but at the same time, 'overdose' the mesocorticolimbic pathway (Cools et al., 2001; Napier et al., 2015). Thus, dopamine induced dysfunction of this circuit may lead to an improper adaptation of reinforcement processing and decision-making towards rewards and to an impaired ability to learn from negative decision outcomes.

One other important factor to consider is the activity state of the dopamine neurons, that is, the proportion of dopamine neurons that are active and their average firing rate pattern. In a normal functioning dopamine system, the overall baseline pattern of neuronal behaviour is thought to maximize the dynamic range of any phasic responses to internal or external stimuli (Hollerman and Grace, 1990). Repeated administration of DAs and other dopaminergic drugs perturb this balance. For example, repeated levodopa or amphetamine administration increases the proportion of active dopamine neurons at baseline (Harden and Grace, 1995; Lodge and Grace, 2008) rendering the system hypersensitive to stimuli. This is because, at baseline, dopamine neurons fire in single-spiking irregular patterns which allows for the bidirectional detection of changes in that spiking pattern – increases or dips (Grace and Bunney, 1984b; Schultz et al., 1997; Schultz, 2016). When a human or animal is exposed to a better-than-expected outcome, this causes dopamine neurons to fire in bursts of activity (Grace and Bunney, 1984a), however the burst firing selectively occurs in those dopamine neurons that are already tonically active. So, the artificially increased proportion of tonically active dopamine neurons may serve to amplify any phasic signals to stimuli (Lodge and Grace, 2006; Grace et al., 2007).

1.11 Dopamine Agonist Administration in Healthy Humans

The research presented thus far on the role of DA medication in the development of GD/ICDs has focused on the PD population. While these findings have be very useful in helping us understand the effects that DAs have on the human brain, it would be useful to try to disentangle the confound of PD disease pathology. Here I will present available data from DA administration studies with healthy humans. Research on the effects of DAs in healthy human participants are rare and are generally restricted to one or two small doses which restricts any analysis to only the acute effects of the drug. Considering that the effects of repeated exposure to DAs differ from those seen following acute administration (Chernoloz et al., 2009), this obviously limits the interpretation of how the drug acts on the human nervous system. For example, acute administration of PPX is associated with behavioural sedation, somnolence, dizziness, nausea (Dooley and Markham, 1998; Wermuth, 1998; Hauser et al., 2000; O'Suilleabhain and Dewey, 2002; Etminan et al., 2003; Silber et al., 2003; Samuels et al., 2006b, a) and a decrease in mood and levels of motivation (Drijgers et al., 2012), whereas long-term PPX therapy increases mood and motivation (Leentjens et al., 2009). However, information gleaned from acute PPX studies in healthy humans may still provide some insights.

Hamidovic et al. (2008) investigated the effect of low doses of PPX on cognitive performance, impulsive behaviour, and mood in 10 healthy men and women. PPX decreased mood (likely due to 6/10 of the participants reporting nausea) and increased subjective reports of cognitive and behavioural sedation. There were no significant changes in impulsivity or cognition, which the authors surmised was due to insufficient dose strength. A more recent study by Yang et al. (2016) also investigated the acute effects of PPX on impulsivity. In their study, healthy participants were given 0.5 mg of PPX (n = 20) or placebo (n = 20). Two hours after

ingestion, impulsivity was assessed using the Go/No-Go task, where in participants are required to either respond on Go-trials or withhold a response on No-Go trials. Each trial type is indicated by visual stimuli. They found that PPX did not affect performance on No-Go trials but substantially increased time-out errors on go trials, indicating that acute PPX actually *decreased* motor impulsivity by slowing reaction times and increasing motor control, although this could be related to the sedative effects of acute PPX administration. Campbell-Meiklejohn et al. (2011) looked at the effect of low dose PPX on loss chasing in a gambling game. Thirty healthy volunteers participated in the study. After receiving PPX, the volunteers reported a decreased in mood and were more likely to attach higher value to the value of the losses that were chased compared to those that were surrendered. This suggests that PPX had a role in enhancing the value of losses that were chased. Riba et al. (2008) conducted a study with 15 healthy male participants who received a single moderate dose injection of PPX before doing a lottery task. These participants also received an antinausea medication, domperidone, 1h prior to PPX administration. The authors found that PPX increased preference for risky choices, particularly after an unexpected big win. Both Pizzagalli et al. (2008) and Santesso et al. (2009) conducted studies testing performance of healthy volunteers in a probabilistic reward task after a single moderate dose of PPX. Evidence from both studies suggest that acute PPX impairs reward learning, slows reaction time, and decreases mood. In another study which investigated the acute effect of PPX on trial-and-error learning, Gallant et al. (2016) found that a single dose of PPX (0.5mg) impaired learning in healthy participants compared to those that received a placebo. Unfortunately, the authors did not conduct an analysis to determine whether the impairments were due to deficits in learning from negative feedback. Lastly, Martens et al. (2021) conducted a study to assess the potential of PPX as an antidepressant. This involved randomly assigning 21

healthy subjects to receive either PPX (peak daily dose of 1mg/kg) for 12-15 days or a placebo after which their brains were scanned using fMRI while looking at emotional facial expressions. They found that, compared to placebo controls, the participants that received PPX exhibited deceased amygdala activation in response to fearful faces compared to happy faces, but had no other antidepressant like effect. This may suggest that PPX has the ability to reduce the impact of negative emotional stimuli. In sum, these studies with healthy human volunteers suggest that PPX administration impairs reinforcement learning, increases risky decision-making, decreases impulsivity when administered acutely, and may decrease negative emotional perceptions, particularly if adverse effects like nausea are counteracted.

1.12 Evidence from Rodent Studies

Results from animal studies investigating the effect of DAs such as PPX and ropinirole on addiction, impulsivity and decision-making are largely in agreement with results from the human literature; DAs promote GD and other behavioural addictions and this effect is consistent across species.

The first thing of note when reviewing the animal literature is that PPX and ropinirole affect animals similarly, likely due to their very similar pharmacological profiles. Both PPX and ropinirole are potent full agonists of dopamine D2 and D3 receptors, with high selectivity for D3 (see Table 1.3). Secondly, PPX and ropinirole both induce decision-making impairments in rats across a wide range of tasks including the rodent version of the IGT (cf. Di Ciano et al., 2015; Tremblay et al., 2017), the rat betting task (Russell et al., 2021), probability discounting tasks (Rokosik and Napier, 2012; Holtz et al., 2016; Pes et al., 2017; Floris et al., 2022), and the 5-choice serial reaction time task (Jiménez-Urbieta et al., 2019). In line with data from human probability discounting studies, increased discounting in rats after repeated PPX administration

appears to be related to a reduction in the perceived negativity of unrewarded events rather than enhancing the value of the rewarded events (Rokosik and Napier, 2012). PPX also increases preference for variable ratio (VR) schedules over FR schedules (Johnson et al., 2011; Johnson et al., 2012) and increases sucrose consumption in a binge eating model (Dardou et al., 2014). A recent study conducted by Orrù et al. (2020) also replicated the finding that PPX increases disadvantageous decision-making, but interestingly this effect was not reversed with acute administrations of D2 or D3 antagonists indicating that the effects of PPX on probability discounting are not the result of acute D2 or D3 receptor activation and that neuroadaptive changes after repeated exposures are likely responsible. Thirdly, PPX and ropinirole can both induce and enhance conditioned place preference when paired with other addictive substances (Riddle et al., 2012; Bertz et al., 2015; Loiodice et al., 2017) although acute doses of ropinirole attenuate conditioned place preference when administered as a single dose after the place preference has already developed (Brancato et al., 2014; Shahzadi et al., 2022). Importantly, the behavioural and cognitive impairments observed after administration of these DAs do not diminish over time and often require repeated administrations to develop (Rokosik and Napier, 2012; Holtz et al., 2016; Pes et al., 2017; Jiménez-Urbieta et al., 2019; Orrù et al., 2020). That said, these biases can be reversed upon PPX withdrawal and reinstate when the drug is reintroduced (Rokosik and Napier, 2012).

Together, the evidence from animal models supports the evidence from the human literature. That is, DAs promote the development of GD and other ICDs by impairing decision-making processes, increasing risk preference, and enhancing the addictive potential of other drugs of abuse. Mild risk-taking/disadvantageous decision-making emerges with acute drug action which is then enhanced after repeated exposures to DAs in both animal models of PD and

in intact, healthy animals. It may be that certain cognitive processes related to decision-making impairments are present upon acute administration of the drug and—through sensitization processes—increase with exposure, but at the same time other processes such as physiological reactivity to risk undergo tolerance.

1.13 Somatic and Neurobiological Correlates of Gambling Disorder

Both functional imaging studies and studies using biological sampling methods have revealed abnormalities of dopaminergic function in several areas related to GD, including the modulation of expectation and reward, appetitive urge, craving and salience, as well as different aspects of impulsivity (Fowler et al., 2007). Gambling is a physiologically arousing activity. When gamblers make a bet, increases in heart rate, blood pressure, salivary cortisol levels, and skin conductance responses (SCR) can be reliably detected (Meyer et al., 2000), particularly if they are in a gambling environment and are using their own money. those with GD exhibit modified physiological responses when gambling, that is, they are generally less physiologically aroused and display fewer indications of stress (Lole et al., 2014). However, this tendency toward decreased arousal is largely accounted for by the sensation-seeking personality trait. In a pair of experiments conducted by Peterson et al. (2008; 2010), the SCR of participants was measured while gambling. The authors found that people who scored high on sensation-seeking experienced diminished increases in SCR compared to low sensation-seekers in the first half of the IGT, particularly in the anticipatory phase (before a decision was made) compared to baseline. Using PET imaging with [^{11}C] raclopride, the authors also found that decreased dopamine receptor availability was found only in those people with GD who also had high levels of sensation-seeking. The authors theorize that the low-sensation-seeking subjects (both in the GD and HC groups) experience higher levels of fear or anxiety when first making a wager which

manifests in the larger sympathetic nervous response detected by SCR monitoring. These subjects eventually lose that fear as the task progresses while high sensation-seeking subjects (primarily in the GD group) begin the task fearlessly and remain fearless throughout the entire task, resulting in the weak SCR responses observed in this group. Another experiment investigating physiological differences conducted by Bergh et al. (1997) found decreases in CSF levels of dopamine but increases in its metabolites 3,4-dihydroxyphenylacetic acid and homovanillic acid, indicating increased dopamine turnover at baseline in a group of people with GD. Together, these studies indicate that people with GD have altered physiological responses while gambling. Biological factors may constitute a vulnerability to GD and provide a window into the disruption of internal sensory feedback to the brain which likely has an impact on risky decision-making and other cognitive processes.

Moving from the peripheral systems to the central nervous system, the ventral striatum, including the NAC, has been known to play a critical role in reward and addiction for decades (Kalivas and Volkow, 2005; Nutt et al., 2015). The ventral striatum receives two main excitatory inputs from the prefrontal cortex and the subiculum. The prefrontal cortex input enables behavioural flexibility, or the ability to shift behavioural focus as task contingencies change (Seamans et al., 1995; Goto and Grace, 2005a, b; Floresco, 2013). The subiculum relates information from the hippocampus to other brain structures containing contextual, episodic details of previous experiences (Squire, 1992) that are used to guide future behaviour. The processing of these two inputs is regulated by the dopamine system. Stimulation of D2 receptors inhibits the input from the prefrontal cortex (which is often, but not always behaviourally inhibitory in nature), whereas D1 receptor stimulation will potentiate hippocampal input. And so, reinforcement driven increases in dopamine efflux would potentiate hippocampal input to the

ventral striatum via D1 receptors and inhibit D2-mediated input from the prefrontal cortex (Sesack and Grace, 2010).

The ventral striatum is a processing hub combining information from cortical and limbic afferents and sends efferent projections to downstream structures that regulate motor and reward-related behaviours (Gruber and McDonald, 2012). This structure is critical for energizing approach related behaviours, but its integrity is also important for inhibition of impulsive behaviours (Roitman and Loriaux, 2014). This dissociation is largely explained by the regional divisions in the ventral striatum, particularly the NAC. The NAC can be divided into two major regions; the NAC core receives information from cortical structures such as the prefrontal cortex (PFC; particularly the dorsal MFC and DLPFC), hippocampus, as well as the thalamus, while the NAC shell receives information primarily from subcortical structures (although there is also significant input from MFC and OFC), namely the amygdala, hypothalamus, and midbrain monoamine nuclei such as the SN, RN, VTA, and locus coeruleus (Scofield et al., 2016). Accordingly, animal studies have generally agreed that the NAC core plays more of an inhibitory role over behaviour, while activation of the shell produces impulsive behaviour (Dalley and Robbins, 2017). For example, when experimenters induce a lesion or deplete the dopamine in the NAC core, animals exhibit increased impulsivity, while the opposite is true of the shell (Diergaarde et al., 2008; Murphy et al., 2008; Besson et al., 2010).

It has been proposed that the excessive dopamine release in the ventral striatum seen in both GD/ICDs and in substance addiction reflects a sensitization of circuits that occurs when repeated exposures to the addictive stimulus bypass the normal mechanisms of habituation (Di Chiara and Bassareo, 2007; Murray et al., 2013). However, addiction has historically been considered a disorder of repeated compulsive drug use. It is often referred to as a ‘habit’

colloquially, and there are decades of research that support the idea that both drug use and disordered gambling become less pleasurable over time and participation in these activities becomes compulsive (Volkow and Fowler, 2000; Hyman and Malenka, 2001; Everitt and Robbins, 2005). Normally, the MFC and ventral striatum are involved in the processing of information early in learning, when outcome is most uncertain, and are thought to have evolved as an integral part of a larger skill acquisition process linked to survival (Clark, Lawrence, Astley-Jones, & Gray, 2009). Specifically, the ventral and neighbouring dorsomedial striatum are responsible for goal-directed emotional-motivational processes that promote approach/avoidance with unexpected or novel sources of reward/punishment (McCullough et al., 1993; Mirenowicz and Schultz, 1994, 1996; Flagel et al., 2011), while the MFC processes contextual information including memories of similar situations (via large afferents from the hippocampus) that helps guide this motivated behaviour (Euston et al., 2012). This in turn provides opportunities for the animal to determine whether there are any stable predictors of reward in the environment (Shizgal and Arvanitogiannis, 2003), which, if any, behaviours the animal needs to perform to procure the reward, and then to practice those behaviours to maximize skill and efficiency (Clark, 2010). However, the process of learning and skill acquisition is resource intensive in terms of the number of cognitive resources involved (visual/auditory attention, working memory, decision-making, etc.) and the metabolic energy required to maintain these processes which could be used to solve other problems. So as learning progresses and skill improves, there is a corresponding increase in reward predictability. This change in predictability is thought to trigger or facilitate a shift in the control of those behaviours from ventral to dorsomedial striatum and finally to dorsolateral striatum (Haber et al., 2000; Porrino et al., 2004; Everitt et al., 2008; Gruber and McDonald, 2012). Once under control of the

dorsal regions of striatum, the reward associations are thought to become fairly inflexible and automatic (Yin et al., 2004; Gerfen and Surmeier, 2011), are characterized by insensitivity to outcome, and the associated behaviours tend to be stereotypical and habit-like (Chambers et al., 2003; Yin et al., 2005; Yin and Knowlton, 2006).

So, given that addiction can be seen as a sensitization of circuits after repeated exposure to the addictive stimulus which bypass the normal mechanisms of habituation, but addiction is also conceived as a process of over consolidation of the habituation system where by addictive behaviours become very habit-like and insensitive to outcomes; how are we to square this circle? Most recent evidence suggests that in addiction, both of these processes of sensitization and habituation are still occurring, however different cognitive and behavioural aspects of this learning process become decoupled (Everitt and Robbins, 2016). Particularly the hedonic pleasure derived from these reinforcers, mediated by the opioid system, undergoes tolerance and the behaviours associated with the seeking and taking of the drug or behaviour (in the case of gambling and other ICDs) become stereotypical and habit-like, which are primarily under the control of the dorsolateral striatum. In contrast, the motivational and attentional aspects, mediated by dopamine, become sensitized over time leading to obsessive thoughts and cravings for the drug or activity (Berridge et al., 2009; Berridge and Robinson, 2016). This is further reinforced by negative reinforcement learning that occurs when substances are consumed or activities are engaged in that alleviate dysphoria and unpleasant compensatory homeostatic responses (Koob and Le Moal, 2001; Koob and Volkow, 2016).

In this context, the increased release of dopamine seen in people with GD could reflect the process of sensitization in response to repeated gambling exposure or a premorbid vulnerability in the ventral striatum (changes in dopamine receptor, transporter, or enzyme

quantities or intrinsic functioning). In the case of people treated with DAs, prolonged exposure to these drugs could further prime this system. By preferentially activating certain dopamine receptor subtypes that engage sensitization processes (involving glutamate mediated long-term potentiation and long-term depression, as well as brain-derived neurotrophic factor-facilitated synaptogenesis) or by providing excessive dopaminergic stimulation to circuits that regulate the individual components of the addiction process, including motivation, reward, habit formation, and impulse control, DAs could shift the balance of this learning/reinforcement/motivational/behavioural system toward one that is more susceptible to the maladaptive changes seen in addiction.

1.14 Human Imaging Studies

A number of human imaging studies have been conducted to identify both the neural networks and neurotransmitter system changes related to GD/ICDs both in PD patients and in otherwise healthy individuals. This section will highlight some of these findings, particularly those investigating dopaminergic changes, dopamine D2 and D3 receptors, and neurophysiological differences between groups of people with GD/ICDs compared to control groups.

Higher synaptic dopamine levels have been demonstrated in the ventral striatum of PD patients with GD/ICDs (Callesen et al., 2013b) compared to matched PD controls after exposure to reward-related cues (O'Sullivan et al., 2011; Joutsa et al., 2015; Payer et al., 2015; Wu et al., 2015). Probably the most recognized investigation into striatal dopamine levels in this population is a PET study conducted by Steeves et al. (2009). In this study, [^{11}C] raclopride, a potent D2/D3 agonist, was used to investigate dopamine release in PD patients with GD. They found that PD patients with GD demonstrated greater decreases in binding potential in the ventral striatum both

during gambling and at baseline compared to control PD patients. This could reflect increased dopamine release, lower baseline levels of D2/D3 receptors or both. Similarly, in a [11C] raclopride PET evaluation of PD patients with DDS, Evans et al. (2006) demonstrated that in response to a single dose of levodopa, PD patients with DDS released more dopamine in the ventral striatum compared to matched PD controls. This effect was also seen in RLS patients treated chronically with DA agonists when 'ON' medication compared to 'OFF' (Abler et al., 2009).

It would appear that people with GD have accumbal dopamine hypersensitivity during gambling, however, an earlier functional magnetic resonance imaging (fMRI) study conducted with GD patients without PD found a decrease in ventral striatal activity in response to positive outcomes during a guessing game compared to healthy controls (Reuter et al., 2005). These opposing findings seem difficult to reconcile, but it could be partly explained by the nature of the tasks in each study. Both experiments used gambling tasks that involved real money; however, the wins were small in the study by Reuter et al. (2005), €1 wins and losses and the overall winnings were €23, while the wins and losses in Steeves et al. (2009) were larger ($1, $3, or $5) and average winnings were $146. The latter task also incorporated stronger sensory stimuli upon wins or losses - flashing lights and accompanying auditory sounds, which are known to be highly physiologically arousing (Dixon et al., 2014b) and may preferentially stimulate D3 receptors (Le Foll et al., 2005) compared to primary rewards. The decrease in striatal activity captured by fMRI may also reflect a more complete picture of the various inputs to the striatum. That is, the neuronal activity in the striatum is not only affected by the amount of mesolimbic dopamine release, but also the various excitatory glutamatergic inputs from the cortex. The PFC in particular appears to be hypoactive both at rest and during active gambling in people with GD,

resulting in a decrease in the magnitude of excitatory stimulation of the target cells in the ventral striatum (Lee et al., 2014). The overall effect could be decreased blood-oxygen-level-dependent (BOLD) activity in the ventral striatum but increased dopamine release as measured by PET.

PET imaging studies of people with high levels of impulsivity and addictions in the general population have shown increased release of dopamine in the ventral striatum in response to amphetamine and methylphenidate challenges (Volkow et al., 1999; Buckholtz et al., 2010). This increase is also seen in fMRI studies where participants with addiction are shown images associated with their particular addiction, including preferred-gambling stimuli (and money) in people with GD, and pornographic images in people with compulsive sexual behaviour (Childress et al., 1999; Steeves et al., 2009; Clark and Limbrick-Oldfield, 2013; Sescousse et al., 2013; Voon et al., 2014b). These same groups often exhibit decreased ventral striatal activation for other, more mundane or abstract rewards (Balodis et al., 2012; Clark and Limbrick-Oldfield, 2013), illustrating a maladaptive increase in the salience of the addictive stimulus and decrease in the salience of other stimuli. Particular attention needs to be paid to the type of task, the nature of the reward and the task timing when interpreting patterns of activity in the PFC and striatum. Large salient rewards and or cues, ecologically appropriate tasks (e.g., slot machine-preferring gamblers playing on slots at a casino with their own money versus doing an abstract risk task in a lab for points) and tasks that are active rather than passive generally produce results that are consistent with hyperactivity in the striatum and some parts of the PFC, while the opposite is true of tasks that the gambler may find less engaging (Rao et al., 2008; Studer et al., 2012; Limbrick-Oldfield et al., 2013; Sescousse et al., 2013; Limbrick-Oldfield et al., 2017).

In line with this, people with GD/ICDs who are imaged while performing abstract risk-taking tasks such as the Balloon Analogue Task, typically exhibit reduced ventral striatal and

PFC activity (Rao et al., 2010; Voon et al., 2011), and increased risk-taking behaviours (but see Claassen et al., 2011). Voon et al. (2011) suggests that in PD patients with ICDs, DAs cause a change in attitude to risky situations by altering unconscious biases toward risk, but only when there is a prospect of gain. When both gain and loss are on the table, the risk preference is not affected. Of note, when the participants in her study were making risky decisions when both gain and loss were possible, the authors observed increases in anterior insula (INS) activity only in the DA medication "ON" condition indicating increased processing of visceromotor stimuli which has been most strongly linked to negative outcome, loss anticipation, and pain (Seymour et al., 2005; Seymour et al., 2007; Craig, 2009), but also to any powerful event regardless of valence that produces arousal in the body (Gogolla, 2017). This may reflect increased arousal in the gain condition, due to the increase in subjective value of the reward. The absence of the effect in the loss condition is puzzling, but it may reflect the overall shift toward focus on gains rather than losses, which could possibly result in blunted INS activity in the loss condition because the INS activates most robustly to the anticipation of losses in healthy participants. The insula and MFC are two cortical regions heavily implicated in emotional decision-making and are both known to receive large visceromotor sensory input (Clark et al., 2008). Activity in the insula (particularly the anterior portion) is decreased in people with addiction when engaged in decision-making tasks and increased when participants are viewing drug-related cues. Moreover, the magnitude of the increase in activity is correlated to the chance of relapse after a period of abstinence (Droutman et al., 2015). Damage to either region produces deficits in patients when making decisions under conditions of ambiguity (e.g., the IGT) and risk (e.g., the Cambridge Gambling Task). Furthermore, there is evidence that in some cases, damage to the insula can disrupt cigarette cravings in nicotine addicts and induce immediate smoking cessation and remain

abstinent. The results of such studies suggest that the insula is critically involved in the conscious anticipation of bodily effects in relations to emotional events, particularly negative outcomes.

As discussed previously, PET studies using radioligand tracers have consistently found decreases in striatal D2/D3 receptors in individuals with substance addiction, and these findings have recently been corroborated in PD patients with ICDs (Payer et al., 2015; Stark et al., 2018; Barbosa et al., 2019). Additionally, in non-addicted subjects, below baseline measures of striatal dopaminergic receptor availability predicts liking for methylphenidate (Volkow et al., 2002) and has likewise been demonstrated in subjects with morbid obesity due to overeating (Volkow et al., 2008). In addition to the well-known decreases in striatal D2 receptors seen in PD patients with GD/ICDs, non-parkinsonian individuals with ICDs as well as people with substance addiction, imaging studies have also revealed a decrease in striatal DAT in these groups that often predates the addiction/ICD (Cilia et al., 2010; Lee et al., 2014; Voon et al., 2014a; Vriend et al., 2014; Smith et al., 2016). In one of these studies, Cilia et al. (2010) using a radioligand, FP-CIT, that is not sensitive to competition from endogenously released dopamine, found evidence that further supports the position that presynaptic DAT are decreased in the ventral striatum (Troiano et al., 2009). This reduction in presynaptic reuptake is consistent with reported increases in dopamine levels in the ventral striatum in GD. Homoeostatic control of striatal dopamine is mediated by both dopamine D2/D3 autoreceptors and DAT proteins located on presynaptic terminals. D2 autoreceptors particularly have also been found to work in concert with DAT, supporting membrane DAT trafficking (Bolan et al., 2007; Lee et al., 2007). Impairment of this homeostatic control over dopamine function in the striatum may be partly responsible for increasing levels of impulsivity, reward sensitivity, and therefore vulnerability to addiction. Ultimately, if D2 autoreceptors and DAT are underperforming at the presynaptic neuron (i.e., unable to effectively

clear the synapse of dopamine), this leads to a longer than normal effect of dopamine on the postsynaptic neuron, which may have an overall effect of increasing attentional, motivational, cognitive, and behavioural focus toward highly rewarding stimuli.

Studies using radiotracers with high affinity for extrastriatal D2/D3 receptors such as [^{18}F] fallypride or [^{11}C] FLB-457 have also provided evidence for dopaminergic dysfunction in regions outside of the striatum in impulsive individuals. Buckholtz et al. (2010) found that decreased D2/D3 autoreceptor availability in the VTA and SN was inversely correlated with impulsivity. Ray et al. (2012) scanned 14 PD patients (7 with a history of GD) while they were performing a monetary task involving real money and compared the D2/D3 radiotracer binding activity in that task to a non-gambling control task. In order to maximize group differences, all patients were given 1mg of PPX, one hour before each scan. The authors found reduced binding potential in the midbrain, a region dominated by dopamine autoreceptors (Khan et al., 1998) in the GD group compared to PD controls. This suggests that excessive striatal dopamine release following gambling rewards in PD patients with PG stems from reduced control over striatal dopamine by midbrain autoreceptors. They also observed increased binding in both the ACC and OFC during gambling in the GD group, indicating that there was greater (primarily) D2 receptor availability in those regions due to decreased tonic levels of dopamine from the acute PPX administration. They theorize that this low DA tone (which correlated with impulsivity scores on the Barratt Impulsiveness Scale) could result in impaired prefrontal control over motivated behaviour and result in impulsive action. In another set of studies which used $H_2{}^{15}O$ PET imaging and fMRI, both van Eimeren et al. (2010) and Voon et al. (2011) found that PD patients with GD/ICDs have impaired prefrontal activity while making risky decisions; findings in line with reduced PFC function. These impairments in executive functioning have also been linked to

DA medications in PD patients (Voon et al., 2010). The dorsal regions of PFC in particular appear to be hypoactive in investigations into substance addiction (Goldstein and Volkow, 2011) (Volkow et al., 2011; Volkow et al., 2012).

The prefrontal cortex plays an integral role in behavioural flexibility, behavioural and outcome monitoring, subjective value estimation, tracking events across time, multimodal sensory and motor integration with abstract goals and values, and working memory. But for the purpose of this paper, I will focus on its role as a top-down manager of behavioural output from the basal ganglia. As previously mentioned, the striatum receives glutamatergic excitatory inputs from various regions of the cortex. These inputs provide a way for the PFC to enhance or diminish the activity in the striatum. In the context of addiction, the consensus from the academic corpus is that inhibitory control over the striatum in particular is impaired, leading to increased impulsivity, altered reinforcement processing, and maladaptive behaviour (Jentsch and Taylor, 1999; Cavedini et al., 2002; Kelley, 2004; Bechara, 2005; Kelley et al., 2005; Schoenbaum et al., 2006; Tanabe et al., 2007; Everitt et al., 2008; Kalivas, 2008; Balodis et al., 2012; Leeman and Potenza, 2012; Limbrick-Oldfield et al., 2013; Moeller et al., 2014; Koob and Volkow, 2016).

Dopamine functioning in the PFC contributes significantly to addiction and impulsivity. However, the direction of the change in dopamine action and the various receptors, proteins, and enzymes involved differs depending on the particular PFC region and the situational context (Torregrossa and Kalivas, 2008). As mentioned in the section on genetic contributions (see section 1.8), polymorphisms of the COMT gene which increase the rate of intracellular dopamine catabolism in the PFC are found more often in people with GD (cf. Vallelunga et al., 2011; Grant et al., 2015) as well as people with higher trait impulsivity (Paloyelis et al., 2010).

The Val substitution at the COMT gene results in a ~40% increase in enzymatic activity and a consequent decrement in PFC dopamine levels (Lotta et al., 1995). This decrease in dopaminergic activity due to the Val allelic variant has been associated with less efficient prefrontal neural signaling and relative deficits in executive functioning (Diaz-Asper et al., 2008; Dumontheil et al., 2011; Farrell et al., 2012). In another study that further supports a hypoactive PFC, PD patients with GD exhibited reduced activation in PFC regions associated with response inhibition and impulse control in response to an apomorphine challenge, which is a potent D1/D2 agonist with particularly high affinity for D2 receptors (van Eimeren et al., 2010). This reduction in PFC activation also correlated with disordered gambling severity in these patients.

In contrast, drugs and drug related-cues that increase dopamine action in the ventral striatum also increase activity in the ventral MFC including the OFC (Volkow et al., 2005; Lin et al., 2006). When observed using fMRI, the MFC typically displays increases in BOLD activity during tasks that involve the processing of uncertain rewards (Fukui et al., 2005) and decreases in BOLD activity as the learning occurs and outcomes become predictable, a pattern which is mirrored in the ventral striatum (Nicola and Malenka, 1998; Nicola and Deadwyler, 2000; Anselme, 2013). These regions also exhibit decreased D2 receptor availability in cocaine addicts (Volkow et al., 1993). So, whether certain PFC regions are hyper- or hypo active in the context of addiction is region-specific. Generally speaking, MFC and OFC are hypersensitive to rewards while more dorsal regions like the ACC and DLPFC are hypoactive. This is likely related to the different connectivity patterns these regions share with the striatum, where ventral and medial PFC structures are more heavily connected to the ventral striatum and the dorsal and lateral PFC structures send more projections to the dorsal regions of the striatum. So, the hyperactivity in the MFC and OFC would enhance the excitatory glutamatergic inputs into the ventral striatum

enhancing motivation and approach, while in contrast the hypoactivity in the dorsal regions of the PFC would produce anaemic excitatory signals to the dorsal regions of the striatum (particularly the dorsomedial striatum) which could impair goal-directed reward and punishment learning.

Other groups that have conducted imaging studies exploring the regional brain activity in people with GD/ICD have found changes in several other cortical and subcortical areas. For example, using resting state SPECT imaging, Cilia et al. (2008) found overactivity in the OFC, hippocampus, amygdala, INS, and ventral pallidum (VP) in PD patients with comorbid GD. The same group found further evidence for a dysfunction in of the brain network implicated in decision making, risk processing, and response inhibition (Cilia et al., 2011). In particular, the authors found a disconnection between the ACC and the striatum in PD patients with GD, whereas there was no such issue in either the PD or healthy control groups. They also found a pattern of functional disconnection between a number of regions, particularly MFC to ACC, posterior cingulate cortex (CG) to ventrolateral PFC, and striatum (STR) to ventrolateral PFC. Furthermore, activity in ventrolateral PFC, hippocampus, CG, superior temporal gyrus, medial superior frontal gyrus, STR, ACC, INS, and supplementary motor area were all negatively correlated with scores on the South Oaks Gambling Scale, a questionnaire commonly used to measure gambling addiction severity. Carriere et al. (2015) found similar functional disconnections (lateralized on the left side only) between the anterior putamen, the inferior temporal gyrus and the anterior CG in PD patients with ICDs.

Together, these results indicate a widespread pattern of dysfunction encompassing many cortical and subcortical structures. In particular, there is evidence for hypoactivity in dorsal and

lateral regions of the PFC and hyperactivity in both ventral and medial regions of the PFC as well as in subcortical structures.

Lastly, there have also been a number of reports of increased rates of impulsivity and GD in patients with PD after receiving deep brain stimulation (DBS) of the subthalamic nucleus (STN; Frank et al., 2007). However, the effects of STN DBS on addictive and impulsive behaviour is complicated. For example, Voon et al. (2007c) reported 8 PD patients with GD whose symptoms resolved after implantation, but noted that two patients had a transient worsening of GD symptoms. However, the authors noted that because of the successful amelioration of their motor symptoms, the patients were able to reduce their medication dose by 75% on average which likely contributed significantly to the alleviation of problematic gambling behaviours. Ardouin et al. (2006) reported very similar results with all seven patients finding GD relief after DBS, two of which had a transient worsening of symptoms. These patients also had an 74% average reduction in dopamine medication. Smeding et al. (2007) described a patient who developed GD after bilateral STN stimulation. The man was prescribed pergolide in conjunction with levodopa/carbidopa and DBS. At a follow-up appointment, the patient disclosed to his neurologist that he was suffering from GD with a preference for slot machines, which started a month after surgery. He also disclosed a history of alcohol abuse at that time. Results of cognitive tests were within the normal range of the PD population, including performance on the Iowa Gambling Task (IGT). As with the other patients described above, his GD and gambling urges ceased after his pergolide medication was tapered and eventually discontinued (cf. Lu et al., 2006). The authors observed that STN stimulation of the most dorsal contact both with and without medication was associated with worse performances on decision making tests compared to the ventral contact. They theorized that chronic STN stimulation in

this dorsal region sensitized the brain to the effects of DAs, perhaps particularly in vulnerable populations, such as those with a history of addictive behaviours. So while, there may be some additive effects of dorsal STN stimulation on decision-making impairments and in some cases a worsening of GD symptoms, the overall effect of STN stimulation is to lessen the reliance on DA medication for motor symptom relief, thereby relieving GD symptoms.

Decision-making is a complex neural process involving the receipt, organization, and processing of complex internal and external sensory stimuli, incorporation of memory of past events, a weighing of immediate needs against goals for the future, and appropriate action selection to achieve those goals involving a large network of cortical and subcortical brain areas. The STN has a well-known role in motor control (Groenewegen, 2003; Kuhn et al., 2008) and accumulating evidence supports the idea that the STN is involved in some aspects of emotional and cognitive processing as well (Marceglia et al., 2011). As mentioned earlier, people with GD often display impairments in decision-making tasks. While several experiments have been conducted using electroencephalography to study these decision-making impairments, the neuroanatomical targets of most of these studies have been, necessarily, focused on cortical structures. STN implantation surgery provides a rare opportunity to study a subcortical structure heavily influenced by dopamine in humans. To this end, Rosa et al. (2013) collected local field potential data from several PD patients who underwent DBS implantation surgery for PD. Eight of these participants had GD and their performance on an economic decision-making task was compared to nine matched PD controls. Unsurprisingly, the participants with GD employed a risky strategy, more frequently choosing the riskier option (the task was designed specifically to reward a safe strategy). When analyzing the neurophysiological data, the authors recorded low frequencies (2–12 Hz) oscillations from the PD patients with GD when making high-conflict

decisions, where the risk discrepancy between two options was the lowest (e.g., choose between 40%/60% success vs. 20%/80% success). The authors suggest that this low frequency oscillation may reflect increased dopaminergic activity and that PD patients with GD may be more likely to exhibit subthalamic activity that makes their decisional threshold highly sensitive to risk. This is interesting because Marceglia et al. (2011) propose that these low frequency oscillations in the STN are particularly related to decision-making processes involving prefrontolimbic circuitry. Taken together, this further supports the idea of a reward system in people with GD that is shifted toward risky decision-making, primarily modulated by increased dopamine efflux (compared to controls) during the moments leading up to and around the risky decision.

1.15 Experimental Overview

The previous sections have summarized the main findings in regard to the effects of schedules of reinforcement on behaviour and reward, risk, and uncertainty – and by extension slot-machines - induce repeated increases in phasic DA release. I have also outlined how DA may interfere with normal dopamine processes such as reinforcement learning which in turn can alter decision-making processes, risk taking, and impulsivity. This dysregulation may also interact with different biological (e.g., genetic polymorphisms) and environmental vulnerabilities ultimately leading to behavioural addiction. With this in mind, the main goal of this thesis is to explore whether RR schedules of reinforcement alone or paired with the D3 preferring DA, PPX, can induce addiction-like behaviour in an animal model.

The first two experiments presented in this thesis aim to address several theoretical questions. First, is repeated, prolonged exposure to RR schedules of reinforcement enough to cause animals to lapse into gambling addiction, as proposed by the Pathways Model? Second, which aspects of addiction (motivation, persistence, inhibition) are most affected by exposure to

these reinforcement schedules? And third, how would the behaviour of the animals in the gambling variation of the three criteria model compare to the behaviour of the animals from the drug addiction literature?

I predicted that rodents trained under a RR schedule would show greater evidence of addiction on all three measures compared to animals trained on the FR schedule. Based on the evidence from previous experiments, I also predicted that most RR-trained animals would show increases in motivation, and smaller numbers would show impairments in inhibition and persistence in the face of increasing levels of punishment. And lastly, I predicted that while the rats in these studies would exhibit the same overall shift toward addiction as that seen in the drug models, the effect of the RR reinforcement would be less powerful than that seen in the drug addiction literature because stimulant drugs such as cocaine are simply more powerful reinforcers. More people exposed to stimulant drugs become addicts than people exposed to gambling (Petry, 2007).

As a follow-up to the first two experiments, I also investigated whether the addiction-like behaviours associated with prolonged exposure to the RR schedule could be amplified by concurrent DA administration. As mentioned above, DA agonists have been associated with high rates of GD in patients with PD. RR schedules of reinforcement repeatedly induce the phasic release of dopamine, which is thought to be critical to why these types of schedules are so enjoyable. Theoretically it is possible that these unpredictable reward schedules interact with DAs, where the DAs essentially prime the brain's reward, motivation, and reinforcement learning systems to respond excessively to these types of reward, and over time shift over to an addiction state.

There is clear evidence that DAs have a role in the development of GD/ICDs in a large minority of patients with PD. DAs increase impulsivity and produce changes in risky behaviours and decision-making in healthy animals, animal models of PD, healthy humans, and human PD patients regardless of GD/ICD status. These medications obviously have some sort of effect on the dopaminergic reward system, however the effects on different regions of the brain are not well understood, particularly the relative effects on D2 and D3 receptors.

With this in mind, I predict that animals that both receive prolonged training on RR schedules and PPX administration would exhibit the highest rates of addiction-like behaviour. Additionally, given the results from the studies discussed above, I predict that rats exposed to prolonged PPX administration would exhibit increases in D3 receptors primarily in reward related regions, namely the NAC, OFC, MFC, INS, STR VP, SN, and VTA and decreases in regions related to inhibition and cognitive control, particularly the ACC and the CG. In contrast, I expect an overall down regulation of D2 receptors in the NAC, OFC, MFC, INS, STR, VP, SN, and VTA, and an upregulation of D2 receptors in the ACC and CG. Lastly, I also expect that these changes would be most evident in those animals exhibiting the strongest addiction-like behaviours.

Chapter 2: Random Ratio Schedules of Reinforcement as an Animal Model of Gambling Disorder

2.1 Abstract

Similar to drugs of abuse, random-ratio reward schedules are highly motivating and, in humans, are thought to foster gambling addiction. Animal gambling models, however, have not yet demonstrated the compulsivity so characteristic of drug addiction. Three criteria have been used to evaluate addiction-like behaviour in drug models: 1) response inhibition when reward is not available 2) persistence under a progressive ratio schedule, in which the response-to-reward ratio is stretched, and 3) persistence in spite of punishment. We tested whether prolonged exposure (6 weeks) to a gambling-like reward schedule would induce addiction-like symptoms in rats. In two studies, separate groups were trained to respond to either random- or fixed-ratio schedules for food reward. In both experiments, subjects on random-ratio schedules showed higher response rates and dramatically shorter pauses after rewards. Tests of addiction-like behaviour, however, were largely negative. Response-rates were not different during cued no-reward periods nor when reward was coupled with punishment. We also found no group differences when food was devalued nor in reinstatement of reward-seeking after a one-week delay. The sole exception to this pattern was that rats in the second experiment showed greater persistence on a progressive ratio test. After experiment two, subjects were also given 10 days of orally administered pramipexole, which caused increased perseveration during progressive ratio testing, especially in the random ratio group. While it is possible that longer training or more appetitive rewards might have led to addiction-like behaviour, our results, on the surface, suggest that random-ratio schedules are motivating but not addictive.

2.2 Introduction

Addiction is characterized by the inability to refrain from engaging in a particular activity, such as taking drugs, eating, or gambling, which persists despite negative consequences (American Psychiatric Association, 2013). This compulsive aspect of addiction is a common feature of animal models of substance abuse. For example, reinstatement—the re-initiation of drug self-administration after a period of abstinence—is used as evidence of substance addiction in many rodent studies (Shaham et al., 2003). Other drug addiction studies have focussed on the escalation of self-administration as a diagnostic criteria (Edwards and Koob, 2013). Yet others have measured the degree to which an animal will persist in drug self-administration despite rising response demands or negative consequences (Deroche-Gamonet et al., 2004; Pelloux et al., 2007; Belin et al., 2008). These animal models of compulsive drug seeking often involve long-term self-administration, facilitating the development of drug seeking as a habitual response (Everitt and Robbins, 2016). One particularly salient example is that of Deroche-Gamonet et al. (2004), which used three behavioural criteria to assess addiction to cocaine: 1) to assess difficulty in refraining from drug seeking, they examined responses during a period when a cue indicated that no reward was available; 2) to assess motivation, they examined the break-point under a progressive ratio schedule (i.e., the ratio at which rats stopped responding); and 3) to assess sensitivity to negative consequences, they measured the willingness to continue self-administration when responses were paired with punishing foot-shock. Interestingly, even after 2 months of daily self-administration with cocaine, only a fifth of all rats showed elevated compulsivity on all three assessment criteria. This vulnerability in only a small fraction of individuals has been replicated in several similar studies (Belin-Rauscent and Belin, 2012a). The

authors argue that this mirrors the situation with human addicts, because only a fraction of humans exposed to a drug of abuse will actually progress to full-blown addiction.

In contrast to drug addiction studies, animal models of gambling addiction have eschewed the compulsive aspect of addiction, focusing instead on deficits in decision making (i.e., "irrational choices") which are thought to underlie problem gambling. For example, one of the most common tasks is the "rodent gambling task", an analog of the human-based Iowa gambling task in which subjects choose between card decks which differ in both the amount and probability of monetary gain or loss (Bechara et al., 1999). The high risk, high yield decks ultimately result in a net loss, and normal subjects quickly learn to avoid these decks whereas problem gamblers are drawn to them (Goudriaan et al., 2005). Rats which preferentially choose high-reward/high-risk options are thought to mimic decision making impairments seen in problem gamblers (Winstanley and Clark, 2016). Others have looked at "delay discounting," which measures the willingness to wait for reward. People with gambling problems typically show less tolerance for delayed reward even when it is substantially larger than an immediate reward, so rats which fail to wait presumably capture this impulsive aspect of problem gambling (Dixon et al., 2003; Madden et al., 2007). Other recent animal studies have looked at the influence of wager size on risk affinity and the "near-miss" phenomenon which is thought to increase the addictiveness of slot-machines (Clark, 2010; Winstanley et al., 2011; Cocker et al., 2012).

Although decision biases may predispose individuals to become gambling addicts, it has been argued that the factor which makes gambling both highly engaging and potentially addictive is the uncertainty of reward. Early behaviourists recognized that random-ratio (RR) schedules, like the payout at a slot machine or video lottery terminal, are highly engaging while

fixed-ratio (FR) schedules (i.e., reward delivered after a fixed number of responses) are not (Skinner and Ferster, 1957; Fantino, 1967; Sherman and Thomas, 1968). Contemporary authors also support this basic finding (Mazur, 1983; Madden et al., 2007; Lagorio and Winger, 2014). Random ratio schedules are also thought to be central to the process whereby gambling becomes addictive. One prominent theory, the Pathways Model (Blaszczynski and Nower, 2002), suggests that exposure to RR schedules is common causal factor in all people with gambling addiction, irrespective of biological or socio-economic risk factors.

Several lines of evidence suggest that dopamine is central to the motivational and addictive properties of RR schedules. Midbrain dopaminergic neurons are famously driven by the difference between expected and actual reward, the so-called "reward prediction error" (Schultz, 2016). This has led some to theorize that the uncertainly of gambling wins maximizes dopamine release, ultimately leading to addiction (Ross et al., 2008). This hypothesis has been supported by several empirical findings. In monkeys, the tonic firing of midbrain dopaminergic neurons is strongest before reward delivered with maximum uncertainty (50% likelihood) (Fiorillo et al., 2003). Similarly, random ratio schedules enhance dopamine release in parts of the human basal ganglia (Zald et al., 2004). Other evidence suggests that gambling-like activities can sensitize the brain to dopamine. Rats trained to expect food reward probabilistically (i.e., with high uncertainty) show higher amphetamine-induced hyperactivity than rats trained with more predictable reward (Singer et al., 2012; Zack et al., 2014). It is worth noting, however, that several rodent studies suggest that poor decision making in gambling tasks is correlated with reduced dopaminergic transmission efficacy (Cocker et al., 2012; da Silva Lobo et al., 2015; Zoratto et al., 2017). Whether this is due to a dissociation of the decision making and compulsive aspects of addiction or other causes is unclear.

Further bolstering the link between dopamine and gambling addiction is the de novo development of gambling and other behavioural addictions in Parkinson's patients given dopamine agonist therapy (Zand, 2008; Weintraub and Claassen, 2017). The D_3 receptor has been specifically implicated in this addiction process and, in fact, the drug with the highest D_3 binding potential, pramipexole dihydrochloride, is associated with the highest rates of behavioural addiction (Zand, 2008; Seeman, 2015).

While it is known that both unpredictable reward and dopamine agonist administration can change risk preferences, decision-making, and motivation levels in animals, to the best of our knowledge no one has tested whether repeated exposure to RR schedules of reinforcement generates addiction-like behaviour per se. In this study, we investigate whether RR schedules of reinforcement are more likely to produce behavioural addition in rats and whether administration of pramipexole dihydrochloride exacerbates addiction symptomatology. Following the design of the cocaine-addiction study of Deroche-Gamonet et al. (2004), rats worked for food reward in standard operant chambers daily for several weeks (which allows for addiction-like behaviour to appear) after which several behavioural measures were assessed. Four of these were derived from the Deroche-Gamonet et al. (2004) study and were used as the main measures of behavioural addiction: 1) the ability to refrain from seeking reward when a cue indicates it is not available 2) motivation to obtain reward as response requirements increase; 3) persistence in seeking reward paired with punishment and 4) reinstatement of responding after a period of withdrawal. Two others, 5) responses rates and 6) post reinforcement pauses, were used to measure motivation when comparing reward schedules (Mazur, 1983). These measures were included to provide information that was comparable to other studies investigating the effects of various reward schedules on animal behaviour. A final test assessed 7) habitual responding after

food reward was devalued. One of the hallmarks of late-stage addiction is that the pursuit of reward becomes habitual (Everitt and Robbins, 2016). Habitual behaviour is often tested in rats using a devaluation test, in which a rat trained on an instrumental task is sated on the specific type of reward earned by the instrumental response (Balleine and O'Doherty, 2010). If the rat's responses decrease after satiation, the behaviour is said to be "goal-directed" because the consequences of action guide behaviour. If not, the behaviour is said to be "habitual". We enquired as to whether rats trained on an RR schedule would become more habitual in their responses than those trained on an FR schedule. We were also interested to see how each of these measures related to each other. Behavioural measures that are strongly intercorrelated may indicate that they are measuring the same underlying process. Conversely, if we found that our measures of addiction are not related to one another, it could mean that different underlying processes and hence, different brain networks, are involved.

The experiment was conducted twice. The second iteration was included to both replicate our findings and extend the duration of the training period from 4 to 6 weeks. An overview of behavioural tests used in each experiment are provided in Table 2.1. We predicted that animals working for unpredictable food reward would exhibit more behavioural markers of addiction parallel to those seen in drug addiction studies (i.e., increased motivation and compulsion) after several weeks than animals working for predictable food reward.

In humans, addiction is diagnosed by assessing how many addiction criterion the individual meets, and a similar approach is used in some rodent studies (Belin-Rauscent and Belin, 2012a). One of our primary goals was to model this study after the cocaine addiction studies of Deroche-Gamonet et al. (2004) so as to draw a direct comparison between our findings and the drug addiction literature. In line with their assessment of cocaine addiction in rats, we

examined the proportion of our animals who scored high in addiction-like responses for each of the three central addiction tests: cued-unavailability, progressive ratio, and progressive aversion. We predicted that a higher proportion of rats trained on an RR schedule of reinforcement would test positive for one or more addiction criteria than those trained on an FR schedule.

Finally, we investigated the effects of PPX on schedule-induced behavioural addiction. Rats trained on FR and RR schedules were exposed to increasing amounts of the dopamine agonist pramipexole dihydrochloride (PPX) while their addiction-like behaviour was assessed. We expected an interaction between PPX and reward schedule, with PPX preferentially exacerbating addiction-like symptoms in the RR animals.

Table 2.1 Overview of behavioural tests used in each experiment

Exp.	Purpose	Response Rate	Post Reinforcement Pause	Cued-No Reward	Progressive Ratio	Progressive Aversion	Devaluation	Reinstatement
1	Test effects of random ratio schedules on addiction-like behaviour	✓	✓	✓	✓		✓	
2	Replication Exp. 1 with longer training	✓	✓	✓	✓	✓	✓	✓
3	Test effects of the $D_{2/3}$ agonist pramipexole	✓	✓	✓	✓		✓	

A list of all behavioural tasks and brief descriptions of the purpose of each experiment are described above. Checkmarks indicate which behavioural tests were included in each experiment.

2.3 Materials and Methods

2.3.1 Experiment 1

2.3.1.1 Subjects and Ethics

Subjects were male Long–Evans rats (n = 16; Charles River Laboratories, Raleigh, NC). Two animals in the control (FR) group were excluded from analysis due to behavioural problems

during training (i.e., chewing on nose-poke hole rather than nose-poking). Animals weighed 295–350 g and were 88 days old at the start of the experiment. Animals were pair-housed in a temperature-controlled colony room under a 12 h reverse light cycle (lights off at 10:00 AM.). All experiments were performed in accordance with the guidelines set by the Canadian Council of Animal Care, and experimental protocols were approved by the University of Lethbridge Animal Welfare Committee.

2.3.1.2 Apparatus and software (data acquisition)

Behavioural testing took place in standard five-hole operant chambers which were enclosed within a ventilated sound-attenuating cabinet (Med Associates Inc., Fairfax, VT). Each chamber was fitted with an array of five response holes positioned 3.5 cm above a bar floor. Each hole contained a horizontal infrared beam as well as stimulus light. Responses were recorded when infrared beams were broken by the animal. At the middle of the opposite wall, a food magazine was also fit with an infrared beam and a tray light where animals could collect food reward. Food magazines delivered food pellets with high sugar content but also containing a balanced nutritional diet (Rodent Purified Dustless Precision Pellets, F0021 45 mg; Bioserv, New Jersey) via an external pellet dispenser. Water was available to the animals *ad libitum* during testing via a water bottle located on the right side of the back wall, adjacent to the food magazine. Chambers were fit with two house lights allowing for chamber illumination in two colors (yellow and blue). All chamber hardware was controlled via by software written in ABET (Lafayette Instruments, Lafayette, MA) using a standard Microsoft Windows computer and Lafayette Instruments interface hardware (ABET 2G starter interface and expansion interfaces).

2.3.1.3 Pre-training, housing, and food restriction

All habituation, pre-training and training sessions took place between 10:00 AM. and 9:00 P.M. seven days per week. Water was available ad libitum. Animals were food restricted to ~85% of their free-feeding weight and were maintained at this weight by daily supplements of standard rat diet, as needed, delivered at least 15 minutes after the end of behavioural testing.

One day prior to habituation, each animal was given small amounts of purified pellets in order to create familiarity with the novel food. Animals were habituated to the operant chamber in a single 30 min pre-training session, during which reward was delivered non-contingently with a variable interval, averaging 60 seconds. Animals were then trained to make a nose-poke response into the central nose-poke aperture in order to earn a single food pellet (FR1 schedule). Operant chambers were illuminated with a blue light during auto-shaping sessions. Illumination of the food magazine accompanied reward presentation in all sessions. Each session lasted 30 min. Rats were moved onto the subsequent pre-training stage either after they earned 100 rewards in 30 min. All animals passed criteria within 3 days.

Following the auto-shaping paradigm, sessions were broken into alternating blocks wherein rats were trained on an FR1 schedule to associate the blue illumination with periods of reward availability and yellow illumination with reward unavailability. During the yellow light periods, the nose poke was not illuminated and responses did not count towards reward. Animals completed this stage when response rates during the cued no-reward period were ≤ 50% of their response rates during the cued-reward period. All animals in Exp. 1 passed the first criteria after one session. During subsequent pre-training sessions, the duration of cued no-reward periods were gradually increased from one to ten minutes. The shorter no-reward periods allowed more reward/no-reward transitions per session, facilitating learning in early sessions.

Upon completion of the pre-training stages, rats were rank ordered according to average response rates during the final pre-training stage. Animals were then assigned in pairs to either the FR or RR group, equalizing baseline response rates between experimental groups.

2.3.1.4 Gambling Task

The main behavioural task in this study involved rats responding for food reward delivered on either a fixed or random schedule of reinforcement. In fixed ratio schedules, animals were required to respond a fixed number of times before obtaining reinforcement. In contrast, random ratio schedules delivered food reward after a random number of responses. Pseudo-random ratio schedules were generated by shuffling a list of all rewarded and unrewarded trials (e.g., 99 rewards among a total of 4950 trials for an RR50 session). The list was randomized repeatedly to make seven different versions of the RR50 schedule which rats rotated through sequentially each week. Having fixed RR50 schedules provided control over both the distribution and number of rewarded trials within each session (i.e., one rat could not experience, by chance, multiple sessions loaded with rewarded trials at the beginning).

Rats were trained over a week to repeatedly nose-poke into the central hole for food reward. Reinforcement schedules for FR rats were increased from FR5 to FR10, FR25, and then FR50, spending two days on each step up to FR50. Similarly, RR rats started on RR5 and increased to RR10, RR25 and RR50. Rats trained on an FR schedule earned 3 purified pellets upon completion of each ratio requirement. Those trained on an RR schedule earned 1, 3, or 5 ($\bar{x}$ = 3) pellets. Sessions contained 99 reward events and lasted until either the animal obtained all rewards or 255 min elapsed. Each session was divided into three cued-reward blocks (blue light) separated by two 10 min cued no-reward blocks (yellow light). Cued no-reward blocks were initiated after animals completed both the 33rd and 66th rewarded trial. If a rat used all 255 min

this would equate to three 45 min cued-reward periods and two 10 min cued-no reward periods. A time-out period of 300 ms was implemented after each poke, forcing rats to withdraw at least once after this period before the next poke. This prevented rats from accidentally achieving rapid, multiple beam breaks while chewing on the edge of the hole. A light at the back of the poke hole was turned off during the time-out period and then on again when the nose-poke was active. Premature responses reset the 300 ms timer.

Following the walk-up on the FR/RR schedules, each group completed 4 weeks of behavioural testing on the FR50 or RR50 schedules. Animals unable to complete all trials within the time limit ran additional sessions so the total number of trials between groups was equivalent.

A variety of behavioural measures were collected during each daily testing session, including the animal's response rate during cued-reward and cued no-reward periods, inter-response intervals, and post reinforcement pauses. Post reinforcement pause times were calculated as the time elapsed between final food magazine exit and the first subsequent nose-poke on the central port.

2.3.1.5 Devaluation Test

Upon completion of the main Gambling Task, rats were assessed for goal-directed behaviour using a food devaluation task. Prior to behavioural testing animals were allowed free access to the purified pellets used in testing for one hour. All rats then completed a single session on the FR50 schedule and performance was compared to data collected from the previous testing session when the rat was not sated. Following the devaluation test, rats completed two additional FR50/RR50 sessions without pre-feeding to allow for responding to recover to baseline levels.

2.3.1.6 Progressive Ratio Test

Finally, animals were assessed for differences in motivational levels using a progressive ratio task. In this task, animals could earn food reward by nose-poking into the central hole. However, the number of responses required to obtain food reward gradually increases throughout the testing session. The blue cue light remained on during the entire session. Individual trial response requirements were computed using the function $PR(x) = \text{round}(r*((x-3)^2/ (104)^2))$, where PR is the number of responses needed to achieve reward, r = ratio value at 100 rewards, set to 1000, and x = reward number, ranging from 1-120. The session lasted until the animal failed to obtain a reward after 30 min or a maximum of 5 h had elapsed. Breakpoint and response rate data was collected for all animals. Average response rates were expressed as a ratio of "baseline" response rates, measured in a standard FR50 or RR50 testing session run on the final day of regular testing. Data from one animal on this test was excluded due to a power-outage during testing.

2.3.2 Experiment 2

Experiment 2 was intended to replicate the first study, using an extended training duration of 6 weeks and more animals. Two other changes are worth noting. First, we switched from nose-poke to lever for responses. The nose-poke has limitations in that a rat chewing on the edge of the hole can trigger a beam break with each bite, creating a rapid series of unintended responses. Second, whereas the first experiment used variable reward in the random-ratio group (1, 3 or 5 pellets), the second experiment used a fixed reward of 3 pellets for each response in both random- and fix-ratio groups. The goal was to eliminate a confounding source of uncertainty in the random-ratio group. Behavioural tests used in Exp. 2 are largely the same as Exp. 1 and are described above in section 2.1. Additional behavioural tests and changes to any

Table 2.2 Experimental timelines

Exp.	Day	Task
	1-17	Pre-training
	18-48	RR50/FR50 Testing
1	49	Devaluation
	52	Progressive Ratio
	1-23	Pre-training
	24-65	RR50/FR50 Testing
	66	Devaluation
2	69	Progressive Ratio
	70-71	Reinstatement
	82	Progressive Aversion
	86	RR50/FR50 Baseline
	87-92	RR50/FR50 Testing with
3		PPX
	93	Devaluation
	96	Progressive Ratio

Separate groups of rats were run for Exp.1 and Exp. 2, but rats from Exp. 2 were the same as those in the pramipexole (PPX) experiment.

tests used in Exp. 1 are described below. See also Table 2.1 for a comparison of the behaviour tests and Table 2.2 for a comparison of the experimental time-lines.

2.3.2.1 Subjects

Subjects were male Long-Evans rats (n = 30; Charles River Laboratories, Raleigh, NC). Four animals (three from the RR group and one from FR) were excluded from analysis, to behavioural problems during training (i.e., chewing on lever rather than pressing with forepaws). Data from the other three animals was excluded due to a hardware issue with the lever in their testing chamber which was discovered late in the testing schedule. Animals weighed 235–265 g and were 78 days old at the start of the experiment. Animals were pair-housed in a temperature-controlled colony room under a 12 h reverse light cycle (lights off at 10:00 AM.).

2.3.2.2 Apparatus

Testing took place in the same chambers as those used for Experiment 1, with the addition of a response lever. The lever (Med Associates ENV-110M) was located adjacent to the food magazine on the left side of the back wall (2.75 cm above the bar floor). A custom-installed backlight within the lever housing took the role of the nose-poke cue light. Shock was delivered via a Lafayette Instruments Shocker (model HSCK100AP) which delivers scrambled shock with a bipolar waveform and 12% duty cycle. The scrambler has a cycle time of 75ms with each grid pair receiving a bipolar pulse of 8.3 ms.

2.3.2.3 Pre-training

Autoshaping and pre-training methods were identical to that in Experiment 1. All animals passed autoshaping criteria within 3 days. Three animals (1 FR and 2 RR) did not meet the first criteria for cued no-reward training and were forced on to the next stage.

2.3.2.4 Progressive Ratio

Progressive ratio testing was conducted the same as for Experiment 1 with a small adjustment to the formula for computing the ratios, so that ratios increased more rapidly. The number of responses require to achieve the x^{th} reward (PR) was computed using the function

$$PR(x) = \text{round}(r*((x-3)^2/ (104)^2))$$

where r = ratio value at 100 rewards, set to 2000, with x ranging from 1-120.

2.3.2.5 Reinstatement Test

This task assesses an animal's propensity to relapse into reward seeking behaviour after a period of withdrawal. After a 5-day rest period (following the Progressive Ratio task), rats were tested for reinstatement of instrumental responding (lever pressing) over two sessions of extinction testing. Specifically, during the first session (cue-induced reinstatement) rats were

placed into a dark operant chamber for 90 min, during which no cue lights were presented and lever-pressing was unrewarded. After this extinction period, non-contingent cue lights associated with reward were presented (blue light and lever light) and remained on for the rest of the session. At the 90 min point and at each 30 min interval thereafter (up to a total of 210 min), the feeder activated and food magazine light turned on but no reward was delivered. The second day of reinstatement testing (reward-induced reinstatement) was identical to the first day except that the animals also received food reward with the presentation of the non-contingent reward-related cues. Rats received one non-contingent purified pellet at the 90 min point, two pellets at 120 min, 4 pellets at 150 minutes, and 8 pellets at 180 minutes. Response rate data was collected from the final 30 min period.

2.3.2.6 Progressive Aversion Test

The progressive aversion task measures the degree to which rats will seek reward despite increasing negative consequences. During these sessions, rats worked for food reward on a FR10 schedule. Cue lights remained the same as those used during the Gambling Task (see Section 2.2.4.) with some minor changes. After the 8th and 9th lever press in each trial, the lever light flashed rapidly (6.67 Hz) signaling delivery of a 1.5 s foot-shock after the next lever press. Foot-shock was delivered after the 9th response and was paired with reward after the 10th response in each trial. The shock current was gradually increased from 0.04mA up to a maximum of 1.24 mA in increments of 0.04mA every three trials. The session lasted until the rat completed 120 trials, failed to obtain a reward after 30 min, or a maximum of 5 h had elapsed. Breakpoint data (i.e., the level of current at which an animal elected to stop responding) was collect for all animals. Average response rates were expressed as a ratio of "baseline" response rates, measured in a standard FR50 or RR50 testing session run on the final day of regular testing.

2.3.2.7 Multi-criterion Assessment of Addiction

Following Deroche-Gamonet et al. (2004), we used the scores obtained in three behavioural tests to assess addiction, namely progressive ratio breakpoints, response rates during the cued no-reward periods, and progressive aversion breakpoints. Each rat was rank-ordered on each of the tasks and tested positive for that criterion if it fell within the 33% highest percentile of the distribution on that test (see Deroche-Gamonet et al. (2004), Supplementary Materials for a discussion on the rationale for addiction measure thresholds).

2.3.3 Drug Administration

The effect of the dopamine D_3 agonist, pramipexole dihydrochloride, on addiction-like behaviours was examined in a final experiment. The enantiomerically pure (~98%) dopamine D2/3 agonist, pramipexole dihydrochloride [(S)-2-amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole dihydrochloride monohydrate], was prescribed by our veterinarian and purchased from a local pharmacy in form of 1 mg tablets which were crushed into a powder.

Drug was administered orally once daily for 10 days by dissolving it in the rats' home cage water bottles. Pair housed rats shared the same bottle (i.e., each bottle contained 2 doses and enough water for two animals). Rats received a set amount of water each day (based on their pre-drug baseline water intake levels, averaged over 5 days) to ensure the full drug dose was ingested. Water restriction commenced the third day after Progressive Aversion testing and continued for the remainder of the experiment (11 days in total). Animals had free access to their home cage water bottles (dosed with pramipexole) except during behavioural testing and for approximately 1h thereafter, during which animals were fed in separate cages. While it is not ideal for rats to share the same bottle, we felt that the proposed method would have the least negative impact on animal welfare and best experimental outcomes. Because water intake is

under strict homeostatic control, each animal is likely to ingest a fairly constant amount of water each day, so fluctuations were expected to be small.

2.3.3.1 Dose-Response Testing

After completing the Progressive Aversion test, rats completed four additional FR50/RR50 sessions to allow for responding to recover to baseline levels. Water restriction started after testing was completed on the third recovery day and baseline response rate data was collected from the fourth session while all rats were water restricted. Oral administration of PPX via homecage water bottles started after the fourth FR50/RR50 recovery session. Rats continued behavioural testing on FR50/RR50 schedules for the following six days while under the influence of increasing doses of drug. Specifically, animals received 0.33 mg/kg/day on days 1 and 2, 0.66 mg/kg/day on days 3 and 4, and 1.0 mg/kg/day on days 5 and 6. Devaluation testing was conducted on day 7 and Progressive Ratio testing on day 10 (see Section 2.2.5. and 2.2.6. for descriptions). Both tests were conducted at the highest (1.0 mg/kg/day) dose of drug.

2.3.4 Correlations Between Behavioural Measures and Dendrograms

We computed the correlation between every pair of measures for each study. Before computing correlations, two tests which showed skewed distributions—cued unavailable reward and reinstatement—were log-transformed to reduce the influence of outliers. Behavioural measures were also transformed so that higher scores indicated higher levels of addiction-like behaviour. Specifically, scores for post reinforcement pauses were multiplied by -1 before computing correlations and distances (this procedure was conducted in Exp. 1 and 2 in this chapter but was not used for Exp. 3 and 4 in Chapter 3).

A dendrogram was used to visualize the degree of relatedness between each of the behavioural measures. Distance scores were calculated between each pair of rows as 1-*r* where *r*

is the Pearson correlation between rows. A distance of near zero meant that the behavioural correlates for those two measures were nearly identical whereas a distance of 1 meant that the measures were unrelated. Values above 1 indicated that the measures were anti-correlated. A dendrogram was then generated from this data using the Unweighted Pair Group Method with Arithmetic Mean (UPGMA) algorithm, in the BMEToolbox (http://www.bioinformatics.org/mbetoolbox/) written for MATLAB (The Mathworks, Natick, MA).

2.4 Results

In order to determine whether prolonged exposure to unpredictable reinforcement could induce addiction-like behaviours, rats were trained to respond for food reward on either random or fixed ratio schedules of reinforcement over four (Exp. 1) or six (Exp. 2) weeks and were then assessed for addiction-like behaviour using a battery of tests.

2.4.1 Group Equivalence in Baseline Response Rates and Total Rewards

We first confirmed that random-ratio (RR) and fixed ratio (FR) groups showed equivalent performance during pre-training, before their experiences diverged. After exclusions (described in Methods), Experiment 1 included 14 rats (RR: 8 rats, FR: 6 rats) while Experiment 2 included 26 rats (RR: 12 rats, FR: 14 rats). For both experiments, there were no differences in responses rates between groups during their final stage of pre-training on an FR1 schedule (Experiment 1: average responses per second for FR group ± standard deviation: 0.2839 ± 0.0227; RR group: 0.3454 ± 0.0757; t-test: $t(12) = -1.673$, $p = 0.12$; Experiment 2: FR group: 0.3752 ± 0.0825; RR group: 0.3738 ± 0.1085; t-test: $t(26) = 0.038$, $p = 0.97$). During extended training on the FR/RR50 schedules, some rats did not complete the maximum of 99 rewarded trials per day. To maintain an equal number of total rewards across groups, some rats were allowed extra training

sessions so that, in the end, there was no significant difference in the total number of rewards achieved between FR and RR groups (Experiment 1: total rewards received by FR group: 3673.33 ± 55.388; RR group: 3671.25 ± 9.146; t-test (equal variances not assumed): t(5.205) = .223, p = 0.832; Experiment 2: FR group: 4728.5 ± 26.229; RR group: 4747.07 ± 18.813; t-test: t (26) = 0.166, p = 0.87).

2.4.2 Comparison of Random- and Fixed Ratio Schedules

2.4.2.1 Random Ratio Schedules of Reinforcement Increase Response Rates. Weekly average response rates for groups of animals were computed by averaging nose pokes (Exp. 1) or lever presses (Exp. 2) over all trials during the cued-reward periods, excluding the trial after reward (see discussion of post reinforcement pause, below). In Exp. 1, average response rates were consistently higher in the RR group across weeks, but a mixed designs ANOVA with schedule as the between subjects factor and week of testing as a repeated measure showed no main effect of schedule (Fig. 2.1a; F (1, 12) = 1.023, p =. 332) nor schedule by week interaction (F (1.964, 23.57) = .585, p = .562; Greenhouse-Geisser corrected); however, there was a significant within-subjects effect of week (F (1.964, 23.57) = 37.415, p < .001; Greenhouse-Geisser corrected), indicating the rats got faster with increased experience on the task.

In Experiment 2, RR rats were faster across all 6 weeks of training, this time significantly so (Fig. 2.1c; main effect on response rate, F (1, 24) = 4.496, p = .045). Again, rats improved across weeks (within subjects effect of week, F (2.468, 59.233) = 31.697, p < .001, Greenhouse-Geisser corrected). Here, there was no reinforcement schedule by week interaction effect (F (2.468, 59.233) = 1.829, p = .161, Greenhouse-Geisser corrected).

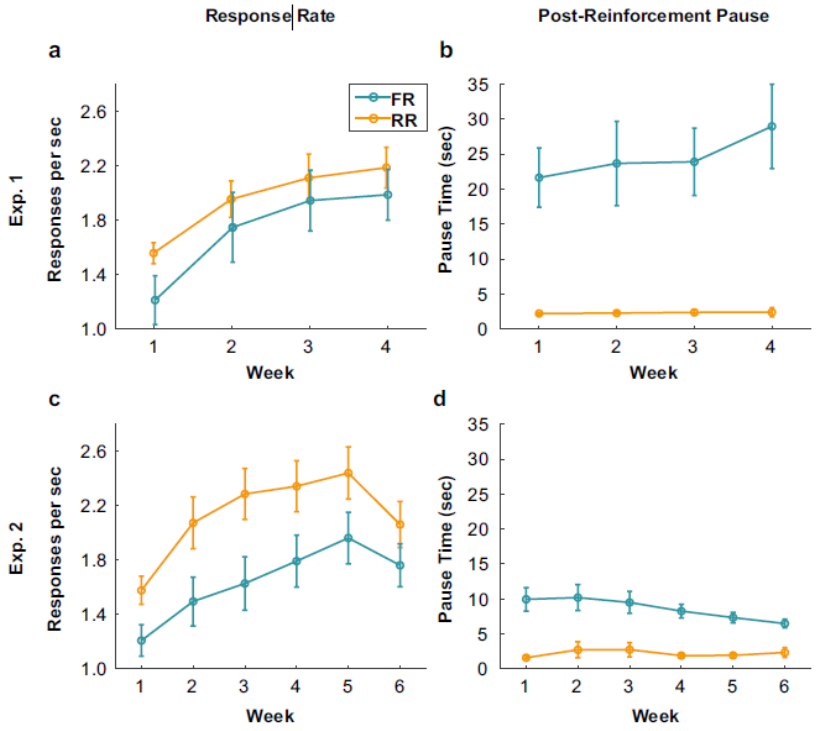

Figure 2.1. Behavioural measures during training on a random or fixed ratio schedule of reinforcement. The first column shows average response rate for each week of training in Experiments 1 (nose-poke) and 2 (lever press). These response rates are calculated for the cued-reward periods and excluded the cued no-reward periods. The second column shows the weekly average post-reinforcement pause for both groups in both experiments.

2.4.2.2 Random Ratio Schedules Decrease Post-Reinforcement Pause Time

We found that in both studies, animals trained on RR schedules exhibited much lower pause times than those on FR schedules over all weeks of testing (Fig. 2.1b and 2.1d). Mixed designs ANOVAs showed that schedule had a significant main effect on the post-reinforcement pause (Exp. 1: $F(1, 12) = 35.174$, $p < .001$; Exp. 2: $F(1, 24) = 29.150$, $p < .001$), however, there was no within-subjects effect of week ($F(1.209, 14.512) = 1.103$, $p = .325$; Exp. 2: $F(2.378, 57.084) = 2.086$, $p = .125$; Greenhouse-Geisser corrected), and no schedule x week interaction (Exp. 1: $F(1.209, 14.512) = 1.011$, $p = .348$; Exp. 2: $F(2.378, 57.084 = 1.691$, $p = .188$; Greenhouse-Geisser corrected).

2.4.2.3 Random Ratio Schedules Do Not Affect Cue-Induced Inhibition of Responding

We computed weekly averaged rates of nose pokes (Exp. 1) or lever presses (Exp. 2) over the first 10 minutes of the cued no-reward period in each session. As shown in Fig. 2.2a and 2.2d, the schedule of reinforcement did not significantly affect rats' response rates in either experiment. A mixed designs ANOVA showed no significant main effect of reward schedule on response rates (Exp. 1: $F(1, 12) = 3.438$, $p = .088$; Exp. 2: $F(1, 24) = .024$, $p = .879$); however, there was a significant within-subjects effect of week (Exp. 1: $F(3, 36) = 23.079$, $p < .001$; Exp. 2: $F(2.777, 66.644) = 29.338$, $p < .001$; Greenhouse-Geisser corrected), showing that rats'

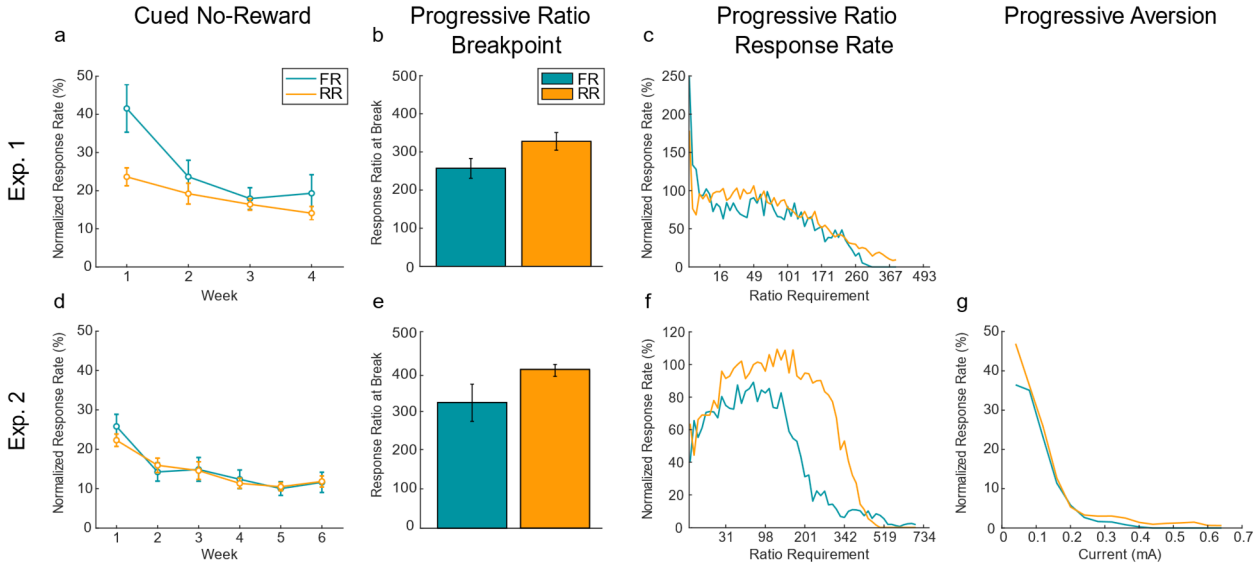

Figure 2.2. Effects of random or fixed ratio reinforcement schedule responses during cued no-reward periods, progressive ratio, and progressive aversion tests. The first column compares persistence in reward-seeking during cued no-reward periods for Experiment 1 and 2. Rates are shown as a percentage of the average response rate during cued-reward periods. Average progressive ratio breakpoints (column 2) and response rates for each ratio requirement (column 3) are also shown for both RR and FR groups. Responses are expressed a percentage of the response rate on the last day of regular testing, during which rats ran on a standard FR50 or RR50 schedule. The fourth column shows response rates for RR and FR groups during a test in which reward was paired with progressively increasing intensities of foot-shock (i.e., "progressive aversion"). As with the progressive ratio test, response rates are expressed as a percentage of those on the baseline testing day.

ability to inhibit responding in a cue-dependent way improved with time on the task. The schedule by week interaction was significant for Experiment 1 ($F (3, 36) = 5.582$, $p = .003$), but not for Experiment 2 ($F (2.777, 66.644) = .923$, $p = .429$; Greenhouse-Geisser corrected).

2.4.2.4 Random Ratio Schedules Modestly Increase Persistence During Progressive Ratio Testing

Our data showed that, on average, RR rats had slightly higher breakpoints on the progressive ratio test compared to FR rats, but this difference was not statistically significant in either experiment (see Fig. 2.2b and 2.2e; Exp. 1: $t (11) = -1.972$, $p = .074$; Exp. 2: $t (15.606) = -1.875$, $p = .080$, equal variances not assumed). However, in Experiment 2, RR rats clearly showed elevated response rates compared to FR rats at higher response ratios (Fig. 2.2c and 2.2f). To test this statistically, we split the progressive ratio session into three equal phases based on required response ratio and binned response rates accordingly. We then ran a mixed design ANOVA comparing response rate as a function of ratio requirement (low, medium, high) and group (FR versus RR). In Experiment 1, we found no significant main effect of group on response rate ($F (1, 11) = 1.289$, $p = .280$) but in Experiment 2, group had a significant effect ($F (1, 24) = 20.468$, $p < .001$). As expected, there was a significant effect of ratio requirement for both experiments, reflecting the fact that all rats reduced response rates at extreme ratios (Exp. 1: $F (2, 22) = 84.795$, $p < .001$; Exp. 2: $F (2, 48) = 246.003$, $p < .001$). The ratio by group interaction was not significant for Experiment 1 ($F (2, 22) = .115$, $p = .892$) but was significantly different for Experiment 2 ($F (2, 48) = 10.016$, $p < .001$). Thus, it appears that schedule of reinforcement has a modest, but significant impact on rats' willingness to work for food reward under progressive ratio schedules, at least in our second experiment.

2.4.2.5 Random Ratio Schedules Do Not Increase Persistence in the Face of Increasing Punishment

Persistence was calculated by averaging individual rats' breakpoints across groups. A one-factor independent samples T-test was used to test for group differences. These data suggest that rats trained on a RR schedule are no more willing to endure increasing levels of foot shock than rats trained on a FR schedule ($t(24) = -.146$, $p = .885$; Fig. 2.2g).

2.4.2.6 Random Ratio Schedules of Reinforcement Do Not Make Behaviour More Habitual

Willingness to work for the devalued reward was calculated by averaging responses over all trials during the cued-reward periods and comparing this to the baseline pre-devaluation data recorded from the last week of regular testing. Surprisingly, in both experiments, the mean

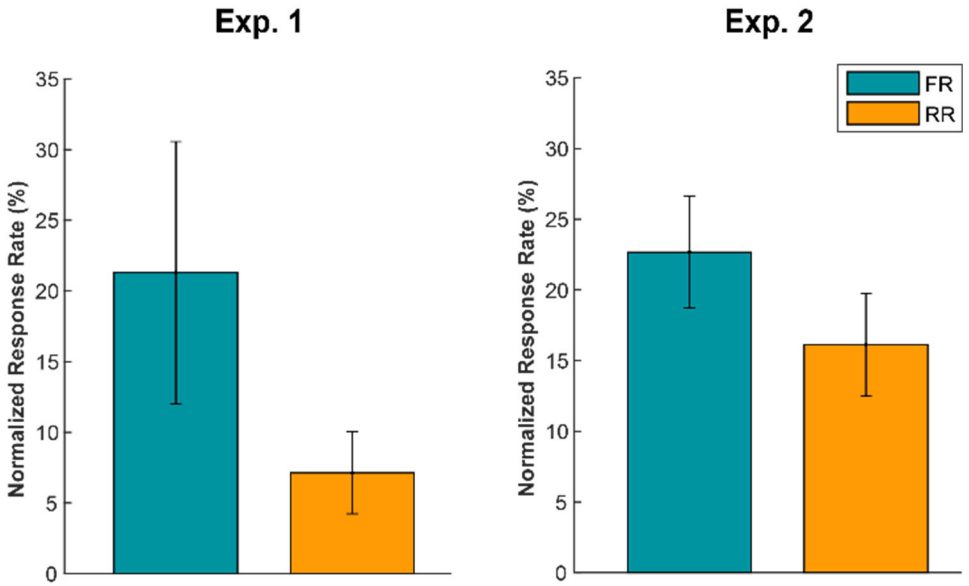

Figure 2.3. Effect of fixed or random ratio schedules on response rates for food after reward devaluation. Response rates are expressed as a percentage of the response rate during the last week of regular testing on an FR50 or RR50 schedule.

response rate after devaluation was lower for the rats trained on the RR schedule (Fig. 2.3); however, this effect did not reach statistical significance in either experiment (Exp. 1: t (12) = 1.644, p = .126; Exp. 2: t (24) = 1.204, p = .240).

2.4.2.7 Random-Ratio Schedules Do Not Increase Reinstatement of Reward Seeking

In Experiment 2, the effect of reward schedules on reinstatement of responding after a period of withdrawal was tested. Each animal's propensity to re-commence responding was calculated using response rate data which were then normalized by dividing by each rat's response rate on the final day of the six-week reinforcement schedule testing. Due to a non-normal distribution of the data, a non-parametric Mann-Whitney U-test was used to assess group differences. We found no significant difference in the mean response rates (mean normalized response rate, FR: 1.859% ± 1.774%; RR: 2.084% ± 3.488%; U = 66.000, p = .374) indicating

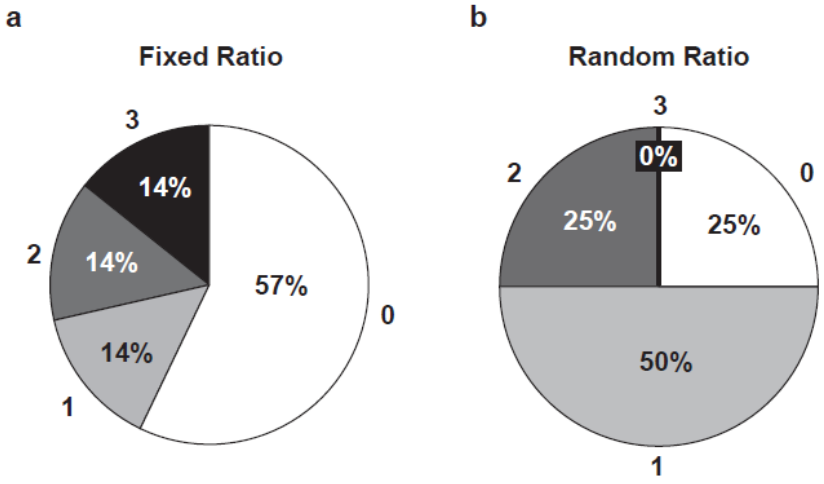

Figure 2.4. Addiction criteria breakdown. Proportion of rats in Experiment 2 that scored positive for zero, one, two, or three addiction-like criteria trained either on a fixed or random ratio schedule of reinforcement. Normalized response rates during the cued no-reward period, progressive ratio breakpoints, and progressive aversion breakpoints were the three criteria used to assess addiction. Percentage of rats are shown inside while number of criteria endorsed is shown on outside

that animals trained on an RR schedule were no more likely than those trained on an FR schedule to reinstate responding after a 5-day period without training.

2.4.2.8 Random Ratio Schedules of Reinforcement Do Not Produce Multi-Criterion "Addiction"

As shown in Figure 2.4, there were far more rats in the RR group endorsing 1 or more addiction-like criteria. However, prior studies have used high scores on all three tests as the criterion for addiction-like behaviour. In our study, only animals in our FR group displayed all three addiction-like symptoms.

2.4.2.9 Analyses of Individual Performance Support a Dissociation Between Motivation and Compulsion

Individual performance of rats during the gambling task and subsequent addiction tests were correlated in order to determine whether there were any relationships between behavioural measures. In experiment 1, the main significant positive correlation was between progressive ratio breakpoints and the post-reinforcement pause (see Fig. 2.5a) this indicates that rats with lower breakpoints on the PR task had higher PRPs, as PRP scores were multiplied by -1 during analysis (see section 2.3.4). In experiment 2, in contrast, rates of responding during both cued reward and cued non-reward, as well as post reinforcement pause times (the PRPs of each animal were again multiplied by -1) and progressive ratio breakpoints were all correlated (see Fig. 2.5c). Specifically, animals that had higher response rates were also likely to have low PRPs, higher rates of responding during the CNR period, and higher breakpoints on the PR task indicating that these measures all likely index a common factor, perhaps motivation. This clustering is apparent in the color plots in Figure 2.5 (left) as well as the dendrograms (right) providing a graphical depiction of the distance between each pair of measures. Reinstatement and, to a lesser extent,

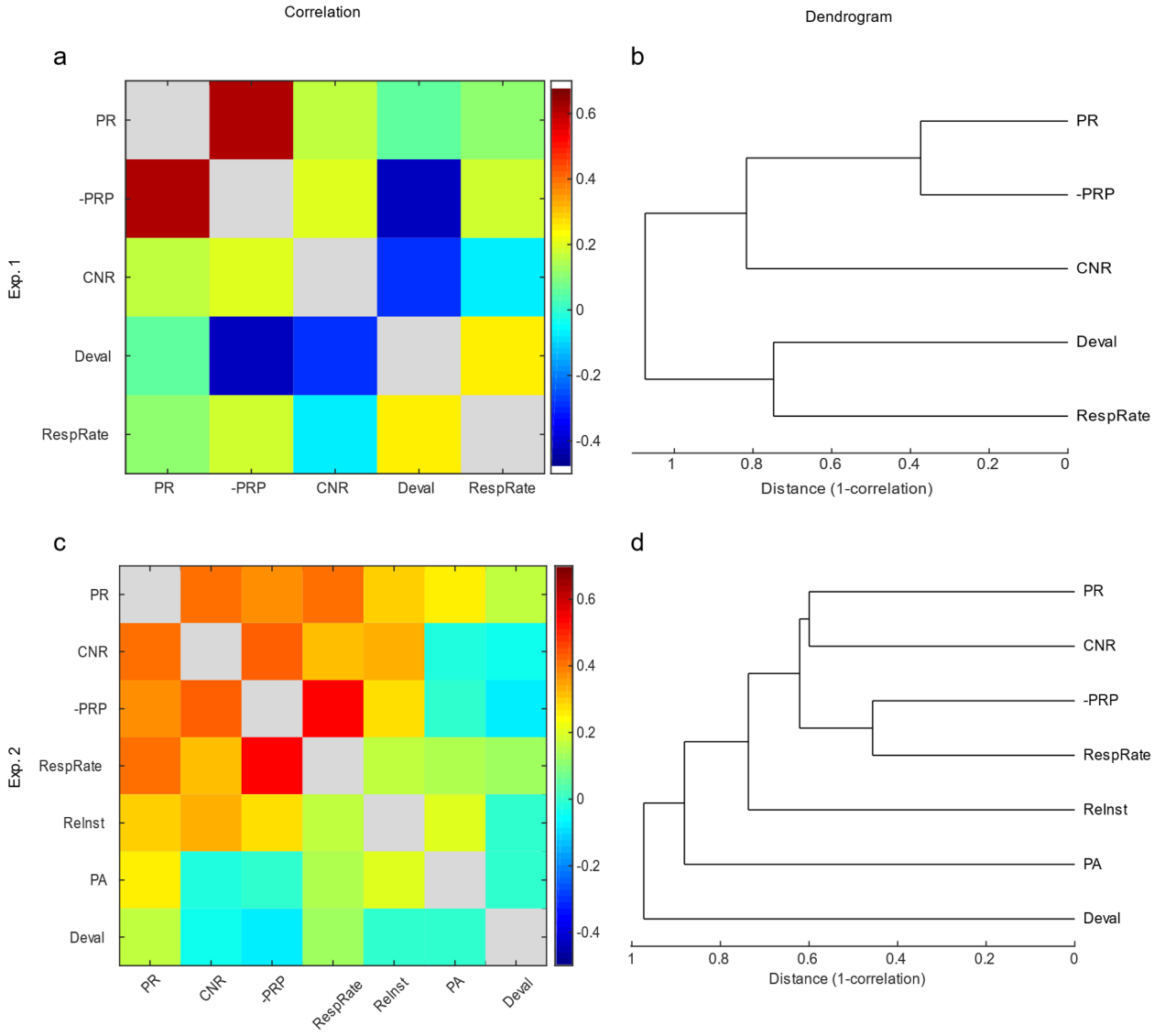

Figure 2.5. Behavioural correlations and dendrograms. Relationships between behavioural measures assessed using individual performance scores on gambling tasks and addiction tests, collapsed across FR and RR groups. Displayed are the correlations between response rates (RespRate), post reinforcement pause times (PRP), progressive ratio (PR) and progressive aversion (PA) breakpoints, normalized response rates during the cued no-reward period (CNR), reinstatement testing (ReInst), and devaluation testing (Deval) for Experiments 1 and 2, as labelled. Color bars show correlation coefficient values. Scores from PRP are inverted, denoted with a (–), so that the highest scores indicated the highest addiction-like behavior. Clustering of behavioural measures as depicted by Unweighted Pair Group Method with Arithmetic Mean (UPGMA) algorithm are shown at right for both experiments.

progressive aversion performance were also modestly correlated with this "motivational" cluster in Experiment 2. Finally, devaluation stands apart in that it was either unrelated to other measures, or, in the case of experiment 1, negatively correlated with both the post—

reinforcement pause and cued no-reward response rate. Devaluation may hence be measuring some other aspect of behaviour separate from motivation and cue-sensitivity.

2.4.3 Effect of Pramipexole on Behavioural Addiction Measures

The effect of short-term oral administration of the dopamine D_3 agonist, pramipexole dihydrochloride (PPX), on behavioural measures of addiction was assessed during an additional ten days of behavioural testing after Experiment 2 using the same rats.

2.4.3.1 Pramipexole Administration Increases Persistence but Not Other Motivation Measures

PPX did not change rats' response rates on either RR or FR schedules when compared to their water-restricted baseline (Fig. 2.6a). A mixed designs ANOVA revealed a significant main effect of reward schedule on response rate ($F(1, 24) = 5.698$, $p = .025$). However, we found neither a within-subjects effect of PPX administration ($F(2.143, 51.436) = .388$, $p = .694$; Greenhouse-Geisser corrected), nor a schedule by PPX interaction ($F(2.143, 51.436) = 1.381$, $p = .261$; Greenhouse-Geisser corrected). Similar analyses showed no effect of PPX on the post-reinforcement pause. As shown in Figure 2.6b, a mixed designs ANOVA showed that reward schedule had a significant effect on pause time ($F(1, 24) = 22.437$, $p < .001$), with decreased pauses in animals trained on a RR schedule. However, we found neither a significant within-subjects effect of PPX administration ($F(3, 72) = .111$, $p = .953$), nor a schedule by PPX interaction ($F(3, 72) = .776$, $p = .511$).

PPX also did not affect response rates during the cued no-reward period (Fig. 2.6c). Using a mixed designs ANOVA, we found that reward schedule did not have a significant main effect on response rate during the cued no-reward period ($F(1, 24) = .041$, $p = .841$). We also did not find a significant within-subjects effect of PPX ($F(3, 72) = 1.744$, $p = .166$), nor was there a

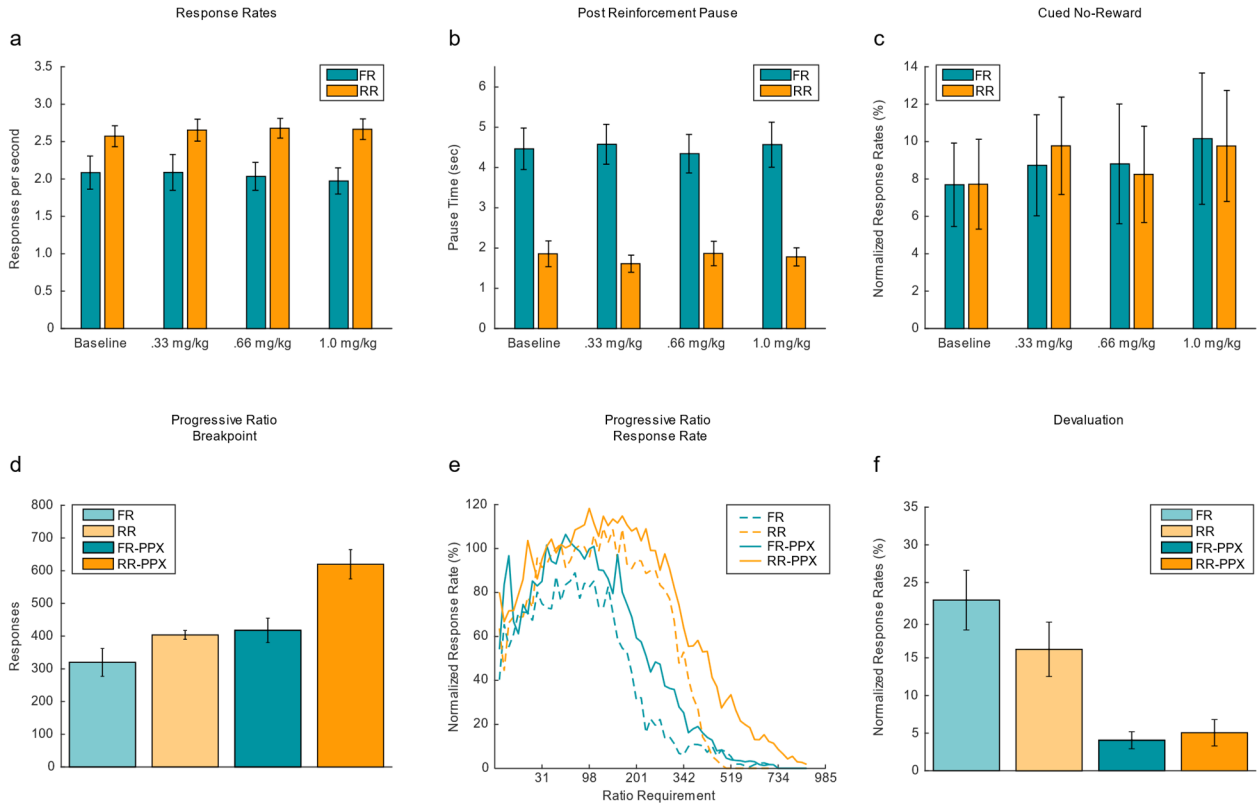

Figure 2.6. Effects of pramipexole on behavioral motivation and persistence measures. Top row shows the effects of low (0.33 mg/kg), medium (0.66 mg/kg), or high (1.0 mg/kg) daily doses of PPX and schedule of reinforcement on response rates, post-reinforcement pauses, and cued no-reward period response rates. Cued no-reward rates are shown as a percentage of the response rate in the periods when reward was available. For the progressive ratio test, both breakpoints (bottom left) and overall response rates at each ratio requirement (bottom middle) are shown. The final plot in lower right shows the effect of PPX and schedule of reinforcement on responding for food after pre-feeding (devaluation). Progressive ratio and devaluation tests were all performed under the high (1.0 mg/kg) PPX dose and compared to previous results from Experiment 2.

schedule by PPX interaction ($F(3, 72) = 1.302$, $p = .281$). A log transformation was performed on the data to correct for skewness.

Animals on PPX did, however, work longer on a progressive ratio schedule (Fig. 2.6d and 2.6e). Breakpoints on the progressive ratio task were compared to baseline progressive ratio breakpoint data obtained when animals were drug-free (and prior to water deprivation). Using a mixed designs ANOVA, we found that reward schedule had a significant main effect on breakpoint ($F(1, 24) = 9.714$, $p = .005$). We also found a significant within-subjects effect of

PPX ($F(1, 24) = 35.067$, $p < .001$), as well as a significant schedule by PPX interaction ($F(1, 24) = 4.973$, $p = .035$).

2.4.3.2 Pramipexole Makes Behaviours Less Habitual During Devaluation

Finally, we examined whether short term PPX administration would decrease goal-directed behaviours in favour of habitual responding by testing animals' willingness to work for food reward after it had been devalued. Rats' response rates were normalized using response rates obtained from the previous day of regular RR/FR testing while animals were on the highest dose of PPX. The results were compared to data collected during the first pre-PPX devaluation test (see section 3.1.6). A mixed designs ANOVA test showed that reward schedule did not have a significant main effect on normalized response rates ($F(1, 24) = .76$, $p = .392$). There was a significant within-subjects effect of PPX administration ($F(1, 24) = 32.924$, $p < .001$), but no significant reinforcement schedule by PPX interaction ($F(1, 24) = 2.117$, $p = .159$). Contrary to our expectations, animals in both groups became more sensitive to reward devaluation after PPX administration, as illustrated in Figure 2.6f. If devaluation is taken as a measure of habitual responding, these data indicate that PPX makes rats *less* habitual in their responding for both RR and FR groups.

2.5 Discussion

In these studies, we aimed to determine whether prolonged exposure to a RR schedule of reinforcement induces addiction-like symptoms similar to those seen in rats given extended experience with drug self-administration (Deroche-Gamonet et al., 2004). Addiction-like behaviour was measured using three primary criteria: 1) difficulty refraining from seeking reward when no reward is available, measured via response rates during a cued no-reward period, 2) increased motivation to obtain food reward, measured via a progressive ratio test, and

3) persistence in seeking reward despite negative consequences, measured by pairing rewarded responses with progressively increasing aversive foot-shock. Confirming previous findings, our experiments clearly demonstrate that RR schedules are more motivating that FR schedules during training but do not produce enduring changes after training. Response rates for non-rewarded trials on the RR schedule were significantly higher in Experiment 2 and trended higher in Experiment 1. Post reinforcement pauses were strikingly lower for rats on the RR schedule in both experiments, consistent with higher motivation. Although, we did not find a statistically significant difference in the progressive ratio breakpoint analysis, results from both studies trended toward significance, and would have met that criteria had we decided to use a one-tailed test based on a strong *a priori* hypothesis. However, in keeping with the goal to make our study as directly comparable as possible to that used in Deroche-Gamonet et al. (2004), we have presented the 2-tailed test results. That said, it was clear that there was a qualitative difference between the groups (see Fig. 2.2, third column) so we ran a second analysis. We found that the schedule-based differences persisted during progressive ratio testing in Experiment 2, with RR animals showing elevated response rates at higher response ratios. The progressive ratio test is the weakest of our three addiction-like criteria because RR rats would have an intrinsic advantage due to their prior experience with larger ratios. In other words, an FR rat who has only experienced a reward ratio of 50 is more likely to be flummoxed by ratios which rapidly exceed this number than a rat trained with varying ratios that could stretch up to 200. Our other two primary tests of addiction-like behaviour, cued no-reward and progressive aversion, showed no differences due to reward schedule. When evaluated in terms of the number of tests in which a given rat scored high for addiction-like behaviour, only rats in the FR group scored in the top third for all three primary addiction criteria (Fig. 2.4). Several other measures of motivation and

compulsion were also analyzed, including response rates during FR or RR training, post reinforcement pauses, devaluation, and reinstatement. Consistent with a lack of addiction-like symptoms, RR animals were no more likely than FR animals to show reinstatement of responding after a period of abstinence nor to show habit-like responding after devaluation. Taken together, these results show that rats under RR schedules show enhanced motivation, but do not develop compulsive, addiction-like behaviour even after intensive daily training for up to 6 weeks.

It is worth noting here that the strongest effect of RR schedules on behaviour appears to be a reduction in the post-reinforcement pause. This is in line with prior animal research comparing FR, RR, and variable-ratio (VR) schedules of reinforcement (Boren, 1973; Priddle-Higson et al., 1976; Webbe and Malagodi, 1978; Mazur, 1983; Crossman et al., 1987). However, this may come as a surprise to some considering that the main findings from human research into the post-reinforcement pause suggests that pause time increases with the value or magnitude of reward (Lowe et al., 1978; Delfabbro and Winefield, 1999; but see Williams et al., 2011; Dixon et al., 2013). If RR schedules are more motivating and rewarding, why is the post-reinforcement pause smaller? It is generally accepted that reinforcement has an inhibiting effect on subsequent responding that increases positively with both with the magnitude of the reinforcer and the size of the work or time requirement (Skinner and Ferster, 1957; Felton and Lyon, 1966; Powell, 1968). While it is true that VR and RR schedules induce shorter pause times overall, prior research indicates that animal behaviour under these schedules also follows this same general rule (Farmer and Schoenfeld, 1967; Priddle-Higson et al., 1976; Crossman et al., 1987; Baron et al., 1992). A compelling explanation for the reduction in the post-reinforcement pause under VR/RR schedules of reinforcement is that pause magnitude is influenced by not only by the

inhibitory properties of the last reinforcement but also the excitatory properties associated with a future reinforcer (Baron et al., 1992). In the case of FR schedules (particularly large ones), just after reward the probability of further reinforcement is low and the distance to the next reinforcement is large. Conversely, the probability and distance to reinforcement is likely interpreted as being greater and closer, respectively, in the case of RR/VR schedules. While it is beyond the scope of this paper, a review by Schlinger et al. (2008) provides an excellent overview and theoretical consideration of the many studies investigating pausing under different schedules of reinforcement while Killen and colleagues have proposed quantitative models (Killeen and Fetterman, 1993; Killeen et al., 2009; Bradshaw and Killeen, 2012).

Why do animals in our experiments showed limited indicators of addiction? Several factors may explain our findings. First, perhaps addiction would have developed if the animals in our study had more exposure to the gambling schedules. Previous experiments that produced addiction phenotypes in rats generally used longer experimental paradigms ranging from ~30 to 100 days (Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004; Pelloux et al., 2007; Belin et al., 2009). So perhaps longer exposure to an RR schedule would induce compulsive responding; however, we have many more response-reward pairings compared to other studies (4200 pairings per rat compared to 1850 pairings in Deroche-Gamonet et al. (2004)). Of course, it is not clear what the appropriate measure of exposure should be. Is it the number of sessions, session length, or the total number of response-reward pairings? Additionally, differences due to cocaine self-administration in most measures used by Deroche-Gamonet et al. (2004) emerge by 35-38 days (e.g. responding during the no-drug period and PR breakpoints); well within our experimental timeline. However, it is worth noting that, in their experiment, differences in responses to reward paired with punishment, measured at 32 and 74 days, were only present at

the later time-point. Compulsion may simply take time to emerge. In our study, all of our continuously acquired measures reach near-asymptotic performance within three weeks, making it hard to justify many additional weeks of daily testing. A second factor which may have limited the development of addiction-like behavior is our use of food reinforcer, which is mild compared to drug reward. However, food is a strong reinforcer and can cause addiction-like symptoms especially when containing high levels of fat, sugar, and salt (Holden, 2001; Hoebel et al., 2009). In fact, sucrose self-administration has been successfully used as an addiction model by at least three research groups (Avena et al., 2008; Diergaarde et al., 2009; Velázquez-Sánchez et al., 2014). Our food reinforcer is high in sugar and fat content and is therefore likely a strong reinforcer in terms of food. We cannot, however, entirely discount the possibility that the amount, type, or lack of variety of food in our experiment lacked the addictive potential of money or drugs. Third, it is worth noting that not all animal studies show addiction-like behaviour, even with cocaine. A study by Waters et al. (2014) which employed the same "three-criteria" model of addiction using cocaine as Deroche-Gamonet and Piazza (2014) found results more similar to ours. That is, they found increased motivation levels, but no increases in compulsivity or drug-seeking in the absence of a drug reinforcer after 65 days of cocaine self-administration. This puts our gambling study results in line with at least some of the drug addiction literature. Lastly, the multi-criterion method used by Deroche-Gamonet and Piazza (2014) artificially limits the number of animals that could be classified as "addicted". As discussed in section 2.3.2.7, each rat was rank ordered on each of the three addiction tests and was scored as positive for that criterion if it fell within the highest 33% of the group distribution. This method does not take into account changes from baseline, for example, it is theoretically possible that nearly all the rats were exhibiting pathological behaviours on each task, but this

method of classification would not be able to capture that reality. For this reason, I chose to not use this method of classification in subsequent experiments presented in Chapter 3.

Our low rates of compulsive behaviour may also have occurred because an addiction-like phenotype develops only in a very small percentage of rats. Due to our relatively small samples, vulnerable rats may simply have been missing in our RR groups. Two animals in Experiment 2 endorsed all three addiction criteria but happen to have been in the FR group. It is possible that these animals were intrinsically different than the rest of their cohort. Theories concerning individual vulnerability to addiction have been gaining traction over the past couple of decades with evidence accumulating in both animal and human studies (Piazza et al., 1989; Chambers et al., 2003; Everitt et al., 2008; Verdejo-Garcia et al., 2008; Everitt, 2014). Increased trait impulsivity, novelty reactivity, and stress have been implicated as factors which increase the chance of an individual developing addiction (Piazza et al., 1989; Belin et al., 2008; Ersche et al., 2010; Velázquez-Sánchez et al., 2014) and increases the likelihood of relapse after a period of abstinence (Shaham et al., 2000; Sinha, 2001). Animals in our study were healthy, not socially isolated, and only experienced minor stress events which may have afforded some measure of protection (Alexander et al., 1978). In short, animals in our experiment may not have had either the environmental or inherited neurological vulnerabilities conducive to developing addiction.

Our analysis of the correlation of behavioural measures across all rats, shown in Figure 2.5, yielded several interesting findings. First, response rates, post reinforcement pauses during training, cued no-reward, and progressive ratio response rates are all high correlated with one-another. This suggests that these variables are all sensitive to some underlying factor, perhaps intrinsic motivation. It also suggests that manipulations, such as reward schedule, which affect one will affect the others in this group. Given this, it is puzzling that RR schedules affected only

three of these variables, but not cued no-reward responses. Second, responses under progressive aversion were only weakly correlated with our motivational variables. This may be because the test is generally insensitive. Indeed, we had very little individual variation in progressive aversion breakpoint scores, which could mean that the schedule used was too steep. Another possibility is that progressive aversion indexes a separate factor. The brain systems which help animals to avoid primary negative reinforcement (i.e., bodily injury) may, in fact, be different than those which allow animals to avoid other forms of negative reinforcement such as time-outs, increased effort, or loss of future reward. Finally, responses during devaluation were unrelated to any other addiction measure. As previously mentioned, addiction is characterized by habitual responses (Everitt and Robbins, 2016) and habitual responses are often measured via a devaluation procedure (Balleine and O'Doherty, 2010). Hence, our results were unexpected. Devaluation is usually measured using two separate responses and two reward types, one of which is devalued (Killcross and Coutureau, 2003). Because rats were only trained with one type of reward in our study, a differential comparison was not possible, which may account for our lack of significant findings. On the other hand, while habitual responding under devaluation has been hypothesized under drug reward, it has yet to be demonstrated, because satiating an animal with drug would essentially result in a lethal overdose. Hence, it remains an open question whether addiction in any form causes habitual responses, at least as measured by responses to devalued reward.

We also tested whether short-term administration of the D_3 receptor preferring dopamine agonist, PPX, intensifies addiction-like symptoms. PPX as well other D_3-preferring agonists have previously been connected to increased incidences of behavioural addictions in humans (Drapier et al., 2006; Imamura et al., 2006; Weintraub et al., 2006a; Voon et al., 2007a; Zand, 2008;

Seeman, 2015) and can increase preference for uncertainty and risky options as well as impulsivity in rodents (Madden et al., 2010; Johnson et al., 2011; Johnson et al., 2012; Tremblay et al., 2017). In our study, PPX did not cause changes in response rates, post-reinforcement pauses, or cued no-reward responses. However, it did increase persistence during progressive ratio testing, and this effect was stronger for the RR group. The effect of dopamine agonists on responding during progressive ratio schedules is mixed in the literature, with some drugs decreasing, increasing, or having no effect on breakpoint (Caine and Koob, 1995; Depoortere et al., 1996; Stafford et al., 1998; Izzo et al., 2001).

Our PPX results come with several important caveats, which must be weighed before drawing firm conclusions. First, we did not observe a dose-response effect for any of the daily acquired measures (i.e., response rates, post-reinforcement pause, and cued no-reward). It may be the case that none of these measures is sensitive to PPX. Another possibility is that PPX takes times to become effective. The reported case studies on human Parkinson's patients suggest that compulsive behaviours don't begin until at least two weeks after the PPX dosage is significantly increased (Dodd et al., 2005; Giladi et al., 2007; Bostwick et al., 2009; Fernández and González, 2009). Another possibility is that our method of administration—mixing it with each rat's drinking water—was not completely effective. Although rats had continuous access to their water, we did not monitor their drinking schedule. Given that PPX has a 3.5 hour half-life in rats (Pharmacia & Upjohn, 1997), this raise the possibility that PPX levels in some rats may have been below effective levels during testing. However, our behaviour observations suggested that the drug was having an effect. That is, rats on PPX showed increased piloerection, increased aggressiveness, increased startle responses, and, in some cases, mild motor symptoms (i.e. falling over). The second caveat is that our two significant effects, on progressive ratio and devaluation,

both confound PPX treatment with water restriction and increased training. In both cases, we compared our PPX results with tests performed earlier in the experiment. Although most of our measures were stable at the end of testing, we cannot rule out the possibility that increased persistence on the progressive ratio test is a by-product of increased training or previous experience with the progressive ratio test. Another factor to consider is that rats receiving PPX, although not water-deprived, were given just enough water to meet their daily needs (thus ensuring they would take the entire dose of PPX). Our earlier tests, in contrast, allowed free access to water. While neither factor seems likely to have dramatically influenced our results, our conclusions from these results must necessarily be tentative. Clearly, further experiments will be needed to evaluate whether PPX coupled with RR schedules might serve as a useful animal model for PPX-induced behavioural addiction in humans.

2.6 Conclusions

Overall, results from our experiments indicate that gambling-like schedules of reinforcement increase motivation to obtain reward, but do not lead to compulsivity in most rats. Particularly striking is the fact that our correlation results show a cluster of measures which we believe indicates motivation and this cluster is clearly influenced by reinforcement schedules, random versus fixed. Further study is needed to determine what factors are needed to tip the balance towards compulsive addiction-like behaviour. Abnormal dopamine processing, increased levels of impulsivity and novelty-reactivity are all potential candidates. Identifying these factors may lead to a better rodent gambling model paralleling those used in drug addiction studies. In turn, this may lead to pharmacological and behavioural interventions to treat and prevent gambling addiction in humans.

Chapter 3: Examining the Effects of Random Ratio Schedules and Pramipexole on D2 and D3 Receptor Expression and Gambling Addiction-like Behaviours

3.1 Abstract

Individuals treated for Parkinson's disease using D3-preferring dopamine agonists develop gambling disorder at much higher rates than the general population. We investigated whether the administration of a D3 agonist, pramipexole (PPX), could induce behaviours consistent with addiction and whether concurrent training on a random ratio (RR) schedule of reinforcement would exacerbate these behaviours. In the third experiment, rats (n = 30) were implanted with either an osmotic pump, which delivered 1.0, 2.0, or 3.0 mg/kg/day of PPX over 28 days, or a dummy pump. After several weeks of training on a RR schedule, animals were assessed for addiction-like behaviours using a battery of behavioural tests. In experiment 4, rats (n = 50) were implanted with either an osmotic pump, which delivered 1.0 mg/kg/day of PPX over 28 days, or a dummy pump. After several weeks of training on either a RR or fixed ratio (FR) schedule, animals were assessed for addiction-like behaviours. Immunofluorescence antibody staining was then used to look for changes in dopamine D2 and D3 receptor expression in brain regions associated with reinforcement and addiction. We found that PPX increased motivation and interfered with rats' ability to limit reward-seeking. Discriminant analysis indicated that D2 receptor expression patterns best discriminated between RR and FR schedules while differences in D3 receptor expression were most useful in classifying whether an animal received PPX or sham surgeries. Both D2 and D3 receptor expression correlated with measures of addiction. Our results suggest that PPX administration on addiction-like behaviour does not interact with RR schedules of reinforcement, contrary to our hypothesis, but rather affects motivation and compulsive tendencies more generally.

3.2 Introduction

Dopamine is well known to have a role in developing and maintaining both substance-based and behavioral addictions. Patients with Parkinson's disease who are treated with drugs that increase dopamine efficacy or availability such as L-DOPA or dopamine agonists report the emergence of behavioral addictions at rates higher than that seen in the general population (Nirenberg and Waters, 2006; Weintraub and Claassen, 2017). The highest incidence of behavioral addictions occurs when patients are prescribed dopamine agonists that are selective for dopamine D3 receptors (Zand, 2008; Seeman, 2015; Castro-Martínez et al., 2018; Napier et al., 2020). In this paper, we investigate whether the administration of the D3-preferring dopamine agonist, pramipexole dihydrochloride (PPX) can induce a gambling addiction-like phenotype in rats.

While it is known that both unpredictable reward and dopamine agonist administration can change risk preferences (Voon et al., 2011; Kobayashi et al., 2019; Soutschek et al., 2020), learning and decision-making (Santesso et al., 2009; Voon et al., 2010), and motivation levels in both animals and humans (Wise, 2004; Dunlop and Nemeroff, 2007; Winstanley et al., 2010), to the best of our knowledge no one has tested whether unpredictable reward delivered on a random ratio (RR) schedule of reinforcement (similar to those used in slot machines) in combination with dopamine agonist medication increases behavioral markers of addiction. In this series of studies, we investigated whether RR schedules of reinforcement were more likely to produce behavioral addiction in rats and whether the administration of PPX exacerbated addiction symptomatology. Following the design of the cocaine-addiction study of Deroche-Gamonet et al. (2004), rats in our study worked for food reward in standard operant chambers daily over the course of several weeks. Rats were then implanted with an osmotic pump which delivered a constant dose of PPX

over a period of 28 days (or were implanted with a dump pump). After recovery from surgery, rats continued training on the operant task for several weeks after which they were assessed for several markers of behavioral addiction. Because unexpected reward increases dopamine release more than predictable reward (Mirenowicz and Schultz, 1994; Schultz et al., 1997), we predicted that animals receiving PPX while working for unpredictable food rewards would exhibit more behavioral markers of addiction

In the second experiment, following behavioural testing, we examined the animals' brains for regional changes in D2 and D3 receptor distribution using immunohistochemical methods. We predicted that rats exposed to prolonged PPX administration would exhibit increases in D3 receptors primarily in reward related regions, namely the NAC, OFC, MFC, INS, STR VP, SN, and VTA and decreases in regions related to inhibition and cognitive control, particularly the ACC and the CG. In contrast, I expect an overall down regulation of D2 receptors in the NAC, OFC, MFC, INS, STR, VP, SN, and VTA, and an upregulation of D2 receptors in the ACC and CG. Lastly, I also expect that these changes would be most evident in those animals exhibiting the strongest addiction-like behaviours.

3.3 Methods

Several methodological changes were made to the task after re-evaluation of the task once Exps. 1 and 2 were completed. Most notably, due to time limitations of the osmotic pumps used to deliver PPX, some of the behavioural assessments found in Exps. 1 and 2 were not conducted in Exps. 3 and 4, specifically reinstatement testing and devaluation testing.

3.3.1 Subjects and Ethics

Subjects in Exp. 3 were male Long-Evans rats (n = 30; Charles River Laboratories, Kingston, NY). Animals weighed 368–486 g and were 174 days old at the start of the

experiment. Subjects in Exp. 4 were male Long-Evans rats (n = 50; Charles River Laboratories, Kingston, NY). These animals weighed 357-486g and were 121 days old at the start of the experiment. Animals were pair-housed in a temperature-controlled colony room under a 12 h reverse light cycle (lights off at 10:00 a.m.). All experiments were performed in accordance with the guidelines set by the Canadian Council of Animal Care, and experimental protocols were approved by the University of Lethbridge Animal Welfare Committee.

3.3.2 Apparatus and Software (Data Acquisition)

The test apparatus has been described in detail elsewhere (Laskowski et al., 2019). Behavioural testing took place in standard operant chambers which were enclosed within a ventilated sound-attenuating cabinet (Med Associates Inc., Fairfax, VT). A custom-installed backlight within the lever housing functioned as a response cue light. All chambers were fit with two house lights allowing for chamber illumination in two colors (yellow and blue). Shock was delivered via a Lafayette Instruments Shocker (model HSCK100AP) which delivers scrambled shock with a bipolar waveform and 12% duty cycle. The scrambler has a cycle time of 75 ms with each grid pair receiving a bipolar pulse of 8.3 ms. All chamber hardware was controlled via by software written in ABET (Lafayette Instruments, Lafayette, MA) using Lafayette Instruments interface hardware (ABET 2G starter interface and expansion interfaces).

3.3.3 Surgery

Animals in Exp. 3 were anesthetized with isoflurane and implanted subcutaneously with either osmotic minipumps (Model 2ML4, 2.5µL per hour delivery rate with a 2mL reservoir volume; ALZET, Cupertino, CA) which delivered PPX at a rate of 1.0, 2.0, or 3.0 mg/kg/day for 28 days or dummy pumps for the control group. Dummy pumps were fabricated on site from 1/2” lennite polyethylene rod, cut to the same dimensions as the osmotic pumps. Animals in Exp.

4 were implanted with either osmotic minipumps which delivered PPX at a rate of 1.0mg/kg/day dummy pumps.

3.3.4 Gambling Task

See Section 2.3 for detailed experimental methodology. Briefly, animals in Exp. 3 were trained to respond (lever-press) for food reward on a RR-50 schedule of reinforcement. Animals in Exp. 4 were trained on either a RR-50 or a FR-50 schedule of reinforcement. In the FR-50 condition, rats are required to lever press 50 times to earn reward. In the RR-50 condition, reward is delivered after a random number of lever presses, but when averaged over a number of trials the average trial-by-trial requirement equals 50. Pseudo-random ratio schedules were generated by shuffling a list of all rewarded and unrewarded trials (e.g., 99 rewards among a total of 4950 trials for an RR50 session). The list was randomized repeatedly to make seven different versions of the RR50 schedule which rats rotated through sequentially each week. Having fixed RR50 schedules provided control over both the distribution and number of rewarded trials within each session (i.e., one rat could not experience, by chance, multiple sessions loaded with rewarded trials at the beginning). Sessions contained 99 reward events and lasted until either the animal obtained all rewards or 255 min elapsed. Each session was divided into three cued-reward blocks (blue light) separated by two 10 min cued no-reward blocks (yellow light). Each group completed 4 weeks of behavioural testing on the FR50 or RR50 schedules. Animals unable to complete all trials within the time limit ran additional sessions so the total number of trials between groups was equivalent. Behavioural measures such as response rates and post-reinforcement pauses were collected during each daily testing session.

3.3.5 Progressive Ratio

Animals were assessed for differences in motivational levels using a progressive ratio task. In this task, animals could earn food reward by nose-poking into the central hole. However, the number of responses required to obtain food reward gradually increases throughout the testing session. The session lasted until the animal failed to obtain a reward after 30 min or a maximum of 5 h had elapsed. Breakpoint data were collected for all animals.

3.3.6 Progressive Aversion Test

The progressive aversion task measures the degree to which rats will seek reward despite increasing negative consequences. During these sessions, rats worked for food reward on a FR-10 schedule. After the 8th and 9th lever press in each trial, the lever light flashed rapidly (6.67 Hz) signaling delivery of a 1.5 s foot-shock after the next lever press. Foot-shock was delivered after the 9th response and was paired with reward after the 10th response in each trial. The shock current was gradually increased from 0.04 mA up to a maximum of 1.24 mA in increments of 0.04 mA every three trials. The session lasted until the rat completed 120 trials, failed to obtain a reward after 30 min, or a maximum of 5 h had elapsed. Breakpoint data (i.e., the level of current at which an animal elected to stop responding) was collect for all animals.

3.3.7 Immunohistochemistry

Rats were transcardially perfused with phosphate-buffered saline (PBS) and 4% paraformaldehyde in PBS. Brains were collected for immunohistochemical analysis. The brains were kept in 4% paraformaldehyde for 24 hours and transferred to a 30% sucrose solution and stored at 4°C until sectioning. Brains were sliced coronally in 40 µm sections on a freezing microtome. Immunohistochemical procedures for D2 and D3 receptors were performed. In brief, sections were fixed on slides, allowed to dry and stored at 4°C until antibody staining began.

For D2 immunostaining, slides were washed twice in PBS for 10 min each and then blocked in 3% Goat serum in .3% Triton-X for 90 min. The sections were incubated for 44-48 hours in primary antibody (1:50 α-DRD2; AB5084P, Millipore Sigma) in PBS + .3% Triton-X + .02% sodium azide at room temperature in a dark humid chamber. Following incubation, slides were given three x 10min washes in PBS + .3% Triton-X. Then sections were incubated with secondary antibody (1:500 Goat α-rabbit-Alexa Fluor 594; A-11037, ThermoFisher Scientific) in PBS + .3% Triton-X + .02% sodium azide for 25 hours in a dark humid chamber. Finally, the sections were washed once for 10 min with PBS + .3% Triton-X and then twice more in a PBS solution for 10 min each and then covered with coverslips with Vectashield H-1000 (Vector Laboratory).

For D3 immunostaining, slides were washed twice in a phosphate buffer solution (PBS) for 10 min each and then blocked in 3% Goat serum in .3% Triton-X for 90 min. The sections were incubated for 44-48 hours in primary antibody (1:500 α-DRD3; AB1786P, Millipore Sigma) in PBS + .3% Triton-X + .02% sodium azide at room temperature in a dark humid chamber. Following incubation, slides were washed three times in PBS + .3% Triton-X for 10 min each, and sections were incubated with secondary antibody (1:500 Goat α-Rabbit-biotinylated; 111-065-003, Jackson Laboratories) in PBS + .3% Triton-X + .02% sodium azide for 25 hours in a dark humid chamber. After the incubation period, slides were washed once in a PBS + .3% Triton-X for 10 min and then twice in a PBS solution for 10 min each. Slides were then quenched in a 1% H_2O_2 in PBS solution for 15 min. This was followed by three x 10 min PBS washes. The slides were then incubated with 1:200 SA-HRP (NEL750001EA, Perkin Elmer) in a TSA-Blocking Buffer (SAT701001EA, Akoya Biosciences) for 2 hours. Slides were then washed three times in Tris Buffered Saline with Tween 20 (TBST) for 10 min each and then

incubated in 1:150 TSA-FITC (SAT701001EA, Akoya Biosciences) in TBST + .0005% H_2O_2 for 1 hour. Finally, the sections were washed three times in TBST for 10 min each and then coverslipped with Vectashield H-1000 (Vector Laboratory).

3.3.8 Image Analysis

Finally, whole slides were imaged using NanoZoomer microscope (NanoZoomer 2.0-RS, HAMAMATSU, JAPAN). We analyzed 9 brain sections for D2 and D3 immunostaining markers for each rat. The images were analyzed using MATLAB and Statistics Toolbox Release 2021b, (The MathWorks, Inc., Natick, MA).

Once images were acquired, each image was normalized so that range of pixel intensities scaled between 0-255 for either the red (D2) or green (D3) channel. Regional tracing was based off of regional divisions delineated in *The Rat Brain in Stereotaxic Coordinates* (Paxinos and Watson, 2007). The tracing was done by an experimenter who was blind to the identity of the rats. Pixel intensity data was then collected for each region of interest and normalized as a percentage of background signal from a region on each slide where D2 and D3 dopamine receptors are not present in significant amounts (i.e., motor cortex for anterior slices; reticular formation for posterior slices; Bentivoglio and Morelli, 2005).

3.4 Results

3.4.1 Experiment 3: PPX Administration Does Not Increase Response Rates

In Exp. 3, weekly average response rates for groups of animals were computed by averaging lever presses over all trials during the cued-reward periods, excluding the trial after reward. A mixed design ANOVA showed that while there was a significant within-subjects effect of time (see Fig. 3.1 left; $F(1, 26) = 29.543$, $p < .001$), there was no main effect of PPX dose ($F(3, 26) = 1.064$, $p = .109$), nor was there a time x PPX dose interaction ($F(3, 26) =$

.1.981, p = .141). Post hoc analysis indicates that there were no individual effects of PPX dose. Taken together this shows that PPX administration did not affect response rates.

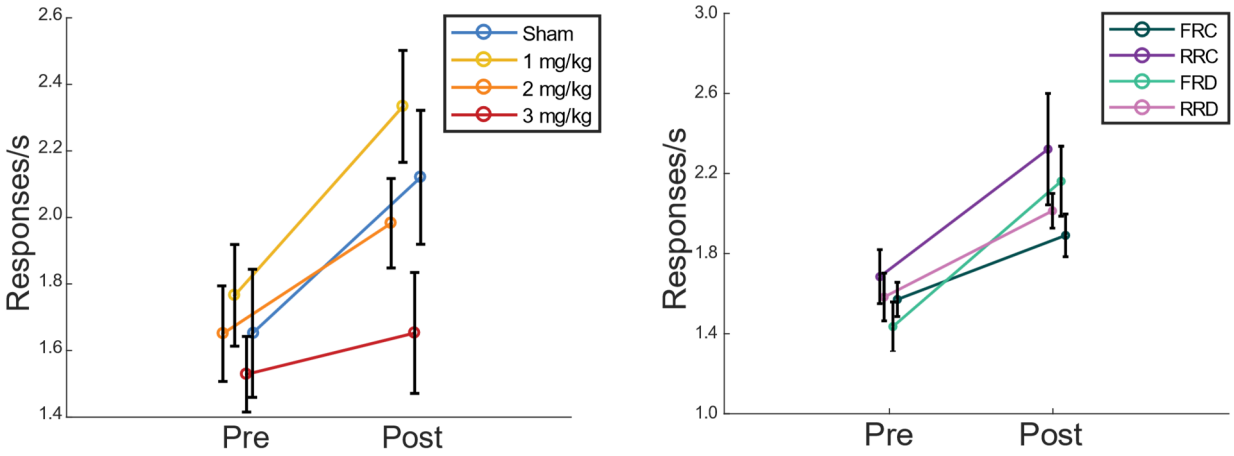

Figure 3.1. Response rates. Average response rate for each experimental group in Exp. 3 (left) and Exp. 4 (right) during the last 4 days of testing prior to surgery (Pre) and the last 4 days of testing after surgery (Post). FRC fixed ratio control, RRC random ratio control, FRD fixed ratio drug, RRD random ratio drug. Data shown are mean ± SEM.

3.4.2 Experiment 4: PPX Administration Increases Response Rates in Rats Trained on Fixed Ratio Schedules

In Exp. 3, average response rates for groups of animals were computed by averaging lever presses over all trials during the cued-reward periods, excluding the trial after reward (Fig. 3.1 right). Using a mixed designs ANOVA with schedule and PPX treatment as the between-subjects factors and time as the repeated measure, we found a within-subjects effect of time ($F(1, 42) = 70.671$, $p < .001$) indicating that all the animals exhibited an increase in response rate after surgery, but there was no main effect of schedule ($F(1, 42) = 1.044$, $p = 0.313$) or PPX treatment ($F(1, 42) = .266$, $p = 0.609$), similar to the results from Exp. 3. There was also no schedule x time interaction ($F(1, 42) = .007$, $p = 0.934$) and no PPX treatment x time interaction ($F(1, 42) = .633$, $p = 0.431$); however, there was a significant time x schedule x PPX treatment

interaction (F (1, 42) = 5.933, p = 0.019), indicating the rats who received PPX treatments and trained on a FR schedule preferentially increased their response rate with increased experience on the task.

3.4.3 Experiment 3: PPX Administration Does Not Decrease Post-Reinforcement Pause Time

In Exp. 3, a mixed design ANOVA showed that while there was a significant within-subjects effect of time (see Fig. 3.2 left; F (1, 26) = 12.304, p = .002), there was no main effect of PPX dose (F (3, 26) = 1.151, p = .117), nor was there a time x PPX dose interaction (F (3, 26) = 1.577, p = .219). Post hoc analysis indicates that there was no individual effect of PPX dose. Taken together this shows that PPX administration did not affect post-reinforcement pause time, however, this is likely due to a floor effect (see section 3.5).

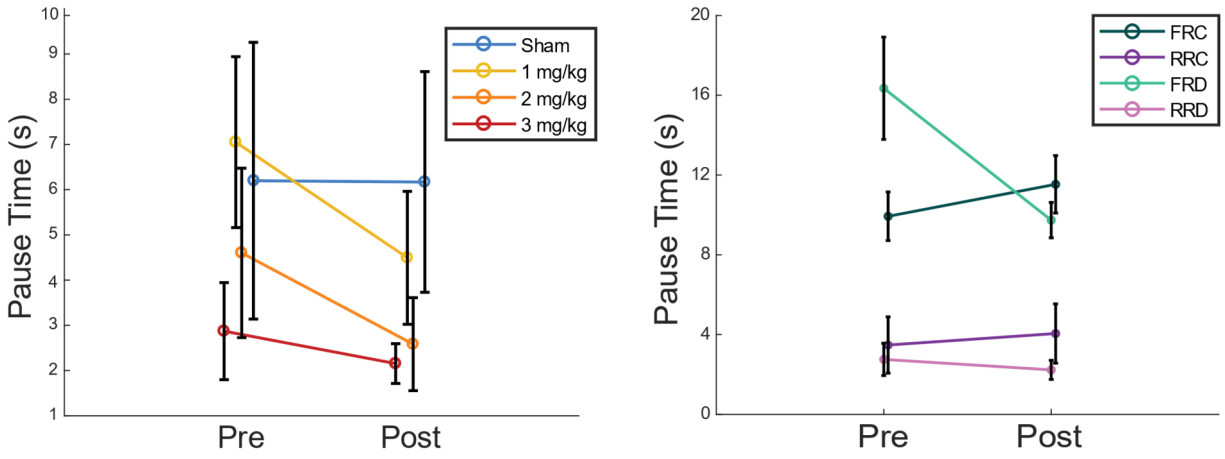

Figure 3.2. Post-reinforcement pauses. Average post reinforcement pause time for each experimental group in Exp. 3 (left) and Exp. 4 (right) during the last 4 days of testing prior to surgery (Pre) and the last 4 days of testing after surgery (Post). These pause times are calculated for the cued-reward periods and excluded the cued no-reward periods. FRC fixed ratio control, RRC random ratio control, FRD fixed ratio drug, RRD random ratio drug. Data shown are mean ± SEM.

3.4.4 Experiment 4: Random Ratio Schedules Decrease Post-Reinforcement Pause Time

In Exp. 4, we found that animals trained on RR schedules exhibited much lower pause times than those on FR schedules and that PPX administration preferentially affected FR rats (Fig. 3.2 right). A mixed designs ANOVA showed that schedule had a significant main effect on the post-reinforcement pause ($F(1, 42) = 52.329$, $p < 0.001$), however, there was no main effect of PPX treatment on pause time ($F(1, 42) = .184$, $p = .670$), nor a schedule x PPX administration interaction ($F(1, 42) = 2.189$, $p = .146$). We also did not find a within-subjects effect of time ($F(1, 42) = 3.328$, $p = 0.075$), and no schedule × time interaction ($F(1, 42) = 3.448$, $p = 0.070$). However, we did observe a strong PPX treatment x time interaction ($F(1, 42 = 11.712$, $p = 0.001$) as well as a schedule x PPX treatment x time interaction ($F(1, 42 = 6.826$, $p = 0.012$) indicating that rats who received PPX treatments and trained on an FR schedule exhibited markedly large decreases in their pause times compared to the other groups. The lack of effect in the RRD group is likely due to a floor effect.

3.4.5 Experiment 3: PPX Administration Decreases Responding During Cued No-Reward Period

In Exp. 3, we computed weekly averaged lever press rates over the first 10 min of the cued no-reward period in each session. As shown in Fig. 3.3 left, the within-subjects effect of time was significantly different from Pre to Post ($F(1, 26) = 15.211$, $p = .001$). A mixed designs ANOVA showed no significant between-subjects effect of PPX dose ($F(3, 26) = 1.630$, $p = .158$), but there was a time x PPX dose interaction ($F(3, 26) = 4.315$, $p = .013$). Post hoc analysis indicates that there was no individual effect of PPX dose. Taken together this shows that those rats that received PPX treatment displayed increasing difficulty inhibiting responding when cues indicated that reward was not available.

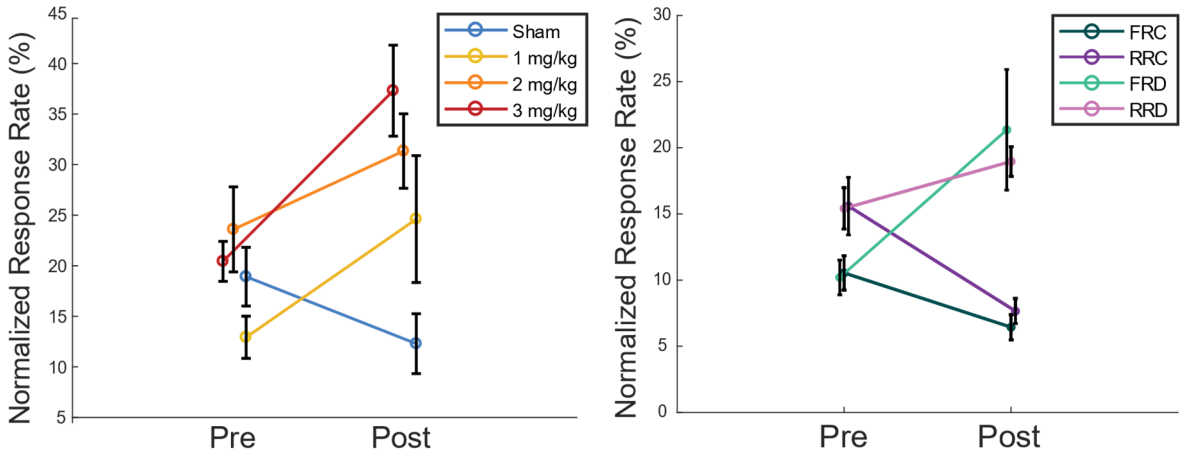

Figure 3.3. Cued No-reward period. Normalized response rates during cued no-reward periods in Exp. 3 (left) and Exp. 4 (right) are shown as a percentage of the average response rate during cued-reward periods. Data shown were analyzed from data collected during the last 4 days of testing prior to surgery (Pre) and the last 4 days of testing after surgery (Post). FRC fixed ratio control, RRC random ratio control, FRD fixed ratio drug, RRD random ratio drug. Data shown are mean ± SEM.

3.4.6 Experiment 4: Both Random Ratio Schedules and PPX Administration Increase Responding During Cued No-Reward Period

In Exp. 4, we computed weekly averaged lever press rates over the first 10 min of the cued no-reward period in each session. As shown in Fig. 3.3 right, the schedule of reinforcement did not significantly affect rats' normalized response rates ($F(1, 42) = 2.130$, $p = .152$), however, there was a strong main effect of PPX administration on responding during the cued no-reward period ($F(1, 42) = 17.029$, $p < .001$). We did not observe a significant schedule x PPX treatment interaction ($F(1, 42) = .305$, $p = .584$). A mixed designs ANOVA showed no significant within-subjects effect of time on normalized response rates ($F(1, 42) = .271$, $p = .605$); however, there were both significant time x schedule ($F(1, 42) = 4.949$, $p = .032$), and time x PPX treatment interactions ($F(1, 42) = 27.034$, $p < .001$), similar to Exp. 3. There was no time x schedule x PPX treatment interaction effect ($F(1, 42) = .542$, $p = .542$). Taken together this shows that those rats that received PPX, particularly if they were in the FR group, displayed increasing difficulty inhibiting responding when cues indicated that reward was not available.

3.4.7 Experiment 3: PPX Administration Increases Persistence During Progressive Ratio Testing

In Exp. 3, univariate ANOVA analysis reveals that PPX dose significantly increases breakpoints on the progressive ratio test (see Fig. 3.4 left; $F(3, 26) = 4.659$, $p = 0.010$). Post hoc analysis using the Tukey method reveals significant differences between the Sham group and the 1.0mg/kg group ($p = 0.024$), the 2.0mg/kg group ($p = 0.040$), as well as the 3.0mg/kg group ($p = 0.015$). This suggests that PPX increases willingness to continue to respond as reward becomes increasingly difficult to earn.

3.4.8 Experiment 4: PPX Increases Motivation During Progressive Ratio Testing

In Exp. 4, Using a univariate ANOVA, analysis of our data shows that rats that received PPX treatment had higher breakpoints on the progressive ratio test compared to our sham control rats (see Fig. 3.4 right; $F(1,42) = 11.272$, $p = 0.002$), in agreement with results from Exp. 3. We did not see changes in either average breakpoint as a result of the schedule of reinforcement on which the animals were trained ($F(1,42) = .696$, $p = 0.409$), nor a schedule x PPX treatment

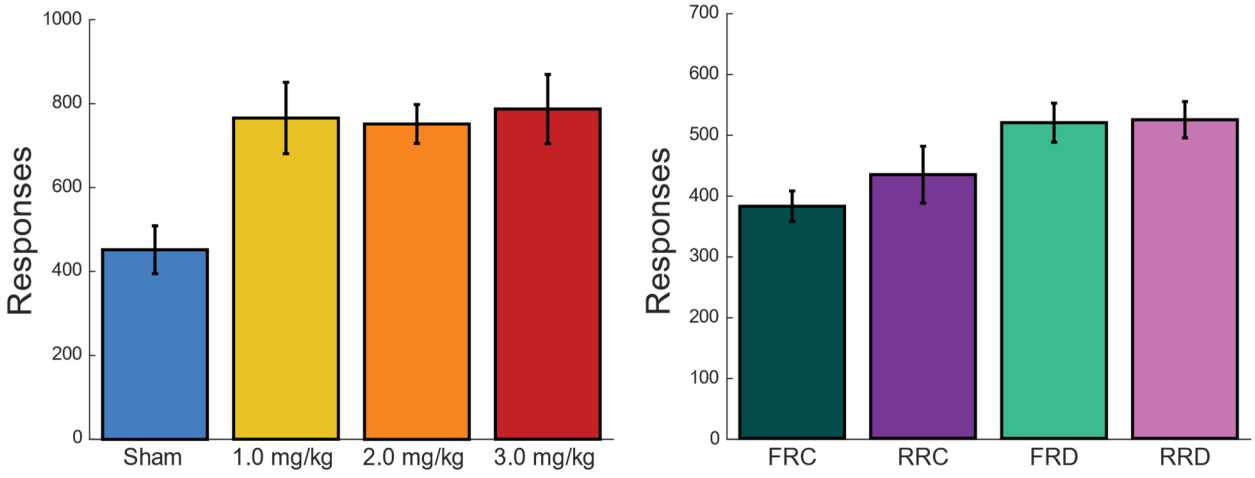

Figure 3.4. Progressive ratio task. Average progressive ratio breakpoints are shown for each experimental group in Exp. 3 (left) and Exp. 4 (right). FRC fixed ratio control, RRC random ratio control, FRD fixed ratio drug, RRD random ratio drug. Data shown are mean ± SEM.

interaction (F (1,42) = .479, p = 0.493) Thus, it appears that PPX administration has a strong impact on rats' willingness to work for food reward under progressive ratio schedules irrespective of the schedule of reinforcement on which they were trained.

3.4.9 Experiment 3: PPX Administration Does Not Increase Persistence in the Face of Increasing Punishment

In Exp. 3, persistence was calculated by averaging individual rats' breakpoints during the progressive aversion task across each experimental group. A univariate ANOVA was used to examine the data for group differences. Our data suggest that PPX dose did not significantly affect rats' willingness to endure increasing levels of foot shock (see Fig. 3.5 left; F (3, 26) = 1.073, p = 0.378). Additionally, post hoc analysis confirms that the dose of PPX also had no significant effect on breakpoint.

3.4.10 Experiment 4: Persistence in the Face of Increasing Punishment is Not Affected by Either Schedule of Reinforcement or PPX Administration

In Exp. 4, Persistence was calculated by averaging individual rats' breakpoints across experimental groups. A univariate ANOVA was used to test for group differences. Our data suggest that neither schedule of reinforcement (F (1,42) = .059, p = 0.810) nor PPX administration (F (1,42) = 1.393, p = 0.245) affected rats' willingness to endure increasing levels of foot shock (see Fig. 3.5 right). There was also no indication of a schedule x PPX administration interaction effect (F (1,42) = .191, p = 0.664).

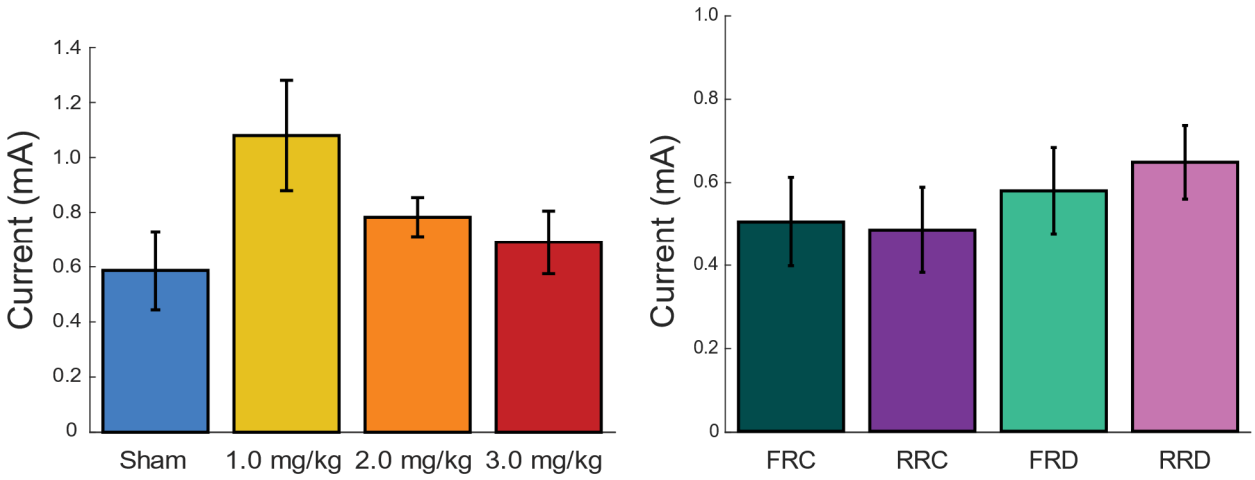

Figure 3.5. Progressive aversion task. Average progressive aversion breakpoints are shown for each experimental group in Exp. 3 (left) and Exp. 4 (right). FRC fixed ratio control, RRC random ratio control, FRD fixed ratio drug, RRD random ratio drug. Data shown are mean ± SEM.

3.4.11 Immunofluorescence Antibody Staining

In order to examine whether the behavioural changes seen as a consequence of prolonged training on FR or RR schedule of reinforcements or PPX administration in our animals were related to changes in dopamine receptor density, we employed immunofluorescence antibody staining to measure the density of D2 and D3 receptors in vitro in several brain regions thought to play a role in motivation and/or addiction.

There were several significant relationships between our behavioural measures and both D2 and D3 regional intensity after correcting for schedule and PPX treatment. For a full breakdown of all correlations, see Fig. 3.7. Firstly, In Exp. 3 we saw a positive correlation between normalized response rates during the CNR period and breakpoints on the PR task ($r(28) = .708$, $p < .001$) there was a trend toward this in Exp. 4, but it was not significant ($r(44) = .273$, $p = .066$). In Exp. 4 there were also significant relationships between responses rates and responding during the CNR period ($r(44) = -.344$, $p = .019$), between response rates and breakpoints during the PA task ($r(44) = .333$, $p = .024$), and between PR breakpoints and PA

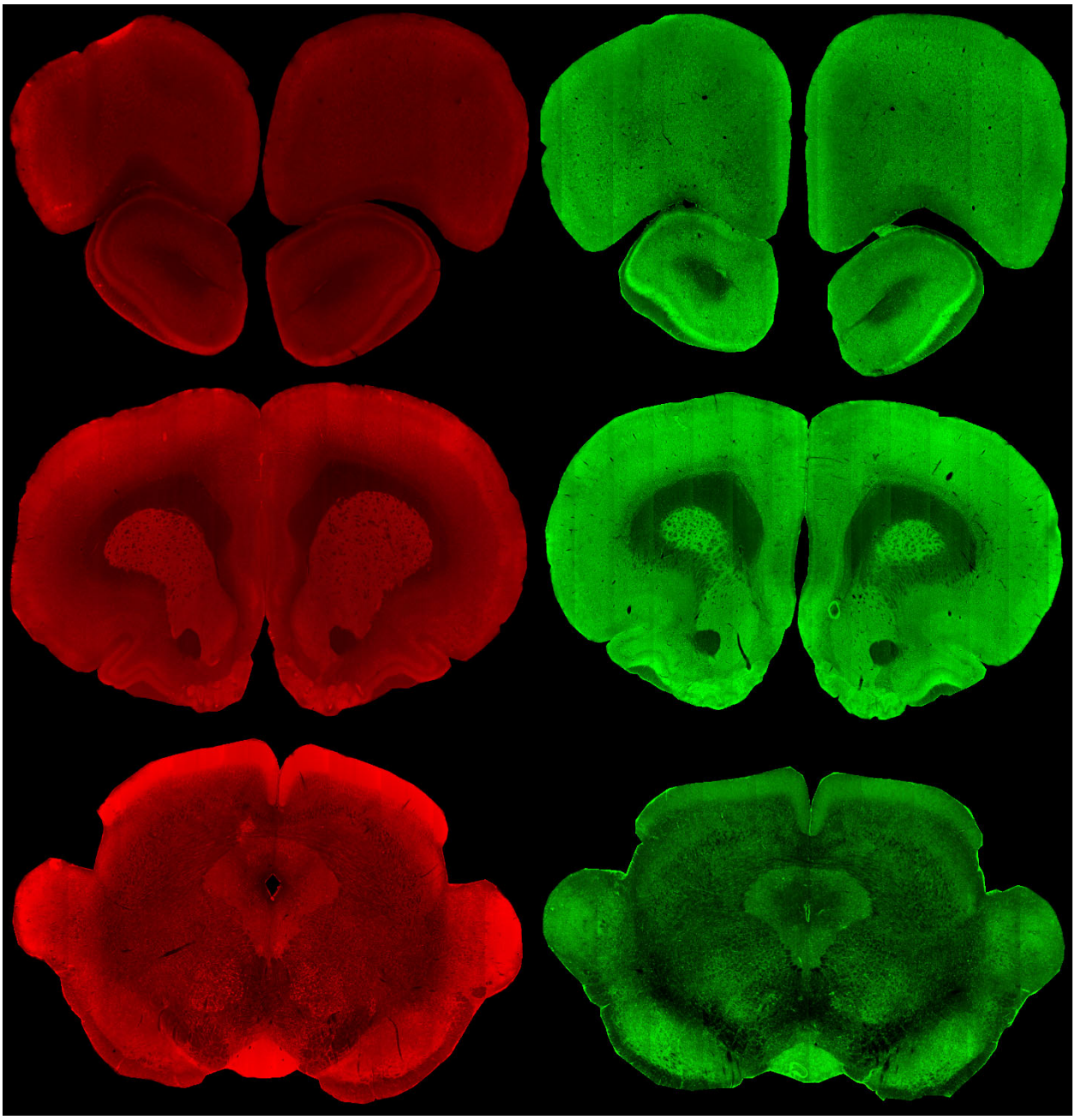

Figure 3.6 Sample immunofluorescence images. Sample images of D2 (left; red) and D3 (right; green) from rats with median receptor expression. Upper images are sample slices from anterior regions of cortex, middle images are at the level of the ventral striatum, and lower images are at the level of the midbrain.

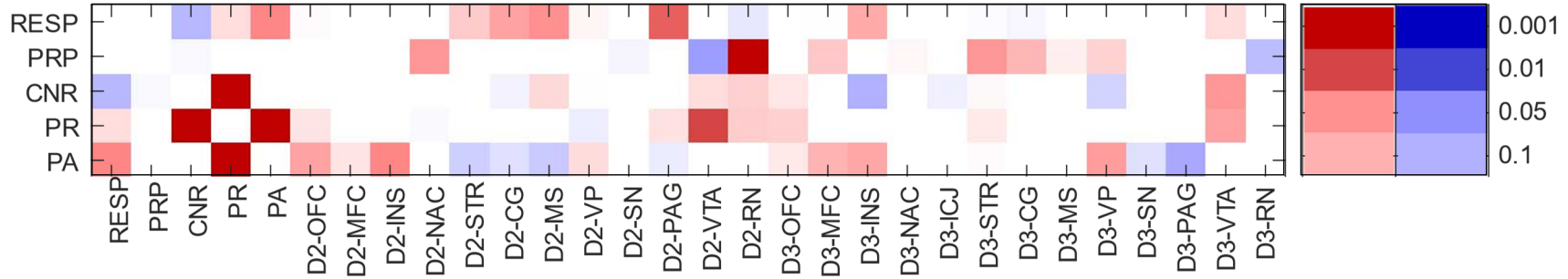

Figure 3.7. Bivariate correlations between behavioural addiction measures and D2/D3 regional signal intensity. Scale bar indicates Pearson correlations scaling between 1 (red) and -1 (blue), color saturation indicates p-value for each pair (darker is more significant). Orbitofrontal cortex (OFC), medial prefrontal cortex (MFC), insular cortex (INS), nucleus accumbens (NAC), Islands of Calleja (ICJ), striatum (STR), cingulate gyrus (CG), medial septum (MS), ventral pallidum (VP), substantia nigra (SN), periaqueductal grey (PAG), ventral tegmental area (VTA), raphe nucleus (RN).

Table 3.1 Discriminative function analysis.

	Group	Eigenvalue	Canonical Correlation	Wilks Lambda	Classification Results	Predictors	Standardized Canonical Discriminant Function Coefficients	Structure Matrix
D2	Schedule	.838	.675	Λ = .544 p = .019	75.6%	VTA	.616	.404
						INS	.690	.354
						RN	-.607	-.342
	Drug Treatment	.431	.549	Λ = .699 p = .266	66.7%	VP	.645	.381
						NAC	.215	.381
						MFC	.109	.309
D3	Schedule	.478	.569	Λ = .677 p = .273	75.6%	RN	.619	.566
						STR	-.338	-.468
						SN	.449	.402
						ICJ	.406	.390
	Drug Treatment	1.201	.739	Λ = .454 p = .004	86.7%	VP	-.659	-.327
						VTA	.597	.313
						OFC	.468	.310
						NAC	-.652	-.301

Only predictors with pooled within-groups correlations above .3 are reported.

breakpoints (r (44) = .385, p = .008) and between breakpoints on the PR and PA tasks (r (44) = .411, p = .005). These relationships were not significant in Exp. 3 (r (28) = .004, p = .983; r (28) = .076, p = .691). In Exp. 4 there were significant positive correlations. Out of 13 areas examined, we found significant correlations between: PRPs and D2 signal expression in both the NAC (r (44) = .321, p = .030) and the RN (r (44) = .449, p = .002), CNR period response rates and D2 signal intensity in the RN (r (44) = .363, p = .013), PR breakpoints and D2 signal intensity in both the VTA (r (44) = .346, p = .019) and the RN (r (44) = .350, p = .017), and finally, PA breakpoints and D2 signal intensity in the INS (r (44) = .322, p = .029). There were also significant positive correlations between PR breakpoints and D3 receptor expression in the CG (r (44) = .292, p = .049), as well as PA breakpoints and D3 receptor intensity in both the INS (r (44) = .332, p = .024) and VP (r (44) = .344, p = .019).We also conducted a discriminant function analysis (see Table 3.1) in order to determine in which regions of the brain the D2 or D3 signal intensity provided the most explained variance in the determination of group membership in either the RR vs. FR (Schedule) groups or the PPX vs. Sham (Drug Treatment) groups. The model was statistically significant for D2 regional signal intensity in predicting group membership for the schedule of reinforcement whereas D3 signal intensity was significant in predicting group membership for drug treatment.

3.5 Discussion

In this series of experiments, we investigated whether prolonged PPX administration would interact with training on a RR schedule of reinforcement to produce a gambling addiction-like phenotype in rats. Interestingly, the only main effect of schedule was on the PRP, which was similar to that seen in Exp 1 and 2 (see section 2.4.2.2). There was also a schedule by PPX interaction in several measures, however contrary to the experimental prediction, this was seen in

the FR group rather than the RR group. It appears that when PPX is administered to an animal that is working for reward on an FR schedule, it reduces or overpowers the differences in behaviour caused by the RR schedule, particularly in the CNR period and the PR task. There area few caveats to this interpretation, particularly in relation to animals' PRP times. Firstly, the effect of the RR schedule is so strong that the animals are already maximizing trial-by-trial response time, spending almost no time pausing between trials. The PRP in these animals is between 2-3s and most of this time is spent consuming the food reward. So even if PPX was having a large effect on the RR group, the animals simply could not initiate the trial any faster than they already were. Secondly, the PPX effect on PRPs may be due to increased locomotor activity. We did observe hyperactivity, stereotyped behaviours, and insomnia in several of the animals, particularly at higher doses. However, PPX did not appear to increase response rates, if anything, the response rates trended lower in the 3mg/kg group in Exp. 3 (see Fig. 3.1). So, we argue that it is unlikely that the reduction in PRP was due to PPX induced hyperactivity.

We also found that while PPX increased motivation to work for food reward, and made it more difficult for rats to withhold responding when cues indicated that reward was not available, it did not cause rats to persevere in the face of increasing levels of punishment in the form of foot-shock. This suggests that D3 receptor agonism largely serves to increase the willingness of animals to work harder and longer for any sort of positive reinforcement, lifting all boats rather than interacting preferentially with unpredictable rewards.

We were also interested in exploring how PPX administration and behavioural training affected the overall amount and distribution of dopamine D2 and D3 receptors in regions of the brain important for processing reward and punishment as well as regions that have been implicated in addiction. We found that overall D2 receptor signal intensity correlated more

strongly with our behavioural measures, which indicate a more direct role of D2 receptors in control over reward-seeking behaviour. This falls in line with other studies that have investigated the relative effects of D2 and D3 agonists on behaviour, with D3 receptors having an effect on motivation (particularly under large ratio/work requirements) and locomotor responding, but overall, less obvious effects on reward-seeking compared to D2 manipulations (Dias et al., 2004; Beninger and Banasikowski, 2008; Cocker et al., 2017; Sokoloff and Le Foll, 2017).

Using a discriminative function analysis, we found that D2 signal in the VTA, INS, and RN provided the best discrimination for whether an animal was trained on a RR or FR schedule, while D3 receptor signal in the VP, VTA, OFC and NAC were relatively strong discriminative power in determining whether an animal received PPX treatment. The main findings of the analysis were not surprising in that D2 signal across all regions was largely associated with the effects due to the training schedule while D3 signal was more associated with the effects due to drug treatment considering that PPX is highly selective for D3 receptors. Those findings notwithstanding, we would like to highlight a few notable findings.

In line with previous studies, we found a relationship between D2 receptors in the VTA and performance on the PR task (Depoortere et al., 1999; Soares-Cunha et al., 2018), with higher signal intensity correlating with higher breakpoints. Findings from experiments investigating the effects of manipulations on VTA D2 receptors and PR breakpoints have largely supported the opposite relationship or have been inconclusive. de Jong et al. (2015) found that decreased D2 autoreceptors in the VTA were associated with increases in breakpoints on the PR task, while systemic or intra-VTA D2 receptor antagonism decreases PR breakpoints (Mobini et al., 2000; Sakamoto et al., 2014; Heath et al., 2015) or has no effect (Vezina, 2004; Peng et al., 2021). Bernosky-Smith et al. (2018) found that D2 receptor knockdown in the VTA enhances choice

impulsivity. Other investigations have found that VTA D2 receptor agonism increases alcohol consumption and sensitizes cocaine-induced locomotor responding (Henry et al., 1998; Nowak et al., 2000), but D2 receptor blockade has also been found to increase amphetamine induced increases in locomotor activity (Tanabe et al., 2004). Regardless, it is clear that VTA D2 receptors are at least necessary for the drug/reward induced increases in PR breakpoints (Elmer et al., 2002; Kruzich et al., 2006). It may be that the changes in D2 receptor density in the VTA due to training on the RR schedule had a larger effect on the D2 receptors present on the GABAergic (Johnson and North, 1992; Steffensen et al., 2008; Galaj et al., 2020) neurons present in the VTA rather than those located on the dopaminergic neurons. Alternatively, we also found increases in D3 receptors in the VTA in our PPX group. Considering that the correlation between D3 receptor intensity and PR was only marginally non-significant in our experiment, changes in the number of D3 receptors (or the ratio of D2:D3) in the VTA could be contributing to the increase in PR breakpoints. Evidence for effects of local D3 manipulations in the VTA are sparse, but Kling-Petersen et al. (1995) reported decreased locomotor activity after infusion of the D3 agonist R-(+)-7-OH-DPAT, but the D3 preferring antagonist, U99194A, had no effect.

A relationship between D2 receptor signal in the INS and performance on the PA tasks also aligns with the body of evidence that posits a central role for the INS in the processing of aversive outcomes. The INS receives dopaminergic input directly from the VTA (Saper, 1982) and communicates reciprocally with the NAC (Allen et al., 1991; Yasui et al., 1991; Chikama et al., 1997), providing the NAC with important integrated sensory input. Increases in D2 receptors in this region could influence the willingness of rats to engage in behaviours that leads to reward (via the glutamatergic projections to the NAC), even if reward is paired with punishment. By changing the processing of cognitive or interoceptive information related to the experience of

punishment, dopaminergic modulation of the INS could decrease the strength of context-aversion associations and thus promote compulsive reward-seeking behaviour (Seif et al., 2013).

Additionally, we observed a strong relationship between D2 receptor signal intensity in the RN and PRP length. Typically, after earning a reward, both animals and humans will pause for a time before initiating the next trial. This pause time scales positively both with the amount of effort required to earn reward (Ferster and Skinner, 1957) and the magnitude or relative value of the reward (Lowe et al., 1974; Mazur, 1983). This suggests that schedule induced changes in D2 receptors likely have an impact on brain 5-HT signalling. Considering the large amount of evidence for the role of 5-HT in impulsivity (particularly motor impulsivity) (Dalley and Roiser, 2012), mood disorders (Martinowich and Lu, 2008), and addiction (Müller and Homberg, 2015), this may be a fruitful line of inquiry for future studies.

As aforementioned, the brain regions which showed the most discriminative differences in D3 receptor signal were the OFC, NAC, VP and VTA. Each of these regions are involved in important reinforcement processing loops. The D3 receptor modulates glutamatergic output from the prefrontal cortex to a variety of subcortical regions (Sokoloff and Le Foll, 2017), notably for the purpose of this discussion, the large glutamatergic projections from the OFC to the medial and ventral striatum including the NAC (Haber and Knutson, 2010; Gruber and McDonald, 2012). D3 receptors in the VP may play and important role in the modulation of dopamine release in the NAC via the pallido-habenular circuit or through afferents to the VTA (Haber et al., 1985; Pribiag et al., 2021).

Limitations of these studies include the inability to differentiate the relative contribution of dopamine receptor signal from autoreceptors or those at postsynaptic sites and the inability localize where the dopamine receptors are located within a region; they may be located on the

principal neurons, interneurons, or possibly glial cells. Another notable limitation of our study concerns the visual cues used in the task. In particular, it has been noted by other researchers that D3 receptors appear to play a role in mediating drug/reward-cue associations (Le Foll et al., 2005; Beninger and Banasikowski, 2008). For example, Barrus and Winstanley (2016) conducted a risky decision-making study, the rIGT, where rats had to choose between four nose-poke holes which were associated with different magnitudes and frequencies of reward and time-out punishment. When these rats were administered the D3 agonist PD128907 they showed marked impairment in the task (choosing the disadvantageous options more frequently), while a D3 antagonist, SB-277011-A, had the opposite effect, but critically these changes were only seen when complex and varied audiovisual cues were present. Although light cues were present in our study, there were no difference in the information provided by the cues on a trial-by-trial basis. Each instrumental response produced the same light flicker, every reward had the same light-paired presentation. It is possible that if our task was designed in such a way so that there were variable amounts of reward that were paired with distinct visual (and perhaps audio) cues, the PPX effect may be enhanced. This option was considered during experimental design; however, we concluded that too many experimental factors would overly complicate the analysis and interpretation of the findings. That said, adding complex audiovisual cues to this task remains a potentially fruitful line of inquiry.

Collectively, our results demonstrate that manipulations of both D2 and D3 receptors via pharmacological interventions or operant conditioning influence rats' reward seeking behaviour, persistence, and motivational levels. Each component of these addiction-related behaviours has a distinct immunohistochemical profile with motivational behaviours involving increased D2 activity in several core monoamine nuclei, compulsive behaviours involving increased D2

receptors in punishment related networks, combined with D3 modulation (generally decreased signal with the exception of the VTA and OFC) in each of the systems. These findings, we hope, will bring a more detailed understanding of how D3 agonists affect dopamine-related reinforcement processing in the brain and how this interacts with repeated engagement with unpredictable rewards like those experienced while gambling.

Chapter 4: Discussion and Synthesis

4.1 Overview and Discussion of Main Findings

The overarching aims of the experiments in this thesis were to investigate whether prolonged exposure to RR schedules of reinforcement would constitute a good animal model of GD as assessed by the 3-criteria model of addiction and whether PPX administration would exacerbate addiction symptomatology. A further aim was to examine the effect of PPX on D2 and D3 receptor expression and the relative contributions of each to rodent behaviour during the task.

Studies 1 and 2 addressed this first aim. Rats in these studies that were trained on RR schedules of reinforcement exhibited increased motivation on the progressive ratio test and had significantly shorter post-reinforcement pause latencies. Response rates were not different between groups, which is consistent with findings from similar studies that found equivalent steady-state performance between VR and FR schedules (Mazur, 1983; Reed, 2011). It should be noted here that rats in both the FR and RR groups displayed consistently high breakpoints on the PR task even in groups that were drug naïve (e.g., exceeding an average of 250 responses in the FR group in Exp. 1, which was the lowest average breakpoint of any group in any of the experiments), much higher than what might be expected. It is possible that the inclusion of the cued-no reward period during the regular testing sessions introduced an element of uncertainty into an otherwise predictable session thus rendering the FR schedule more appetitive, and more similar to the RR schedule, than intended. I would argue that given the obvious differences in the PRP between FR and RR schedules, that they animals are experiencing the schedules differently. Rather, the effect on PR breakpoints is likely a consequence of a build up of tolerance in the animals to long stretches of time between rewards. An FR-50 schedule is quite onerous for a rat

and without a number of pretraining stages which progressively increase the ratio requirements in stages, most rats would extinguish responding before they reached 50 lever presses. In effect, I trained all of the animals to tolerate hard work for their food, which is reflected in their willingness to endure high ratio requirements on the PR task.

In regard to the other addiction measures, responding during the cued no-reward periods and progressive aversion breakpoints were similar between groups. Only a handful of animals were positive for all three addiction criteria, which is to be expected, however, these animals were equally likely to belong to the FR-trained group as the RR group. Overall, this indicates that while RR schedules are motivating (i.e., they decrease PRPs and increase PR breakpoints), long-term exposure to these schedules does not result in a pattern of behaviour that is consistent with GD.

While it is possible that in a very large group of animals (probably several hundred), we would see more animals in the RR group testing positive for addiction, at this time it appears that RR schedules are no more likely to generate addiction than FR schedules. This argues against the primary behavioural conditioning pathway in the Pathways Model of gambling addiction (Blaszczynski and Nower, 2002). That said, it should be noted that Blaszczynski and Nower themselves expect that few gamblers develop GD via this pathway. They also write that the behaviourally conditioned subgroup reports the least severe gambling problems of all subgroups, displays minimal levels of psychopathology, responds well to treatment, and requires minimal intervention. This group is typically introduced to gambling through social contacts who also gamble frequently. In this subgroup, the behavioural and psychological conditioning via repeated reinforcement events likely interacts with some underlying latent vulnerability to produce GD.

There is ample evidence for shared genetic, biological, and genetic vulnerabilities among people with GD, ICDs, and substance addiction. Many of the genetic and neurobiological risk factors involve some perturbation of monoamine systems in the brain, particularly dopamine. A growing body of evidence, primarily from PD research, proposes that one very powerful risk factor for GD/ICDs is prolonged exposure to DA medication. Experiments 3 and 4 investigated this claim.

Animals in Exp. 3 were trained to respond to food reward on a RR schedule of reinforcement for several weeks, after which they were implanted with osmotic pumps that delivered either 1mg/kg/day, 2mg/kg/day, or 3mg/kg/day of PPX over the course of 28 days. After implantation, animals continued to respond for food daily and were then assessed for addiction-like behaviours. Control animals were implanted with a dummy pump. Animals that received PPX exhibited increases in motivation as evidenced by increased progressive ratio breakpoints and decreased post-reinforcement pause times. PPX administration was also associated with increases in responding during the cued no-reward period, while sham animals exhibited a decrease in responding during the same period. There was a trend in the 1.0mg/kg/day group toward increased breakpoints on the progressive aversion task, but this was non-significant after controlling for multiple comparisons. Overall, PPX both increased motivation and responding during periods when reward was not available, but did not have a significant effect on punishment sensitivity in animals trained on an RR schedule of reinforcement.

In a follow up experiment, I was interested in investigating whether the effects of PPX seen in Exp. 3 were specific to RR schedules. So, in Exp. 4 animals were trained to respond for food reward on either a RR or FR schedule of reinforcement daily for several weeks. Each group

was then split and half were implanted with a dummy pump or an osmotic pump that delivered 1mg/kg/day of PPX over 28 days. During that time, animals continued daily training and were then assessed for addiction-like behaviours. Similar to the results from Exp. 3, PPX increased progressive ratio breakpoints and decreased post-reinforcement pause latencies. Rats also responded more during the cued no-reward period. These effects were seen in both the RR and FR groups, indicating that PPX does not interact with the RR schedule of reinforcement. PPX did not significantly affect breakpoints on the progressive aversion task. In sum, similar to Exp. 3, PPX increased motivation and responding during the CNR period. However, this effect appears to affect all animals that received PPX equally, regardless of whether they were trained on an RR or FR schedule of reinforcement, contrary to my initial prediction. Lastly, again similar to the results from Exp. 3, PPX did not affect the punishment sensitivity of any of the animals.

The pattern of results obtained from Exp. 3 and 4 suggest that DA agonists work to enhance motivation for all repetitively reinforced behaviours, regardless of whether they are expected or unexpected. Alternatively, given the large ratio requirements involved, it is possible that the FR schedules were perceived by the rats as being similar to the RR schedules. There is evidence that at high ratio requirements, animals stop perceiving the behavioural requirements as discrete events where a certain number of instrumental responses are needed to obtain reward, but rather treat them like interval schedules where a certain period of time must elapse while they behaviourally respond (Gibbon, 1977; Meck and Church, 1983; Killeen and Fetterman, 1988; Killeen and Fetterman, 1993; Cliff et al., 2019). With this in mind, if the FR schedule is perceived as a time to reward, the perception of the reward schedule may be variable as it depends on the rat's current response rate. However, when looking at the PRPs between the two groups, it becomes obvious that the rats are responding to the two schedules differently.

There appears to be evidence to support the first of the above-mentioned theories—that is that DA agonists work to enhance motivation for all repetitively reinforced behaviours—embedded within the ICD phenomenology itself. As discussed in Chapter 1, ICDs encompass a constellation of addictive and compulsive syndromes such as GD, hypersexuality, compulsive shopping/buying, DDS, and binge eating. DAs appear to increase the incidence of all of these disorders in patient populations. While an argument could be made that compulsive shopping/buying shares some unpredictable reward elements with gambling, many of the other disorders do not; and while GD and hypersexuality were the most often reported ICDs in many of the early studies of ICDs in PD, hypersexuality and hobbyism have risen in prominence more recently. The increased reporting of higher incidences of GD and hypersexuality early on may be in part due to their highly disruptive nature. Both disorders are likely to be noticed by family members/caregivers and cause conflict in the home, even if there are attempts to hide the behaviours, as is often the case with GD. This makes these disorders more likely to be reported to the neurologist compared to shopping, eating, or hobbyism, which are considered to be more normal activities to engage in by both the PD patients and their families/caregivers, and thus less likely to be reported (Garcia-Ruiz et al., 2014). When awareness of the link between DRT and ICDs became widespread in the medical community and clinicians began routinely monitoring their patients for ICDs, much higher rates of all ICDs, but particularly hobbyism and hypersexuality were recorded. This suggests that DRT, and particularly DAs, increase engagement in all pleasurable activities. So, in that context, the results from Exp. 3 and 4 are better explained by a mechanism in which PPX works by enhancing all rewarded behaviours more or less equally.

When considering possible mechanisms by which DAs could be acting on the brain to produce the changes in behaviour seen in these experiments, it is worth considering how dopaminergic neurons behave normally and how this is affected by the introduction of an exogenous receptor agonist. In normal conditions, the temporal structure of neuronal firing dictates the temporal profile of presynaptic release of dopamine, subsequent pre- and postsynaptic receptor activation, and signal transduction. When DAs are introduced, the normal moment-to-moment control over dopamine transmission is perturbed. As discussed in sections 1.5 and 1.6, PPX activates both D2 and D3 postsynaptic receptors which inhibit the cAMP-dependant protein kinase pathway, and D2 and D3 autoreceptors that regulate the release of dopamine from presynaptic terminals. The affinity of PPX for the D2 and D3 receptors rivals that of dopamine itself (Mierau and Schingnitz, 1992; Sokoloff et al., 1992; Mierau et al., 1995; Coldwell et al., 1999), and so competes effectively with dopamine for receptor binding. So, because DAs act on dopamine receptors in a sustained, tonic fashion, their presence masks the moment-to-moment dynamics imparted by the phasic firing of presynaptic dopaminergic neurons. In this way, the DAs enhance the effects produced by the activation of these receptors that are normally associated with the tonic firing of presynaptic dopamine neurons. Tonic firing has been linked to changes in motivational magnitude with increased firing related to increased motivation (Berridge, 2007; Salamone, 2007). This fits with the results from the progressive ratio task, where PPX-treated rats in these studies were willing to work harder and longer to obtain food reward. The phasic firing of dopamine neurons, on the other hand, is critical for reinforcement learning processes. Spikes in firing rates signal a positive error prediction while pauses in firing signal a negative error prediction. These signals relate outcome feedback tied to behaviours and allow for behavioural adjustments to changing reward-related contingencies

(Schultz, 2002). So, by tonically activating the D2/D3 receptors and both elevating and stabilizing the receptor-mediated effects, DAs reduce the ability of the presynaptic neurons to signal changes in outcomes, particularly negative outcomes (Frank et al., 2004; Frank et al., 2007; Cohen and Frank, 2009). In risky decision-making tasks, this generally manifests as an insensitivity to losses. In their article, Rokosik and Napier (2012) argue that the increased discounting seen in rats after repeated PPX administration is likely due to a reduction in the perceived negativity to unrewarded events rather than enhancing the value of the rewarded events. While the main behavioural task used in the experiments conducted in this thesis does not contain a probability discounting component, I will argue that the increased responding by PPX-treated rats during the cued no-reward period is a manifestation that is consistent with insensitivity to losses. When rats respond during this period, if they have some expectation of reward after some number of instrumental responses, then the excessively long period of responding without receiving any reward could be interpreted as a reward omission. PPX, however, could be degrading the salience of these omissions. If the phasic dopamine omission signal is weak, these rats may continue to respond for a longer period of time before the extinction of responding occurs.

One issue with this interpretation is that all animals were assessed for sensitivity to the change in task contingencies as cued by the change in house light colour, during the pretraining phase of the study. Before animals were permitted to continue on to the main task, they had to exhibit at least a 50% reduction in responding during this period to demonstrate that they had learned the house light-cue/food-reward association. So, if this association was well learned, then the animals should have no expectation of reward during the cued no-reward period and there should be no dip in tonic dopamine signalling. However, when looking closer at the data during

this period, I have noted that all rats across all four experiments continued to respond at least somewhat during this period, particularly in the first minute after the cue-light change. There is no indication that once the light changes, the animals immediately cease responding. It appears that all rats take some time to extinguish their behaviour. It may be that rather than simply using the light-cue to signal an appropriate change in behaviour, the rats tune into the reward-feedback information to guide their behaviour. Once the animals had experienced a few reward-omission events (it typically takes an animal 30-45 sec of responding to earn a reward), that omission served as a cue for response cessation. The house-light, rather than serving as a signal to stop responding, was used as a signal to reinitiate responding after the 10 minutes elapsed. In this light, the presence of a DA would disrupt the omission-related feedback that the rats are using at the start of the cued-no reward period and retard behavioural cessation, a pattern that was present in this data. That said, theoretically, if PPX had been on board during the training phase of this task when rats were first learning the task contingencies, the effect on responding during the cued no-reward period could be even more profound.

This insensitivity to reward omission brings up another issue, if DAs were impairing learning from negative feed-back, why were the rats that were treated with PPX not more impaired on the progressive aversion task? There are several possible answers to this; firstly, experiencing an omission of an expected reward is not the same as receiving a punishment. They are different neurological processes that engage different neural circuitry and are mediated by different neurotransmitter systems (Ashton, 2002; Wrase et al., 2007). For example, positive and negative punishment signalling relies more heavily on norepinephrine and substance P, whereas positive and negative reward systems rely more heavily on dopamine. In reality, most of the major neurotransmitters are involved in both processes, but the specific types of receptors and

their distribution patterns across the different neural circuits differentiate them. So, while DAs may impair learning from reward omission, they may not have as large of an effect on punishment learning. This is buttressed by the findings from a study where PD patients both on and off DA medication gambled in two conditions (1) where they could either gain money or receive nothing and (2) where they could gain or lose money, or receive nothing (Voon et al., 2011). The authors of this study found that DAs only caused a change in attitude to risky situations when the prospect of gain was present; if the prospect of losing money was on the table, then risk preference was not affected. Secondly, it is possible that the DA was either not administered for long enough or that the dose was not sufficiently large enough to impair reinforcement learning to such an extent as to interfere with punishment learning processes. While, some of the effects of DAs are seen almost immediately, many of the more serious changes in behaviour and cognition are seen only after neuroadaptive changes have taken place. It is possible that this process of adaptation was incomplete. However, in the context of all the studies using PPX in rats published thus far, the duration of exposure to the drug in the studies presented here is quite long (most other studies administer PPX over the course of ~2 weeks compared to 4 weeks in these experiments). Thirdly, these studies are some of the only ones available that use osmotic pumps to deliver PPX at a sustained rate over the course of many weeks. In most other studies the rats are repeatedly injected with PPX before testing and the drug is allowed to wash out between sessions. This produces a moderate pulsatile effect which is known to engage certain neuroadaptive changes that may have affected results in other studies and are absent in these experiments. Arguing against this however, is evidence from PD studies investigating this phenomenon that has generally agreed that because of the long half-life of PPX and other DA medications used in the treatment of PD, the neuroadaptive changes due to

pulsatile stimulation of postsynaptic neurons, such as those seen with levodopa, are largely absent with DAs. Finally, although not significant, PPX did increase the progressive aversion breakpoint somewhat in Exp. 3 and 4, and when PPX was administered orally for a shorter duration (10 days) in Exp. 2 it caused a decrease in responding during the progressive aversion task, which is more in line with the effects of short term/acute PPX administration. That is, when administered acutely, PPX produces sedation, low affect, and low motivation, which we observed in our rats in the first week after implantation. This suggests that PPX had some impact on punishment learning and persistence, but the effect may have not been powerful enough to counteract the intensity and reinforcement strength of a powerful nociceptive stimulus such as the electrical shock used in these studies.

The third major aim in this thesis was to investigate how prolonged exposure to RR schedules of reinforcement and PPX administration affected D2 and D3 receptors in the brains of rats with the overall goal of elucidating the relative contribution of each of these receptors to addiction-like behaviour. Which receptors mediate the behavioural effects of PPX is unclear. As discussed above, PPX is a full agonist at both D2 and D3 receptors with a 7-30-fold higher affinity for the D3 receptor over D2 (Dooley and Markham, 1998; Collins et al., 2007; Eisenreich et al., 2010; Antonini and Calandrella, 2011). However, the therapeutic doses used in PD likely also involve significant D2 receptor activation (Deutschländer et al., 2016) and there is evidence that 1.0 mg/kg of PPX is enough to stimulate both D2 and D3 receptors in rats (Collins et al., 2007), thus it was likely that activation of either or both receptors contributed to the behavioural changes seen in the rats in these experiments. Evidence from the immunofluorescence antibody staining in Exp. 4 supports this proposition.

Statistical analysis of the changes in both D2 and D3 receptors in various reward and addiction related regions yielded some important findings. First, PPX treatment had a stronger impact on the overall levels of D3 receptors compared to D2, which is not surprising considering the relative binding affinities. The regions that exhibited the largest changes and contributed the most to the statistical model were the VP, VTA, OFC, and NAC. When comparing animals that received PPX to controls, both D2 and D3 receptors were decreased in the VP but D3 was much more affected. I also observed an increase in D3 (but not D2) receptor expression in the VTA. Both D2 and D3 receptor expression was increased in the OFC, but the effect was stronger for D3 receptors. Finally, there was a decrease in D2 (but not D3) expression in the NAC.

The second main finding was that changes in D2 receptor expression were more closely related to schedule of reinforcement. That is, regional D2 receptor expression accounted for more variance in determining group classification between RR rats and FR rats. The regions that contributed the most to this statistical model were the VTA, INS, and RN. When comparing animals that trained on the RR schedule to those trained on the FR schedule, there was an overall increase in D2 (but not D3) receptors in both the VTA and INS. Finally, in the RN, D2 receptors were decreased but D3 receptors were increased.

The changes in D2 and D3 expression also correlated with several behavioural measures on the task. Post reinforcement pauses were positively correlated to both D2 receptor expression in the NAC and the RN. That is, the lower the D2 expression in these areas, the smaller the pause time. Responding during the cued-no reward period was also positively associated with D2 receptor expression in the RN. Progressive ratio breakpoints were positively correlated with D2 receptors in the VTA and RN and D3 receptors in the CG. Lastly, breakpoints on the progressive

aversion task were positively correlated with both D2 and D3 receptors in the INS and D3 receptors expression in the VP.

Overall, these results are consistent with general dysregulation of the mesolimbic dopaminergic circuit. Decreases in striatal D2 receptors were associated with faster trial initiation and increased task motivation. This is consistent with the addiction literature indicating a relationship between decreased striatal D2 receptor expression and increased addiction severity, increased craving, increased cue reactivity, and increased likelihood of relapse. Increases in D2 receptors in the INS were associated with increased breakpoints during the progressive aversion task. This finding is also parsimonious with the role of the insula in signalling expectations of negative outcomes. Theoretically, increased D2 postsynaptic receptors in the insula could decrease the firing rate of glutamatergic neurons that project to the NAC core by promoting the opening of K+ ion channels. This decrease in excitatory input to the core may then cause a release of the inhibitory control that the core has on the shell, resulting in increased impulsivity in the face of anticipated punishment. Several behavioural measures (i.e., PRP, CNR responding, and PR breakpoint) were correlated with D2 expression in the RN. This finding is particularly interesting in that it suggests a significant interaction between dopamine and serotonin in regulating these behaviours. Serotonin's role in mediating impulsive behaviours is well established (Coccaro, 1989; Lesch and Merschdorf, 2000; Winstanley et al., 2005; Dalley and Roiser, 2012). The particular effects that decreased D2 receptors have on serotonergic signalling require more investigation to delineate, but it suggests that there may be impairments in the ability to regulate activity in this area. Lastly, there were significant decreases in D3 receptor expression in the VP that positively correlated with breakpoints on the progressive aversion task. Neurons in the ventral pallidum normally have high levels of both D2 and D3

receptor expression (Contreras et al., 1987; Beckstead et al., 1988; Richfield et al., 1989; Tziortzi et al., 2011). This region is a key regulator of both reward- and punishment-related behaviour (Root et al., 2015; Saga et al., 2017; Fujimoto et al., 2019; Wulff et al., 2019) and is heavily interconnected with the NAC, lateral habenula, amygdala, the STN and the MFC. It also receives dopaminergic and serotonergic input from the VTA and RN respectively. Decreases in D3 receptor expression in this region likely influences both reward and punishment processes. To illustrate this, Pribiag et al. (2021) conducted a series of studies with mice and found that genetic knockdown of D3 receptor expression in the VP reduced activity in the VTA and subsequent DA release in the NAC shell, decreasing the likelihood of cocaine relapse. Moreover, inhibition the D3 expressing VP projection or reduction of D3 receptor signalling to the lateral habenula suppressed cocaine-seeking behaviour after a period of abstinence. This suggests that increased D3 signalling in this region promotes addiction-like behaviours. Furthermore, Payer et al. (2014) reported increased levels of D3 receptor binding in cocaine dependent individuals. This complements the findings from Exp. 4 in that increased D3 receptor expression in the VP was associated with higher progressive aversion breakpoints. It should be noted that because the antibody staining used in this study does not differentiate between pre- and postsynaptic dopamine receptors, it is difficult to say for certain what the effect these changes in dopamine receptor levels have on the overall activity of the brain regions involved. More investigations would need to be conducted to further differentiate the relative effects of pre- and postsynaptic D3 effects.

The last point I will address is that although the association between DAs and GD/ICDs has been reported consistently in the literature, it remains controversial as to whether the effects are dose dependent or follow an all-or-none pattern. The findings from this study may help to

explain why investigations into the prevalence of GD/ICDs in PD patient populations have not found a relationship between DA dose and ICDs. It is possible that the effect of DAs on the development of GD/ICDs work in several stages, where a certain threshold of D3 receptor binding is needed for the ICD to develop (i.e., D3 receptors may normally act as breaking mechanism for D1/D2-mediated behavioural dysregulation). Once the D3 receptor system is sufficiently perturbed, increasing levels of tonic D1/D2 receptor activation then scale with behavioural dysregulation. So, in the case of D3-preffering DA medication, the D3 receptors are saturated at relatively low doses but D1 and D2 receptors may not yet be unduly affected. It is at this point introduction of levodopa causes subsequent increases in endogenous dopamine that activate D2 receptors, which may or may not interact with some underlying neurobiological vulnerability. As the dose of levodopa increases with disease progression, D2 receptors become saturated, further impairing reward related feedback mechanisms. This then followed by activation of D1 receptors which promote active reward-seeking type behaviours. At this point the pathological behaviours begin to manifest which are associated with specific environmental contexts (e.g., problematic gambling behaviours may become evident if the individual is exposed to slot machines at a casino), and worsen with increasing levels of levodopa rather than DA dosage.

4.2 Limitations and Considerations

There are a number of limitations to consider with these studies. One concern is that the reinforcer used in the study, food, is not a strong enough reinforcer to induce addiction. However, sucrose self-administration has been successfully used as an addiction model by several groups (Avena et al., 2006, 2008; Diergaarde et al., 2009; Domingo-Rodriguez et al., 2020). In the study conducted by Avena et al. (2008), rats exhibited several symptoms of

addiction including binging, withdrawal, and craving. Additionally, binge-eating is one of the ICDs that develops in PD patients after prolonged DA treatment. Moreover, as discussed in section 1.12, both PPX and ropinirole impair decision-making in rats and shift animals towards a preference for unpredictable or risky outcomes. Importantly, this occurred regardless of the reinforcer involved, for example Rokosik and Napier (2012) used ICSS as a reinforcer, whereas Johnson et al. (2011) used food reward. This evidence supports the position that highly palatable food is a sufficient reinforcer. Another concern is the lack of a wager. Gambling involves wagering something of value in return for the chance of receiving something of larger value. While the animals in these tasks obviously do not wager money, they are giving up valuable time and energy. An animal making a choice to press a lever incurs a small cost in terms of energy, experienced subjectively as effort. Additionally, according to foraging theory, every action has an opportunity cost, an alternate action which might have led to higher caloric or reproductive return (Pyke, 1984). These costs are admittedly small on a trial-by-trial basis, but over hundreds of thousands of responses, as is the case in these studies, the costs add up. Second, animal models are meant to capture an important facet of GD, not to perfectly replicate human gambling. For example, we will never be able to capture socioeconomic factors such as race and poverty in an animal model (Williams et al., 2021). Instead, the aim is to study the brain and behavioral responses to reward schedules, which are just one piece (albeit a very important one) of gambling addiction. Third, when considering another highly motivating recreational pursuit, video games, the alluring components of these games are also driven, at least in part, by the unpredictability of reward (Hellman et al., 2013; Nagle et al., 2014). Because an explicit wager is not essential to the addictive potential of these games, it may not be for gambling, either.

It must also be acknowledged that the RR schedule of reinforcement does not capture all facets of the gambling experience or even just of slot-machines. Modern slot machines employ several other mechanisms, such as losses disguised as wins and near misses, that further increase gambling frequency and time spent on the machine (Dixon et al., 2013; Templeton et al., 2015). There are also environmental and social factors to consider. Casinos are exciting environments that are designed to entice players to spend their time and money within these establishments. Gambling behaviour is not only rewarded monetarily when a gambler wins a big jackpot but also socially – casino employees and other gamblers will come an congratulate the winner - friends, family and coworkers may further reinforce the win later on. It is possible that these additional experiences are necessary to fully engage the addictive process. However, rather than a difference of kind, it is likely that these additional factors affect the degree to which people lapse into addiction.

Another technical limitation of the study is that only D2 and D3 receptors were assessed. This limits the conclusions that can be drawn about the overall changes in the dopamine reward system. Further investigations should include tests for D1 receptors, DAT, COMT and MAO, in combination with methods to assess both tonic and phasic dopamine levels during the task. Another technical issue mentioned previously is that the staining method used here does not differentiate between pre- and postsynaptic receptors so it is difficult to discern exactly how the changes in D2 and D3 receptors are ultimately affecting signal transmission.

Another obvious concern is that GD/ICDs may only develop in individuals when there is already a pre-existing dopaminergic pathology, as is the case in PD. There is a case for PD patients having increased frontal lobe dysfunction that could impair their ability to control behavioural impulses and their ability to appreciate the consequences of their actions. Although

many cognitive processes are affected by PD, the cognitive impairments associated with PD are often described as a disorder of frontal executive function (Owen et al., 1992; Robbins et al., 1994). Studies into these impairments usually focus on two broad categories: (1) functions of attentional control such as working memory, planning and task- or set-switching and (2) reward-based control of behaviours and the management of risk. There are clear abnormalities within both categories but the nature of the deficit depends on a complex interaction between the specific task conditions, disease severity, genetic and neurobiological variations and treatment (Rowe et al., 2008). Several studies have noted these same deficits in PD patients with GD (Ribacoba et al., 2010) and it is well known that people with GD also have deficits in a few tasks that rely on frontal lobe executive functions (Cavedini et al., 2002; Kalechstein et al., 2007). It is therefore a reasonable conjecture that the frontal lobe, and general dopamine system dysfunction caused by PD may constitute a unique vulnerability to GD.

Supporting this, is evidence from studies of post mortem brain tissue of PD patients that indicate the apart from the well-known depletion of DA, PD also causes decreases in norepinephrine and serotonin (Politis et al., 2010; Goldstein et al., 2011). Both of these neurotransmitters are involved in frontal inhibition processes and depletion of either one of these neurotransmitters is correlated with impaired inhibitory control. Moreover, PD is also associated both with decreased frontal grey matter and decreases in white matter integrity between the frontal cortex and the striatum (Zeighami et al., 2015; Chen et al., 2016; Dadar et al., 2018; de Schipper et al., 2019), both of which result in decreased prefrontal control of behaviour. These changes may further contribute to an increase in the reported incidence of impulsivity (both motor and choice/reflection impulsivity) in PD patients. So, as discussed in sections 1.5 and 1.7, dopaminergic medications such as levodopa (and to a lesser extent DAs), initiate a process of

neural sensitization that mediate compulsive medication use in DDS and arguably incentive sensitization in GD/ICDs. Due to the underlying neurodegeneration and resultant cognitive decline that occurs in PD, it is likely that patients would have a reduced ability to control impulsive reward-seeking behaviours associated with the sensitization and to cognitively apprehend the impacts of their behaviour (Giovannoni et al., 2000; Avanzi et al., 2004).

However, there are several arguments against the idea the PD patients are particularly vulnerable group. Firstly, untreated patients with de novo PD show similar ICD prevalence rates compared to the general population, so it is unlikely that there are many shared heritability factors between ICDs and PD. Evidence from genetic and human imaging studies suggest that PD patients that go on to develop an ICD have similar premorbid neurobiological vulnerabilities to healthy people in the general population that develop ICDs (Shaffer et al., 2004; da Silva Lobo et al., 2007; da Silva Lobo and Kennedy, 2009; Smith et al., 2016). Secondly, the observed personality characterises of PD patients suggest a population that is particularly *unlikely* to develop GD or another ICD. General population studies have associated GD with high levels of novelty seeking and impulsivity, characterised by exploratory-type behaviours, excitement in novel situations, rapid decision-making and extravagance (Cloninger et al., 1993; Kim and Grant, 2001; Slutske et al., 2005; Mishra et al., 2010). Alternatively, the personalities of PD patients are characterized by low levels of novelty-seeking, accompanied by thoughtful, careful decision-making and a calm temperament (Menza et al., 1993; Voon et al., 2007b; Dagher and Robbins, 2009; Poletti and Bonuccelli, 2012). There is no evidence that untreated PD patients are more likely to develop GD/ICDs and it is worth considering that PD patients are almost unique in terms of their long-term exposure to DAs. Interestingly, D2 receptor expression is upregulated in PD and the D3 receptor is downregulated (Ryoo et al., 1998), whereas studies of post-mortem

brain tissue in individuals with addiction generally indicate the opposite pattern (Staley and Mash, 1996; Segal et al., 1997; Tupala et al., 2001; Volkow et al., 2003). This further supports the idea that PD patients may be uniquely protected against the harmful effects of DAs rather than being particularly susceptible to them. This leads into the final argument against PD pathology generating a particularly vulnerability to the development of GD/ICDs; DAs are used to treat a handful of other disorders and GD/ICDs are elevated in those populations as well.

Although most reports of GD and ICDs come from the PD patient population, there is increasing evidence of these disorders connected to DA use in the treatment of other disorders such as restless legs syndrome, fibromyalgia, and prolactinoma (Davie, 2007; Driver-Dunckley et al., 2007; Evans and Butzkueven, 2007; Quickfall and Suchowersky, 2007; Tippmann-Peikert et al., 2007; Falhammar and Yarker, 2009; Pourcher et al., 2009; Dang et al., 2011; Martinkova et al., 2011; Strejilevich et al., 2011; Lipford and Silber, 2012; Bancos et al., 2014; Grall-Bronnec et al., 2018; Dogansen et al., 2019). Restless legs syndrome is a sensorimotor disorder that involves the unpleasant sensations in the legs combined with a strong urge to move the legs in order to alleviate those feelings. Fibromyalgia is a condition that involves widespread chronic feelings of pain and fatigue. Both of these conditions are treated with dopamine agonists, particularly restless legs syndrome. Ondo and Lai (2007) interviewed patients with PD, restless legs syndrome, or both and found an overall ICD prevalence rate of 19.7%, with the highest rates seen for gambling (10%) and compulsive shopping/buying (8.7%) and lower rates for hypersexuality (3.7%). Initially, there appeared to be a greater rate of ICDs in the PD population, but after controlling for the medication dose - PD patients are generally prescribed higher doses of DAs - the difference was non-significant. Holman (2009) reported a .7% overall rate of ICDs (1.5% in those patients that were prescribed DAs) when reviewing the charts of 3006

fibromyalgia patients. Of the 3006 patients, 1356 had received at least one dose of a DA, nearly all of which were PPX. Similar to what is seen with PD patients with GD/ICDs and in the general population, patients with restless legs syndrome who have comorbid GD/ICDs exhibit increased levels of impulsivity as assessed by the Barrett Impulsiveness Scale (Dang et al., 2011). These reports suggest that DAs have the capacity to induce GD and other ICDs independent of the neuropathology for which the drug is being used, and that the DA related effects involve dysregulation of general reward processes.

4.3 Conclusions

RR schedules of reinforcement are highly motivating to animals, but alone are not likely to promote addiction. Generally, some other factor such an exogenous drug or an underlying genetic or neurophysiological vulnerability appears to be needed to push animals over into an addition-like phenotype. DA medications appear to be just such a factor. The D3 preferring DA, PPX, induced widespread alterations in both D2 and D3 receptor expression in regions of the brain associated with reward, motivation, punishment, and inhibition of behaviour. Prolonged training on RR schedules of reinforcement also produced changes in the dopamine receptor expression, primarily D2 receptors. Furthermore, these changes in receptor expression correlated with the animals' addiction-related behaviours. It is likely that PPX and other DAs interfere with the normal functioning of dopamine neurons by tonically stimulating the D2 and D3 receptors which result in learning impairments from negative feedback. The neuroadaptive changes that occur as a consequence to this stimulation promote a shift in the animals' decision-making biases over into a more risk-seeking profile because the negative outcomes from losing are less powerful reinforcers and thus less able to influence reward-related behaviours.

In terms of the theoretical framework motivating the line of questioning in this thesis, it appears that there is little evidence for the behaviourally conditioned pathway in the Pathways Model, when examined using intact healthy animals. It is likely that humans that fall into this category either have some sort of underlying inherited biological vulnerability or possibly interactions with exogenous substances that went undetected. As discussed in section 1.4, patients often hide GD/ICD symptoms and both current and former problematic substance use from clinicians, even when questioned directly. When an exogenous substance that increases tonic dopamine levels is introduced, the animals exhibit more signs of an addiction phenotype. This phenotype shares some features in common with the third pathway in the Pathways Model, the antisocial impulsivist subtype. These gamblers are characterized by a family history of problem gambling, high levels of impulsivity, and co-morbid substance dependence (Blaszczynski, 2000). However, these gamblers also display more severe dysfunction and are typically treatment resistant (Blaszczynski and Nower, 2002). It may be that the behaviourally conditioned subtype is a less severe form of the antisocial impulsivist subtype. In this light, these individuals would likely have a family history of substance abuse and/or GD/ICDs and moderately increased trait impulsivity that is exacerbated by gambling and substance use, however they would lack the antisocial and narcissistic personality traits associated with the more severe, widespread dysfunction seen in the antisocial impulsivist subtype such as criminal activity, affective instability, and suicidal ideation.

Taken together, the results from these studies suggest that responding for unpredictable reward is likely not a harmful pursuit for the majority of individuals and that simple exposure to repeated unexpected rewards does not often lead to GD unless there is some other factor at play. This could be an underlying biological/genetic vulnerability or the addition of an exogenous

drug. It should be noted here, that although these series of experiments capture some aspects of the gambling experience in humans, these tasks do not capture all of the various aspects of the typical EGM/VLT/slot-machine (e.g., betting money, losses disguised as wins, near misses, etc.). However, the evidence presented in this thesis does point to some implications for the gambling industry and gambling policy. Particularly the relationship between gambling and substances that increase tonic activation of dopamine receptors such as alcohol. There is high comorbidity between GD and substance abuse (McGrath and Barrett, 2009; Lorains et al., 2011) and while many of these substances are not as specialized in their affect on dopamine signalling as DAs, they all still have an overall effect of increasing tonic levels of dopamine which may disrupt the reinforcement learning processes discussed throughout this thesis. With this in mind, it may be of particular interest to policy makers, academics, and clinicians to take note of the interaction between gambling and drug use. Alcohol consumption in particular, is often encouraged in casinos. It is well known that this drug not only increases tonic dopamine levels (Di Chiara, 1997), but also decreases prefrontal inhibition (Lawrence et al., 2009; Abernathy et al., 2010) – a particularly dangerous mix according to the evidence provided in this thesis.

Lastly, DAs appear to disrupt reward learning and yoked motivational processes which promote narrowed reward seeking behaviours. The effect is not gambling specific, but appears to have the most impact on behaviours linked with repeated, high intensity positive reinforcement and hedonistic pleasure. Importantly, the reinforcer is often abstract and difficult to satiate via normal regulatory homeostatic feedback mechanisms. In the case of gambling the reinforcer is money and social cache, as well as the subsequent primary reinforcers (i.e., food, sex, shelter, etc.). In the case of hypersexuality, viewing pornography or the excitement of sexual conquest serve as secondary reinforcers with sexual pleasure as a primary reinforcer. Compulsive

shopping also involves abstract rewards such as excitement in the hunt for a good deal as well as social reinforcement from peers in the form of compliments. Recent trends also support this position, with increased rates of addiction-like behaviours related to social media use (Hou et al., 2019) and online gaming (Young, 2009), both of which are heavily reinforced via social feedback as well as more traditional goal-oriented reinforcement mechanisms in the case of gaming. The lone exception appears to be binge eating, for which there are robust homeostatic regulatory mechanisms (Saper et al., 2002) and the by-product of overeating, weight gain is culturally condemned rather than lauded. On the other hand, it should be noted that the process of weight gain is a relatively slow process and so the accumulation of negative effects may be discounted at a greater rate compared to gambling losses or money spent during shopping binges. Overall, while gambling may not be unique in its ability or propensity to induce an addictive disorder, it remains one of the few activities - particularly the continuous forms of gambling – that have the capacity to do so in significant numbers and therefore should be treated with caution.

This series of experiments has improved our understanding of the neurobiological mechanisms involved in GD, painting a complex picture of the relationship between dopamine receptor expression, reward-seeking behaviours, and the characteristics of reward delivery. As a better understanding of the specific neurobiological contributions to disordered gambling behaviours develops, these insights can be capitalized on with the aim of improving prevention and treatment strategies. It through such efforts that the lives of many individuals currently experiencing or at risk of gambling problems can be improved.

REFERENCES

Abernathy K, Chandler LJ, Woodward JJ (2010) Alcohol and the prefrontal cortex. International review of neurobiology 91:289-320.

Abler B, Hahlbrock R, Unrath A, Gron G, Kassubek J (2009) At-risk for pathological gambling: imaging neural reward processing under chronic dopamine agonists. Brain 132:2396-2402.

Alessi SM, Petry NM (2003) Pathological gambling severity is associated with impulsivity in a delay discounting procedure. Behavioural Processes 64:345-354.

Alexander BK, Coambs RB, Hadaway PF (1978) The effect of housing and gender on morphine self-administration in rats. Psychopharmacology (Berl) 58:175-179.

Allen GV, Saper CB, Hurley KM, Cechetto DF (1991) Organization of visceral and limbic connections in the insular cortex of the rat. The Journal of Comparative Neurology 311:1-16.

American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders (4th ed., Text Revision). Washington, DC: American Psychiatric Association.

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Association.

Anselme P (2013) Dopamine, motivation, and the evolutionary significance of gambling-like behaviour. Behavioural Brain Research 256:1-4.

Antonini A, Poewe W (2007) Fibrotic heart-valve reactions to dopamine-agonist treatment in Parkinson's disease. Lancet neurology 6:826-829.

Antonini A, Calandrella D (2011) Pharmacokinetic evaluation of pramipexole. Expert Opinion on Drug Metabolism & Toxicology 7:1307-1314.

Antonini A, Tolosa E, Mizuno Y, Yamamoto M, Poewe WH (2009) A reassessment of risks and benefits of dopamine agonists in Parkinson's disease. Lancet neurology 8:929-937.

Ardouin C, Voon V, Worbe Y, Abouazar N, Czernecki V, Hosseini H, Pelissolo A, Moro E, Lhommée E, Lang AE, Agid Y, Benabid A-L, Pollak P, Mallet L, Krack P (2006) Pathological gambling in Parkinson's disease improves on chronic subthalamic nucleus stimulation. Movement Disorders 21:1941-1946.

Ashton H (2002) Reward and punishment systems. In: Neurochemistry of Consciousness: Neurotransmitters in Mind (Perry E, Ashton H, Young A, eds), p 83. Amsterdam, The Netherlands: John Benjamins Publishing Company.

Avanzi M, Uber E, Bonfà F (2004) Pathological gambling in two patients on dopamine replacement therapy for Parkinson’s disease. Neurological Sciences 25:98-101.

Avanzi M, Baratti M, Cabrini S, Uber E, Brighetti G, Bonfà F (2006) Prevalence of pathological gambling in patients with Parkinson's disease. Movement disorders: official journal of the Movement Disorder Society 21:2068-2072.

Avena NM, Rada P, Hoebel BG (2006) Sugar bingeing in rats. Current protocols in neuroscience / editorial board, Jacqueline N Crawley [et al] Chapter 9:Unit9 23C.

Avena NM, Rada P, Hoebel BG (2008) Evidence for sugar addiction: Behavioral and neurochemical effects of intermittent, excessive sugar intake. Neuroscience and biobehavioral reviews 32:20-39.

Balleine BW, O'Doherty JP (2010) Human and rodent homologies in action control: corticostriatal determinants of goal-directed and habitual action. Neuropsychopharmacology 35:48-69.

Balodis IM, Kober H, Worhunsky PD, Stevens MC, Pearlson GD, Potenza MN (2012) Diminished frontostriatal activity during processing of monetary rewards and losses in pathological gambling. Biol Psychiatry 71:749-757.

Bancos I, Nannenga MR, Bostwick JM, Silber MH, Erickson D, Nippoldt TB (2014) Impulse control disorders in patients with dopamine agonist-treated prolactinomas and nonfunctioning pituitary adenomas: a case-control study. Clinical endocrinology (Oxford) 80:863-868.

Barbosa P, Hapuarachchi B, Djamshidian A, Strand K, Lees AJ, de Silva R, Holton JL, Warner TT (2019) Lower nucleus accumbens α-synuclein load and D3 receptor levels in Parkinson's disease with impulsive compulsive behaviours. Brain (London, England : 1878) 142:3580-3591.

Barns Neurauter MP, Rickards H, Cavanna AE (2010) The prevalence and clinical characteristics of pathological gambling in Parkinson's disease: An evidence-based review. Functional Neurology 25:9-13.

Baron A, Mikorski J, Schlund M (1992) Reinforcement magnitude and pausing on progressive-ratio schedules. Journal of the Experimental Analysis of Behavior 58:377-388.

Barrus MM, Winstanley CA (2016) Dopamine D3 receptors modulate the ability of win-paired cues to increase risky choice in a rat gambling task. Journal of Neuroscience 36:785-794.

Beaulieu-Boire I, Lang AE (2015) Behavioral effects of levodopa. Movement disorders 30:90-102.

Bechara A (1997) Deciding Advantageously Before Knowing the Advantageous strategy.

Bechara A (2005) Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. Nat Neurosci 8:1458-1463.

Bechara A, Tranel D, Damasio H (2000) Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. Brain 123:2189-2202.

Bechara A, Damasio AR, Damasio H, Anderson SW (1994) Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 50:7-15.

Bechara A, Damasio H, Tranel D, Damasio AR (1997) Deciding advantageously before knowing the advantageous strategy. Science 275:1293-1295.

Bechara A, Damasio H, Damasio AR, Lee GP (1999) Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. The Journal of Neuroscience 19:5473-5481.

Beckstead RM, Wooten GF, Trugman JM (1988) Distribution of D1 and D2 dopamine receptors in the basal ganglia of the cat determined by quantitative autoradiography. Journal of comparative neurology (1911) 268:131-145.

Becona E (1997) Pathological Gambling in Spanish children and adolescents: An emerging problem. Psychological reports 81:275-287.

Belin-Rauscent A, Belin D (2012a) Animal models of drug addiction In: Addictions - From Pathophysiology to Treatment. Poitiers, France: Université de Poitiers.

Belin-Rauscent A, Belin D (2012b) Animal models of drug addiction. In: Addictions - From Pathophysiology to Treatment. Poitiers, France: Université de Poitiers.

Belin D, Balado E, Piazza PV, Deroche-Gamonet V (2009) Pattern of intake and drug craving predict the development of cocaine addiction-like behavior in rats. Biological Psychiatry 65:863-868.

Belin D, Mar AC, Dalley JW, Robbins TW, Everitt BJ (2008) High impulsivity predicts the switch to compulsive cocaine-taking. Science 320:1352-1355.

Beninger RJ, Banasikowski TJ (2008) Dopaminergic mechanism of reward-related incentive learning: Focus on the dopamine D(3) receptor. Neurotoxicity Research 14:57-70.

Bentivoglio M, Morelli M (2005) The organization and circuits of mesencephalic dopaminergic neurons and the distribution of dopamine receptors in the brain. In: Handbook of Chemical Neuroanatomy (S.B. Dunnett MBAB, Hökfelt T, eds), pp 1-107: Elsevier.

Berger C, Mehrhoff FW, Beier KM, Meinck HM (2003) Sexual delinquency and Parkinson's disease. Nervenarzt 74:370.

Bergh C, Eklund T, Södersten P, Nordin C (1997) Altered dopamine function in pathological gambling. Psychological Medicine 27:473-475.

Berke JD, Hyman SE (2000) Addiction, dopamine, and the molecular mechanisms of memory. In, pp 515-532. United States: Elsevier Inc.

Bernosky-Smith KA, Qiu YY, Feja M, Lee YB, Loughlin B, Li JX, Bass CE (2018) Ventral tegmental area D2 receptor knockdown enhances choice impulsivity in a delay-discounting task in rats. Behav Brain Res 341:129-134.

Berridge KC (2007) The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology (Berl) 191:391-431.

Berridge KC, Robinson TE (2016) Liking, wanting, and the incentive-sensitization theory of addiction. Am Psychol 71:670-679.

Berridge KC, Robinson TE, Aldridge JW (2009) Dissecting components of reward: 'liking', 'wanting', and learning. Curr Opin Pharmacol 9:65-73.

Bertz JW, Chen J, Woods JH (2015) Effects of pramipexole on the acquisition of responding with opioid-conditioned reinforcement in the rat. Psychopharmacology (Berl) 232:209-221.

Besson M, Belin D, McNamara R, Theobald DE, Castel A, Beckett VL, Crittenden BM, Newman AH, Everitt BJ, Robbins TW, Dalley JW (2010) Dissociable control of impulsivity in rats by dopamine d2/3 receptors in the core and shell subregions of the nucleus accumbens. Neuropsychopharmacology 35:560-569.

Bézard E, Ferry S, Mach U, Stark H, Leriche L, Boraud T, Gross C, Sokoloff P (2003) Attenuation of levodopa-induced dyskinesia by normalizing dopamine D3 receptor function. Nature medicine 9:762-767.

Binde P, Romild U, Volberg RA (2017) Forms of gambling, gambling involvement and problem gambling: evidence from a Swedish population survey. International Gambling Studies 17:490-507.

Black DW (2007) A review of compulsive buying disorder. World psychiatry 6:14-18.

Black DW, Moyer T (1998) Clinical features and psychiatric comorbidity of subjects with pathological gambling behavior. Psychiatric services (Washington, DC) 49:1434-1439.

Blaszczynski A (2000) Pathways to pathological gambling: Identifying typologies. Journal of Gambling Issues.

Blaszczynski A, Nower L (2002) A pathways model of problem and pathological gambling. Addiction 97:487-499.

Blaszczynski A, Steel Z, McConaghy N (1997) Impulsivity in pathological gambling: the antisocial impulsivist. Addiction (Abingdon, England) 92:75-87.

Bódi N, Kéri S, Nagy H, Moustafa A, Myers CE, Daw N, Dibó G, Takáts A, Bereczki D, Gluck MA (2009) Reward-learning and the novelty-seeking personality: a between- and within-subjects study of the effects of dopamine agonists on young Parkinson's patients. Brain (London, England : 1878) 132:2385-2395.

Boileau I, Payer D, Chugani B, Lobo DSS, Houle S, Wilson AA, Warsh J, Kish SJ, Zack M (2013) In vivo evidence for greater amphetamine-induced dopamine release in pathological gambling: a positron emission tomography study with [11C]-(+)-PHNO. Molecular Psychiatry 19:1305-1313.

Boileau I, Guttman M, Rusjan P, Adams JR, Houle S, Tong J, Hornykiewicz O, Furukawa Y, Wilson AA, Kapur S, Kish SJ (2009) Decreased binding of the D3 dopamine receptor-preferring ligand [11C]-(+)-PHNO in drug-naïve Parkinson's disease. Brain (London, England : 1878) 132:1366-1375.

Boileau I, Payer D, Houle S, Behzadi A, Rusjan PM, Tong J, Wilkins D, Selby P, George TP, Zack M, Furukawa Y, McCluskey T, Wilson AA, Kish SJ (2012) Higher binding of the dopamine D3 receptor-preferring ligand [11C]-(+)-propyl-hexahydro-naphtho-oxazin in methamphetamine polydrug users: A positron emission tomography study. The Journal of Neuroscience 32:1353-1359.

Bolan EA, Kivell B, Jaligam V, Oz M, Jayanthi LD, Han Y, Sen N, Urizar E, Gomes I, Devi LA, Ramamoorthy S, Javitch JA, Zapata A, Shippenberg TS (2007) D2 receptors regulate dopamine transporter function via an extracellular signal-regulated kinases 1 and 2-dependent and phosphoinositide 3 kinase-independent mechanism. Molecular pharmacology 71:1222.

Bonci A, Bernardi G, Grillner P, Mercuri NB (2003) The dopamine-containing neuron: maestro or simple musician in the orchestra of addiction? Trends in pharmacological sciences 24:172-177.

Bordet R, Ridray S, Carboni S, Diaz J, Sokoloff P, Schwartz JC (1997) Induction of dopamine D3 receptor expression as a mechanism of behavioral sensitization to levodopa. Proceedings of National Academy of Sciences of the United States of America 94:3363-3367.

Boren MCP (1973) Fixed-ratio and variable-ratio schedules of brief stimuli in second-order schedules of matching to sample. Journal of the Experimental Analysis of Behavior 20:219-233.

Bostwick JM, Hecksel KA, Stevens SR, Bower JH, Ahlskog JE (2009) Frequency of new-onset pathologic compulsive gambling or hypersexuality after drug treatment of idiopathic Parkinson Disease. Mayo Clinic Proceedings 84:310-316.

Bradshaw CM, Killeen PR (2012) A theory of behaviour on progressive ratio schedules, with applications in behavioural pharmacology. Psychopharmacology (Berl) 222:549-564.

Brancato A, Plescia F, Marino RAM, Maniaci G, Navarra M, Cannizzaro C (2014) Involvement of dopamine D2 receptors in addictive-like behaviour for acetaldehyde. PloS one 9:e99454.

Brevers D, Cleeremans A, Goudriaan AE, Bechara A, Kornreich C, Verbanck P, Noel X (2012) Decision making under ambiguity but not under risk is related to problem gambling severity. Psychiatry Res 200:568-574.

Brewer JA, Potenza MN (2008) The neurobiology and genetics of impulse control disorders: relationships to drug addictions. Biochem Pharmacol 75:63-75.

Buckholtz JW, Treadway MT, Cowan RL, Woodward ND, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Shelby ES, Smith CE, Kessler RM, Zald DH (2010) Dopaminergic network differences in human impulsivity. Science 329:532.

Caine SB, Koob GF (1995) Pretreatment with the dopamine agonist 7-OH-DPAT shifts the cocaine self-administration dose-effect function to the left under different schedules in the rat. Behavioural Pharmacology 6:333-347.

Callesen MB, Weintraub D, Damholdt MF, Møller A (2013a) Impulsive and compulsive behaviors among Danish patients with Parkinson's disease: Prevalence, depression, and personality. Parkinsonism & related disorders 20:22-26.

Callesen MB, Hansen KV, Gjedde A, Linnet J, Møller A (2013b) Dopaminergic and clinical correlates of pathological gambling in Parkinson's Disease: A case report. Frontiers in Behavioral Neuroscience 7.

Campbell-Meiklejohn D, Wakeley J, Herbert V, Cook J, Scollo P, Ray MK, Selvaraj S, Passingham RE, Cowen P, Rogers RD (2011) Serotonin and dopamine play complementary roles in gambling to recover losses. Neuropsychopharmacology 36:402-410.

Cannas A, Solla P, Floris G, Tacconi P, Loi D, Marcia E, Marrosu MG (2006) Hypersexual behaviour, frotteurism and delusional jealousy in a young parkinsonian patient during dopaminergic therapy with pergolide: A rare case of iatrogenic paraphilia. Progress in neuro-psychopharmacology & biological psychiatry 30:1539-1541.

Carriere N, Lopes R, Defebvre L, Delmaire C, Dujardin K (2015) Impaired corticostriatal connectivity in impulse control disorders in Parkinson disease. Neurology 84:2116.

Castro-Martínez XH, García-Ruiz PJ, Martínez-García C, Martínez-Castrillo JC, Vela L, Mata M, Martínez-Torres I, Feliz-Feliz C, Palau F, Hoenicka J (2018) Behavioral addictions in early-onset Parkinson disease are associated with DRD3 variants. Parkinsonism Relat Disord 49:100-103.

Cavedini P, Riboldi G, Keller R, D'Annucci A, Bellodi L (2002) Frontal lobe dysfunction in pathological gambling patients. Biol Psychiatry 51:334-341.

Chambers RA, Taylor JR, Potenza MN (2003) Developmental neurocircuitry of motivation in adolescence: A critical period of addiction vulnerability. The American Journal of Psychiatry 160.

Chen F-X, Kang D-Z, Chen F-Y, Liu Y, Wu G, Li X, Yu L-H, Lin Y-X, Lin Z-Y (2016) Gray matter atrophy associated with mild cognitive impairment in Parkinson's disease. Neuroscience letters 617:160-165.

Chernoloz O, Mansari ME, Blier P (2009) Sustained administration of pramipexole modifies the spontaneous firing of dopamine, norepinephrine, and serotonin neurons in the rat brain. Neuropsychopharmacology 34:651-661.

Chikama M, McFarland NR, Amaral D, Haber SN (1997) Insular cortical projections to functional regions of the striatum correlate with cortical cytoarchitectonic organization in the primate. The Journal of Neuroscience 17:9686-9705.

Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP (1999) Limbic activation during cue-induced cocaine craving. American Journal of Psychiatry 156:11-18.

Chowdhury NS, Livesey EJ, Blaszczynski A, Harris JA (2017) Pathological gambling and motor impulsivity: a systematic review with meta-analysis. Journal of gambling studies / co-sponsored by the National Council on Problem Gambling and Institute for the Study of Gambling and Commercial Gaming 33:1213-1239.

Christensen DR, Williams RJ, Ofori-Dei SM (2019) The multidimensional structure of problem gambling: An evaluation of four gambling categorization instruments from an international online survey of gamblers. Journal of gambling studies / co-sponsored by the National Council on Problem Gambling and Institute for the Study of Gambling and Commercial Gaming 35:1079-1108.

Cilia R, Siri C, Marotta G, Isaias IU, de Gaspari D, Canesi M, Pezzoli G, Antonini A (2008) Functional abnormalities underlying pathological gambling in parkinson disease. Archives of Neurology 65:1604-1611.

Cilia R, Ko JH, Cho SS, van Eimeren T, Marotta G, Pellecchia G, Pezzoli G, Antonini A, Strafella AP (2010) Reduced dopamine transporter density in the ventral striatum of patients with Parkinson's disease and pathological gambling. Neurobiology of Disease 39:98-104.

Cilia R, Cho SS, van Eimeren T, Marotta G, Siri C, Ko JH, Pellecchia G, Pezzoli G, Antonini A, Strafella AP (2011) Pathological gambling in patients with Parkinson's disease is associated with fronto-striatal disconnection: A path modeling analysis. Movement Disorders 26:225-233.

Cilia R, Siri C, Canesi M, Zecchinelli AL, De Gaspari D, Natuzzi F, Tesei S, Meucci N, Mariani CB, Sacilotto G, Zini M, Ruffmann C, Pezzoli G (2014) Dopamine dysregulation syndrome in Parkinson's disease: from clinical and neuropsychological characterisation to management and long-term outcome. Journal of neurology, neurosurgery and psychiatry 85:311-318.

Claassen DO, van den Wildenberg WPM, Ridderinkhof KR, Jessup CK, Harrison MB, Wooten GF, Wylie SA (2011) The risky business of dopamine agonists in Parkinson Disease and Impulse Control Disorders. Behavioral neuroscience 125:492-500.

Clark L (2010) Decision-making during gambling: an integration of cognitive and psychobiological approaches. Philosophical transactions of the Royal Society of London Series B, Biological sciences 365:319-330.

Clark L, Limbrick-Oldfield EH (2013) Disordered gambling: a behavioral addiction. Curr Opin Neurobiol 23:655-659.

Clark L, Bechara A, Damasio H, Aitken MR, Sahakian BJ, Robbins TW (2008) Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. Brain 131:1311-1322.

Cliff JH, Jackson SMK, McEwan JS, Bizo LA (2019) Weber's Law and the Scalar Property of Timing: A Test of Canine Timing. Animals (Basel) 9.

Cloninger CR, Svrakic DM, Przybeck TR (1993) A psychobiological model of temperament and character. Archives of general psychiatry 50:975.

Coccaro EF (1989) Central serotonin and impulsive aggression. The British Journal of Psychiatry 155:52-62.

Cocker PJ, Winstanley CA (2015) Irrational beliefs, biases and gambling: Exploring the role of animal models in elucidating vulnerabilities for the development of pathological gambling. Behavioural brain research 279:259-273.

Cocker PJ, Tremblay M, Kaur S, Winstanley CA (2017) Chronic administration of the dopamine D2/3 agonist ropinirole invigorates performance of a rodent slot machine task, potentially indicative of less distractible or compulsive-like gambling behaviour. Psychopharmacology 234:137-153.

Cocker PJ, Dinelle K, Kornelson R, Sossi V, Winstanley CA (2012) Irrational choice under uncertainty correlates with lower striatal D(2/3) receptor binding in rats. The Journal of Neuroscience 32:15450-15457.

Cohen MX, Frank MJ (2009) Neurocomputational models of basal ganglia function in learning, memory and choice. Behav Brain Res 199:141-156.

Coldwell MC, Boyfield I, Brown T, Hagan JJ, Middlemiss DN (1999) Comparison of the functional potencies of ropinirole and other dopamine receptor agonists at human D2(long), D3 and D4.4 receptors expressed in Chinese hamster ovary cells. British journal of pharmacology 127:1696-1702.

Collins GT, Hauck Newman A, Grundt P, Rice KC, Husbands SM, Chauvignac C, Chen J, Wang S, Woods JH (2007) Yawning and hypothermia in rats : Effects of dopamine D3 and D2 agonists and antagonists. Psychopharmacologia 193:159-170.

Comings DE, Rosenthal RJ, Lesieur HR, Rugle LJ, Muhleman D, Chiu C, Dietz G, Gade R (1996) A study of the dopamine D2 receptor gene in pathological gambling. Pharmacogenetics 6:223-234.

Comings DE, Gade R, Wu S, Chiu C, Dietz G, Muhleman D, Saucier G, Ferry L, Rosenthal RJ, Lesieur HR, Rugle LJ, MacMurray P (1997) Studies of the potential role of the dopamine D1 receptor gene in addictive behaviors. Molecular Psychiatry 2:44-56.

Comings DE, Gonzalez N, Wu S, Gade R, Muhleman D, Saucier G, Johnson P, Verde R, Rosenthal RJ, Lesieur HR, Rugle LJ, Miller WB, MacMurray JP (1999) Studies of the 48 bp repeat polymorphism of the DRD4 gene in impulsive, compulsive, addictive behaviors: Tourette syndrome, ADHD, pathological gambling, and substance abuse. American journal of medical genetics 88:358-368.

Comings DE, Gade-Andavolu R, Gonzalez N, Wu S, Muhleman D, Chen C, Koh P, Farwell K, Blake H, Dietz G, MacMurray JP, Lesieur HR, Rugle LJ, Rosenthal RJ (2001) The additive effect of neurotransmitter genes in pathological gambling. Clinical genetics 60:107-116.

Constantinescu R (2008) Update on the use of pramipexole in the treatment of Parkinson's disease. Neuropsychiatric Disease and Treatment 4:337-352.

Contreras PC, Quirion R, Gehlert DR, Contreras ML, O'Donohue TL (1987) Autoradiographic distribution of non-dopaminergic binding sites labeled by [3H]haloperidol in rat brain. Neuroscience letters 75:133.

Cools R, Altamirano L, D'Esposito M (2006) Reversal learning in Parkinson's disease depends on medication status and outcome valence. Neuropsychologia 44:1663-1673.

Cools R, Barker RA, Sahakian BJ, Robbins TW (2001) Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. Cerebral cortex (New York, NY 1991) 11:1136-1143.

Corvol J-C, Artaud F, Cormier-Dequaire F, Rascol O, Durif F, Derkinderen P, Marques A-R, Bourdain F, Brandel J-P, Pico F (2018) Longitudinal analysis of impulse control disorders in Parkinson disease. Neurology 91:e189-e201.

Costall B, Naylor RJ (1975) The behavioural effects of dopamine applied intracerebrally to areas of the mesolimbic system. European journal of pharmacology 32:87-92.

Craig AD (2009) How do you feel--now? The anterior insula and human awareness. Nat Rev Neurosci 10:59-70.

Crockford D, Quickfall J, Currie S, Furtado S, Suchowersky O, el-Guebaly N (2008) Prevalence of Problem and Pathological Gambling in Parkinson's Disease. Journal of gambling studies / co-sponsored by the National Council on Problem Gambling and Institute for the Study of Gambling and Commercial Gaming 24:411-422.

Crossman EK, Bonem EJ, Phelps BJ (1987) A comparison of response patterns on fixed-, variable-, and random-ratio schedules. Journal of the Experimental Analysis of Behavior 48:395-406.

da Silva Lobo DS, Kennedy JL (2006) The genetics of gambling and behavioral addictions. CNS Spectrums 11:931-939.

da Silva Lobo DS, Kennedy JL (2009) Genetic aspects of pathological gambling: a complex disorder with shared genetic vulnerabilities. Addiction 104:1454-1465.

da Silva Lobo DS, Casey DM, el-Guebaly N, Kennedy JL (2011) Genetic pathways in addictions: Associations with pathological gambling. In: Society of Biological Psychiatry Annual Meeting.

da Silva Lobo DS, Vallada HP, Knight J, Martins SS, Tavares H, Gentil V, Kennedy JL (2007) Dopamine genes and pathological gambling in discordant sib-pairs. Journal of gambling studies / co-sponsored by the National Council on Problem Gambling and Institute for the Study of Gambling and Commercial Gaming 23:421-433.

da Silva Lobo DS, Aleksandrova L, Knight J, Casey DM, el-Guebaly N, Nobrega JN, Kennedy JL (2015) Addiction-related genes in gambling disorders: New insights from parallel human and pre-clinical models. Molecular Psychiatry 20:1002-1010.

da Silva Lobo DS, Souza RP, Tong RP, Casey DM, Hodgins DC, Smith GJ, Williams RJ, Schopflocher DP, Wood RT, el-Guebaly N, Kennedy JL (2010) Association of functional variants in the dopamine D2-like receptors with risk for gambling behaviour in healthy Caucasian subjects. Biological Psychiatry 85:33-37.

Dadar M, Zeighami Y, Yau Y, Fereshtehnejad SM, Maranzano J, Postuma RB, Dagher A, Collins DL (2018) White matter hyperintensities are linked to future cognitive decline in de novo Parkinson's disease patients. NeuroImage Clinical 20:892-900.

Dagher A, Robbins TW (2009) Personality, addiction, dopamine: Insights from Parkinson's disease. Neuron 61:502-510.

Dalley JW, Roiser JP (2012) Dopamine, serotonin and impulsivity. Neuroscience 215:42-58.

Dalley JW, Robbins TW (2017) Fractionating impulsivity: neuropsychiatric implications. Nature reviews Neuroscience 18:158-171.

Dalley JW, Fryer TD, Brichard L, Robinson ES, Theobald DE, Laane K, Pena Y, Murphy ER, Shah Y, Probst K, Abakumova I, Aigbirhio FI, Richards HK, Hong Y, Baron JC, Everitt BJ, Robbins TW (2007) Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. Science 315:1267-1270.

Dang D, Cunnington D, Swieca J (2011) The emergence of devastating impulse control disorders during dopamine agonist therapy of the restless legs syndrome. Clinical neuropharmacology 34:66.

Dardou D, Chassain C, Durif F (2014) Chronic pramipexole treatment increases tolerance for sucrose in normal and ventral tegmental lesioned rats. Frontiers in neuroscience 8:437-437.

Davie M (2007) Pathological gambling associated with cabergoline therapy in a patient with a pituitary prolactinoma. The Journal of Neuropsychiatry and Clinical Neurosciences 19:473-474.

de Jong JW, Roelofs TJM, Mol FMU, Hillen AEJ, Meijboom KE, Luijendijk MCM, van der Eerden HAM, Garner KM, Vanderschuren LJMJ, Adan RAH (2015) Reducing ventral tegmental dopamine D2 receptor expression selectively boosts incentive motivation. Neuropsychopharmacology 40:2085-2095.

de Schipper LJ, Hafkemeijer A, Bouts M, van der Grond J, Marinus J, Henselmans JML, van Hilten JJ (2019) Age- and disease-related cerebral white matter changes in patients with Parkinson's disease. Neurobiol Aging 80:203-209.

Delfabbro PH, Winefield AH (1999) Poker-machine gambling: An analysis of within session characteristics. British Journal of Psychology 90:425-439.

Depoortere R, Perrault G, Sanger DJ (1996) Behavioural effects in the rat of the putative dopamine D3 receptor agonist 7-OH-DPAT: Comparison with quinpirole and apomorphine. Psychopharmacology (Berl) 124:231-240.

Depoortere R, Perrault G, Sanger DJ (1999) Intracranial self-stimulation under a progressive-ratio schedule in rats: effects of strength of stimulation, d-amphetamine, 7-OH-DPAT and haloperidol. Psychopharmacology 142:221-229.

Deroche-Gamonet V, Piazza PV (2014) Psychobiology of cocaine addiction: Contribution of a multi-symptomatic animal model of loss of control. Neuropharmacology 76 Pt B:437-449.

Deroche-Gamonet V, Belin D, Piazza PV (2004) Evidence for addiction-like behavior in the rat. Science 305:1014-1017.

Deutschländer A, la Fougère C, Boetzel K, Albert NL, Gildehaus F-J, Bartenstein P, Xiong G, Cumming P (2016) Occupancy of pramipexole (Sifrol) at cerebral dopamine D2/3 receptors in Parkinson's disease patients. NeuroImage clinical 12:41-46.

Di Chiara G (1997) Alcohol and dopamine. Alcohol Health Res World 21:108-114.

Di Chiara G, Bassareo V (2007) Reward system and addiction: what dopamine does and doesn’t do. Current opinion in pharmacology 7:69-76.

Di Ciano P, Pushparaj A, Kim A, Hatch J, Masood T, Ramzi A, Khaled MATM, Boileau I, Winstanley CA, Le Foll B (2015) The impact of selective dopamine D2, D3 and D4 ligands on the Rat Gambling Task. PLoS ONE 10:e0136267.

Dias C, Lachize S, Boilet V, Huitelec E, Cador M (2004) Differential effects of dopaminergic agents on locomotor sensitisation and on the reinstatement of cocaine-seeking and food-seeking behaviour. Psychopharmacology (Berl) 175:414-427.

Diaz-Asper CM, Goldberg TE, Kolachana BS, Straub RE, Egan MF, Weinberger DR (2008) Genetic variation in catechol-O-methyltransferase: effects on working memory in schizophrenic patients, their siblings, and healthy controls. Biological psychiatry (1969) 63:72-79.

Diergaarde L, Pattij T, Nawijn L, Schoffelmeer AN, De Vries TJ (2009) Trait impulsivity predicts escalation of sucrose seeking and hypersensitivity to sucrose-associated stimuli. Behavioral neuroscience 123:794-803.

Diergaarde L, Pattij T, Poortvliet I, Hogenboom F, de Vries W, Schoffelmeer AN, De Vries TJ (2008) Impulsive choice and impulsive action predict vulnerability to distinct stages of nicotine seeking in rats. Biol Psychiatry 63:301-308.

Dixon MJ, MacLaren V, Jarick M, Fugelsang JA, Harrigan KA (2013) The frustrating effects of just missing the jackpot: Slot machine near-misses trigger large skin conductance responses, but no post-reinforcement pauses. Journal of gambling studies / co-sponsored by the National Council on Problem Gambling and Institute for the Study of Gambling and Commercial Gaming 29:661-674.

Dixon MJ, Graydon C, Harrigan KA, Wojtowicz L, Siu V, Fugelsang JA (2014a) The allure of multi-line games in modern slot machines. Addiction 109:1920-1928.

Dixon MJ, Harrigan KA, Santesso DL, Graydon C, Fugelsang JA, Collins K (2014b) The impact of sound in modern multiline video slot machine play. Journal of gambling studies / co-sponsored by the National Council on Problem Gambling and Institute for the Study of Gambling and Commercial Gaming 30:913-929.

Dixon MR, Marley J, Jacobs EA (2003) Delay discounting by pathological gamblers. Journal of Applied Behavior Analysis 36:449-458.

Dodd ML, Klos KJ, Bower JH, Geda YE, Josephs KA, Ahlskog JE (2005) Pathological gambling caused by drugs used to treat Parkinson disease. Archives of Neurology 62:1377-1381.

Dogansen SC, Cikrikcili U, Oruk G, Kutbay NO, Tanrikulu S, Hekimsoy Z, Hadzalic A, Gorar S, Omma T, Mert M, Akbaba G, Yalin GY, Bayram F, Ozkan M, Yarman S (2019) Dopamine agonist-induced impulse control disorders in patients with prolactinoma: A cross-sectional multicenter study. The journal of clinical endocrinology and metabolism 104:2527-2534.

Domingo-Rodriguez L, Ruiz de Azua I, Dominguez E, Senabre E, Serra I, Kummer S, Navandar M, Baddenhausen S, Hofmann C, Andero R, Gerber S, Navarrete M, Dierssen M, Lutz B, Martín-García E, Maldonado R (2020) A specific prelimbic-nucleus accumbens pathway

controls resilience versus vulnerability to food addiction. Nature communications 11:782-782.

Dooley M, Markham A (1998) Pramipexole. A review of its use in the management of early and advanced Parkinson's Disease. Drugs & Aging 12:495-514.

Drapier D, Drapier S, Sauleau P, Derkinderen P, Damier P, Allain H, Vérin M, Millet B (2006) Pathological gambling secondary to dopaminergic therapy in Parkinson's disease. Psychiatry Research 144:241-244.

Drijgers RL, Verhey FRJ, Tissingh G, van Domburg PHMF, Aalten P, Leentjens AFG (2012) The role of the dopaminergic system in mood, motivation and cognition in Parkinson's disease: A double blind randomized placebo-controlled experimental challenge with pramipexole and methylphenidate. Journal of the neurological sciences 320:121-126.

Driver-Dunckley E, Samanta J, Stacy M (2003) Pathological gambling associated with dopamine agonist therapy in Parkinson's disease. Neurology 61:422.

Driver-Dunckley E, Noble BN, Hentz JG, Evidente VGH, Caviness JN, Parish J, Krahn L, Adler CH (2007) Gambling and increased sexual desire with dopaminergic medications in restless legs syndrome. Clinical neuropharmacology 30:249.

Droutman V, Read SJ, Bechara A (2015) Revisiting the role of the insula in addiction. Trends Cogn Sci 19:414-420.

Dumontheil I, Roggeman C, Ziermans T, Peyrard-Janvid M, Matsson H, Kere J, Klingberg T (2011) Influence of the COMT genotype on working memory and brain activity changes during development. Biological psychiatry (1969) 70:222-229.

Dunlop BW, Nemeroff CB (2007) The role of dopamine in the pathophysiology of depression. Archives of General Psychiatry 64:327-337.

Edwards S, Koob GF (2013) Escalation of drug self-administration as a hallmark of persistent addiction liability. Behavioural Pharmacology 24:356-362.

Eisen SA, Lin N, Lyons MJ, Scherrer JF, Griffith K, True WR, Goldberg J, Tsuang MT (1998) Familial influences on gambling behavior: an analysis of 3359 twin pairs. Addiction 93:1375-1384.

Eisen SA, Slutske WS, Lyons MJ, Lassman J, Xian H, Toomey R, Chantarujikapong S, Tsuang MT (2001) The genetics of pathological gambling. Seminars in Clinical Neuropsychiatry 6:195-204.

Eisenreich W, Sommer B, Hartter S, Jost WH (2010) Pramipexole extended release: A novel treatment option in Parkinson's disease. Parkinson's Disease 2010:1-7.

Elmer GI, Pieper JO, Rubinstein M, Low MJ, Grandy DK, Wise RA (2002) Failure of intravenous morphine to serve as an effective instrumental reinforcer in dopamine D2 receptor knock-out mice. The Journal of Neuroscience 22:1-6.

Ersche KD, Turton AJ, Pradhan S, Bullmore ET, Robbins TW (2010) Drug addiction endophenotypes: Impulsive versus sensation-seeking personality traits. Biological Psychiatry 68:770-773.

Erskine HE, Whiteford HA (2018) Epidemiology of binge eating disorder. Current opinion in psychiatry 31:462.

Etminan M, Gill S, Samii A (2003) Comparison of the risk of adverse events with pramipexole and ropinirole in patients with Parkinson's disease: a meta-analysis. Drug safety 26:439.

Euston DR, Gruber AJ, McNaughton BL (2012) The role of medial prefrontal cortex in memory and decision making. Neuron 76:1057-1070.

Evans AH, Butzkueven H (2007) Dopamine agonist-induced pathological gambling in restless legs syndrome due to multiple sclerosis. Movement disorders 22:590-591.

Evans AH, Katzenschlager R, Paviour D, O'Sullivan JD, Appel S, Lawrence AD, Lees AJ (2004) Punding in Parkinson's disease: Its relation to the dopamine dysregulation syndrome. Movement disorders 19:397-405.

Evans AH, Pavese N, Lawrence AD, Tai YF, Appel S, Doder M, Brooks DJ, Lees AJ, Piccini P (2006) Compulsive drug use linked to sensitized ventral striatal dopamine transmission. Annals of neurology 59:852-858.

Everitt BJ (2014) Neural and psychological mechanisms underlying compulsive drug seeking habits and drug memories - indications for novel treatments of addiction. European Journal of Neuroscience 40:2163-2182.

Everitt BJ, Robbins TW (2005) Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nature Neuroscience 8:1481-1489.

Everitt BJ, Robbins TW (2016) Drug addiction: Updating actions to habits to compulsions ten years on. Annual Review of Psychology 67:23-50.

Everitt BJ, Belin D, Economidou D, Pelloux Y, Dalley JW, Robbins TW (2008) Review. Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. Philosophical transactions of the Royal Society of London Series B, Biological sciences 363:3125-3135.

Falhammar H, Yarker JY (2009) Pathological gambling and hypersexuality in cabergoline-treated prolactinoma. Medical journal of Australia 190:97-97.

Fantino E (1967) Preference for mixed- versus fixed-ratio schedules. Journal of the Experimental Analysis of Behavior 10:35-43.

Farmer J, Schoenfeld WN (1967) Response rates under varying probability of reinforcement. Psychonomic Science 7:173-174.

Farre M, Cami J (1991) Pharmacokinetic considerations in abuse liability evaluation. Addiction (Abingdon, England) 86:1601-1606.

Farrell SM, Tunbridge EM, Braeutigam S, Harrison PJ (2012) COMT Val158Met genotype determines the direction of cognitive effects produced by catechol-O-methyltransferase inhibition. Biological Psychiatry 71:538-544.

Fasano A, Petrovic I (2010) Insights into pathophysiology of punding reveal possible treatment strategies. Molecular psychiatry 15:560-573.

Felton M, Lyon DO (1966) The post-reinforcement pause. Journal of the Experimental Analysis of Behavior 9:131-134.

Fernández FM, González TM (2009) Pathological gambling and hypersexuality due to dopaminergic treatment in Parkinson's disease. Actas Españolas de Psiquiatría 37:118-122.

Fernandez HH, Durso R (1998) Clozapine for dopaminergic-induced paraphilias in Parkinson's disease. Movement disorders 13:597.

Fernandez HH, Chen JJ (2007) Monoamine Oxidase-B inhibition in the treatment of Parkinson's Disease. Pharmacotherapy 27:174S-185S.

Ferster CB, Skinner BF (1957) Schedules of reinforcement. Engelwood Cliffs, NJ: Prentice-Hall.

Fiorillo CD, Tobler PN, Schultz W (2003) Discrete coding of reward probability and uncertainty by dopamine neurons. Science 299:1898-1902.

Flagel SB, Clark JJ, Robinson TE, Mayo L, Czuj A, Willuhn I, Akers CA, Clinton SM, Phillips PE, Akil H (2011) A selective role for dopamine in stimulus-reward learning. Nature 469:53-57.

Floresco SB (2013) Prefrontal dopamine and behavioral flexibility: shifting from an "inverted-U" toward a family of functions. Front Neurosci 7:62.

Floris G, Scheggi S, Pes R, Bortolato M (2022) The steroidogenic inhibitor finasteride reverses pramipexole-induced alterations in probability discounting. Brain research bulletin 181:157-166.

Forbush KT, Shaw M, Graeber MA, Hovick L, Meyer VJ, Moser DJ, Bayless J, Watson D, Black DW (2008) Neuropsychological characteristics and personality traits in pathological gambling. CNS spectrums 13:306-315.

Fowler JS, Volkow ND, Kassed CA, Chang L (2007) Imaging the addicted human brain. Science and Practice Perspectives 3:4-16.

Frank MJ, Seeberger LC, O'Reilly R C (2004) By carrot or by stick: Cognitive reinforcement learning in parkinsonism. Science 306:1940-1943.

Frank MJ, Samanta J, Moustafa AA, Sherman SJ (2007) Hold your horses: Impulsivity, deep brain stimulation, and medication in Parkinsonism. Science.

Fujimoto A, Hori Y, Nagai Y, Kikuchi E, Oyama K, Suhara T, Minamimoto T (2019) Signaling incentive and drive in the primate ventral pallidum for motivational control of goal-directed action. The Journal of neuroscience 39:1793-1804.

Fukui H, Murai T, Fukuyama H, Hayashi T, Hanakawa T (2005) Functional activity related to risk anticipation during performance of the Iowa Gambling Task. Neuroimage 24:253-259.

Galaj E, Han X, Shen H, Jordan CJ, He Y, Humburg B, Bi G-H, Xi Z-X (2020) Dissecting the role of GABA neurons in the VTA versus SNr in opioid reward. The Journal of Neuroscience 40:8853-8869.

Gallagher DA, O'Sullivan SS, Evans AH, Lees AJ, Schrag A (2007) Pathological gambling in Parkinson's disease: Risk factors and differences from dopamine dysregulation. An analysis of published case series. Movement disorders 22:1757-1763.

Gallant H, Vo A, Seergobin KN, MacDonald PA (2016) Pramipexole impairs stimulus-response learning in healthy young adults. Frontiers in Neuroscience 10:374.

Garcia-Ruiz PJ, Martinez Castrillo JC, Alonso-Canovas A, Herranz Barcenas A, Vela L, Sanchez Alonso P, Mata M, Olmedilla Gonzalez N, Mahillo Fernandez I (2014) Impulse control disorder in patients with Parkinson's disease under dopamine agonist therapy: a multicentre study. Journal of neurology, neurosurgery and psychiatry 85:840-844.

Gerfen CR, Surmeier DJ (2011) Modulation of striatal projection systems by dopamine. Annual Review of Neuroscience 34:441-466.

Gerfen CR, Engber TM, Mahan LC, Susel Z, Chase TN, Monsma FJ, Sibley DR (1990) D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. Science (American Association for the Advancement of Science) 250:1429-1432.

Gibbon J (1977) Scalar expectancy theory and Weber's law in animal timing. Psychological review 84:279.

Giladi N, Weitzman N, Schreiber S, Shabtai H, Peretz C (2007) New onset heightened interest or drive for gambling, shopping, eating or sexual activity in patients with Parkinson's disease: The role of dopamine agonist treatment and age at motor symptoms onset. Journal of Psychopharmacology 21:501-506.

Giovannoni G, O'Sullivan JD, Turner K, Manson AJ, Lees AJ (2000) Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. J Neurol Neurosurg Psychiatry 68:423-428.

Gogolla N (2017) The insular cortex. Current Biology 27:R580-R586.

Goldstein DS, Sullivan P, Holmes C, Kopin IJ, Basile MJ, Mash DC (2011) Catechols in post-mortem brain of patients with Parkinson disease. European journal of neurology 18:703-710.

Goldstein RZ, Volkow ND (2011) Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat Rev Neurosci 12:652-669.

Goodwin FK (1971) Psychiatric side effects of levodopa in man. JAMA : the journal of the American Medical Association 218:1915.

Goole J, Amighi K (2009) Levodopa delivery systems for the treatment of Parkinson's disease: An overview. International journal of pharmaceutics 380:1-15.

Goto Y, Grace AA (2005a) Dopaminergic modulation of limbic and cortical drive of nucleus accumbens in goal-directed behavior. Nat Neurosci 8:805-812.

Goto Y, Grace AA (2005b) Dopamine-dependent interactions between limbic and prefrontal cortical plasticity in the nucleus accumbens: disruption by cocaine sensitization. Neuron 47:255-266.

Goudriaan AE, Oosterlaan J, de Beurs E, van den Brink W (2005) Decision making in pathological gambling: A comparison between pathological gamblers, alcohol dependents, persons with Tourette syndrome, and normal controls. Brain Research Cognitive Brain Research 23:137-151.

Grace AA, Bunney BS (1984a) The control of firing pattern in nigral dopamine neurons: burst firing. The Journal of neuroscience 4:2877-2890.

Grace AA, Bunney BS (1984b) The control of firing pattern in nigral dopamine neurons: single spike firing. The Journal of neuroscience 4:2866-2876.

Grace AA, Floresco SB, Goto Y, Lodge DJ (2007) Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. Trends Neurosci 30:220-227.

Graff-Guerrero A, Willeit M, Ginovart N, Mamo D, Mizrahi R, Rusjan P, Vitcu I, Seeman P, Wilson AA, Kapur S (2008) Brain region binding of the D2/3 agonist [11C]-(+)-PHNO and the D2/3 antagonist [11C]raclopride in healthy humans. Human brain mapping 29:400-410.

Graff-Guerrero A, Redden L, Abi-Saab W, Katz DA, Houle S, Barsoum P, Bhathena A, Palaparthy R, Saltarelli MD, Kapur S (2010) Blockade of [11C](+)-PHNO binding in

human subjects by the dopamine D3 receptor antagonist ABT-925. The international journal of neuropsychopharmacology 13:273-287.

Grall-Bronnec M, Victorri-Vigneau C, Donnio Y, Leboucher J, Rousselet M, Thiabaud E, Zreika N, Derkinderen P, Challet-Bouju G (2018) Dopamine agonists and impulse control disorders: A complex association. Drug safety 41:19-75.

Grant JE, Leppink EW, Redden SA, Odlaug BL, Chamberlain SR (2015) COMT genotype, gambling activity, and cognition. Journal of psychiatric research 68:371-376.

Groenewegen HJ (2003) The basal ganglia and motor control. Neural Plast 10:107-120.

Grosset KA, Macphee G, Pal G, Stewart D, Watt A, Davie J, Grosset DG (2006) Problematic gambling on dopamine agonists: Not such a rarity. Movement Disorders 21:2206-2208.

Gruber AJ, McDonald RJ (2012) Context, emotion, and the strategic pursuit of goals: interactions among multiple brain systems controlling motivated behavior. Front Behav Neurosci 6.

Gschwandtner U, Aston J, Renaud S, Fuhr P (2001) Pathologic gambling in patients with Parkinson's disease. Clinical Neuropharmacology 24:170.

Guillin O, Diaz J, Carroll P, Griffon N, Schwartz J-C, Sokoloff P (2001) BDNF controls dopamine D3 receptor expression and triggers behavioural sensitization. Nature (London) 411:86-89.

Gurevich EV, Joyce JN (1999) Distribution of dopamine D3 receptor expressing neurons in the human forebrain: Comparison with D2 receptor expressing neurons. Neuropsychopharmacology 20:60-80.

Haber SN, Knutson B (2010) The reward circuit: Linking primate anatomy and human imaging. Neuropsychopharmacology 35:4-26.

Haber SN, Fudge JL, McFarland NR (2000) Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. The Journal of Neuroscience 20:2369-2382.

Haber SN, Groenewegen HJ, Grove EA, Nauta WJ (1985) Efferent connections of the ventral pallidum: Evidence of a dual striato pallidofugal pathway. The Journal of Comparative Neurology 235:322-335.

Hametner E-M, Seppi K, Poewe W (2012) Role and clinical utility of pramipexole extended release in the treatment of early Parkinson's disease. Clinical Interventions in Aging:83.

Hamidovic A, Kang UJ, de Wit H (2008) Effects of low to moderate acute doses of pramipexole on impulsivity and cognition in healthy volunteers. J Clin Psychopharmacol 28:45-51.

Harden DG, Grace AA (1995) Activation of dopamine cell firing by repeated L-DOPA administration to dopamine-depleted rats: its potential role in mediating the therapeutic response to L-DOPA treatment. The Journal of neuroscience 15:6157-6166.

Harrigan K, Collins K, Dixon MJ, Fugelsang J (2010) Addictive gameplay: what casual game designers can learn from slot machine research. In, pp 127-133: ACM.

Hassan A, Bower JH, Kumar N, Matsumoto JY, Fealey RD, Josephs KA, Ahlskog JE (2011) Dopamine agonist-triggered pathological behaviors: Surveillance in the PD clinic reveals high frequencies. Parkinsonism & related disorders 17:260-264.

Hauser RA, Gauger L, Anderson WM, Zesiewicz TA (2000) Pramipexole-induced somnolence and episodes of daytime sleep. Movement disorders 15:658-663.

Heath CJ, Bussey TJ, Saksida LM (2015) Motivational assessment of mice using the touchscreen operant testing system: effects of dopaminergic drugs. Psychopharmacology 232:4043-4057.

Hellman M, Schoenmakers TM, Nordstrom BR, Van Holst RJ (2013) Is there such a thing as online video game addiction? A cross-disciplinary review. Addiction Research & Theory 21:102-112.

Henry DJ, Hu XT, White FJ (1998) Adaptations in the mesoaccumbens dopamine system resulting from repeated administration of dopamine D1 and D2 receptor-selective agonists : relevance to cocaine sensitization. Psychopharmacologia 140:233-242.

Herrero MT, Augood SJ, Hirsch EC, Javoy-Agid F, Luquin MR, Agid Y, Obeso JA, Emson PC (1995) Effects of l-DOPA on preproenkephalin and preprotachykinin gene expression in the MPTP-treated monkey striatum. Neuroscience 68:1189-1198.

Hoebel BG, Avena NM, Bocarsly ME, Rada P (2009) Natural addiction: A behavioral and circuit model based on sugar addiction in rats. Journal of addiction medicine 3:33-41.

Holden C (2001) 'Behavioral' addictions: Do they exist? Science 294:980-982.

Hollerman JR, Grace AA (1990) The effects of dopamine-depleting brain lesions on the electrophysiological activity of rat substantia nigra dopamine neurons. Brain research 533:203.

Holloway RG et al. (2004) Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. Archives of neurology (Chicago) 61:1044.

Holman AJ (2009) Impulse Control Disorder behaviors associated with pramipexole used to treat fibromyalgia. Journal of gambling studies / co-sponsored by the National Council on Problem Gambling and Institute for the Study of Gambling and Commercial Gaming 25:425-431.

Holtz NA, Tedford SE, Persons AL, Grasso SA, Napier TC (2016) Pharmacologically distinct pramipexole-mediated akinesia vs. risk-taking in a rat model of Parkinson's disease. Progress in neuro-psychopharmacology & biological psychiatry 70:77-84.

Hou Y, Xiong D, Jiang T, Song L, Wang Q (2019) Social media addiction: Its impact, mediation, and intervention. Cyberpsychology: Journal of psychosocial research on cyberspace 13.

Housden CR, O'Sullivan SS, Joyce EM, Lees AJ, Roiser JP (2010) Intact reward learning but elevated delay discounting in Parkinson's disease patients with impulsive-compulsive spectrum behaviors. Neuropsychopharmacology 35:2155-2164.

Hyman SE, Malenka RC (2001) Addiction and the brain: The neurobiology of compulsion and its persistence. Nature Reviews Neuroscience 2:695-703.

Ibanez A, Perez De Castro I, Fernandez-Piqueras J, Blanco C, Saiz-Ruiz J (2000) Pathological gambling and DNA polymorphic markers at MAO-A and MAO-B genes. Molecular psychiatry 5:105-109.

Imamura A, Uitti RJ, Wszolek ZK (2006) Dopamine agonist therapy for Parkinson disease and pathological gambling. Parkinsonism & Related Disorders 12:506-508.

Isaias IU, Siri C, Cilia R, De Gaspari D, Pezzoli G, Antonini A (2008) The relationship between impulsivity and impulse control disorders in Parkinson's disease. Movement disorders 23:411-415.

Izzo E, Orsini C, Koob GF, Pulvirenti L (2001) A dopamine partial agonist and antagonist block amphetamine self-administration in a progressive ratio schedule. Pharmacology, Biochemistry and Behavior 68:701-708.

Jeanblanc J, He D-Y, McGough NNH, Logrip ML, Phamluong K, Janak PH, Ron D (2006) The dopamine D3 receptor is part of a homeostatic pathway regulating ethanol consumption. The Journal of neuroscience 26:1457-1464.

Jeanneteau F, Funalot B, Jankovic J, Deng H, Lagarde JP, Lucotte G, Sokoloff P (2006) A functional variant of the dopamine D3 receptor is associated with risk and age-at-onset of essential tremor. Proc Natl Acad Sci U S A 103:10753-10758.

Jentsch JD, Taylor JR (1999) Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. Psychopharmacologia 146:373-390.

Jiménez-Jiménez FJ, Sayed Y, García-Soldevilla MA, Barcenilla B (2002) Possible zoophilia associated with dopaminergic therapy in Parkinson Disease. Annals of Pharmacotherapy 36:1178-1179.

Jiménez-Urbieta H, Gago B, Quiroga-Varela A, Rodríguez-Chinchilla T, Merino-Galán L, Oregi A, Belloso-Iguerategui A, Delgado-Alvarado M, Navalpotro-Gómez I, Marin C, Fernagut P-O, Rodríguez-Oroz MC (2019) Pramipexole-induced impulsivity in mildparkinsonian

rats: a model of impulse control disorders in Parkinson's disease. Neurobiology of aging 75:126-135.

Johnson PS, Madden GJ, Stein JS (2012) Effects of acute pramipexole on male rats' preference for gambling-like rewards II. Experimental and Clinical Psychopharmacology 20:167-172.

Johnson PS, Madden GJ, Brewer AT, Pinkston JW, Fowler SC (2011) Effects of acute pramipexole on preference for gambling-like schedules of reinforcement in rats. Psychopharmacology 213:11-18.

Johnson SW, North RA (1992) Two types of neurone in the rat ventral tegmental area and their synaptic inputs. J Physiol 450:455-468.

Jolkkonen J, Jenner P, Marsden CD (1995) l-DOPA reverses altered gene expression of substance P but not enkephalin in the caudate-putamen of common marmosets treated with MPTP. Brain research Molecular brain research 32:297-307.

Joutsa J, Voon V, Johansson J, Niemelä S, Bergman J, Kaasinen V (2015) Dopaminergic function and intertemporal choice. Translational psychiatry 5:e491-e491.

Kalechstein AD, Fong T, Rosenthal RJ, Davis A, Vanyo H, Newton TF (2007) Pathological gamblers demonstrate frontal lobe impairment consistent with that of methamphetamine-dependent individuals. The Journal of Neuropsychiatry and Clinical Neurosciences 19:298-303.

Kalivas PW (2008) Addiction as a pathology in prefrontal cortical regulation of corticostriatal habit circuitry. Neurotox Res 14:185-189.

Kalivas PW, Volkow ND (2005) The neural basis of addiction: A pathology of motivation and choice. Am J Psychiatry 162:1403-1413.

Katzenschlager R (2011) Dopaminergic dysregulation syndrome in Parkinson's disease. Journal of the neurological sciences 310:271-275.

Kawa AB, Bentzley BS, Robinson TE (2016) Less is more: Prolonged intermittent access cocaine self-administration produces incentive-sensitization and addiction-like behavior. Psychopharmacology (Berl) 233:3587-3602.

Kelley AE (2004) Ventral striatal control of appetitive motivation: role in ingestive behavior and reward-related learning. Neurosci Biobehav Rev 27:765-776.

Kelley AE, Baldo BA, Pratt WE, Will MJ (2005) Corticostriatal-hypothalamic circuitry and food motivation: integration of energy, action and reward. Physiol Behav 86:773-795.

Khan ZU, Mrzljak L, Gutierrez A, de la Calle A, Goldman-Rakic PS (1998) Prominence of the dopamine D2 short isoform in dopaminergic pathways. Proceedings of the National Academy of Sciences - PNAS 95:7731-7736.

Killcross S, Coutureau E (2003) Coordination of actions and habits in the medial prefrontal cortex of rats. Cerebral Cortex 13:400-408.

Killeen PR, Fetterman JG (1988) A behavioral theory of timing. Psychological review 95:274.

Killeen PR, Fetterman JG (1993) The behavioral theory of timing: Transition analyses. Journal of the Experimental Analysis of Behavior 59:411-422.

Killeen PR, Posadas-Sanchez D, Johansen EB, Thrailkill EA (2009) Progressive ratio schedules of reinforcement. Journal of Experimental Psychology Animal Behavior Processes 35:35-50.

Kim SW, Grant JE (2001) Personality dimensions in pathological gambling disorder and obsessive–compulsive disorder. Psychiatry research 104:205-212.

Kish SJ, Shannak K, Hornykiewicz O (1988) Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. The New England journal of medicine 318:876-880.

Kling-Petersen T, Ljung E, Svensson K (1995) Effects on locomotor activity after local application of D3 preferring compounds in discrete areas of the rat brain. Journal of neural transmission General section 102:209.

Klos KJ, Bower JH, Josephs KA, Matsumoto JY, Ahlskog JE (2005) Pathological hypersexuality predominantly linked to adjuvant dopamine agonist therapy in Parkinson's disease and multiple system atrophy. Parkinsonism & Related Disorders 11:381-386.

Kobayashi S, Asano K, Matsuda N, Yoshikazu U (2019) Dopaminergic influences on risk preferences of Parkinson’s disease patients. Cognitive, Affective, & Behavioral Neuroscience 19.

Koob GF, Le Moal M (2001) Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 24:97-129.

Koob GF, Volkow N (2016) Neurobiology of addiction: A neurocircuitry analysis. Lancet Psychiatry 3:760-773.

Koran LM, Faber RJ, Aboujaoude E, Large MD, Serpe RT (2006) Estimated prevalence of compulsive buying behavior in the United States. The American journal of psychiatry 163:1806-1812.

Kraemmer J, Smith K, Weintraub D, Guillemot V, Nalls MA, Cormier-Dequaire F, Moszer I, Brice A, Singleton AB, Corvol J-C (2016) Clinical-genetic model predicts incident impulse control disorders in Parkinson's disease. Journal of neurology, neurosurgery and psychiatry 87:1106-1111.

Kruzich PJ, Mitchell SH, Younkin A, Grandy DK (2006) Dopamine D2 receptors mediate reversal learning in male C57BL/6J mice. Cognitive, Affective, & Behavioral Neuroscience 6:86-90.

Kuhn AA, Kempf F, Brucke C, Gaynor Doyle L, Martinez-Torres I, Pogosyan A, Trottenberg T, Kupsch A, Schneider G-H, Hariz MI, Vandenberghe W, Nuttin B, Brown P (2008) High-frequency stimulation of the subthalamic nucleus suppresses oscillatory beta activity in patients with Parkinson's disease in parallel with improvement in motor performance. The Journal of neuroscience 28:6165-6173.

Kulisevsky J, Pascual-Sedano B, Barbanoj M, Gironell A, Pagonabarraga J, García-Sánchez C (2007) Acute effects of immediate and controlled-release levodopa on mood in Parkinson's disease: A double-blind study. Movement disorders 22:62-67.

Kurlan R (2004) Disabling repetitive behaviors in Parkinson's disease. Movement disorders 19:433-437.

Kuzma JM, Black DW (2008) Epidemiology, prevalence, and natural history of compulsive sexual behavior. The Psychiatric clinics of North America 31:603.

Lagorio CH, Winger G (2014) Random-ratio schedules produce greater demand for i.v. drug administration than fixed-ratio schedules in rhesus monkeys. Psychopharmacology (Berl) 231:2981-2988.

Laskowski CS, Dorchak DL, Ward KM, Christensen DR, Euston DR (2019) Can slot-machine reward schedules induce gambling addiction in rats? Journal of gambling studies / co-sponsored by the National Council on Problem Gambling and Institute for the Study of Gambling and Commercial Gaming 35:887-914.

Lawrence AD, Evans AH, Lees AJ (2003) Compulsive use of dopamine replacement therapy in Parkinson's disease: reward systems gone awry? Lancet neurology 2:595-604.

Lawrence AJ, Luty J, Bogdan NA, Sahakian BJ, Clark L (2009) Impulsivity and response inhibition in alcohol dependence and problem gambling. Psychopharmacology (Berl) 207:163-172.

Le Foll B, Schwartz JC, Sokoloff P (2003) Disruption of nicotine conditioning by dopamine D3 receptor ligands. Molecular psychiatry 8:225-230.

Le Foll B, Goldberg SR, Sokoloff P (2005) The dopamine D3 receptor and drug dependence: Effects on reward or beyond? Neuropharmacology 49:525-541.

Le Foll B, Francès H, Diaz J, Schwartz J-C, Sokoloff P (2002) Role of the dopamine D3 receptor in reactivity to cocaine-associated cues in mice. The European journal of neuroscience 15:2016-2026.

Ledgerwood DM, Orr ES, Kaploun KA, Milosevic A, Frisch GR, Rupcich N, Lundahl LH (2012) Executive function in pathological gamblers and healthy controls. Journal of

gambling studies / co-sponsored by the National Council on Problem Gambling and Institute for the Study of Gambling and Commercial Gaming 28:89-103.

Lee B, London E, Poldrack RA, Farahi J, Nacca A, Monterosso JR, Mumford JA, Bokarius AV, Dahlbom M, Mukherjee J, Bilder RM, Brody AL, Mandelkern MA (2009a) Striatal dopamine D2/D3 receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. The Journal of neuroscience 29:14734-14740.

Lee FJS, Pei L, Moszczynska A, Vukusic B, Fletcher PJ, Liu F (2007) Dopamine transporter cell surface localization facilitated by a direct interaction with the dopamine D2 receptor. The EMBO journal 26:2127-2136.

Lee J-Y, Jeon BS, Kim H-J, Park S-S (2012) Genetic variant of HTR2A associates with risk of impulse control and repetitive behaviors in Parkinson's disease. Parkinsonism & related disorders 18:76-78.

Lee J-Y, Lee EK, Park SS, Lim J-Y, Kim HJ, Kim JS, Jeon BS (2009b) Association of DRD3 and GRIN2B with impulse control and related behaviors in Parkinson's disease. Movement disorders 24:1803-1810.

Lee J-Y, Kim J-M, Kim JW, Cho J, Lee WY, Kim H-J, Jeon BS (2010) Association between the dose of dopaminergic medication and the behavioral disturbances in Parkinson disease. Parkinsonism & related disorders 16:202-207.

Lee J-Y, Seo SH, Kim YK, Yoo HB, Kim YE, Song IC, Lee JS, Jeon BS (2014) Extrastriatal dopaminergic changes in Parkinson's disease patients with impulse control disorders. Journal of Neurology, Neurosurgery & Psychiatry 85:23-30.

Leeman RF, Potenza MN (2011) Impulse control disorders in Parkinson's disease: clinical characteristics and implications. Neuropsychiatry (London) 1:133-147.

Leeman RF, Potenza MN (2012) Similarities and differences between pathological gambling and substance use disorders: a focus on impulsivity and compulsivity. Psychopharmacology (Berl) 219:469-490.

Leentjens AFGMDP, Koester JP, Fruh B, Shephard DTSBM, Barone PMDP, Houben JJGMP (2009) The effect of pramipexole on mood and motivational symptoms in parkinson's disease: A meta-analysis of placebo-controlled studies. Clinical therapeutics 31:89-98.

Lesch KP, Merschdorf U (2000) Impulsivity, aggression, and serotonin: a molecular psychobiological perspective. Behavioral sciences & the law 18:581-604.

Lévesque D, Martres MP, Diaz J, Griffon N, Lammers CH, Sokoloff P, Schwartz JC (1995) A paradoxical regulation of the dopamine D3 receptor expression suggests the involvement of an anterograde factor from dopamine neurons. Proceedings of the National Academy of Sciences - PNAS 92:1719-1723.

Limbrick-Oldfield EH, van Holst RJ, Clark L (2013) Fronto-striatal dysregulation in drug addiction and pathological gambling: Consistent inconsistencies? NeuroImage Clinical 2:385-393.

Limbrick-Oldfield EH, Mick I, Cocks RE, McGonigle J, Sharman SP, Goldstone AP, Stokes PRA, Waldman A, Erritzoe D, Bowden-Jones H, Nutt D, Lingford-Hughes A, Clark L (2017) Neural substrates of cue reactivity and craving in gambling disorder. Translational Psychiatry 7:e992-e992.

Lin S-K, Pan WHT, Yeh P-H (2006) Prefrontal dopamine efflux during exposure to drug-associated contextual cues in rats with prior repeated methamphetamine. Brain research bulletin 71:365-371.

Lind PA, Zhu G, Montgomery GW, Madden PA, Heath AC, Martin NG, Slutske WS (2013) Genome-wide association study of a quantitative disordered gambling trait. Addict Biol 18:511-522.

Lipford MC, Silber MH (2012) Long-term use of pramipexole in the management of restless legs syndrome. Sleep medicine 13:1280-1285.

Liu YZ, Tang BS, Yan XX, Liu J, Ouyang DS, Nie LN, Fan L, Li Z, Ji W, Hu DL, Wang D, Zhou HH (2009) Association of the DRD2 and DRD3 polymorphisms with response to pramipexole in Parkinson's disease patients. Eur J Clin Pharmacol 65:679-683.

Lodge DJ, Grace AA (2006) The hippocampus modulates dopamine neuron responsivity by regulating the intensity of phasic neuron activation. Neuropsychopharmacology 31:1356-1361.

Lodge DJ, Grace AA (2008) Amphetamine activation of hippocampal drive of mesolimbic dopamine neurons: a mechanism of behavioral sensitization. The Journal of neuroscience 28:7876-7882.

Loiodice S, McGhan P, Gryshkova V, Fleurance R, Dardou D, Hafidi A, Nogueira da Costa A, Durif F (2017) Striatal changes underlie MPEP-mediated suppression of the acquisition and expression of pramipexole-induced place preference in an alpha-synuclein rat model of Parkinson’s disease. Journal of psychopharmacology (Oxford) 31:1323-1333.

Lole L, Gonsalvez CJ, Barry RJ, Blaszczynski A (2014) Problem gamblers are hyposensitive to wins: An analysis of skin conductance responses during actual gambling on electronic gaming machines. Psychophysiology 51:556-564.

Lorains FK, Cowlishaw S, Thomas SA (2011) Prevalence of comorbid disorders in problem and pathological gambling: systematic review and meta-analysis of population surveys. Addiction (Abingdon, England) 106:490-498.

Lotta T, Vidgren J, Tilgmann C, Ulmanen I, Melen K, Julkunen I, Taskinen J (1995) Kinetics of human soluble and membrane-bound catechol O-methyltransferase: A revised

mechanism and description of the thermolabile variant of the enzyme. Biochemistry (Easton) 34:4202-4210.

Lowe CF, Davey GCL, Harzem P (1974) Effects of reinforcement magnitude on interval and ratio schedules. Journal of the Experimental Analysis of Behavior 22:553-560.

Lowe CF, Harzem P, Bagshaw M (1978) Species differences in temporal control of behaviour II: Human performance. Journal of the Experimental Analysis of Behavior 29:351-361.

Lu C, Bharmal A, Suchowersky O (2006) Gambling and Parkinson Disease. Archives of Neurology 63:298-298.

Madden GJ, Ewan EE, Lagorio CH (2007) Toward an animal model of gambling: Delay discounting and the allure of unpredictable outcomes. Journal of gambling studies / co-sponsored by the National Council on Problem Gambling and Institute for the Study of Gambling and Commercial Gaming 23:63-83.

Madden GJ, Petry NM, Johnson PS (2009) Pathological gamblers discount probabilistic rewards less steeply than matched controls. Exp Clin Psychopharmacol 17:283-290.

Madden GJ, Johnson PS, Brewer AT, Pinkston JW, Fowler SC (2010) Effects of pramipexole on impulsive choice in male wistar rats. Experimental and Clinical Psychopharmacology 18:267-276.

Maj J, Rogóz Z, Margas W, Kata M, Dziedzicka-Wasylewska M (2000) The effect of repeated treatment with pramipexole on the central dopamine D_3 system. Journal of Neural Transmission 107:1369-1379.

Mamikonyan E, Siderowf AD, Duda JE, Potenza MN, Horn S, Stern MB, Weintraub D (2008) Long-term follow-up of impulse control disorders in Parkinson's disease. Mov Disord 23:75-80.

Marceglia S, Fumagalli M, Priori A (2011) What neurophysiological recordings tell us about cognitive and behavioral functions of the human subthalamic nucleus. Expert review of neurotherapeutics 11:139.

Martens MAG, Kaltenboeck A, Halahakoon DC, Browning M, Cowen PJ, Harmer CJ (2021) An experimental medicine investigation of the effects of subacute pramipexole treatment on emotional information processing in healthy volunteers. Pharmaceuticals 14:800.

Martinez D, Narendran R, Foltin RW, Slifstein M, Hwang D-R, Broft A, Huang Y, Cooper TB, Fischman MW, Kleber HD, Laruelle M (2007) Amphetamine-induced dopamine release: markedly blunted in cocaine dependence and predictive of the choice to self-administer cocaine. The American journal of psychiatry 164:622-629.

Martinez D, Gil R, Slifstein M, Hwang D-R, Huang Y, Perez A, Kegeles L, Talbot P, Evans S, Krystal J, Laruelle M, Abi-Dargham A (2005) Alcohol dependence is associated with

blunted dopamine transmission in the ventral striatum. Biological psychiatry (1969) 58:779-786.

Martinkova J, Trejbalova L, Sasikova M, Benetin J, Valkovic P (2011) Impulse control disorders associated with dopaminergic medication in patients with pituitary adenomas. Clinical neuropharmacology 34:179.

Martinowich K, Lu B (2008) Interaction between BDNF and Serotonin: Role in Mood Disorders. Neuropsychopharmacology 33:73-83.

Mascia P, Neugebauer NM, Brown J, Bubula N, Nesbitt KM, Kennedy RT, Vezina P (2019) Exposure to conditions of uncertainty promotes the pursuit of amphetamine. Neuropsychopharmacology 44:274-280.

Mash DC (1997a) D3 receptor binding in human brain during cocaine overdose. Molecular psychiatry 2:5.

Mash DC (1997b) Are neuroadaptations in D3 dopamine receptors linked to the development of cocaine dependence? Molecular psychiatry 2:7-8.

Mayo Clinic (n.d.) Drugs and Supplements. In.

Mazur JE (1983) Steady-state performance on fixed-, mixed-, and random-ratio schedules. Journal of the Experimental Analysis of Behavior 39:293-307.

Mazur JE (1986) Fixed and variable ratios and delays: further tests of an equivalence rule. J Exp Psychol Anim Behav Process 12:116-124.

McCullough LD, Cousins MS, Salamone JD (1993) The role of nucleus accumbens dopamine in responding on a continuous reinforcement operant schedule: A neurochemical and behavioral study. Pharmacology, Biochemistry, and Behavior 46:581-586.

McGrath DS, Barrett SP (2009) The comorbidity of tobacco smoking and gambling: A review of the literature. Drug and alcohol review 28:676-681.

McKerchar TL, Renda CR (2012) Delay and probability discounting in humans: An overview. The Psychological Record 62:817-834.

Meck WH, Church RM (1983) A mode control model of counting and timing processes. Journal of experimental psychology: animal behavior processes 9:320.

Menza MA, Golbe LI, Cody RA, Forman NE (1993) Dopamine-related personality traits in Parkinson's disease. Neurology 43:505-505.

Meyer G, Hauffa BP, Schedlowski M, Pawlak C, Stadler MA, Exton MS (2000) Casino gambling increases heart rate and salivary cortisol in regular gamblers. Biological Psychiatry 48:948-953.

Michalczuk R, Bowden-Jones H, Verdejo-Garcia A, Clark L (2011) Impulsivity and cognitive distortions in pathological gamblers attending the UK National Problem Gambling Clinic: a preliminary report. Psychol Med 41:2625-2635.

Mierau J, Schingnitz G (1992) Biochemical and pharmacological studies on pramipexole, a potent and selective dopamine D2 receptor agonist. European Journal of Pharmacology 215:161-170.

Mierau J, Schneider FJ, Ensinger HA, Chio CL, Lajiness ME, Huff RM (1995) Pramipexole binding and activation of cloned and expressed dopamine D2, D3 and D4 receptors. European journal of pharmacology 290:29-36.

Mirenowicz J, Schultz W (1994) Importance of unpredictability for reward responses in primate dopamine neurons. Journal of Neurophysiology 72:1024-1027.

Mirenowicz J, Schultz W (1996) Preferential activation of midbrain dopamine neurons by appetitive rather than aversive stimuli. Nature 379:449-451.

Mishra S, Lalumière ML, Williams RJ (2010) Gambling as a form of risk-taking: Individual differences in personality, risk-accepting attitudes, and behavioral preferences for risk. Personality and individual differences 49:616-621.

Missale C, Nash SR, Robinson SW, Jaber M, Caron MG (1998) Dopamine receptors: from structure to function. Physiological Reviews 78:189-225.

Mobini S, Chiang TJ, Ho MY, Bradshaw CM, Szabadi E (2000) Comparison of the effects of clozapine, haloperidol, chlorpromazine and d-amphetamine on performance on a time-constrained progressive ratio schedule and on locomotor behaviour in the rat. Psychopharmacologia 152:47-54.

Moeller SJ, Frobose MI, Konova AB, Misyrlis M, Parvaz MA, Goldstein RZ, Alia-Klein N (2014) Common and distinct neural correlates of inhibitory dysregulation: Stroop fMRI study of cocaine addiction and intermittent explosive disorder. Journal of Psychiatric Research 58:55-62.

Molina JA, Sáinz-Artiga MJ, Fraile A, Jiménez-Jiménez FJ, Villanueva C, Ortí-Pareja M, Bermejo-P F (2000) Pathologic gambling in Parkinson's disease: A behavioral manifestation of pharmacologic treatment? Movement disorders 15:869-872.

Montastruc JL, Schmitt L, Bagheri H (2003) Pathological gambling behavior in a patient with Parkinson's disease treated with levodopa and bromocriptine. Revue Neurologique (Paris) 159:441-443.

Moore TJ, Glenmullen J, Mattison DR (2014) Reports of pathological gambling, hypersexuality, and compulsive shopping associated with dopamine receptor agonist drugs. JAMA internal medicine 174:1930.

Morgan D, Grant KA, Gage HD, Mach RH, Kaplan JR, Prioleau O, Nader SH, Buchheimer N, Ehrenkaufer RL, Nader MA (2002) Social dominance in monkeys: dopamine D2 receptors and cocaine self-administration. Nature neuroscience 5:169-174.

Müller CP, Homberg JR (2015) The role of serotonin in drug use and addiction. Behavioural brain research 277:146-192.

Munhoz RP, Fabiani G, Becker N, Teive HAG (2009) Increased frequency and range of sexual behavior in a patient with Parkinson's disease after use of pramipexole: a case report. The Journal of Sexual Medicine 6:1177-1180.

Murphy ER, Robinson ES, Theobald DE, Dalley JW, Robbins TW (2008) Contrasting effects of selective lesions of nucleus accumbens core or shell on inhibitory control and amphetamine-induced impulsive behaviour. Eur J Neurosci 28:353-363.

Murray AM, Ryoo HL, Gurevich E, Joyce JN (1994) Localization of dopamine D_3 receptors to mesolimbic and D_2 receptors to mesostriatal regions of human forebrain. Proceedings of National Academy of Sciences of the United States of America 91:11271-11275.

Murray JE, Dilleen R, Pelloux Y, Economidou D, Dalley JW, Belin D, Everitt BJ (2013) Increased impulsivity retards the transition to dorsolateral striatal dopamine control of cocaine seeking. Biol Psychiatry.

Nader MA, Morgan D, Gage HD, Nader SH, Calhoun TL, Buchheimer N, Ehrenkaufer R, Mach RH (2006) PET imaging of dopamine D2 receptors during chronic cocaine self-administration in monkeys. Nature neuroscience 9:1050-1056.

Nagle A, Wolf P, Riener R, Novak D (2014) The use of player-centered positive reinforcement to schedule in-game rewards inreases enjoyment and performance in a serious game. International Journal of Serious Games 1:35-47.

Napier TC, Kirby A, Persons AL (2020) The role of dopamine pharmacotherapy and addiction-like behaviors in Parkinson’s disease. Progress in Neuropsychopharmacology & Biological Psychiatry 102:109942.

Napier TC, Corvol J-C, Grace AA, Roitman JD, Rowe J, Voon V, Strafella AP (2015) Linking neuroscience with modern concepts of impulse control disorders in Parkinson's disease. Movement disorders 30:141-149.

Neisewander JL, Fuchs RA, Tran-Nguyen LTL, Weber SM, Coffey GP, Joyce JN (2004) Increases in dopamine D3 receptor binding in rats receiving a cocaine challenge at various time points after cocaine self-administration: implications for cocaine-seeking behavior. Neuropsychopharmacology (New York, NY) 29:1479.

Nicola SM, Malenka RC (1998) Modulation of synaptic transmission by dopamine and norepinephrine in ventral but not dorsal striatum. Journal of Neurophysiology 79:1768-1776.

Nicola SM, Deadwyler SA (2000) Firing rate of nucleus accumbens neurons is dopamine-dependent and reflects the timing of cocaine-seeking behavior in rats on a progressive ratio schedule of reinforcement. The Journal of Neuroscience 20:5526-5537.

Nirenberg M, Waters C (2006) Compulsive eating and weight gain related to dopamine agonist use. Movement Disorders 21:524-529.

Nombela C, Rittman T, Robbins TW, Rowe JB (2014) Multiple modes of impulsivity in Parkinson's disease. PloS one 9:e85747-e85747.

Nowak KL, McBride WJ, Lumeng L, Li TK, Murphy JM (2000) Involvement of dopamine D2 autoreceptors in the ventral tegmental area on alcohol and saccharin intake of the alcohol-preferring P Rat. Alcoholism, clinical and experimental research 24:476-483.

Nutt DJ, Lingford-Hughes A, Erritzoe D, Stokes PRA (2015) The dopamine theory of addiction: 40 years of highs and lows. Nature Reviews Neuroscience 16:305-312.

O'Suilleabhain PE, Dewey RB, Jr. (2002) Contributions of dopaminergic drugs and disease severity to daytime sleepiness in Parkinson disease. JAMA : the journal of the American Medical Association 288:1214.

O'Sullivan SS, Wu K, Politis M, Lawrence AD, Evans AH, Bose SK, Djamshidian A, Lees AJ, Piccini P (2011) Cue-induced striatal dopamine release in Parkinson's disease-associated impulsive-compulsive behaviours. Brain (London, England : 1878) 134:969-978.

Obeso I, Wilkinson L, Casabona E, Bringas ML, Álvarez M, Álvarez L, Pavón N, Rodríguez-Oroz M-C, Macías R, Obeso JA, Jahanshahi M (2011) Deficits in inhibitory control and conflict resolution on cognitive and motor tasks in Parkinson’s disease. Experimental brain research 212:371-384.

Olanow CW et al. (2004) Levodopa in the treatment of Parkinson's disease: Current controversies. Movement disorders 19:997-1005.

Ondo WG, Lai D (2007) Predictors of impulsivity and reward seeking behavior with dopamine agonists. Parkinsonism & related disorders 14:28-32.

Orrù M, Strathman HJ, Floris G, Scheggi S, Levant B, Bortolato M (2020) The adverse effects of pramipexole on probability discounting are not reversed by acute D2 or D3 receptor antagonism. European neuropsychopharmacology 32:104-119.

Owen AM, James M, Leigh PN, Summers BA, Marsden CD, Quinn NP, Lange KW, Robbins TW (1992) Fronto-striatal cognitive deficits at different stages of Parkinson’s disease. Brain (London, England : 1878) 115:1727-1751.

Paloyelis Y, Asherson P, Mehta MA, Faraone SV, Kuntsi J (2010) DAT1 and COMT effects on delay discounting and trait impulsivity in male adolescents with attention deficit/hyperactivity disorder and healthy controls. Neuropsychopharmacology (New York, NY) 35:2414-2426.

Parkinson Study Group (2000) Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomized controlled trial. Parkinson Study Group. JAMA : the journal of the American Medical Association 284:1931.

Paxinos G, Watson C (2007) The Rat Brain in Stereotaxic Coordinates, 6th Edition. San Diego, CA: Academic Press.

Payer DE, Behzadi A, Kish SJ, Houle S, Wilson AA, Rusjan PM, Tong J, Selby P, George TP, McCluskey T, Boileau I (2014) Heightened D3 dopamine receptor levels in cocaine dependence and contributions to the addiction behavioral phenotype: A positron emission tomography study with [11C]-+-PHNO. Neuropsychopharmacology 39:311-318.

Payer DE, Guttman M, Kish SJ, Tong J, Strafella A, Zack M, Adams JR, Rusjan P, Houle S, Furukawa Y, Wilson AA, Boileau I (2015) [11C]-(+)-PHNO PET imaging of dopamine D2/3 receptors in Parkinson's disease with impulse control disorders. Movement disorders 30:160-166.

Pelloux Y, Everitt BJ, Dickinson A (2007) Compulsive drug seeking by rats under punishment: Effects of drug taking history. Psychopharmacology 194:127-137.

Peng B, Xu Q, Liu J, Guo S, Borgland SL, Liu S (2021) Corticosterone attenuates reward-seeking behavior and increases anxiety via D2 receptor signaling in ventral tegmental area dopamine neurons. The Journal of Neuroscience 41:1566-1581.

Perez-Lloret S, Rey MV, Fabre N, Ory F, Spampinato U, Montastruc J-L, Rascol O (2012) Do Parkinson's disease patients disclose their adverse events spontaneously? European journal of clinical pharmacology 68:857-865.

Pérez de Castro I, Ibáñez A, Saiz-Ruiz J, Fernández-Piqueras J (1999) Genetic contribution to pathological gambling: possible association between a functional DNA polymorphism at the serotonin transporter gene (5-HTT) and affected men. Pharmacogenetics (London) 9:397.

Pérez de Castro I, Ibáñez A, Saiz-Ruiz J, Fernández-Piqueras J (2002) Concurrent positive association between pathological gambling and functional DNA polymorphisms at the MAO-A and the 5-HT transporter genes. Molecular psychiatry 7:927-928.

Pérez de Castro I, Ibáñez A, Torres P, Sáiz-Ruiz J, Fernández-Piqueras J (1997) Genetic association study between pathological gambling and a functional DNA polymorphism at the D4 receptor gene. Pharmacogenetics (London) 7:345.

Perez Lloret S, Rascol O (2010) Pramipexole extended-release (once-daily formulation) for the treatment of Parkinson's disease. Expert Opinion on Pharmacotherapy 11:2221-2230.

Pes R, Godar SC, Fox AT, Burgeno LM, Strathman HJ, Jarmolowicz DP, Devoto P, Levant B, Phillips PE, Fowler SC, Bortolato M (2017) Pramipexole enhances disadvantageous decision-making: Lack of relation to changes in phasic dopamine release. Neuropharmacology 114:77-87.

Peterson E, Moeller A, Linnet J, Doudet D, Hansen KV, Rodell A, Gjedde A (2008) Dopamine and skin conductance response to gambling. NeuroImage 41.

Peterson E, Moller A, Doudet DJ, Bailey CJ, Hansen KV, Rodell A, Linnet J, Gjedde A (2010) Pathological gambling: relation of skin conductance response to dopaminergic neurotransmission and sensation-seeking. Eur Neuropsychopharmacol 20:766-775.

Petry NM (2007) Gambling and substance use disorders: current status and future directions. The American journal on addictions 16:1-9.

Pharmacia & Upjohn I (1997) Mirapex (Pramipexole Dihydrochloride) Tablets Drug Approval Package. In.

Piazza PV, Deminiere JM, Le Moal M, Simon H (1989) Factors that predict individual vulnerability to amphetamine self-administration. Science 245:1511-1513.

Pignatti R, Brioschi A, Mauro A, Zamarian L, Wenter J, Semenza C (2012) Selective IGT decision-making impairment in a patient with juvenile Parkinson's disease and pathological gambling: A role for dopaminergic therapy? Neurocase 18:503-513.

Pinna F, Dell'Osso B, Di Nicola M, Janiri L, Altamura AC, Carpiniello B, Hollander E (2015) Behavioural addictions and the transition from DSM-IV-TR to DSM-5. Journal of Psychopathology 21:380-389.

Pizzagalli DA, Evins AE, Schetter EC, Frank MJ, Pajtas PE, Santesso DL, Culhane M (2008) Single dose of a dopamine agonist impairs reinforcement learning in humans: Behavioral evidence from a laboratory-based measure of reward responsiveness. Psychopharmacologia 196:221-232.

Poletti M, Bonuccelli U (2012) Impulse control disorders in Parkinson' disease: the role of personality and cognitive status. Journal of neurology 259:2269-2277.

Politis M, Wu K, Loane C, Kiferle L, Molloy S, Brooks DJ, Piccini P (2010) Staging of serotonergic dysfunction in Parkinson's Disease: An in vivo 11C-DASB PET study. Neurobiology of disease 40:216-221.

Pontone G, Williams JR, Bassett SS, Marsh L (2006) Clinical features associated with impulse control disorders in Parkinson disease. Neurology 67:1258.

Porrino LJ, Lyons D, Smith HR, Daunais JB, Nader MA (2004) Cocaine self-administration produces a progressive involvement of limbic, association, and sensorimotor striatal domains. The Journal of neuroscience 24:3554-3562.

Pourcher E, Rémillard S, Cohen H (2009) Compulsive habits in restless legs syndrome patients under dopaminergic treatment. Journal of the neurological sciences 290:52-56.

Powell RW (1968) The effect of small sequential changes in fixed-ratio size upon the post-reinforcement pause. Journal of the Experimental Analysis of Behavior 11:589-593.

Pribiag H, Shin S, Wang EH-J, Sun F, Datta P, Okamoto A, Guss H, Jain A, Wang X-Y, De Freitas B, Honma P, Pate S, Lilascharoen V, Li Y, Lim BK (2021) Ventral pallidum DRD3 potentiates a pallido-habenular circuit driving accumbal dopamine release and cocaine seeking. Neuron 109:2065-2182.

Priddle-Higson PJ, Lowe CF, Harzem P (1976) Aftereffects of reinforcement on variable-ratio schedules. Journal of the Experimental Analysis of Behavior 25:347-354.

Pyke GH (1984) Optimal foraging theory: a critical review. Annual review of ecology and systematics 15:523-575.

Quickfall J, Suchowersky O (2007) Pathological gambling associated with dopamine agonist use in restless legs syndrome. Parkinsonism Relat Disord 13:535-536.

Ramirez-Zamora A, Gee L, Boyd J, Biller J (2016) Treatment of impulse control disorders in Parkinson's disease: Practical considerations and future directions. Expert Rev Neurother 16:389-399.

Rao H, Korczykowski M, Pluta J, Hoang A, Detre JA (2008) Neural correlates of voluntary and involuntary risk taking in the human brain: an fMRI Study of the Balloon Analog Risk Task (BART). Neuroimage 42:902-910.

Rao H, Mamikonyan E, Detre JA, Siderowf AD, Stern MB, Potenza MN, Weintraub D (2010) Decreased ventral striatal activity with impulse control disorders in Parkinson's disease. Movement disorders 25:1660-1669.

Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE (2000) A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. The New England journal of medicine 342:1484-1491.

Rasmussen VG, Poulsen SH, Dupont E, Østergaard K, Safikhany G, Egeblad H (2008) Heart valve disease associated with treatment with ergot-derived dopamine agonists: a clinical and echocardiographic study of patients with Parkinson’s disease. Journal of internal medicine 263:90-98.

Ray NJ, Miyasaki JM, Zurowski M, Ko JH, Cho SS, Pellecchia G, Antonelli F, Houle S, Lang AE, Strafella AP (2012) Extrastriatal dopaminergic abnormalities of DA homeostasis in Parkinson's patients with medication-induced pathological gambling: a [11C] FLB-457 and PET study. Neurobiol Dis 48:519-525.

Reed P (2011) An experimental analysis of steady-state response rate components on variable ratio and variable interval schedules of reinforcement. J Exp Psychol Anim Behav Process 37:1-9.

Repp AC, Deitz SM (1975) A comparison of fixed-ratio and variable-ratio token-production schedules with human subjects. The Psychological Record 25:131-137.

Reuter J, Raedler T, Rose M, Hand I, Glascher J, Buchel C (2005) Pathological gambling is linked to reduced activation of the mesolimbic reward system. Nat Neurosci 8:147-148.

Riba J, Krämer UM, Heldmann M, Richter S, Münte TF (2008) Dopamine agonist increases risk taking but blunts reward-related brain activity. PloS one 3:e2479-e2479.

Ribacoba R, Menendez Gonzalez M, Herrera E, Martinez-Rivera M, Cuetos F (2010) Frontal dysfunction in Parkinson's disease patients with pathological gambling. In: 20th ENS Meeting, p 399. Berlin, Germany.

Richfield EK, Penney JB, Young AB (1989) Anatomical and affinity state comparisons between dopamine D1 and D2 receptors in the rat central nervous system. Neuroscience 30:767.

Richmond-Rakerd LS, Slutske WS, Heath AC, Martin NG (2014) Genetic and environmental influences on the ages of drinking and gambling initiation: evidence for distinct aetiologies and sex differences. Addiction 109:323-331.

Richtand NM, Goldsmith RJ, Nolan JE, Berger SP (2001a) The D3 dopamine receptor and substance dependence. Journal of addictive diseases 20:19-32.

Richtand NM, Woods SC, Berger SP, Strakowski SM (2001b) D3 dopamine receptor, behavioral sensitization, and psychosis. Neuroscience and biobehavioral reviews 25:427-443.

Riddle JL, Rokosik SL, Napier TC (2012) Pramipexole- and methamphetamine-induced reward-mediated behavior in a rodent model of Parkinson's disease and controls. Behav Brain Res 233:15-23.

Ridley R (1994) The psychology of perseverative and stereotyped behaviour. Progress in neurobiology 44:221-231.

Riley DE (2002) Reversible transvestic fetishism in a man with Parkinson's disease treated with selegiline. Clinical neuropharmacology 25:234.

Robbins TW, James M, Owen AM, Lange KW, Lees AJ, Leigh PN, Marsden CD, Quinn NP, Summers BA (1994) Cognitive deficits in progressive supranuclear palsy, Parkinson's disease, and multiple system atrophy in tests sensitive to frontal lobe dysfunction. Journal of neurology, neurosurgery and psychiatry 57:79-88.

Robinson TE, Kolb B (1997) Persistent structural modifications in nucleus accumbens and prefrontal cortex neurons produced by previous experience with amphetamine. J Neurosci 17:8491-8497.

Robinson TE, Kolb B (2004) Structural plasticity associated with exposure to drugs of abuse. Neuropharmacology 47 Suppl 1:33-46.

Roitman JD, Loriaux AL (2014) Nucleus accumbens responses differentiate execution and restraint in reward-directed behavior. Journal of neurophysiology 111:350-360.

Rokosik SL, Napier TC (2012) Pramipexole-induced increased probabilistic discounting: comparison between a rodent model of Parkinson's disease and controls. Neuropsychopharmacology 37:1397-1408.

Root DH, Melendez RI, Zaborszky L, Napier TC (2015) The ventral pallidum: Subregion-specific functional anatomy and roles in motivated behaviors. Progress in neurobiology 130:29-70.

Rosa M, Fumagalli M, Giannicola G, Marceglia S, Lucchiari C, Servello D, Franzini A, Pacchetti C, Romito L, Albanese A, Porta M, Pravettoni G, Priori A (2013) Pathological gambling in Parkinson's disease: subthalamic oscillations during economics decisions. Mov Disord 28:1644-1652.

Ross D, Sharp C, Vuchinich RE, Spurrett D (2008) Midbrain mutiny: The picoeconomics and neuroeconomics of disordered gambling: Economic theory and cognitive science. Cambridge, MA, US: MIT Press.

Rossi M, Gerschcovich ER, de Achaval D, Perez-Lloret S, Cerquetti D, Cammarota A, InÃ©s Nouzeilles M, Fahrer R, Merello M, Leiguarda R (2010) Decision-making in Parkinson's disease patients with and without pathological gambling. European Journal of Neurology 17:97-102.

Rowe JB, Hughes L, Ghosh BCP, Eckstein D, Williams-Gray CH, Fallon S, Barker RA, Owen AM (2008) Parkinson's disease and dopaminergic therapy—differential effects on movement, reward and cognition. Brain (London, England : 1878) 131:2094-2105.

Russell B, Barrus MM, Tremblay M, Ma L, Hrelja K, Wong C, Hynes TJ, Hobson S, Grottick AJ, Winstanley CA (2021) GPR52 agonists attenuate ropinirole-induced preference for uncertain outcomes. Behavioral neuroscience 135:8.

Ryoo HL, Pierrotti D, Joyce JN (1998) Dopamine D3 receptor is decreased and D2 receptor is elevated in the striatum of Parkinson's disease. Movement disorders: official journal of the Movement Disorder Society 13:788-797.

Saga Y, Richard A, Sgambato-Faure V, Hoshi E, Tobler PN, Tremblay L (2017) Ventral pallidum encodes contextual information and controls aversive behaviors. Cerebral cortex (New York, NY 1991) 27:2528-2543.

Sakamoto K, Matsumura S, Okafuji Y, Eguchi A, Yoneda T, Mizushige T, Tsuzuki S, Inoue K, Fushiki T (2014) The opioid system contributes to the acquisition of reinforcement for dietary fat but is not required for its maintenance. Physiology & behavior 138:227-235.

Salamone JD (2007) Functions of mesolimbic dopamine: changing concepts and shifting paradigms. Psychopharmacology 191:389-389.

Samuels ER, Hou RH, Langley RW, Szabadi E, Bradshaw CM (2006a) Comparison of pramipexole and modafinil on arousal, autonomic, and endocrine functions in healthy volunteers. Journal of psychopharmacology (Oxford) 20:756-770.

Samuels ER, Hou RH, Langley RW, Szabadi E, Bradshaw CM (2006b) Comparison of pramipexole and amisulpride on alertness, autonomic and endocrine functions in healthy volunteers. Psychopharmacologia 187:498-510.

Santesso DL, Evins AE, Frank MJ, Schetter EC, Bogdan R, Pizzagalli DA (2009) Single dose of a dopamine agonist impairs reinforcement learning in humans: evidence from event-related potentials and computational modeling of striatal-cortical function. Hum Brain Mapp 30:1963-1976.

Saper CB (1982) Convergence of autonomic and limbic connections in the insular cortex of the rat. The Journal of Comparative Neurology 210:163-173.

Saper CB, Chou TC, Elmquist JK (2002) The need to feed: homeostatic and hedonic control of eating. Neuron 36:199-211.

Schlinger HD, Derenne A, Baron A (2008) What 50 years of research tell us about pausing under ratio schedules of reinforcement. The Behavior Analyst 31:39-60.

Schoenbaum G, Roesch MR, Stalnaker TA (2006) Orbitofrontal cortex, decision-making and drug addiction. Trends Neurosci 29:116-124.

Schreiber L, Odlaug B, Grant J (2011) Impulse control disorders: updated review of clinical characteristics and pharmacological management. Frontiers in Psychiatry 21:1-11.

Schultz W (1997) Dopamine neurons and their role in reward mechanisms. Current Opinion in Neurobiology 7:191-197.

Schultz W (2002) Getting formal with dopamine and reward. Neuron 36:241-263.

Schultz W (2016) Dopamine reward prediction-error signalling: A two-component response. Nature Reviews Neuroscience 17:183-195.

Schultz W, Dayan P, Montague PR (1997) A neural substrate of prediction and reward. Science 275:1593-1599.

Scofield M, Heinsbroek J, Gipson C, Kupchik Y, Spencer S, Smith A, Roberts-Wolfe D, Kalivas P (2016) The nucleus accumbens: Mechanisms of addiction across drug classes reflect the importance of glutamate homeostasis. Pharmacological Reviews 68:816-871.

Seamans JK, Floresco SB, Phillips AG (1995) Functional differences between the prelimbic and anterior cingulate regions of the rat prefrontal cortex. Behavioral neuroscience 109:1063-1073.

Seedat S, Kesler S, Niehaus DJH, Stein DJ (2000) Pathological gambling behaviour: Emergence secondary to treatment of Parkinson's disease with dopaminergic agents. Depression and Anxiety 11:185-186.

Seeman P (2015) Parkinson's disease treatment may cause impulse-control disorder via dopamine D3 receptors. Synapse 69:183-189.

Segal DM, Moraes CT, Mash DC (1997) Up-regulation of D3 dopamine receptor mRNA in the nucleus accumbens of human cocaine fatalities. Brain Research Molecular Brain Research 45:335-339.

Seif T, Chang S-J, Simms JA, Gibb SL, Dadgar J, Chen BT, Harvey BK, Ron D, Messing RO, Bonci A, Hopf FW (2013) Cortical activation of accumbens hyperpolarization-active NMDARs mediates aversion-resistant alcohol intake. Nature Neuroscience 16:1094-1100.

Sesack SR, Grace AA (2010) Cortico-basal ganglia reward network: Microcircuitry. Neuropsychopharmacology 35:27-47.

Sescousse G, Barbalat G, Domenech P, Dreher JC (2013) Imbalance in the sensitivity to different types of rewards in pathological gambling. Brain 136:2527-2538.

Sesia T, Bizup B, Grace AA (2013) Evaluation of animal models of obsessive-compulsive disorder: correlation with phasic dopamine neuron activity. The international journal of neuropsychopharmacology 16:1295-1307.

Seymour B, Singer T, Dolan R (2007) The neurobiology of punishment. Nature Reviews Neuroscience 8:300-311.

Seymour B, O'Doherty JP, Koltzenburg M, Wiech K, Frackowiak R, Friston K, Dolan R (2005) Opponent appetitive-aversive neural processes underlie predictive learning of pain relief. Nat Neurosci 8:1234-1240.

Shaffer HJ, Martin R (2011) Disordered gambling: Etiology, trajectory, and clinical considerations. Annual review of clinical psychology 7:483-510.

Shaffer HJ, Hall MN, Vander Bilt J (1999) Estimating the prevalence of disordered gambling behavior in the United States and Canada: a research synthesis. American journal of public health (1971) 89:1369-1376.

Shaffer HJ, LaPlante DA, LaBrie RA, Kidman RC, Donato AN, Stanton MV (2004) Toward a syndrome model of addiction: multiple expressions, common etiology. Harvard review of psychiatry 12:367.

Shaham Y, Erb S, Stewart J (2000) Stress-induced relapse to heroin and cocaine seeking in rats: A review. Brain Research Reviews 33:13-33.

Shaham Y, Shalev U, Lu L, De Wit H, Stewart J (2003) The reinstatement model of drug relapse: History, methodology and major findings. Psychopharmacology (Berl) 168:3-20.

Shahzadi A, Yunusoglu O, Karabulut E, Sonmez H, Yazici Z (2022) Influence of selective dopamine agonist ropinirole on conditioned place preference and somatic signs of morphine withdrawal in rats. Frontiers in behavioral neuroscience 16:855241-855241.

Shaw CA, Hodgins DC, Williams RJ, Belanger YD, Christensen DR, el-Guebaly N, McGrath DS, Nicoll F, Smith GJ, Stevens RMG (2022) Gambling in Canada during the COVID lockdown: Prospective national survey. Journal of gambling studies / co-sponsored by the National Council on Problem Gambling and Institute for the Study of Gambling and Commercial Gaming 38:371-396.

Sherman JA, Thomas JR (1968) Some factors controlling preference between fixed-ratio and variable-ratio schedules of reinforcement. Journal of the Experimental Analysis of Behavior 11:689-702.

Shizgal P, Arvanitogiannis A (2003) Gambling on dopamine. Science 299:1856-1858.

Silber MH, Girish M, Izurieta R (2003) Pramipexole in the management of restless legs syndrome: An extended study. Sleep (New York, NY) 26:819-821.

Singer BF, Scott-Railton J, Vezina P (2012) Unpredictable saccharin reinforcement enhances locomotor responding to amphetamine. Behavioural Brain Research 226:340-344.

Singh A, Kandimala G, Dewey RB, O'Suilleabhain P (2007) Risk factors for pathologic gambling and other compulsions among Parkinson's disease patients taking dopamine agonists. Journal of clinical neuroscience 14:1178-1181.

Sinha R (2001) How does stress increase risk of drug abuse and relapse? Psychopharmacology (Berl) 158:343-359.

Skinner BF (1953) Science and human behavior. Oxford, England: Macmillan.

Skinner BF, Ferster CB (1957) Schedules of Reinforcement. Engelwood Cliffs, NJ: Prentice-Hall.

Slutske WS, Caspi A, Moffitt TE, Poulton R (2005) Personality and problem gambling: a prospective study of a birth cohort of young adults. Arch Gen Psychiatry 62:769-775.

Slutske WS, Zhu G, Meier MH, Martin NG (2010) Genetic and environmental influences on disordered gambling in men and women. Archives of General Psychiatry 67:624-630.

Slutske WS, Eisen S, True WR, Lyons MJ, Goldberg J, Tsuang M (2000) Common genetic vulnerability for pathological gambling and alcohol dependence in men. Archives of General Psychiatry 57:666-673.

Smeding HM, Goudriaan AE, Foncke EM, Schuurman PR, Speelman JD, Schmand B (2007) Pathological gambling after bilateral subthalamic nucleus stimulation in Parkinson disease. J Neurol Neurosurg Psychiatry 78:517-519.

Smith KM, Xie SX, Weintraub D (2016) Incident impulse control disorder symptoms and dopamine transporter imaging in Parkinson disease. Journal of neurology, neurosurgery and psychiatry 87:864-870.

Soares-Cunha C, Coimbra B, Domingues AV, Vasconcelos N, Sousa N, Rodrigues AJ (2018) Nucleus accumbens microcircuit underlying D2-MSN-Driven increase in motivation. eNeuro:ENEURO-0386.

Sokoloff P, Le Foll B (2017) The dopamine D3 receptor, a quarter century later. European Journal of Neuroscience 45:2-19.

Sokoloff P, Giros B, Martres MP, Bouthenet ML, Schwartz JC (1990) Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics. Nature 347:146-151.

Sokoloff P, Andrieux M, Besançon R, Pilon C, Martres MP, Giros B, Schwartz JC (1992) Pharmacology of human dopamine D3 receptor expressed in a mammalian cell line: comparison with D2 receptor. European journal of pharmacology 225:331.

Sokolowski JD, Conlan AN, Salamone JD (1998) A microdialysis study of nucleus accumbens core and shell dopamine during operant responding in the rat. Neuroscience 86:1001-1009.

Solla P, Cannas A, Corona M, Marrosu MG, Marrosu F (2013) Dopamine dysregulation syndrome in Parkinson's disease patients with unsatisfactory switching from immediate to extended release pramipexole: a further clue to incentive sensitization mechanisms? Behav Neurol 27:563-566.

Soutschek A, Gvozdanovic G, Kozak R, Duvvuri S, de Martinis N, Harele B, Gray DL, Fehr E, Jetter A, Tobler PN (2020) Dopaminergic D1 receptor stimulation affects effort and risk preferences. Biological Psychiatry 87:678-685.

Squire LR (1992) Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol Rev 99:195-231.

St Onge JR, Floresco SB (2009) Dopaminergic modulation of risk-based decision making. Neuropsychopharmacology 34:681-697.

Stafford D, LeSage MG, Glowa JR (1998) Progressive-ratio schedules of drug delivery in the analysis of drug self-administration: A review. Psychopharmacology (Berl) 139:169-184.

Staley JK, Mash DC (1996) Adaptive increase in D3 dopamine receptors in the brain reward circuits of human cocaine fatalities. The Journal of Neuroscience 16:6100-6106.

Stark AJ, Smith CT, Lin Y-C, Petersen KJ, Trujillo P, van Wouwe NC, Kang H, Donahue MJ, Kessler RM, Zald DH, Claassen DO (2018) Nigrostriatal and mesolimbic D2/3 receptor expression in Parkinson's disease patients with compulsive reward-driven behaviors. The Journal of neuroscience 38:3230-3239.

Steel Z, Blaszczynski A (1998) Impulsivity, personality disorders and pathological gambling severity. Addiction 93:895-905.

Steeves TD, Miyasaki J, Zurowski M, Lang AE, Pellecchia G, Van Eimeren T, Rusjan P, Houle S, Strafella AP (2009) Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [11C] raclopride PET study. Brain 132:1376-1385.

Steffensen C, Mægbæk ML, Laurberg P, Andersen M, Kistorp C, Nørrelund H, Dal J, Jørgensen JOL (2014) Dopamin agonist treatment and fibrotic heart valve disease in hyperprolactinaemia patients. Ugeskrift for læger 176:58.

Steffensen SC, Taylor SR, Horton ML, Barber EN, Lyle LT, Stobbs SH, Allison DW (2008) Cocaine disinhibits dopamine neurons in the ventral tegmental area via use-dependent blockade of GABA neuron voltage-sensitive sodium channels. The European journal of neuroscience 28:2028-2040.

Strejilevich SA, Martino DJ, Igoa A, Manes F (2011) Pathological gambling in a bipolar patient treated with pramipexole. The journal of neuropsychiatry and clinical neurosciences 23:E2-E3.

Striegel-Moore RH, Franko DL (2003) Epidemiology of binge eating disorder. The International journal of eating disorders 34:S19-S29.

Studer B, Apergis-Schoute AM, Robbins TW, Clark L (2012) What are the odds? The neural correlates of active choice during gambling. Front Neurosci 6:46.

Tanabe J, Thompson L, Claus E, Dalwani M, Hutchison K, Banich MT (2007) Prefrontal cortex activity is reduced in gambling and nongambling substance users during decision-making. Hum Brain Mapp 28:1276-1286.

Tanabe LM, Suto N, Creekmore E, Steinmiller CL, Vezina P (2004) Blockade of D2 dopamine receptors in the VTA induces a long-lasting enhancement of the locomotor activating effects of amphetamine. Behav Pharmacol 15:387-395.

Templeton JA, Dixon MJ, Harrigan KA, Fugelsang JA (2015) Upping the reinforcement rate by playing the maximum lines in multi-line slot machine play. J Gambl Stud 31:949-964.

Tippmann-Peikert M, Park JG, Boeve BF, Shepard JW, Silber MH (2007) Pathologic gambling in patients with restless legs syndrome treated with dopaminergic agonists. Neurology 68:301.

Torregrossa MM, Kalivas PW (2008) Microdialysis and the neurochemistry of addiction: Microdialysis: Recent Developments. Pharmacology, biochemistry and behavior 90:261-272.

Tremblay M, Silveira MM, Kaur S, Hosking JG, Adams WK, Baunez C, Winstanley CA (2017) Chronic D2/3 agonist ropinirole treatment increases preference for uncertainty in rats regardless of baseline choice patterns. European Journal of Neuroscience 45:159-166.

Troiano AR, de la Fuente-Fernandez R, Sossi V, Schulzer M, Mak E, Ruth TJ, Stoessl AJ (2009) PET demonstrates reduced dopamine transporter expression in PD with dyskinesias. Neurology 72:1211.

Tupala E, Hall H, Bergström K, Särkioja T, Räsänen P, Mantere T, Callaway J, Hiltunen J, J. T (2001) Dopamine D(2)/D(3)-receptor and transporter densities in nucleus accumbens and amygdala of type 1 and 2 alcoholics. Molecular Psychiatry 6:261-267.

Tziortzi AC, Searle GE, Tzimopoulou S, Salinas C, Beaver JD, Jenkinson M, Laruelle M, Rabiner EA, Gunn RN (2011) Imaging dopamine receptors in humans with [11C]-(+)-PHNO: Dissection of D3 signal and anatomy. NeuroImage (Orlando, Fla) 54:264-277.

Vallelunga A, Flaibani R, Formento-Dojot P, Biundo R, Facchini S, Antonini A (2011) Role of genetic polymorphisms of the dopaminergic system in Parkinson's disease patients with impulse control disorders. Parkinsonism & related disorders 18:397-399.

van Eimeren T, Ballanger B, Pellecchia G, Miyasaki JM, Lang AE, Strafella AP (2009) Dopamine agonists diminish value sensitivity of the orbitofrontal cortex: A trigger for pathological gambling in Parkinson's disease? Neuropsychopharmacology 34:2758-2766.

van Eimeren T, Pellecchia G, Cilia R, Ballanger B, Steeves TD, Houle S, Miyasaki JM, Zurowski M, Lang AE, Strafella AP (2010) Drug-induced deactivation of inhibitory networks predicts pathological gambling in PD. Neurology 75:1711-1716.

Vanderschuren LJ, Everitt BJ (2004) Drug seeking becomes compulsive after prolonged cocaine self-administration. Science 305:1017-1019.

Vela L, Martínez Castrillo JC, García Ruiz P, Gasca-Salas C, Macías Macías Y, Pérez Fernández E, Ybot I, Lopez Valdés E, Kurtis MM, Posada Rodriguez IJ, Mata M, Ruiz Huete C, Eimil M, Borrue C, del Val J, López-Manzanares L, Sebastian AR, Marasescu R (2016) The high prevalence of impulse control behaviors in patients with early-onset Parkinson's disease: A cross-sectional multicenter study. Journal of the neurological sciences 368:150-154.

Velázquez-Sánchez C, Ferragud A, Moore CF, Everitt BJ, Sabino V, Cottone P (2014) High trait impulsivity predicts food addiction-like behavior in the rat. Neuropsychopharmacology 39:2463-2472.

Vengeliene V, Leonardi-Essmann F, Perreau-Lenz S, Gebicke-Haerter P, Drescher K, Gross G, Spanagel R (2006) The dopamine D3 receptor plays an essential role in alcohol-seeking and relapse. The FASEB journal 20:2223-2233.

Verdejo-Garcia A, Lawrence AJ, Clark L (2008) Impulsivity as a vulnerability marker for substance-use disorders: Review of findings from high-risk research, problem gamblers and genetic association studies. Neuroscience and biobehavioral reviews 32:777-810.

Vezina P (2004) Sensitization of midbrain dopamine neuron reactivity and the self-administration of psychomotor stimulant drugs. In, pp 827-839. Oxford: Elsevier Ltd.

Vogel HP, Schiffter R (1983) Hypersexuality--a complication of dopaminergic therapy in Parkinson's disease. Pharmacopsychiatria 16:107.

Volkow ND, Fowler JS (2000) Addiction, a disease of compulsion and drive: Involvement of the orbitofrontal cortex. Cerebral Cortex 10:318-325.

Volkow ND, Morales M (2015) The brain on drugs: From reward to addiction. Cell 162:712-725.

Volkow ND, Fowler JS, Wang GJ (2003) The addicted human brain: Insights from imaging studies. The Journal of Clinical Investigation 111:1444-1451.

Volkow ND, Wang G-J, Fowler JS, Tomasi D (2012) Addiction circuitry in the human brain. Annual review of pharmacology and toxicology 52:321-336.

Volkow ND, Wang G-J, Fowler JS, Tomasi D, Telang F, Brookhaven National L (2011) Addiction: Beyond dopamine reward circuitry. Proceedings of the National Academy of Sciences - PNAS 108:15037-15042.

Volkow ND, Fowler JS, Wang GJ, Hitzemann R, Logan J, Schlyer DJ, Dewey SL, Wolf AP (1993) Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. Synapse 14:169-177.

Volkow ND, Wang G-J, Fowler JS, Hitzemann R, Angrist B, Gatley SJ, Logan J, Ding Y-S, Pappas N (1999) Association of methylphenidate-induced craving with changes in right striato-orbitofrontal metabolism in cocaine abusers: implications in addiction. The American journal of psychiatry 156:19-26.

Volkow ND, Wang G-J, Ma Y, Fowler JS, Wong C, Ding Y-S, Hitzemann R, Swanson JM, Kalivas P (2005) Activation of orbital and medial prefrontal cortex by methylphenidate in cocaine-addicted subjects but not in controls: relevance to addiction. The Journal of neuroscience 25:3932-3939.

Volkow ND, Wang G-J, Fowler JS, Thanos P, Logan J, Gatley SJ, Gifford A, Ding Y-S, Wong C, Pappas N (2002) Brain DA D2 receptors predict reinforcing effects of stimulants in humans: Replication study. Synapse (New York, NY) 46:79-82.

Volkow ND, Wang G-J, Telang F, Fowler JS, Thanos PK, Logan J, Alexoff D, Ding Y-S, Wong C, Ma Y, Pradhan K (2008) Low dopamine striatal D2 receptors are associated with prefrontal metabolism in obese subjects: Possible contributing factors. NeuroImage (Orlando, Fla) 42:1537-1543.

Volkow ND, Chang L, Wang GJ, Fowler JS, Ding YS, Sedler M, Logan J, Franceschi D, Gatley J, Hitzemann R, Gifford A, Wong C, Pappas N (2001) Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. The American Journal of Psychiatry 158:2015-2021.

Voon V, Fox SH (2007) Medication-related impulse control and repetitive behaviors in Parkinson disease. Archives of neurology (Chicago) 64:1089.

Voon V, Potenza MN, Thomsen T (2007a) Medication-related impulse control and repetitive behaviors in Parkinson's disease. Current opinion in neurology 20:484-492.

Voon V, Hassan K, Zurowski M, Duff-Canning S, de Souza M, Fox S, Lang AE, Miyasaki J (2006) Prospective prevalence of pathologic gambling and medication association in Parkinson disease. Neurology 66:1750.

Voon V, Gao J, Brezing C, Symmonds M, Ekanayake V, Fernandez H, Dolan RJ, Hallett M (2011) Dopamine agonists and risk: Impulse control disorders in Parkinson's disease. Brain 134:1438-1446.

Voon V, Thomsen T, Miyasaki JM, de Souza M, Shafro A, Fox SH, Duff-Canning S, Lang AE, Zurowski M (2007b) Factors associated with dopaminergic drug-related pathological gambling in Parkinson disease. Archives of Neurology 64:212-216.

Voon V, Rizos A, Chakravartty R, Mulholland N, Robinson S, Howell NA, Harrison N, Vivian G, Ray Chaudhuri K (2014a) Impulse control disorders in Parkinson's disease: decreased striatal dopamine transporter levels. Journal of neurology, neurosurgery and psychiatry 85:148-152.

Voon V, Reynolds B, Brezing C, Gallea C, Skaljic M, Ekanayake V, Fernandez H, Potenza MN, Dolan RJ, Hallett M (2010) Impulsive choice and response in dopamine agonist-related impulse control behaviors. Psychopharmacology (Berl) 207:645-659.

Voon V, Mole TB, Banca P, Porter L, Morris L, Mitchell S, Lapa TR, Karr J, Harrison NA, Potenza MN, Irvine M (2014b) Neural correlates of sexual cue reactivity in individuals with and without compulsive sexual behaviours. PloS one 9:e102419-e102419.

Voon V, Ardouin C, Worbe J, Czernecki V, Abouazzar N, Hosseini H, Pelissolo A, Moro E, Lhommee E, Agid Y, Benabid A, Pollak P, Mallet L, Krack P (2007c) The effects of subthalamic deep brain stimulation on pathological gambling in Parkinson disease: A multicenter case series. The Journal of Neuropsychiatry and Clinical Neurosciences 19:223.

Vriend C, Nordbeck AH, Booij J, van der Werf YD, Pattij T, Voorn P, Raijmakers P, Foncke EMJ, van de Giessen E, Berendse HW, van den Heuvel OA (2014) Reduced dopamine transporter binding predates impulse control disorders in Parkinson's disease. Movement disorders 29:904-911.

Walker SE, Abbott MW, Gray RJ (2012) Knowledge, views and experiences of gambling and gambling-related harms in different ethnic and socio-economic groups in New Zealand. Australian and New Zealand journal of public health 36:153-159.

Waters RP, Moorman DE, Young AB, Feltenstein MW, See RE (2014) Assessment of a proposed "three-criteria" cocaine addiction model for use in reinstatement studies with rats. Psychopharmacology (Berl) 231:3197-3205.

Webbe FM, Malagodi EF (1978) Second-order schedules of token reinforcement: Comparisons of performance under fixed-ratio and variable-ratio exchange schedules. Journal of the Experimental Analysis of Behavior 30:219-224.

Weintraub D, Claassen DO (2017) Impulse control and related disorders in Parkinson's disease. International Review of Neurobiology 133:679-717.

Weintraub D, Mamikonyan E (2019) Impulse control disorders in Parkinson's Disease. American Journal of Psychiatry 176:5-11.

Weintraub D, Siderowf AD, Potenza MN, Goveas J, Morales KH, Duda JE, Moberg PJ, Stern MB (2006a) Association of dopamine agonist use with impulse control disorders in Parkinson disease. Arch Neurol 63:969-973.

Weintraub D, Siderowf AD, Potenza MN, Goveas J, Morales KH, Duda JE, Moberg PJ, Stern MB (2006b) Association of dopamine agonist use with impulse control disorders in Parkinson disease. Archives of Neurology 63:969-973.

Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, Whetteckey J, Wunderlich GR, Lang AE (2010) Impulse control disorders in Parkinson Disease. A Cross-sectional study of 3090 patients. Archives of Neurology 67:589-595.

Weintraub D, Hoops S, Shea JA, Lyons KE, Pahwa R, Driver-Dunckley ED, Adler CH, Potenza MN, Miyasaki J, Siderowf AD, Duda JE, Hurtig HI, Colcher A, Horn SS, Stern MB, Voon V (2009) Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease. Movement disorders 24:1461-1467.

Wermuth L (1998) A double-blind, placebo-controlled, randomized, multi-center study of pramipexole in advanced Parkinson's disease. European Journal of Neurology 5:235-242.

Williams DC, Saunders KJ, Perone M (2011) Extended pausing by humans on multiple fixed-ratio schedules with varied reinforcer magnitude and response requirements. J Exp Anal Behav 95:203-220.

Williams RJ, Volberg RA, Stevens RMG (2012) The population prevalence of problem gambling: methodological influences, standardized rates, jurisdictional differences, and worldwide trends. In: Report prepared for the Ontario Problem Gambling Research Centre and the Ontario Ministry of Health and Long Term Care.

Williams RJ, Leonard CA, Belanger YD, Christensen DR, el-Guebaly N, Hodgins DC, McGrath DS, Nicoll F, Stevens RMG (2021) Gambling and problem gambling in Canada in 2018: Prevalence and changes since 2002. The Canadian Journal of Psychiatry 66:485-494.

Winstanley CA, Clark L (2016) Translational models of gambling-related decision making. Current Topics in Behavioral Neursciences 28:93-120.

Winstanley CA, Cocker PJ, Rogers RD (2011) Dopamine modulates reward expectancy during performance of a slot machine task in rats: Evidence for a 'near-miss' effect. Neuropsychopharmacology 36:913-925.

Winstanley CA, Theobald DE, Dalley JW, Robbins TW (2005) Interactions between serotonin and dopamine in the control of impulsive choice in rats: therapeutic implications for impulse control disorders. Neuropsychopharmacology 30:669-682.

Winstanley CA, Zeeb FD, Bedard A, Fu K, Lai B, Steele C, Wong AC (2010) Dopaminergic modulation of the orbitofrontal cortex affects attention, motivation and impulsive responding in rats performing the five-choice serial reaction time task. Behav Brain Res 210:263-272.

Wise RA (2004) Dopamine, learning and motivation. Nature Reviews Neuroscience 5:483-494.

Wolters EC, van der Werf YD, van den Heuvel OA (2008) Parkinson's disease-related disorders in the impulsive-compulsive spectrum. Journal of neurology 255:48-56.

Wrase J, Kahnt T, Schlagenhauf F, Beck A, Cohen MX, Knutson B, Heinz A (2007) Different neural systems adjust motor behavior in response to reward and punishment. Neuroimage 36:1253-1262.

Wu K, Politis M, O'Sullivan SS, Lawrence AD, Warsi S, Bose S, Lees AJ, Piccini P (2015) Single versus multiple impulse control disorders in Parkinson's disease: an 11C-raclopride positron emission tomography study of reward cue-evoked striatal dopamine release. Journal of neurology 262:1504-1514.

Wulff AB, Tooley J, Marconi LJ, Creed MC (2019) Ventral pallidal modulation of aversion processing. Brain research 1713:62-69.

Yang XQ, Glizer D, Vo A, Seergobin KN, MacDonald PA (2016) Pramipexole increases go timeouts but not no-go errors in healthy volunteers. Frontiers in Human Neuroscience 10:523.

Yasui Y, Breder CD, Saper CB, Cechetto DF (1991) Autonomic responses and efferent pathways from the insular cortex in the rat. The Journal of Comparative Neurology 303:355-374.

Yin HH, Knowlton BJ (2006) The role of the basal ganglia in habit formation. Nat Rev Neurosci 7:464-476.

Yin HH, Knowlton BJ, Balleine BW (2004) Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. European Journal of Neuroscience 19:181-189.

Yin HH, Ostlund SB, Knowlton BJ, Balleine BW (2005) The role of the dorsomedial striatum in instrumental conditioning. Eur J Neurosci 22:513-523.

Young K (2009) Understanding online gaming addiction and treatment issues for adolescents. The American journal of family therapy 37:355-372.

Zack M, Featherstone RE, Mathewson S, Fletcher PJ (2014) Chronic exposure to a gambling-like schedule of reward predictive stimuli can promote sensitization to amphetamine in rats. Frontiers in Behavioral Neuroscience 8:36.

Zald DH, Boileau I, El-Dearedy W, Gunn R, McGlone F, Dichter GS, Dagher A (2004) Dopamine transmission in the human striatum during monetary reward tasks. The Journal of Neuroscience 24:4105-4112.

Zand R (2008) Is dopamine agonist therapy associated with developing pathological gambling in Parkinson's disease patients? European Neurology 59:183-186.

Zeeb FD, Robbins TW, Winstanley CA (2009) Serotonergic and dopaminergic modulation of gambling behavior as assessed using a novel rat gambling task. Neuropsychopharmacology 34:2329-2343.

Zeighami Y, Ulla M, Iturria-Medina Y, Dadar M, Zhang Y, Larcher KM, Fonov V, Evans AC, Collins DL, Dagher A (2015) Network structure of brain atrophy in de novo Parkinson's disease. Elife 4.

Zoratto F, Romano E, Pascale E, Pucci M, Falconi A, Dell'Osso B, Maccarrone M, Laviola G, D'Addario C, Adriani W (2017) Down-regulation of serotonin and dopamine transporter genes in individual rats expressing a gambling-prone profile: A possible role for epigenetic mechanisms. Neuroscience 340:101-116.