# Genetics, Drugs, and Cognitive Control: Uncovering Individual Differences in Substance Dependence

by

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BA., Vancouver Island University, 2004
MSc., University of Victoria, 2007

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in the Department of Psychology

# Supervisory Committee

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# Abstract

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Why is it that only some people who use drugs actually become addicted? In fact, addiction depends on a complicated process involving a confluence of risk factors related to biology, cognition, behaviour, and personality. Notably, all addictive drugs act on a neural system for reinforcement learning called the midbrain dopamine system, which projects to and regulates the brain's system for cognitive control, called frontal cortex and basal ganglia. Further, the development and expression of the dopamine system is determined in part by genetic factors that vary across individuals such that dopamine related genes are partly responsible for addiction-proneness. Taken together, these observations suggest that the cognitive and behavioral impairments associated with substance abuse result from the impact of disrupted dopamine signals on frontal brain areas involved in cognitive control: By acting on the abnormal reinforcement learning system of the genetically vulnerable, addictive drugs hijack the control system to reinforce maladaptive drug-taking behaviors.

The goal of this research was to investigate this hypothesis by conducting a series of experiments that assayed the integrity of the dopamine system and its neural targets involved in cognitive control and decision making in young adults using a combination of electrophysiological, behavioral, and genetic assays together with surveys of substance use and personality. First, this research demonstrated that substance dependent individuals produce an abnormal Reward-positivity, an electrophysiological measure of a cortical mechanism for dopamine-dependent reward processing and cognitive control, and behaved abnormally on a decision making task that is diagnostic of dopamine dysfunction. Second, several dopamine-related neural pathways underlying individual

differences in substance dependence were identified and modeled, providing a theoretical framework for bridging the gap between genes and behavior in drug addiction. Third, the neural mechanisms that underlie individual differences in decision making function and dysfunction were identified, revealing possible risk factors in the decision making system. In sum, these results illustrate how future interventions might be individually tailored for specific genetic, cognitive and personality profiles.

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# Acknowledgments

This dissertation is a personal accomplishment that can be shared by those individuals who have provided me with tremendous support, wisdom, and inspiration throughout the last several years. First and foremost, I can't express enough gratitude to my supervisor Dr. Clay Holroyd for allowing me to stand on his shoulders and teach me to be a scientist. Clay, my future students will be lucky that I had such a great mentor to learn from. I look forward to our continued friendship, and research endeavours. I am also grateful to the members of my dissertation committee for their guidance and support. Over the years, Drs. Tim Stockwell, Gordon Barnes, and Patrick Macleod have provided me with exceptional training in different but complementary ways. Tim and Gordon, I will cherish our times together on the golf course. I also want to thank Dr. Mike Hunter for his invaluable statistical guidance since my first day of graduate school. To my fellow graduate students in the CABS and IMPART program, and members of the LCC lab, thank you for stimulating discussions about research and for making the basement of Cornett a great research environment to work in. I gratefully acknowledge members of Edgewood Addiction Treatment Centre, who were able to support our project despite their busy jobs in addiction treatment care. Finally, words cannot express my gratitude, appreciation, and thanks to my family and friends for all their love and support throughout all my travels in life. And to Brent, you ain't heavy, you're my brother. My heart and passion would not have been in this line of research if it wasn't for you.

# Dedication

To Melanie, **I S***aw* **A***n* **A***ngel* **C***ome*...

# General Introduction

Why do some individuals lose control over their substance use? For instance, being presented with a cold beer on a hot day can potentially be rewarding, and a person might have the automatic response to consume it. But when such behaviour conflicts with internal goals (e.g., driving home safely or fulfilling a previous commitment not to drink alcohol), one might inhibit that prepotent response. This choice ability is often termed 'cognitive control' and is defined as the ongoing process of monitoring and controlling thoughts and actions in order to adaptively guide behaviour to meet current and future goals. Yet, for individuals who suffer from severe drug dependence, this ability does not function optimally, and drug related behaviours and goals persist despite catastrophic consequences on personal health, finances, and social relationships. Needless to say, cognitive control and decision making is of longstanding interest to researchers investigating substance dependence, as it is often compromised in individuals with this disorder.

In fact, substance dependence is a major public health concern, with a 12 month prevalence rate in North America of more that 4-9% of the general population (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). In Canada, tobacco alone is consumed by an estimated 15-20% of the population (Health Canada, 2008), and 20% of all drinkers engage in hazardous alcohol use (Canadian Executive Council on Addictions., 2004). The total cost to society−in terms of the burden placed on the Canadian health care system, law enforcement, and workplace productivity−is estimated to be about $40 billion per year (Rehm, Taylor, & Room, 2006). As noted by the Canadian Centre on Substance Abuse,

"Behind the dollar figure is a dramatic toll measured in tens of thousands of deaths, hundreds of thousands of years of productive life lost, and millions of days spent in hospital" (Rehm et al., 2006). Experts suggest that if we are to make substantial inroads in addressing this major public health concern, a better understanding of the neural and cognitive basis underlying individual differences in the vulnerability to drugs and the transition to addiction is critical as it frames how we must ultimately develop strategies to treat this disorder (Leshner, 1997). But in order to arrive at this stage of treatment development, it would first require understanding how important individual variables underlying substance abuse conspire to make that person addicted in the first place.

Over the last several decades, multidisciplinary efforts in addictions research have indicated that substance dependence results from a confluence of risk factors related to biology, cognition, personality, genetics, mental health, sex/gender, culture, and the social environment (Miller & Carroll, 2006). Thus, a simple single-factor theory of addiction would appear unlikely, and it appears inevitable that the next stage in addictions research will need to integrate these levels of analysis in order to construct a multi-dimensional, cognitive-neuroscientific profile of addiction. But despite decades of research, a causal model of addiction that incorporates these multiple levels of analysis remains to be created. Such an approach would appear to be critical for furthering the development of new therapeutic treatments and clinical management for addiction. But in light of the complexities faced, there is as yet little direct evidence in humans of the neuroadaptive mechanisms that mediate the transition from occasional, controlled drug use to the impaired control that characterizes severe dependence (Hyman, 2007). Thus, a better understanding of the biological and cognitive mechanisms that underlie this maladaptive

transitional process could act as a pivotal point within the confluence of risk factors that encompass this disorder, and ultimately help alleviate this public health scourge.

Drawing on recent biologically-inspired theories of cognitive control, decision making, and reinforcement learning, the present thesis is aimed at exploring the relationship between these theories and addiction from a cognitive neuroscience perspective. Particular emphasis is placed on deconstructing the genetic, biological, cognitive, behavioural and personality-related factors underlying individual differences in the vulnerability to drugs and the transition to addiction. This thesis is motivated by five inter-related areas of investigation. **First**, personality studies indicate that individuals characterized by depression, impulsivity, sensation-seeking and other traits exhibit a relatively greater probability of becoming addicted (Goldstein et al., 2005; Kreek, Nielsen, Butelman, & LaForge, 2005; Goldstein et al., 2007a). **Second**, biological studies indicate that addiction is in fact a disorder of cognitive control and decision making: All addictive drugs act on a neural system for reinforcement learning called the midbrain dopamine system, which projects to and regulates the brain's system for cognitive control and decision making, namely anterior cingulate cortex and basal ganglia (Volkow, Fowler, Wolf, & Gillespi, 1990; Volkow & Li, 2005; Goldstein et al., 2007c; Volkow, Fowler, Wang, Baler, & Telang, 2009; Volkow, 2008). **Third**, genetic studies indicate that the development and expression of the dopamine system is determined in part by genetic factors that vary across individuals such that dopamine-related genes are partly responsible for addiction-proneness (Volkow et al., 1993; Volkow et al., 2001; Volkow et al., 2002). **Fourth**, a recent theory by Holroyd and Coles (2002), the "reinforcement learning theory of the ERN" or RL-ERN theory, holds that the impact of these dopamine signals on the

anterior cingulate cortex elicits a component of the event-related brain potential (ERP) called the "Reward-positivity", and that the anterior cingulate cortex uses these signals for the adaptive modification of behavior according to principles of reinforcement learning. **Fifth,** the Basal Ganglia Go/NoGo model (Frank et al. 2004) proposes that dopaminergic signaling in the basal ganglia can facilitate or suppress action representations during a Probabilistic Selection Task (PST): phasic bursts of dopamine activity facilitate approach learning by reinforcing striatal connections that express D1 receptors (the "Go" pathway), whereas phasic dips in dopamine activity facilitate avoidance learning by reinforcing striatal connections that express D2 receptors (the "NoGo" pathway).

Based on these areas of investigation, the thesis of this research is that drug addiction involves cognitive and behavioral impairments associated with the impact of disrupted dopamine signals on frontal (i.e. anterior cingulate cortex and orbitofrontal cortex) and subcortical (i.e. basal ganglia) brain areas involved in cognitive control and decision making: By acting on the abnormal reinforcement learning system of the genetically vulnerable, addictive drugs hijack the control system to reinforce maladaptive drug-taking behaviors and goals. The functional consequence of this maladaptive process is the *loss of cognitive control*: the impaired ability to regulate and control one's decision-making, in that many substance abusers are unable to regulate their maladaptive drug-taking behavior despite appearing to want to do so. This hypothesis can be directly tested by combining the allelic association method of behavioural genetics with the methods of modern cognitive neuroscience in the context of contemporary theories of cognitive control, decision making and reinforcement learning. Here I present a series of three experiments that 1) examined whether substance abusers produce abnormal dopamine-

related reinforcement learning signals cortically and subcortically; 2) investigated the issue of causality, whether people who abuse substances are characterized in part by genetic abnormalities that a) render the dopamine system vulnerable to the potentiating effects of addictive drugs, or b) underlie personality traits associated with drug abuse; and 3) assessed the impact of addiction therapy on dopamine mechanisms of reinforcement learning, which are believed to constitute the primary neurobiological cause of addiction.

## Reinforcement Learning and Cognitive Control

How we learn from rewards and punishments is fundamental to theories of reinforcement learning. The subject of reinforcement learning is learning what to do−how to map states to actions−to maximize future rewards and avoid punishments (for review, see Sutton & Barto, 1998). The ability to function optimally in this context crucially depends on learning the contingencies between behaviour and reinforcement. That is, we monitor how the environment responds to our actions and seek to influence what happens through trial-and-error search for behaviours that maximize rewards. Exploration of these relationships produces a wealth of information about cause and effect, the consequences of actions, and what to do in order to achieve goals (Sutton & Barto, 1998). In the past, theoretical and empirical investigations into this fundamental principle have provided insight into the laws that govern the functional relationship between action and consequence. One very influential law is *Thorndike's Law of Effect*:

> *"Of several responses made to the same situation, those which are accompanied or closely followed by satisfaction to the animal will, other things being equal, be more firmly connected with the situation, so that, when it recurs, they will be more likely to recur; those which are accompanied or closely followed by discomfort to the animal will, other things being equal, have their connections with that situation weakened, so that, when it recurs, they will be less likely to occur. The greater the satisfaction or discomfort, the greater the strengthening or weakening of the bond."*
> Thorndike, 1911, p.244.

In other words, if an action is followed by a reward (positive feedback) then that action will likely be performed again, whereas if the action is followed by a punishment (negative feedback) then that action will not likely be performed again (for review, see Catania, 1999). Today, recent advances in the field of cognitive neuroscience have provided researchers with a window onto the neural and cognitive mechanisms that underlie reinforcement learning, particularly our ability to detect rewards, learn to predict future rewards from past experience, and use reward information to learn, choose, prepare and execute goal-directed behaviour.

One of the most fascinating aspects of human cognition is the relationship between reinforcement learning and cognitive control. Cognitive control is a broad and general construct that refers to the functions needed for the deliberate control of thought, emotion and actions in order to guide an organism to meet current and future goals (i.e., goal-directed behavior) (Miller & Cohen, 2001). These control functions are particularly invoked in situations that require selecting, organizing, and monitoring processes such as "inhibition", "planning", "set shifting", "flexibility", and "problem solving". While a remarkable feature of the human cognitive system is its ability to configure itself for the performance of specific tasks through appropriate adjustments of these functions, how the cognitive control system utilizes mechanisms for reinforcement learning remains poorly

understood. Yet, over the last decade, Schultz and colleagues, (1998), Holroyd & Coles, (2002), and Frank and colleagues (2004) have developed a theoretical framework to understand and empirically investigate cognitive control from the perspective of reinforcement learning.

In particular, multiple lines of evidence indicate that an important role of the midbrain dopamine system is to provide reinforcement learning signals to brain structures involved in cognitive control and decision making (Schultz, 2002) , the net effect of which is to guide the flow of activity along neural pathways that establish the proper mappings between inputs, internal states, and outputs needed to perform a given task. More so, animal and human studies highlight the role of the anterior cingulate cortex and basal ganglia in many aspects of reinforcement learning (i.e. coding stimulus–reward value, predicting future reward, and integrating reward predictions to guide behavior (Holroyd & Coles, 2002; Frank, Seeberger, & O'reilly, 2004; Frank & Claus, 2006).

## The Midbrain Dopamine System

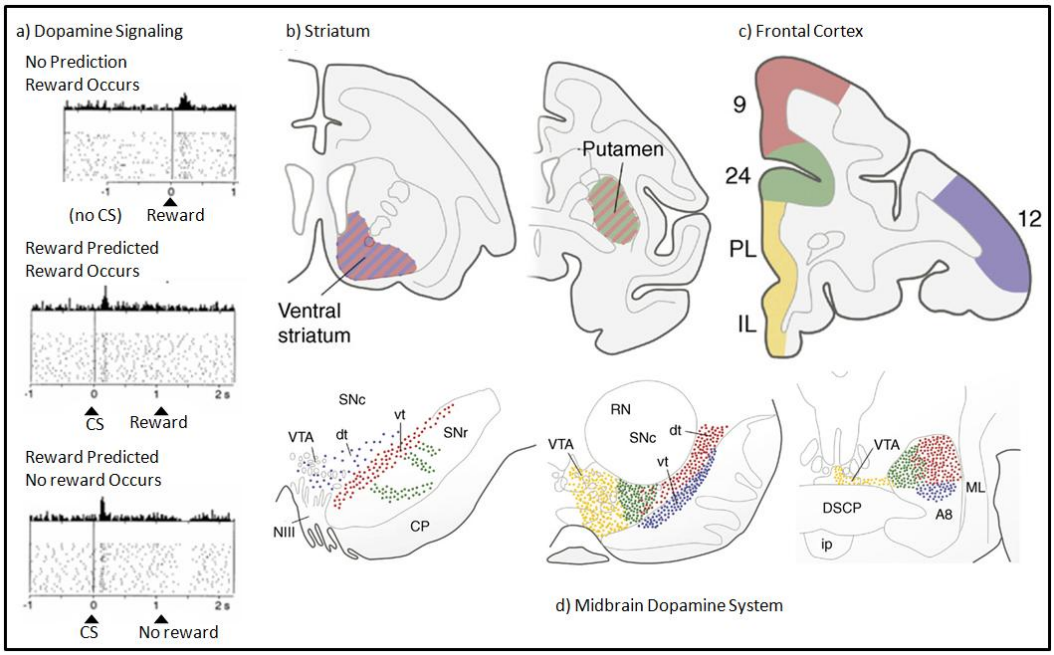


**Figure 1. The midbrain dopamine system and its neural targets. A) Dopamine RPE signals. Raster plots depict dopamine cell activity during individual trials; histograms depict activity pooled across trials. CS = conditioned stimulus, s = second. Adapted from: Schultz (1998). Distribution of midbrain DA neurons (d) projecting to striatal (b) and cortical (c) areas in the primate. Abbreviations: CP, cerebral peduncle; DSCP, decussation of the superior cerebellar peduncle; dt, dorsal tier; IL, infralimbic area of the frontal cortex; ip, interpeduncular nucleus; ML, medial lemniscus; NIII, occulomotor nerve exit; PL, prelinbic area of the frontal cortex; RN, red nucleus; vt, ventral tier; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; VTA, ventral tegmental area. Broadman area 24 (dorsal anterior cingulate cortex), 12 (orbital frontal cortex), 9 (dorsal lateral prefrontal cortex). Adapted from: Björklund and Dunnett, (2007).**

Dopamine (DA) producing neurons comprise a major neuromodulatory system in the brain that is important for motor function, arousal, motivation, emotion, learning, and memory. While DA neurons have been classified into nine distinct nuclei: A8–A16, it is often presumed, as a convenient heuristic, that the mesencephalon contains two major DA nuclei subtypes: the substantia nigra pars compacta (A9) projecting to the striatum along

the nigrostriatal pathway, and the ventral tegmental area (A10) projecting to limbic and cortical areas along mesolimbic and mesocortical pathways (see Figure 1) (reviewed by (Bjorklund & Dunnett, 2007). Not surprisingly, because each of these neural targets of the DA system modulate distinct aspects of cognition and behaviour, alterations in the DA system are linked to numerous neurological and psychiatric disorders ranging from Parkinson's disease to schizophrenia (Maia & Frank, 2011). In recent years, the fundamental biological role of DA in cognitive control, decision making and reinforcement learning are becoming increasingly understood, and as a result, have rekindled interest by many biomedical researchers and clinicians investigating substance dependence. Much of this interest has been motivated by the influential hypothesis that the functional role of the midbrain DA system and its neural targets are to detect rewards, learn to predict future rewards from past experience and use reward information to learn, choose, prepare and execute goal-directed behaviour (Schultz, 2002).

In a seminal study, Schultz and colleagues (1997), using electrophysiological techniques to record the activity of individual midbrain DA neurons in primates learning to perform simple delayed response tasks, demonstrated that DA neurons respond to changes in the prediction of the "goodness" of ongoing events. In brief, when a primate was required to press a lever every time a conditioned stimulus (CS) appeared (a green light), the presentation of the reward elicited a phasic increase in DA cell activity (i.e., a burst of action potentials; Figure. 1, top left). Critically, once the primate had learned to perform the task correctly, the phasic increase in DA activity occurred at the time of the CS, and not at the reward itself. Thus, this finding demonstrated that with learning, the DA signal "propagates back in time" from the point at which the reward is delivered to the onset of

the CS that predicts it (Figure. 1, middle left). It has been suggested that these signals appear to amplify the "incentive salience" or "wanting" of rewards, thereby increasing the frequency and intensity of behaviour that leads to the acquisition of rewarding objects (Schultz, 2002). It is important to note that this process is distinct from the affective enjoyment or "liking" of the reward when consumed (McClure, Daw, & Montague, 2003). Of particular relevance here is the observation that omission of an expected reward leads to a transient cessation in DA neuronal activity (~ 100 ms) that occurs precisely at the same time that the reward would otherwise have been delivered (Figure. 1, bottom left ) (Schultz, 2002). Thus, the midbrain DA system becomes active in anticipation of a forthcoming reward, rather than upon delivery of the reward itself, and becomes relatively de-activated when an anticipated reward fails to materialize. These observations have profoundly influenced contemporary notions regarding the role of DA in reinforcement learning (Schultz, 2002).

The primary conclusion from these earlier studies was that phasic increases in DA activity, seen as bursts of action potentials, are elicited when events are "better than expected", and phasic decreases of DA activity, seen as transient cessations from baseline firing rate, are elicited when events are "worse than expected" (Schultz, 1997; Schultz, Dayan, & Montague, 1997; Schultz, 2002). Thus, the midbrain DA system becomes active in anticipation of a forthcoming reward, rather than upon delivery of the reward itself, and becomes relatively de-activated when an anticipated reward fails to materialize. In support of this view, DA is considered to play an important role in the coordination and regulation of long term potentiation (LTP) and depression (LTD) by acting in a bidirectional manner[1]

[1] LTP is a long-lasting enhancement in signal transmission between two neurons that results from stimulating them synchronously. It is one of several phenomena underlying synaptic plasticity, the ability of chemical

(Wickens, Begg, & Arbuthnott, 1996; Calabresi et al., 2000; Reynolds & Wickens, 2002). To accomplish this, (i) DA exerts stimulatory effects via D1 receptors subtypes (D1, D5), and inhibitory effects via D2 receptors subtypes ($D2_S$, $D2_L$, D3, D4); (ii) the role of tonic (background) DA levels are different from that of phasic (or event-related) DA release; and (iii) optimal DA levels are required for best performance (Trantham-Davidson, Neely, Lavin, & Seamans, 2004; Seamans & Yang, 2004; Floresco, West, Ash, Moore, & Grace, 2003; Goto, Otani, & Grace, 2007; Grace, 1991; Onn, Wang, Lin, & Grace, 2006). The two signaling modes (tonic, phasic) are further distinguished due to different affinities of DA receptors (Wall et al., 2011; Goto et al., 2007). Phasic bursts, which tend to be elicited within 50 ms to 110 ms in response to salient environmental events (e.g. unexpected rewards), and last approximately 200 ms or less (Schultz, 2002), preferentially activates low affinity D1 receptors, which are driven primarily by excitatory glutamatergic inputs in response to salient environmental events (Goto & Grace, 2005; Grace, Floresco, Goto, & Lodge, 2007). Specifically, postsynaptic D1 stimulation facilitates and prolongs an excitatory effect on neural firing (Lewis & O'Donnell, 2000), leading to the facilitation and maintenance of LTP of task relevant input or actions (Calabresi et al., 2000). By contrast, tonic DA level may be sufficient to strongly activate high-affinity D2/D4 receptors, but weakly activate low-affinity D1 receptors. In particular, tonically facilitated D2/D4 activity appears to dampen and suppress neuronal activity either via an excitation of inhibitory interneurons or, pre/postsynaptic D2/D4 stimulation (Goto & Grace, 2005; Grace et al., 2007), inadvertently impacting phasic signaling (Gorelova, Seamans, & Yang,

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synapses to change their strength. As long-term memories are thought to be encoded by modification of synaptic strength, LTP has been widely considered one of the major cellular mechanisms that underlie learning and memory. LTD is the opposing process to LTP, an activity-dependent reduction in the efficacy of neuronal synapses (Sheynikhovich, Otani, & Arleo, 2011; Calabresi et al., 2000).

2002). Release of this suppression of neural activity is facilitated by transient dips in DA mediated by pauses in DA neuron activity, such as those observed following omission of anticipated reward (Schultz, 1998; Schultz, 1999). Depressions in the firing of DA neurons have a similar latency to phasic bursts to rewards, but with a longer duration (Schultz, 2002). Importantly, it has been proposed that insufficient time of DA exposure results in no plasticity or LTD (Sheynikhovich et al., 2011). Yet, others claim that low DA levels actually prevents LTP and induces LTD in D1 containing striatal cells, and facilitates LTP in D2 containing striatal cells (Shen et al. 2008).

This fundamental complementarity of tonic and phasic DA transmission and reciprocity of D2 and D1 receptor stimulation is supported by detailed cellular studies and biophysical modeling. In particular, differential localization of D2/D1 receptor types can give rise to the separation of signaling modes. For example, one hypothesis suggested that D2 receptors in prefrontal cortex are preferentially activated by phasic DA activity, and D1 receptors are preferentially activated by tonic DA activity (Seamans & Yang, 2004). Another hypothesis states that phasic bursts in DA neurons in response to behaviorally relevant stimuli trigger the phasic component of DA release onto postsynaptic D1 targets in subcortical regions. In contrast, tonic DA levels are proposed to regulate the amplitude of the phasic DA response via stimulation of highly sensitive DA terminal D2 autoreceptors. In this way, low tonic DA release would set the sensitivity of the DA system to behaviorally activating stimuli. Summaries of the tonic–phasic DA hypothesis are published elsewhere (Bilder, Volavka, Lachman, & Grace, 2004a; Floresco et al., 2003; Grace, 1991).

These mechanisms highlight the important role of DA in adjusting associative strengths between stimuli and responses for the purpose of gradually optimizing behavior to reach goals. Furthermore, several groups of investigators have noted similarities between the phasic activity of the midbrain DA system and a particular reinforcement learning signal called a temporal difference error or reward prediction errors (RPE), which is associated with a generalization of the Rescorla-Wagner learning rule to the continuous time domain (Schultz, 1997). RPEs are computed as the difference between the experienced "value" of ongoing events and the predicted value of those events. A positive RPE indicates that an event has greater value than originally predicted, whereas a negative RPE indicates that an event has less value than predicted. These observations suggest that the midbrain DA neurons carry a RPE signal to their neural targets, where the signal is used for the purpose of action selection and reinforcement learning. Importantly, these RPEs appear to be utilized by cortical structures (especially orbital frontal cortex, dorsolateral prefrontal cortex and anterior cingulate cortex) (Holroyd & Coles, 2002) and the basal ganglia (Frank et al., 2004) for the purpose of cognitive control and decision making. How these RPE signals shape the structure and function of these neural targets are becoming increasingly understood, and will be discussed in more detail below.

*Genetic Variation in Dopaminergic Expression.* Importantly, dysregulated DA function and altered DA expression are considered to be involved in the biology of several psychiatric disorders such as substance dependence proneness (Volkow et al., 1993; Volkow et al., 2001; Volkow et al., 2002). The DRD2 gene (DRD2) itself has remained a candidate in genetic studies of many psychiatric and neurological diseases (Amadeo et al., 2000; Noble, 2003), although there is limited information as to how the known variations

in the gene would translate into a vulnerability to disease. Nevertheless, it has been suggested that addiction vulnerability is a symptom of a 'reward deficiency syndrome', which is comprised of a spectrum of impulsive, compulsive, and addictive disorders that are based on a common genetic deficiency in the dopamine D2 receptor (Blum et al., 1995; Comings & Blum, 2000). Notably, of all the known dopamine related polymorphisms, the *A1 allele of the TaqI (A1/A2) SNP (rs1800497) of the DRD2 gene,* has been studied extensively as a candidate gene implicated in substance abuse (Noble, 2000a) , novelty seeking (Kazantseva, Gaysina, Malykh, & Khusnutdinova, 2011) and recently, impaired error learning (Klein et al., 2007). People who carry the A1 variant express fewer striatal D2 receptors. However, several studies have failed to find an association between the Taq1A SNPs and D2 density, and the Taq1A effects on D2 expression have been proposed to be a result of an indirect association with C957T SNP of the DRD2 gene (Zhang et al., 2007; Laruelle, Gelernter, & Innis, 1998; Lucht & Rosskopf, 2008). In particular, the *C allele of the C957T (C/T) SNP (rs6277)* (Hirvonen et al., 2009; Hirvonen et al., 2004; but see Duan et al., 2003), and recently, the *T allele of the promoter Zhang_SNP-2 (C/T) (rs12364283)* (Zhang et al., 2007) of the DRD2 gene, have been identified to cause a reduction in striatal D2 receptor expression and binding potential. It has been suggested that individuals with low D2 expression are likely to repeat behaviors that result in increased dopamine levels in order to compensate for a chronically low "reward" state. Consistent with this idea, studies have shown that healthy individuals with relatively few striatal D2 receptors report relatively greater pleasure from psychostimulant administration , while individuals with higher levels of D2 receptors experienced the stimulant as "too much" and unpleasant (Volkow et al., 1999a; Volkow et al., 1999b). Further, a relative

paucity of striatal D2 receptors have been found in cocaine abusers, which was also found to be associated with decreased anterior cingulate and orbital frontal cortex metabolism (Volkow et al., 2009; Volkow, Fowler, & Wang, 1999). Together, these findings suggest that low D2 availability may result in smaller reward-induced activity in regions critical for cognitive control, thereby resulting in a decreased sensitivity to natural reinforcers.

Further, there has been an emerging literature examining genetic variations in the DRD4 gene in the context of personality traits (i.e. sensation seeking and impulsivity), addiction-related phenotypes (i.e. drinking and alcohol craving), cognitive control (i.e. error monitoring), and psychiatric disorders (Oak, Oldenhof, & Van Tol, 2000). In animal studies, expressions of D4 receptors have been shown to modulate exploratory behavior as well as drug sensitivity (Dulawa, Grandy, Low, Paulus, & Geyer, 1999; Rubinstein et al., 1997). For example, DRD4 knockout mice display hypersensitivity to drugs of abuse such as ethanol, cocaine and methamphetamine (Rubinstein et al., 1997), show decreased behavioral exploration of novel stimuli (Dulawa et al., 1999), perform better than their wild-type litter mates on complex motor tasks (Rubinstein et al., 1997), and show enhanced cortical glutamate neuronal activity (Rubinstein et al., 2001), supporting the idea that DRD4 receptors normally act as inhibitors of neuronal activity. In human studies, because the D4 receptor has been show to be preferentially expressed in limbic and prefrontal systems, it has been implicated with emotional function, motivation, planning, and reward processing, and has been extensively studied as a candidate gene for novelty seeking traits, attention deficit hyperactivity disorder, schizophrenia, and recently, substance dependence (Oak et al., 2000). In particular, there has been a number of studies focusing on the ‘long’ allele (VNTR-L = 7 or more repeats, VNTR-S =6 or less repeats) of

the variable number of tandem repeats (VNTR) polymorphism in exon III (McGeary, 2009) because of its functional effects on the D4 receptor. In particular, when compared to VNTR-S, evidence suggests that VNTR-L demonstrates a blunted intracellular response to dopamine, does not appear to bind dopamine antagonists and agonists with great affinity, and are associated with attenuated inhibition of intracellular signal transduction (Oak et al., 2000). Consistent with this evidence, studies have shown that carriers of VNTR-L are associated with greater transient brain responses (e.g. cingulate cortex, prefrontal cortex) and behavioral reactivity (e.g., stronger craving, more arousal) to drug-related cues, suggesting its role in the development and expression of incentive salience, craving, and relapse vulnerability (McGeary, 2009; Mackillop, Menges, McGeary, & Lisman, 2007; Hutchison, McGeary, Smolen, Bryan, & Swift, 2002). More importantly, two recent studies demonstrated that the effect of a VNTR on substance abuse is mediated by the personality trait of sensation seeking, building on the idea of specific pathways of risk associated with genetic influences on alcohol use and abuse phenotypes (Ray et al., 2009; Laucht, Becker, Blomeyer, & Schmidt, 2007).

In parallel, other studies have shown that the promoter -521 (C/T) SNP (rs1800955) of the DRD4 gene, with the T allele resulting in 40% less transcriptional efficiency (Okuyama, Ishiguro, Toru, & Arinami, 1999) impacts prefrontal functioning related to performance monitoring (Marco-Pallares et al., 2009; Kramer et al., 2007). For example, Kramer et al. (2007) demonstrated that carriers of the T allele of the promoter -521 (C/T) SNP produced an increased cortical response after both choice errors and failed inhibitions, suggesting distinct effects of the DRD4 polymorphism on error monitoring processes. Similarly, an fMRI study found a correlation between the insertion allele

variant of the indel -1217G ins/del (-/G) (rs12720364) DRD4 polymorphism gene, and greater conflict monitoring activation in the anterior cingulate cortex (Fan, Fossella, Sommer, Wu, & Posner, 2003; Fossella et al., 2002). Because the variants of the DRD4 gene appear to influence activity of anterior cingulate cortex, a cortical region strongly implicated in both substance dependence (Goldstein et al., 2007c; Peoples, 2002) and high-level cognitive control of motor behavior, (Holroyd & Coles, 2008; Holroyd & Coles, 2002), the DRD4 gene would an appropriate candidate to investigate cognitive control and substance dependence.

Finally, as a number of studies indicate, the Catechol-O-methyltransferase (COMT) gene has been linked to both prefrontal cortex functioning and addiction (Beuten, Payne, Ma, & Li, 2006; Horowitz et al., 2000; Meyer-Lindenberg et al., 2005; Tammimaki & Mannisto, 2010). COMT is an enzyme which plays a crucial role in the metabolism of DA in the synaptic cleft. In particular, the val158met polymorphism accounts for a four-fold variation in DA catabolism (Matsumoto et al., 2003; Chen et al., 2004; Meyer-Lindenberg et al., 2005; Grace, 1991; Bilder, Volavka, Lachman, & Grace, 2004), such that the Val/Val (increase in COMT activity) and Met/Met (decrease in COMT activity) polymorphism are thought to decrease and increase, respectively, tonic dopamine levels in frontal cortex, while the VAL/MET have intermediate levels of COMT activity. Because dopamine is believed to regulate the working memory functions of prefrontal cortex (Cools & D'Esposito, 2011; Jones, 2002), the COMT enzyme modulates working memory in prefrontal cortex via its effect on dopamine levels (Meyer-Lindenberg et al., 2005; Meyer-Lindenberg et al., 2006). For example, one study demonstrated that subjects with only the MET allele made significantly fewer errors on the Wisconsin Card Sort Test, a

task demanding cognitive flexibility, than did subjects with the VAL allele (Malhotra et al., 2002). Additionally, a recent study has indicated that the COMT gene may modulate the ability to adjust behavior rapidly following negative feedback (Frank, Moustafa, Haughey, Curran, & Hutchison, 2007), and thought to reflect exploratory adjustments to gather information given uncertainty about reward statistics (regardless of outcome valence) (Frank et al. 2009).

. Because the COMT gene has been linked to a number of prefrontal functions, including cognitive flexibility and working memory, it has been recently proposed to be genetic risk factor in the vulnerability to addiction, such as opioid (Oosterhuis et al., 2008), nicotine (Beuten et al., 2006)), and cannabis (Baransel Isir et al., 2008; but see Tammimaki & Mannisto, 2010).

**Anterior Cingulate Cortex, Cognitive Control, and the Reward-positivity**

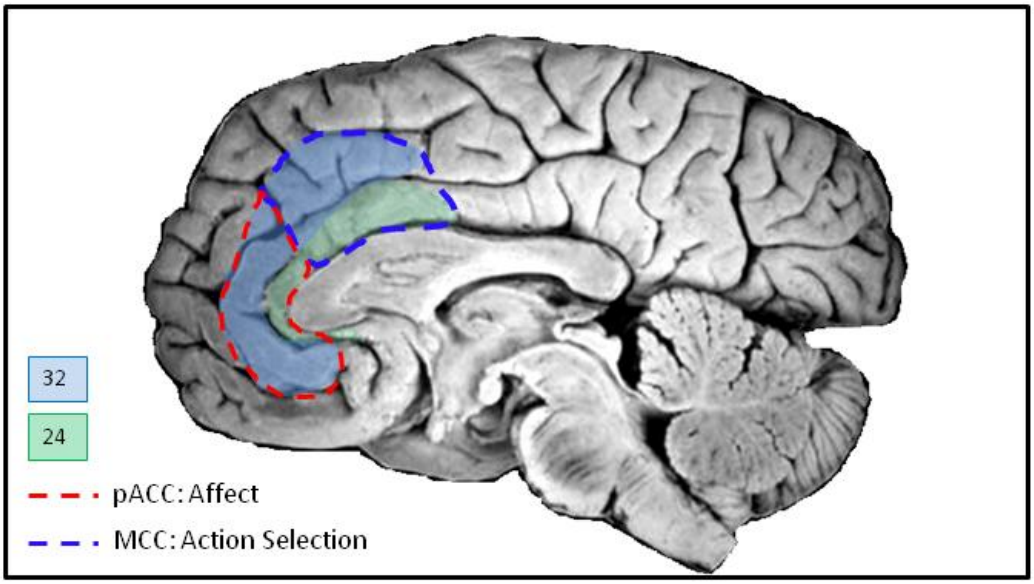

**Figure 2. The Anterior Cingulate Cortex. The anterior cingulate cortex can be divided anatomically into Brodmann area 32 (Blue), and Brodmann area 24 (Green) and functionally into perigenual (pACC: red dashed line) and mid-anterior cingulate (MCC: blue dashed line) regions.**

The anterior cingulate cortex (ACC) is the frontal part of the cingulate cortex and includes Broadmann's areas 24 (Figure 2 Green) and 32 (Figure 2 Blue). The inner border of Area 32, the cingulate sulcus, composes about half of its surface, and its ventral border extends along the rostral sulcus almost to the margin of the frontal lobe. Area 24 forms an arc around the genu of corpus callosum, and its outer border corresponds approximately to the cingulate sulcus. According to recent anatomical evidence (e.g. cytology, imaging, and connectivity), the ACC is actually the perigenual region (Figure 2: red dashed border), and considered separate from the mid-anterior cingulate region (Figure 2: Blue dashed border) (Vogt, Nimchinsky, Vogt, & Hof, 1995; Vogt, Berger, & Derbyshire, 2003; Vogt, 2009). In particular, the anterior and posterior midcingulate cortex is the posterior part of Areas 24 and 32, and contains the cingulate motor neurons (From this point forward, the thesis focuses on the anterior midcingluate region, which will be termed the "ACC" to be consistent with previous work).

The cytoarchitecture of Area 24 of the ACC is characterized by a reduced or absent layer 4 and a well-developed layer 5 containing large pyramidal neurons, whereas Area 32 contains layer 4 and its layer 5 houses smaller pyramidal neurons. Additionally, the cingulate motor area is somatotopically mapped and stimulation evokes movement, supporting its role in motor control (Allman, Hakeem, & Watson, 2002). The pyramidal neurons have extensive dendritic arborizations: a single apical dendrite extending towards the pial surface of the cortex and bifurcates extensively in layer 1 making numerous

connections, and multiple basal dendrites extending from the cell body. These neurons receive widespread afferent projections from several brain regions, including the amygdala, hippocampus, ventral striatum, orbital frontal cortex, prefrontal cortex, and the anterior insular cortex (Beckmann, Johansen-Berg, & Rushworth, 2009; Vogt, Finch, & Olson, 1992; Vogt, Rosene, & Pandya, 1979; Vogt, Rosene, & Peters, 1981; Vogt & Miller, 1983; Vogt & Pandya, 1987; Vogt, Vogt, Farber, & Bush, 2005; Vogt, 2009). From the cell body, a single axon projects towards several areas concerned with directing motor behavior, such as the basal ganglia, supplementary motor area, primary motor area, or spinal cord (Vogt, Wiley, & Jensen, 1995). Critically, the ACC receives one of the richest dopaminergic innervations of any cortical area (Gaspar, Berger, Febvret, Vigny, & Henry, 1989). Because of the diversity of cortical and subcortical inputs and outputs, the ACC affords a critical pathway devoted to the regulation of motivational factors that influence motor control. In other words, the ACC is considered a neural locus where motor intentions are transformed into action (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001).

Over the last two decades, a number of theories have been proposed attempting to explain the role of ACC in behavior. These theories can be loosely grouped into the following categories: (1) Reinforcement learning, (2) Cognitive Control, and (3) Motivation (Holroyd & Yeung, 2011). In regards to reinforcement learning, it is proposed that the ACC composes part of a larger system for reinforcement learning, such that reinforcement learning signals, believed to be carried by the DA system, shape the connectivity and function of neurons in the ACC for the adaptive modification of behavior according to reinforcement learning principles: the reinforcement learning theory of ACC

function (Holroyd & Coles, 2002). Several lines of research support this view: ACC neurons have been found to be involved in revising estimates of action values (Rushworth, Buckley, Behrens, Walton, & Bannerman, 2007), in registering positive and negative reward prediction errors (Matsumoto, Matsumoto, Abe, & Tanaka, 2007), and in guiding voluntary choices based on the history of actions and outcomes (Kennerley, Walton, Behrens, Buckley, & Rushworth, 2006; Walton, Croxson, Behrens, Kennerley, & Rushworth, 2007; Seo & Lee, 2007). Furthermore, the ACC may have an important role in maintaining action–outcome associations when the action is probabilistically associated with an outcome (Paulus & Frank, 2006; Rushworth, Walton, Kennerley, & Bannerman, 2004). More so, deactivating the ACC by injecting the forelimb part with muscimol has been shown to impair an animal's ability to switch to alternative, more task-appropriate behaviors following negative feedback (Shima & Tanji, 1998).

Alternatively, others argue that the role of the ACC is in decision making and the deployment of cognitive control, particularly in monitoring response conflict and recruiting additional control mechanisms to resolve that conflict: the conflict-monitoring hypothesis of ACC function (Botvinick, Cohen, & Carter, 2004; Botvinick, Braver, Barch, Carter, & Cohen, 2001). A substantial amount of evidence from neuroimaging data supports this view, demonstrating that the ACC is activated by conflict-inducing events, where conflict is defined as the simultaneous activation of competing neural processes (e.g., trial-to-trial changes in behavior such as increasing the strength of top-down control following experienced response conflict) (Yeung, Botvinick, & Cohen, 2004). Yet, others propose the ACC provides a global "energizing" factor or motivation necessary to support effortful goal directed behavior: the motivation theory of the ACC (Walton, Bannerman,

Alterescu, & Rushworth, 2003; Walton, Kennerley, Bannerman, Phillips, & Rushworth, 2006). For example, human neuropsychological studies have shown that ACC lesions can produce a condition called akinetic mutism, in which the afflicted person appears to lack the will or motivation to generate behavior, even though he or she is physically capable of doing so (Freemon, 1971; Devinsky, Morrell, & Vogt, 1995; Mega & Cohenour, 1997). In animals studies, damage to the ACC in rats reduced the likelihood of effortful choices, particularly when animals are required to exert greater effort to obtain a larger reward (Walton, Bannerman, & Rushworth, 2002; Walton, Rudebeck, Bannerman, & Rushworth, 2007).

Although each of these theories has been viewed as incomplete and unable to explain all of the ACC data, the theories are not incompatible with each other. In an attempt to reconcile these theories into a formal, unified theoretical framework, Holroyd and Yeung (2012) proposed a theory that the function of the ACC is more concerned with the selection and maintenance of the task itself than with the minutia of task execution. According to this view, the ACC selects and executes goal-directed temporally extended sequences of actions according to principles of hierarchical reinforcement learning (Holroyd & Yeung, 2012). On the one hand, the ACC is responsible for selecting and maintaining high-level "options" that map sequences of relatively primitive actions from initial states to goal states. In particular, options represent action policies comprised of sequences of simple, primitive actions and can be defined by their associated goal states and the set of initiation states that trigger the options. On the other hand, other systems execute those options (dorsal lateral prefrontal cortex and dorsal striatum), and evaluate progress toward the options' goal-states (orbital frontal cortex, ventral striatum), which is

consistent with the existing concepts about the computational function of these cognitive control systems, with which the ACC interacts. Critically, by extending the Reinforcement Learning Theory of the ERN originally proposed by Holroyd and Coles (2002), the current idea proposed that the ACC is trained to recognize the appropriate option by reinforcement learning signals conveyed to it via the DA system.

This theory proposed by Holroyd and Yeung (2012) is consistent with existing theories of dopamine modulation of several frontal cortex functions (i.e. reward processing, working memory). In particular, it is considered that optimal levels of tonic dopamine improves frontal stability of neural patterns representing items (or goals) (Durstewitz & Seamans, 2002; Cohen, Braver, & Brown, 2002), whereas optimal phasic signaling works as a gating mechanism to store relevant inputs (i.e. rewards) in the cognitive control system (Braver & Cohen, 1999). As described above, D1 receptors are preferentially activated by event-related phasic bursts of dopamine activity and facilitate and maintain synaptic plasticity of task relevant input or actions. In contrast, D2/D4 receptor activation, promoted by tonic activity of DA, favors response flexibility and task switching. These network dynamics may constitute an option selection and maintenance function of the ACC, as described by the hierarchical reinforcement learning framework (Holroyd & Yeung, 2012): D1 activation could facilitate the gating of a high-valued option into working memory (option selection), whereas D2/D4 activation could maintain that information in working memory until the option is completed (option maintenance).

*Reward-positivity*. Evidence for the role of the ACC in reinforcement learning and cognitive control in humans comes from observations of the event-related brain potential (ERP). When measured as the difference between the error-related and correct-related

ERPs, the "reward-positivity" is characterized by a negative deflection at frontal-central recording sites that peaks approximately 250 ms following feedback presentation (Miltner, Braun, & Coles, 1997; Holroyd, Pakzad-Vaezi, & Krigolson, 2008; Baker & Holroyd, 2011b) (Figure 3). Source localization procedures have indicated that the Reward-positivity is produced in or near the ACC (e.g., Hewig et al., 2007; Miltner et al., 1997). In accordance with the aforementioned notions, it has been proposed that negative (cessation in DA activity) and positive (phasic burst in DA activity) RPE signals respectively disinhibit and inhibit the apical dendrites of the motor neurons in the ACC, giving rise to differential activity in this area (Holroyd & Coles, 2002). Based on this idea, Holroyd and Coles (2002) proposed this differential in ACC activity between dopaminergic RPE signals contribute to the generation of the reward-positivity. In particular, the N200 is elicited by activity related to unexpected task-relevant events in general, including unexpected positive feedback, and is considered activity that is intrinsic to the ACC. But following unpredicted rewards, the N200 is suppressed by extrinsically applied positive RPE signals, resulting in an ERP component called the reward-positivity. It is important to point out that previous work termed the difference between the error-related and correct-related ERPs as the "feedback ERN" (fERN), but because of the recent observations that the difference in fERN amplitude between reward and error trials results from a positive-going deflection, I will use the term the reward positivity. In other words, the Reward-positivity indexes a mechanism for reward processing in ACC and is hypothesized to reflect the impact of dopaminergic positive RPE signals on ACC for the purpose of facilitating adaptive decision-making. Specifically, a Reward-positivity may

occur following unexpected rewards when a positive RPE signal carried by the DA system inhibits the apical dendrites of the motor neurons in the ACC (Holroyd et al., 2008a).

Indeed, recent studies suggest that the N200 and the reward-positivity are distinguishable ERP components but may co-occur (Baker & Holroyd, 2011b). As a case in point, a recent comparison of the negative deflections following error feedback and infrequent oddball stimuli suggests that these ERP components are in fact the same phenomenon (Pakzad-Vaezi, & Krigolson, 2008). In addition, Baker and Holroyd (2011) demonstrated that the N200 was linked to conflict processing whereas the reward-positivity indexed the processing of rewards. These observations motivated the proposal that the difference in N200 amplitude between reward and error trials results from a positive-going deflection elicited by reward feedback, and not by errors as originally proposed .

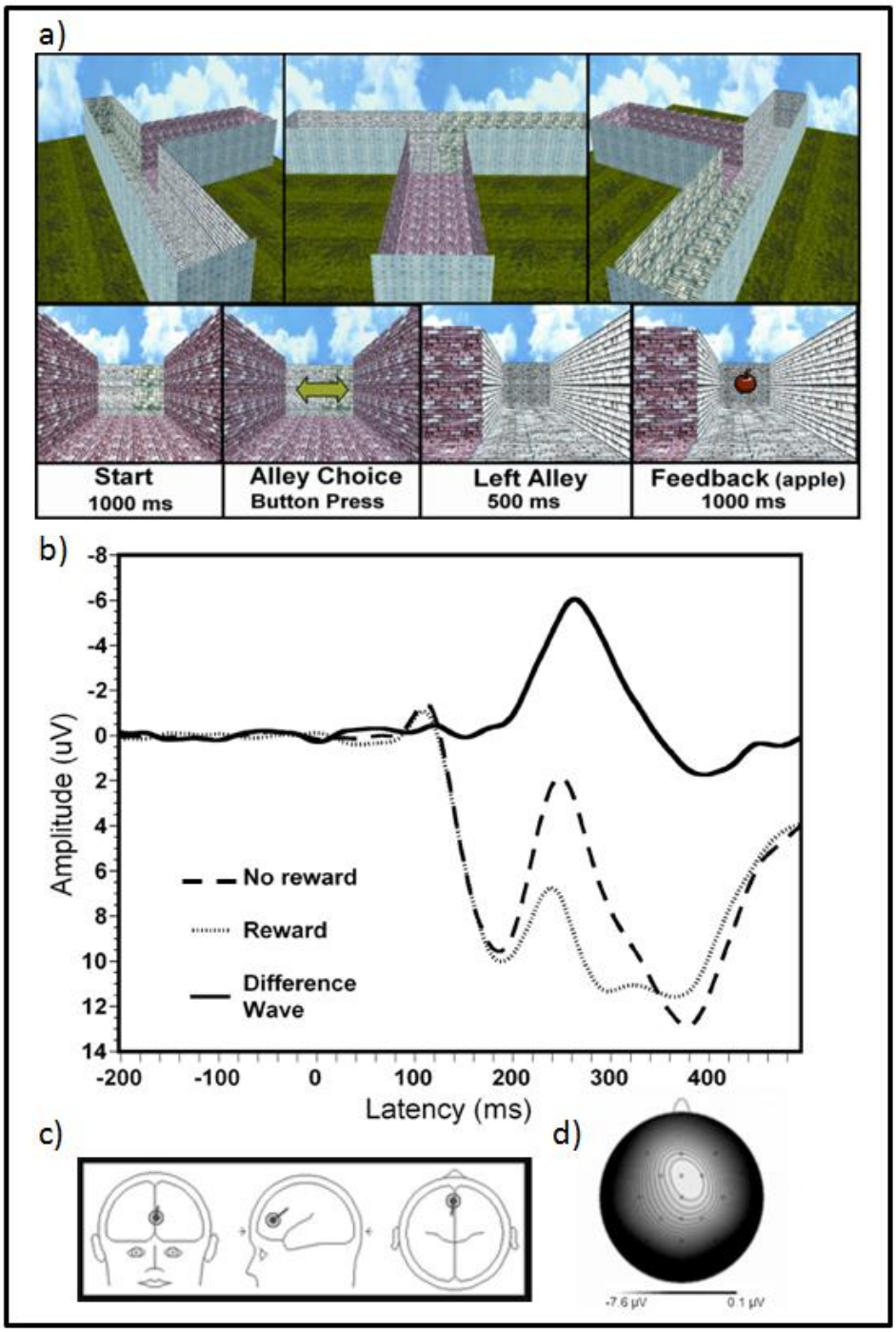


**Figure 3. The Reward-positivity. a) The Virtual T-Maze task, a guessing/reinforcement learning task that elicits robust reward-positivities. Top: Three views of T-Maze from above. Bottom: Sequence of events comprising an example trial of the T-maze Task; stimulus durations are indicated at the bottom of each panel. The double arrow remained visible until the button press. Participants navigated the virtual T-Maze by pressing left and right buttons**

**corresponding to images of a left and right alley presented on a computer screen. After each response an image of the chosen alley appeared, followed by a feedback stimulus (apple or orange) indicating whether the participant received 0 or 5 cents on that trial; unbeknownst to the participants, the feedback was random and equiprobable. Please note that the size of the arrow was magnified in this figure for the purpose of exposition. b) ERP data associated with frontal-central electrode channel FCz. Grand-average ERPs associated with Reward (dotted lines) and No-reward (dashed lines) outcomes and associated difference waves (black solid lines) corresponding to the Reward-positivity. 0 ms corresponds to time of feedback delivery. Negative voltages are plotted up by convention. c) Dipole source localization results of the BESA analysis of the Reward-positivity, localized to the medial frontal cortex, in the approximate region of ACC. d) Scalp voltage map associated with the peak value of the Reward-positivity at electrode FCz.**

Like the dopamine RPE signals, the Reward-positivity is sensitive to events that first indicate when events are better or worse than expected (Holroyd & Coles, 2002; Holroyd & Krigolson, 2007; Baker & Holroyd, 2009; Holroyd, Krigolson, Baker, Lee, & Gibson, 2009). For example, Baker and Holroyd (2009) used a pseudo-RL task where a predictive cue (i.e. reward, no-reward, neutral) was presented before the corresponding feedback stimulus. Participants were informed that if a 'reward' predictive cue appeared, it would indicate that they would receive a reward at the end of the trial; a 'no-reward' predictive cue would indicate no reward at the end of the trial; and a 'neutral' predictive cue was uninformative and would not predict the outcome at the end of the trial. The authors found that a Reward-positivity was elicited to the cues predicting their outcome, and not to the presentation of the feedback itself. Further, when a neutral predictive cue was presented (containing no predictive information), the Reward-positivity was only elicited at the presentation of the feedback cue. Further, genetic (Marco-Pallares et al., 2009), pharmacological and neuropsychological (Overbeek, Nieuwenhuis, &

Ridderinkhof, 2005) evidence implicates dopamine in Reward-positivity production, although the specific mechanism is still debated (Jocham & Ullsperger, 2009). In sum, the reward-positivity is hypothesized to reflect the impact of dopaminergic RPE signals on ACC for the purpose of reinforcing temporally extended sequences of actions (or options) (Holroyd & Yeung, 2012).

In sum, the Reward-positivity provides several attractive characteristics for investigation: 1) an electrophysiological approach that allows for examining the temporal and spectral dynamics of brain electrical activity, providing a means for uncovering fundamental neurocognitive mechanisms related to reinforcement learning and cognitive control, linking human and animal research, and possibly improving clinical diagnosis and treatment assessment; 2) the Reward-positivity is based on an biological plausible model of the role of the DA system and the ACC in reinforcement learning and cognitive control, allowing for explicit inferences about the neural mechanisms that give rise to the generation of this electrophysiological marker (Holroyd & Coles, 2002; Holroyd & Yeung, 2012); 3) the Reward-positivity provides a means for operationally defining a neural mechanism for reward processing via latency, amplitude, and frequency; 4) the virtual T-maze, a decision making task in which subjects navigate a simple maze to gain rewards, has been shown to elicit robust Reward-positivities, and has been used in both typical (Baker & Holroyd, 2009) and atypical populations (Holroyd, Baker, Kerns, & Muller, 2008); 5) genetic analysis showed substantial heritability of the Reward-positivity, supporting it's roles in serving as a endophenotype for genetic studies of personality traits and psychopathology associated with abnormal regulation of behaviour (Anokhin, Golosheykin, & Heath, 2008; Olvet & Hajcak, 2008); and 6) several studies have

demonstrated that the Reward-positivity has excellent test-retest reliability−separated by 2-6 weeks, and as long as 1 to 2 years− suggesting that the Reward-positivity is a stable, trait-like neural measure (Olvet & Hajcak, 2009; Weinberg & Hajcak, 2011).

Note that despite its positive characteristics, the pseudo trial-and-error tasks (e.g., the virtual T-maze) used to elicit the reward-positivity comes with a limitation. Consistent with standard practice the feedback stimuli in the T-maze task are delivered at random, providing a means to identify the reward-positivity using the difference wave approach (Holroyd & Coles, 2002; Holroyd & Krigolson, 2007; Baker & Holroyd, 2009; Holroyd et al., 2009), but for this reason the task does not provide a meaningful performance measure.

**The Basal Ganglia, Decision Making, and the Go/NoGo Model**

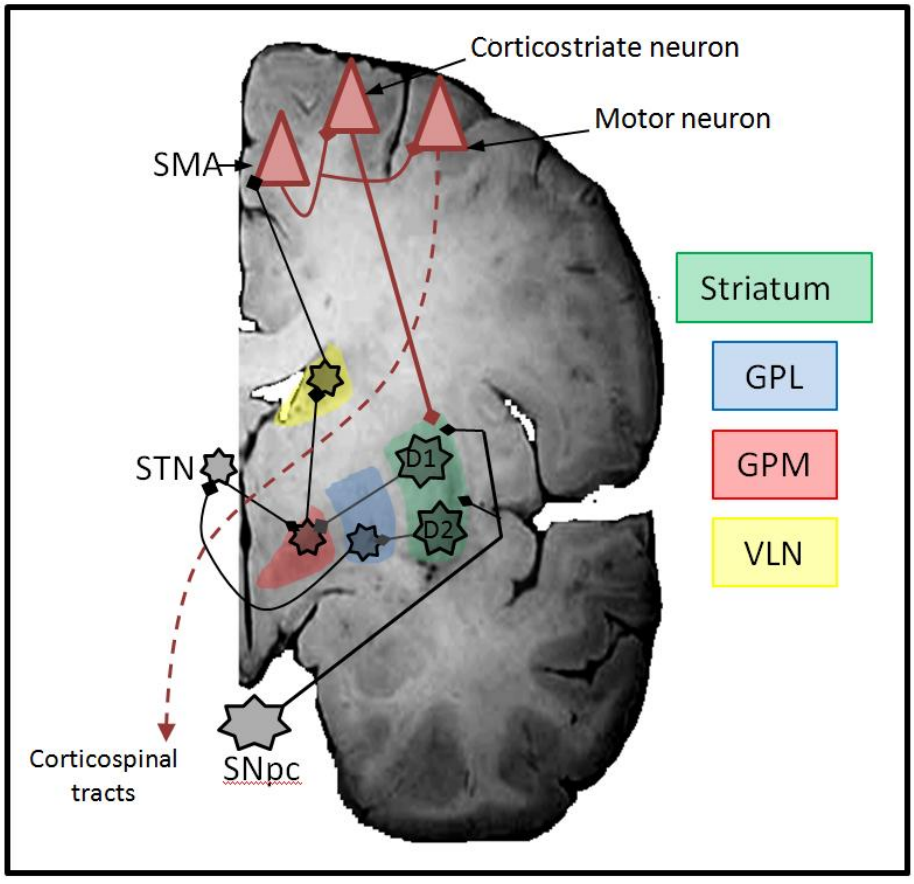

**Figure 4. Coronal section illustrating the basal ganglia motor loop. The two pathways "Go" and "NoGo" are denoted by striatal D1 and D2 receptors types. The corticostriate pathway are exicatory utilizing glutamate. The nigrostriatal neuron (SNpc→striatum) utilizes DA which is excitatory via D1 receptors on target medial pallidal neurons (GPM), and inhibitory via D2 receptors on lateral pallidal neurons (GPL). Supplementary Motor Area (SMA), Substantia Nigra pars compacta (SNpc), Subthalamic Nucleus (STN), ventral lateral nucleus of thalamus (VLN).**

The term basal ganglia is used to designate the areas of the base of the forebrain and midbrain known to be involved in the control of movement (Arsalidou, Duerden, & Taylor, 2012; Harsay et al., 2011). It includes the *striatum* (caudate nucleus, putamen, nucleus accumbens), the *pallidum* (globus pallidus, which comprises a lateral and medial segment, the latter known as substantia nigra pars reticulata), the *subthalamic nucleus*, and *substantia nigra pars compacta* (Figure 4). In the striatum, the cellular distribution of D1 and D2 receptors have been described in detail (Svenningsson et al., 2004; Gerfen et al., 1990; Bertorello, Hopfield, Aperia, & Greengard, 1990; Surmeier, Song, & Yan, 1996; Aizman et al., 2000). D2 receptors are found on dopaminergic nerve terminals (presynaptic D2 autoreceptors) and postsynaptically on GABAergic medium spiny neurons as well as on cholinergic interneurons. D1 receptors are predominantly expressed postsynaptically on GABAergic medium spiny neurons. Anatomical studies have shown that striatonigral neurons contain high levels of D1 receptors, whereas striatopallidal neurons predominantly express D2 receptors. Although the levels of D1 and D2 receptors differ between striatal projection neurons, there is biochemical and physiological evidence supporting the idea that many of them possess both D1 and D2 receptors (for review, see Gerfen & Surmeier, 2011).

The circuitry of the basal ganglia have been shown to be critical for several cognitive, motor, and emotional functions, and are integral components of complex functional/anatomical loops underlying reinforcement learning and decision-making (Arsalidou et al., 2012; Cohen & Frank, 2008). For example, numerous studies demonstrate that the dopaminergic projection from the ventral tegmental area to the nucleus accumbens plays a central role in the brain's reward system and motivation (Di Chiara G., 2002; Kalivas & Nakamura, 1999). More so, its circuitry can facilitate or suppress action representations in the frontal cortex, such that representations that are more goal-relevant or have a higher probability of being rewarded are strengthened, whereas representations that are less goal-relevant or have a lower probability of reward are weakened (Frank, 2011; Cohen & Frank, 2009; Frank, 2005; Frank et al., 2004). Critically, dopaminergic RPE signals plays a pivotal role in this process by modulating both excitatory and inhibitory signals in complementary ways (Cohen & Frank, 2008).

An illustration of the dichotomous function of DA receptor signaling in the striatal Go and No Go pathways have been modeled in humans. According to an influential neurocomputational model of decision making, "the Basal Ganglia Go/NoGo model", dopaminergic signaling in the basal ganglia can facilitate or suppress these action representations: phasic bursts of dopamine activity facilitate reward learning by reinforcing striatal connections that express D1 receptors (the "Go/Approach" pathway), whereas phasic dips in dopamine activity facilitate avoidance learning by reinforcing striatal connections that express D2 receptors (the "NoGo/Avoidance" pathway). In particular, in vivo recordings during reinforcement learning tasks reveal that rewards elicit an increase in DA neuron firing and an increase in DA release in the striatum. At the same

time, visual stimuli and motor actions produce an excitatory cortical activity that is transmitted via an increase in glutamate release in the striatum from pyramidal neurons. According to the Go/NoGo model, strengthening of synaptic connections in striatal neurons in a "Go" or direct pathway occurs when glutamatergic input (a stimulus or movement signal originating from the cortex) and DA input (a reward signal originating from the DA system) are received simultaneously (Frank & Fossella, 2011). Repetitive pairing of these two signals strengthens the connection between cortical and striatal cells. Equally important is that synaptic plasticity does not occur in response to DA or glutamate signals alone (Daw & Touretzky, 2002). Further, the strengthening of the connections is caused by activation of biochemical signalling pathways inside the striatal cells and a persistent increase in the size of the glutamatergic excitatory postsynaptic currents of medium spiny interneurons, which together facilitates LTP (Wall et al., 2011; Lindskog, Kim, Wikstrom, Blackwell, & Kotaleski, 2006). In contrast, when tonic DA levels are reduced, neurons in a "NoGo" or indirect pathway are relieved of tonic DA suppression leading to a disengagement, or inhibition of ongoing behavior, which facilitates LTD (Meyer-Lindenberg et al., 2007; Svenningsson et al., 2004), and LTP resulting from reduced D2 receptor stimulation during DA dips in the NoGo pathway (Shen et al. 2008). These observations support the hypothesis that synaptic plasticity of D1/D2 expressing neurons underlies reinforcement learning in this particular circuitry. Therefore, the net result of DA release or suppression in the striatum via these synaptic triads is to enhance/reduce excitation of cortical neurons, thus reinforcing/extinguishing a particular pattern of neural firing. A selective focusing of target neurons via DA signalling ensures that the strongest firing neurons are facilitated and others are inhibited.

*Probabilistic Learning Task.* Empirically, the Go/NoGo model predictions are typically tested with the Probabilistic Selection Task (PST), a trial-and-error learning task in which subjects are required to learn three concurrent discriminations (stimulus pairs AB, CD and EF), rewarded with schedules of 80%/20%, 70%/30% and 60%/40%, respectively. In a subsequent Test Phase, the subjects are asked to select between novel combinations of the original stimuli without feedback (Figure 6). Subjects who are more accurate at picking the stimulus that was most frequently rewarded (the "Good Stimulus") are classified as "Positive Learners" whereas subjects who are more accurate at avoiding the stimulus that was most frequently punished (the "Bad Stimulus") are classified as "Negative Learners" (Frank, D'Lauro, & Curran, 2007). The PST has provided insight into individual differences related to reinforcement learning (Cohen & Frank, 2008), genetics (Frank, Doll, Oas-Terpstra, & Moreno, 2009; Frank & Hutchison, 2009; Frank et al., 2007; Frank et al., 2007), normal aging (Frank & Kong, 2008), "top-down" modulation by orbital frontal cortex and anterior cingulate cortex (Paulus & Frank, 2006; Frank & Claus, 2006), pharmaceutical manipulations (Frank & O'reilly, 2006), and psychiatric conditions (especially, Parkinson's disease, attention-deficit hyperactivity disorder, and schizophrenia; for review, see Maia & Frank, 2011) (Figure 5).

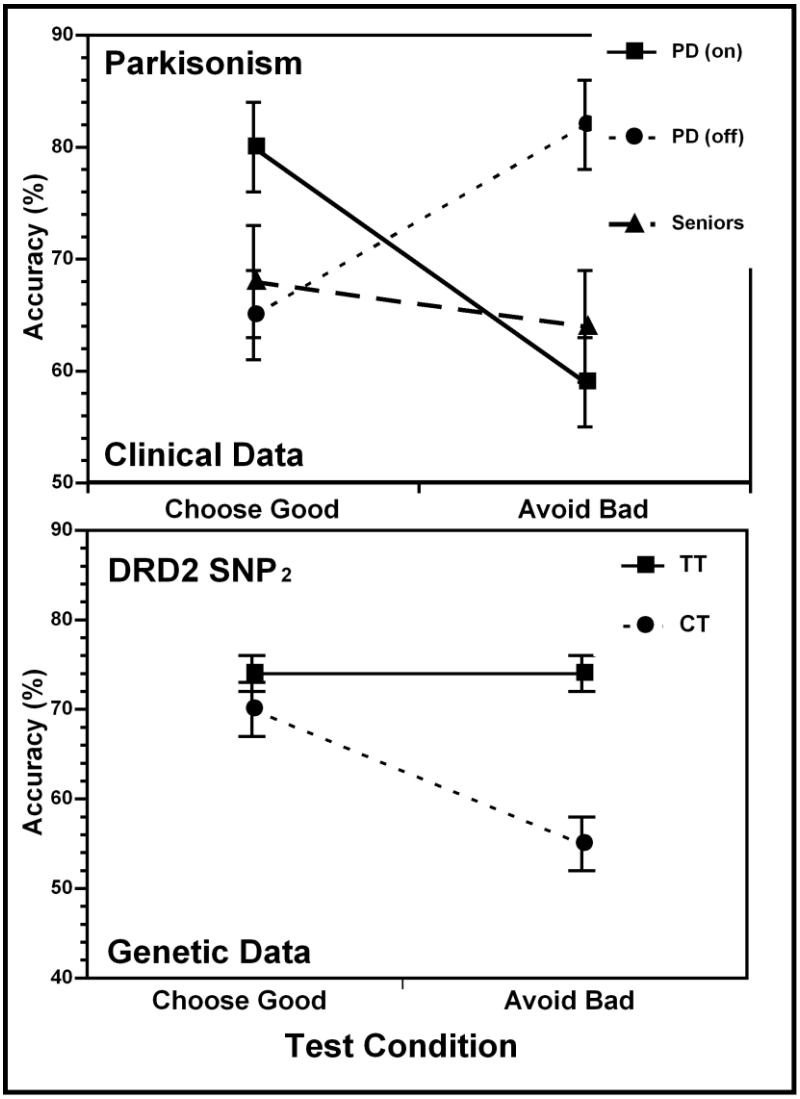


**Figure 5. Probabilistic Selection Task. Top: Behavioral findings in Parkison's patients (PD) on/off medication supporting model predictions (adapted from Frank et al., 2004). Bottom: An example of DRD2 effects on accuracy in Choose Good (approach) and Avoid Bad (avoidance) conditions supporting model predictions (adapted from Frank and Hutchison, 2009) (note, error bars may not be exact to previous reports).**

In particular, genetic studies show that the ability to learn from positive or negative reinforcement can be predicted by variability related to single nucleotide polymorphisms (SNPs) affecting D1 and D2 gene expression in the Go/Approach and NoGo/Avoid pathways . For example, studies have been shown to be consistent with Go/NoGo model

prediction that reduced striatal D2 density should be associated with impaired accuracy on Avoid trials together with spared accuracy on Approach trials in the PST (Frank et al., 2009; Frank & Hutchison, 2009; Frank et al., 2007; Frank et al., 2007; Klein et al., 2007). Similarly, the Go/NoGo model further predicts that good performance on Approach trials should be associated with enhanced efficacy of striatal D1 receptors, as for example modulated by the PPP1R1B gene (Frank et al., 2007). The Go/NoGo model is also being utilized to investigate psychiatric and neurological disorders that involve disturbances of the midbrain dopamine system and basal ganglia, in particular, Parkinson's disease, attention-deficit hyperactivity disorder, and schizophrenia. The model predicts that disruption in dopaminergic signaling in the basal ganglia Go and NoGo pathway can selectively impair approach and avoidance learning on the PST (Maia & Frank, 2011). For example, the model predicts that people with Parkinson's disease will be more accurate on Avoid than Approach trials of the PST while off medication due to a diminished dopamine signal, and more accurate on Approach than Avoid trials while on medication due to an enhanced dopamine signal, findings that have been confirmed empirically (Frank et al., 2004). Further, because of the relationship between addiction and impaired decision making, Maia and Frank (2011) have recently proposed that the Go/NoGo model can provide important insights into addiction. For instance, optogenetic findings in mice demonstrate that direct or indirect pathway stimulation during drug administration increases or decreases the reinforcing effects of the drug, respectively (Lobo et al, 2010), suggesting that reduced indirect relative to direct pathway activity could be a risk factor for addiction (Maia and Frank, 2011).

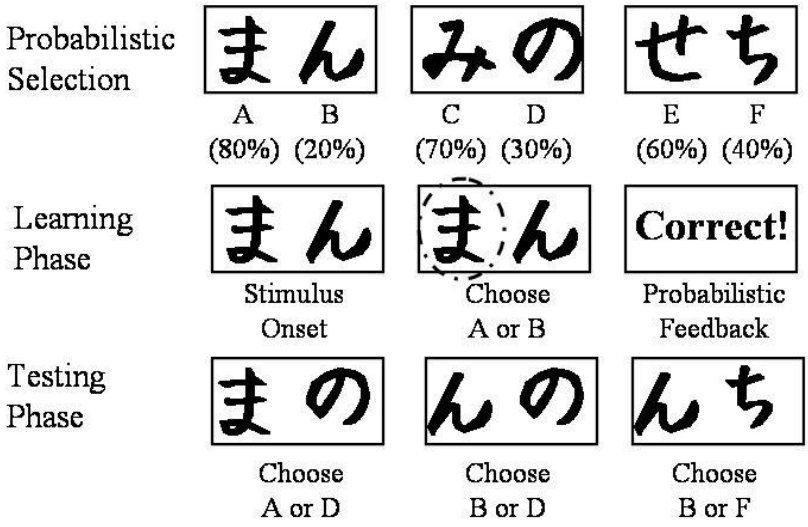


**Figure 6. Probabilistic Selection Task. Top row: Stimuli and reward probabilities (percent positive feedback). Middle row: Schematic of an example trial during the learning phase. Bottom row: Schematic of an example trial during the test phase. In brief, during an initial Learning Phase participants are exposed to three pairs of stimuli presented in random order. The response mappings are probabilistic such that one stimulus in each of the three pairs is rewarded on 80%, 70%, and 60% of the trials, respectively, with the remaining stimulus in each pair rewarded on the complementary percentage of trials. Participants are required to learn by trial-and-error to choose the more frequently rewarded stimulus over the alternative in each pair. Critically, they could do so either by learning that particular stimuli were associated with relatively more reward, by learning that particular stimuli were associated with relatively more punishment, or both. During the Test Phase participants are exposed to all possible combinations of these stimuli in a random order and are required to select the symbol in each pair that they believed to be correct, but without receiving any feedback about their choices.**

In sum, the PST provides several attractive characteristics for assessing reinforcement learning and decision making: (1) the PST is based on an neurocomputational model of reinforcement learning that accounts for individual differences in decision-making ability, allowing for explicit inferences about the neural mechanisms that give rise to approach and avoidance learning; (2) although approach vs.

avoidance learning is not directly observable in the PST, the PST provides a means for differentiating between approach and avoidance learning via accuracy and reaction time during a Test Phase (Frank et al. 2005; Frank et al. 2007, Cohen and Frank, 2009); and (3) the PST has been used in both typical and atypical populations. However, the PST has a few limitations: (1) its psychometric properties remains undetermined (Ragland et al., 2012; Ragland et al., 2009), and (2) the stimulus probabilities are not optimal for extracting the reward-positivity using the difference wave approach, or other ERP components effected by stimulus frequency (Holroyd & Krigolson, 2007; Holroyd et al., 2009).

## Substance Dependence: Loss of Cognitive Control

"Addiction" is an old psychological term that has been defined and studied from multiple perspectives. Its definition originated in Roman law, such that the word *addictus* was given to a person who was as a bond slave to a creditor; or *addicto,* which suggested devotion, as in *senatus, cui me simper addixi* ('the senate, to which I am always devoted") (Lewis and Short, 1879; Alexander and Schweighofer, 1998). And for centuries more, "addiction" has traditionally been referred to as the state of being "given over" or intensely involved with any activity, as shown by the 1933 Oxford English Dictionary definition: "a formal giving over or delivery by sentence of court"−a surrender or dedication of any one to a master; and "The state of being (self-) addicted or given to a habit or pursuit"−devotion" (Murray, Bradley, Cragie, & Onions, 1933, p.104; Alexander and Schweighofer, 1998). It wasn't until the late 19$^{th}$ century that its contemporary meaning emerged, being more restrictive than the traditional one in three ways: it linked addiction

to *harmful* involvements with drugs that produce *withdrawal symptoms or tolerance*. In other words, addiction is not defined specifically, but rather has become associated to the problems linked to the drug use itself.

Today, the Diagnostic and Statistical Manual of Mental Disorders, (Fourth Edition) Text Revision (American Psychiatric Association, 2000) separately divides substance-related disorders into two groups: *Substance Use Disorders*, which include substance dependence, described as "a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues use of the substance despite significant substance-related problems", and substance abuse, characterized by "a maladaptive pattern of substance use manifested by recurrent and significant adverse consequences related to the repeated use of substances"; and *Substance-induced Disorders*, which encompass substance intoxication, substance withdrawal, and other psychiatric syndromes that are the direct pathophysiological consequence of use of a substance. Addiction to alcohol and drugs are typically diagnosed using seven criteria for substance dependence. To be diagnosed, the person would have to have at least three of the criteria within the same year. The first two criteria, tolerance and withdrawal, are central to "physiological dependence" on a drug. A person can be diagnosed with substance dependence either with or without the "physiological dependence," although a person is at greater risk of medical problems and relapse if they do have "physiological dependence." The seven criteria for substance dependence are:

(1) Tolerance, as defined by either of the following:
   a. A need for markedly increased amounts of the substance to achieve intoxication or desired effect.
   b. Markedly diminished effect with continued use of the same amount of the substance.

(2) Withdrawal, as manifested by either of the following:
   a. The characteristic withdrawal syndrome for the substance (withdrawal symptoms vary with the substance, but some symptoms may include increased heart rate, shaking, insomnia, fatigue , and irritability).
   b. The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.

(3) The substance is often taken in larger amounts or over a longer period than was intended.

(4) There is a persistent desire or unsuccessful efforts to cut down or control substance use.

(5) A great deal of time is spent in activities necessary to obtain the substance (such as visiting multiple doctors or driving long distances), use the substance (such as chain smoking) or recover from its effects.

(6) Important social, occupational, or recreational activities are given up or reduced because of substance use.

(7) The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

An important caveat is that a majority of persons who use substances abuse more than one at a time, which complicates this traditional diagnosis. Further, using these criteria, the word "addiction" has been defined differently depending on one's perspective, reflecting a fundamental ambiguity in its definition. For example, from a behavioral perspective, drug addiction is defined as repeated self-administration of a drug (e.g. alcohol, nicotine, cocaine, cannabis, heroin) despite attempts to abstain from its use. From a cognitive perspective, drug addiction is understood in terms of the poor decision-making underlying the adverse medical and social consequences associated with substance abuse. From a biological perspective, addiction is understood mainly as a disturbance of the

midbrain dopamine system/brain reward system by addictive drugs. And from a preclinical perspective, addiction is defined by a compulsive desire to use the drug, escalation of drug dosage to maintain the desired effects, neglect of alternative or natural rewards, and difficulty to abstain or to curtail drug use despite the firm resolution to quit and/or the catastrophic consequences on personal health, finances, and social relationships.

Despite the complexities in its meaning, the cardinal feature of substance dependence–continued drug consumption despite its long-term adverse consequences–is indicative of abnormal decision making and cognitive control. In fact, contemporary theories of addiction emphasize deficits in cognitive control, reinforcement learning and decision making (Redish, Jensen, & Johnson, 2008; Berke & Hyman, 2000; Hyman, 2007; Hyman, Malenka, & Nestler, 2006; Hyman, 2005). Thus, because a clinical diagnosis does not establish the cognitive and biological significance, nor identify a mechanism of vulnerability, as described by the contemporary theories of addiction, a cognitive neuroscience perspective may provide a valuable strategy for extending a clinical diagnosis with cognitive neuroscience data.

As described above, the midbrain DA system projects to all of the structures of the cognitive control and decision making network including the ACC and basal ganglia, and thus may be considered to be the lynchpin of this system, the neural nexus of substance dependence. Accordingly, drugs of abuse effectively increase the magnitude of the positive RPEs carried by the midbrain DA system by raising extracellular dopamine levels either directly or indirectly (Di Chiara G. & Imperato, 1988), thereby augmenting the size of the elicited positive RPE signals (Rice & Cragg, 2004). Whereas natural rewards and external cues associated with reward produce transient increases in dopamine neuron

activity only when these events are unexpected, addictive drugs and drug-related cues increase dopamine levels even when these events are entirely expected. In turn, these exaggerated signals induce changes to synaptic connectivity (Hyman et al., 2006) that rewire and disrupt the neural targets of the midbrain dopamine system (Robinson & Kolb, 2004; Homayoun & Moghaddam, 2006), causing the motivational value of states that precede drug consumption to grow without bound (Redish, 2004). It has been proposed that the disruption of RPE signals by addictive drugs would in fact upset the normal function of basal ganglia and ACC and may precipitate the abnormal decision-making processes that are characteristic of substance abuse (Kalivas & Volkow, 2005). Moreover, because these brain areas implement neural processes that are central to cognitive control and decision making—including goal-directed action selection, response activation and inhibition, performance monitoring, and reward-based learning (Holroyd & Coles, 2002; Cohen & Frank, 2008; Cohen et al., 2002; Miller & Cohen, 2001)—addictive drugs are sometimes said to "usurp" the cognitive control system (Hyman, 2007). In other words, the control system withdraws control over behaviors that it should inhibit, and facilitates behaviors that it should not. Inevitably, the consequence of overconsumption of drugs of abuse can result in a desensitization to the drug's reinforcing effect, hypersensitivity to drug-associated stimuli (i.e. drug 'wanting'), and a decrease in the reinforcing strength of alternative reinforcers or reward allostasis (Koob & Le, 2008; Koob & Le, 1997; Koob, 1996). The functional consequence of this maladaptive learning process is that drug rewards become overvalued at the expense of other natural rewards, contributing to compulsion and to a marked narrowing of life goals to obtaining and using drugs (Hyman et al., 2006).

Supporting this idea, behavioral experiments have revealed that many of the decision making and cognitive control functions associated with the DA system are impaired in people who abuse substances (Redish et al., 2008). For example, substance abusers make relatively risky decisions (Bechara & Damasio, 2002; Bechara, Dolan, & Hindes, 2002; Bechara, 2003), discount the value of future drug rewards more than they do future monetary rewards (Madden, Bickel, & Jacobs, 1999; see also Goldstein et al., 2007b; Goldstein et al., 2007a; Goldstein et al., 2007c; Volkow & Li, 2005), and are generally insensitive to the delayed consequences of their actions (Petry, Bickel, & Arnett, 1998). Unsurprisingly, neuroimaging studies point toward impaired ACC and basal ganglia processing in this population (Peoples, 2002; Hyman et al., 2006; Koob, 1999; Redish et al., 2008). For example, substance dependent individuals exhibit symptoms associated with insults to the ACC, including anhedonia (absence of pleasure), and an inability to make adaptive decisions regarding future actions, observations that are paralleled by a reduced hemodynamic response in ACC to natural rewards, and striking defects in both blood flow and gray matter density in that region (Peoples, 2002). Further, abnormalities in the fiber tracts connecting the orbitofrontal cortex and ACC to limbic structures (i.e. amygdale) have been observed in some cocaine addicts, suggesting a dysruglation of emotional control (Lim, Choi, Pomara, Wolkin, & Rotrosen, 2002).

Recent reports suggest that basal ganglia are involved in the maintenance of drug-seeking behavior under a second-order schedule of reinforcement and might be important for addiction (Everitt et al., 2008; Belin, Jonkman, Dickinson, Robbins, & Everitt, 2009; Belin, Mar, Dalley, Robbins, & Everitt, 2008; Belin & Everitt, 2008). For example, although in most people the basal ganglia compute “fictive error signals” for lost

opportunities, that information is not actually utilized to guide subsequent decision making in smokers as it is in non-smokers; and the neural response to reward prediction error signals is larger for sated smokers than for unsated smokers (Chiu, Lohrenz, & Montague, 2008). Moreover, low D2 receptor binding in the ventral striatum predicts the magnitude of cocaine intake escalation and compulsive cocaine intake when rats are given extended access to cocaine (Dalley et al., 2007). In compulsive cocaine users, individual differences in craving after methylphenidate injection have also been demonstrated and are correlated with increased metabolic activity in the striatum and orbitofrontal cortex (Volkow et al., 1999a). These results suggest that the ACC and basal ganglia may underlie both the vulnerability to the positive reinforcing effects of substances and the vulnerability to the transition from goal-directed to compulsive drug seeking.

## Individual Differences in Substance Dependence

Concerning the susceptibility to substance dependence, individual differences play an important role observed in the propensity to self administer drugs, the sensitivity to drug-associated cues, the severity of the withdrawal state, and the ability to quit (for review, see Koob, 2006; George & Koob, 2010). In particular, one area that has shown much promise with respect to explaining individual differences underlying substance dependence is that focusing on personality traits. For instance, several personality factors, such as anxiety sensitivity, depression-proneness, impulsivity, and sensation seeking have been shown to be associated with risk for substance use disorders and play an important role in the development and maintenance of several forms of psychopathology associated with susceptibility to drug abuse (Mackie, Castellanos-Ryan, & Conrod, 2011; Conrod &

Woicik, 2002). Interestingly, a growing body of research suggests these personality traits are mediated by dopamine-mediated abnormalities, and thus, to some extent, influence the functioning of brain reinforcement systems and their susceptibility to the reinforcing effects of drugs of abuse (Lemenager et al., 2011; McGeary, 2009; Goldstein et al., 2005; Kreek et al., 2005; Franques, Auriacombe, & Tignol, 2000; Noble, 2000a)

As reviewed by Conrod and colleagues (2002), personality traits related to sensation seeking and impulsivity are associated with heavy drinking, drinking in situations where heavy drinking is condoned, difficulties in regulating alcohol intake, frequency of drinking problems and high extroversion. Specifically, individuals high in impulsivity and novelty seeking have been shown to be less sensitive to negative consequences, make more risky decisions, and display poor performance on decision making tasks (Zuckerman & Kuhlman, 2000; Zuckerman, Ball, & Black, 1990; Zuckerman, 1990; Zuckerman, 1988). Animal and human studies indicate that impulsivity and novelty seeking are a pre-existing vulnerability marker for substance dependence mediated in part by genetic polymorphisms that code for the expression of the DA system (Verdejo-Garcia, Lawrence, & Clark, 2008; Noel et al., 2011; Noble, 2003; Noble, 2000b; Noble, 1998). In contrast, personality traits related to anxiety and depression appear associated with drinking alone, drinking in response to unpleasant emotions and conflict with others, drinking problems, a preoccupation with drinking, worries about controlling drinking, and high neuroticism (Conrod & Woicik, 2002). Further, a recent study provided evidence that depressed individuals were found to be hypersensitive to punishment (Cavanagh, Bismark, Frank, & Allen, 2011), and anxious individuals appear to exhibit a preference for low risk options, or risk aversion, during decision making (Maner & Schmidt, 2006; Mitte, 2008;

Raghunathan & Pham, 1999). As such, each different personality risk factor is likely to access a subset of the constellation of vulnerabilities in the cognitive control and decision making system and likely to define the importance of individual differences in the vulnerability to drugs and the transition to addiction

## Summary and Specific Aims

In sum, these observations suggest that substance dependence involves a confluence of biological, behavioral, cognitive, and personality-related factors. Notably, all addictive drugs act on a neural system for reinforcement learning called the midbrain DA system, which projects to and regulates the brain's system for cognitive control, and decision making, namely ACC and basal-ganglia. Further, the development and expression of the dopamine system is determined in part by genetic factors that vary across individuals such that dopamine-related genes are partly responsible for addiction-proneness. Taken together, these observations suggest that the cognitive and behavioral impairments associated with substance abuse result from the impact of disrupted DA signals on frontal brain areas involved in cognitive control: By acting on the abnormal reinforcement learning system of the genetically vulnerable, addictive drugs hijack the control system to reinforce maladaptive drug-taking behaviors. The functional consequence of this maladaptive process is the *loss of cognitive control*: the impaired ability to regulate and control one's decision-making, in that many substance abusers are unable to regulate their maladaptive drug-taking behavior despite appearing to want to do so. The goal of this research was to investigate this hypothesis by conducting a series of experiments that assayed the integrity of the DA system and its neural targets involved in

cognitive control and decision making, namely ACC and basal ganglia, using a combination of electrophysiological, behavioral, and genetic assays together with surveys of substance use and personality.

This thesis reports the findings of three experiments utilizing the Reinforcement Learning Theory of the ACC (Holroyd and Coles, 2002) and the Go/NoGo model (Frank et al., 2004) as a conceptual framework, which link cognitive control and reinforcement learning to neural mechanisms in the ACC, basal ganglia, and the DA system, and have applied measures that are commonly viewed to be highly sensitive to the integrity of the DA system (Reward-positivity, PST performance, genetics) to a population with a suspected impairment of that system: substance dependent individuals. To this end, the proposed research addressed the following **Specific Aims** using these **Operational Definitions**:

## Operational Definitions

It is common practice in psychological sciences to devote an operational definition to the specific variable of investigation. In the present case, substance dependence, cognitive control, and decision-making are each defined in terms of the specific theory, neural process and validation measure used to determine its presence and degree.

First, this thesis rests on the cardinal feature of substance dependence–continued drug consumption despite its long-term adverse consequences–which appears indicative of abnormal decision making and cognitive control, and central to the idea of *loss of control*. Here, the construct of substance dependence was defined as: *patterns of substance use (frequency) that impose a significant cost on the individual, are difficult to interrupt, and*

*are likely to recur following interruption.* In line with this definition, substance dependence was measured using the Global Continuum of Substance Risk score (GCRs) of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (Humeniuk & Ali, 2006), a validated screening test developed by the World Health Organization (WHO) for identifying the degree of problematic substance use (i.e. tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants, sedatives, hallucinogens, inhalants, opioids and "other drugs"), especially in individuals who use multiple substances. For each substance listed, the following questions were scored according to the ASSIST guidelines (Humeniuk et al., 2008), and scores combined to derive the GCR score.

1. Have you ever used Substance A?
   tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants, sedatives, hallucinogens, inhalants, opioids and "other drugs"
2. Used in the past three months?
3. During the past three months, how often have you had a strong desire or urge to use this substance?
4. During the past three months, how often has your use of this substance led to health, social, legal, or financial problems?
5. During the past three months, how often have you failed to do what was normally expected of you because of your use of this substance?
6. Has a friend or relative or anyone else EVER expressed concern about your use of this substance?
7. Have you ever tried and failed to control, cut down or stop using this substance?

The GCR scores were used as a continuous variable throughout the statistical analysis. In addition, participants were classified as either Substance Dependent,

Moderately-dependent or Non-dependent according to their GCR scores. Specifically, participants with GCR scores falling within the bottom, middle and top quartiles of the sample were classified as Non-dependent, Moderately dependent, and Substance Dependent, respectively. Cut-offs score established in previous validation studies of the ASSIST for these groups were used for comparison: Non-dependent (score < 15), Moderate-dependent (score 16-39) and Dependent (score > 39.5) (Newcombe, Humeniuk, & Ali, 2005).

Second, the construct of cognitive control as a function of ACC was defined as: *the ability to select and execute goal-directed temporally extended sequences of actions.* Cognitive control by this definition was measured using the reward-positivity, and Reinforcement Learning Theory of the ACC as its conceptual framework. Specifically, the reward-positivity was used to access the impact of positive RPE signals carried by the midbrain DA system onto motor areas in ACC, where they are utilized to associate values of extended sequences of action for the purpose of cognitive control and reinforcement learning (Holroyd & Coles, 2002; Holroyd & Yeung, 2012).

The reward-positivity is typically quantified for each electrode and participant by measuring the peak or mean amplitude of the difference wave constructed by subtracting the reward ERPs from the corresponding no reward ERPs. The difference-wave approach is used to isolate the reward-positivity from other ERP components that may overlap with it, such as the N2 and P3, providing a relatively pure measure of the brain's differential activity to reward vs. no reward feedback (Luck, 2005). Otherwise, it would be difficult to determine if any differences observed between the reward and no reward trials were due to a difference in the amplitude of the reward-positivity or due to differences in some other

ERP component. The reward-positivity by this measurement is characterized by a negative deflection at frontal-central recording sites, namely FCz, that peaks approximately 250 ms following feedback presentation (Figure. 3). The reward-positivity is commonly studied using pseudo trial-and-error learning tasks, such as the "virtual T-maze" shown in Figure. 3.

Third, the construct of decision making as a function of the basal ganglia was defined as: *the ability to learn from positive and negative feedback by facilitating and suppressing action representations during reinforcement learning and decision making.* Decision making by this definition was measured using performance on the PST and the "Basal Ganglia Go/NoGo model" as its conceptual framework (Frank et al. 2004). Specifically, accuracy on Approach trials during the PST Test Phase was used to assess the impact of positive RPEs carried by the midbrain DA systems onto striatal D1 receptors in the "Go" pathway. Accuracy on Avoidance trials during the PST Test Phase was used to assess the impact of negative RPEs carried by the midbrain DA systems onto striatal D2 receptors in the "No/Go" pathway (for more details, see PST section).

In further detail, PST behavioral measures commonly studied are Test Phase accuracy and reaction time. As mentioned above, participants can be classified as either "Positive Learners" (learning from positive feedback) or "Negative Learners" (learning from negative feedback) according to their performance in the Test Phase on "Approach trials" that involved the A stimulus (the "Good Stimulus"; AC, AD, AE, AF) relative to "Avoid trials" that involved the B stimulus (the "Bad Stimulus", BC, BD, BE, BF). Response conflict can also be assessed by comparing accuracy and reaction times for test pairs with similar reinforcement values (e.g., 80 vs. 70%, High Conflict) with those of

pairs having more easily discriminable values (e.g., 80 vs. 30%, Low Conflict) and separately for High Conflict Approach trials (AC, AE, CE) trials and High Conflict Avoid trials (BD, BF, DF), called "Win–win" (Approach) and "Lose–lose" (Avoid) trials, respectively (Frank et al., 2007; Cavanagh et al., 2010).

Because the midbrain DA system projects to the ACC and basal ganglia, and thus may be considered to be the lynchpin of the reinforcement learning system, and the development and expression of the DA system is determined in part by genetic factors that vary across individuals such that dopamine-related genes are partly responsible for addiction-proneness, I included the construct of *genetic vulnerability* as a function of the midbrain DA system: *a genetically determined variation in a neural or behavioural response to rewards or punishments.* Genetic vulnerability by this definition was measured using single nucleotide polymorphisms (SNPs) associated with genes that code for the expression of the DA system. Specifically, I selected genetic polymorphisms that regulate

i) *D4 expression*: promoter -521 (C/T) SNP (rs1800955), the indel -1217G ins/del (-/G) (rs12720364), and the variable number of tandem repeats (VNTR) polymorphism (long/short) in exon III of the DRD4 gene

ii) *D2 expression*: (TaqI (A1/A2) SNP (rs1800497), C957T (C/T) SNP (rs6277), and promoter $SNP_2$ (C/T) (rs12364283) (Zhang et al., 2007) of the DRD2 gene

iii) *D1 efficacy*: (M12 (rs907094) and the M04 (rs879606) SNP of the PPP1R1B gene

iv) *DA catabolism*: a gene associated with the expression of the *Catechol-O-methyltransferase (COMT) enzyme* (the Val158Met polymorphism (rs4680) of the COMT gene

| Gene | DRD2 | | | | | | | | PPP1R1B (DARPP-32 protein) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SNP | Taq1A | | | C957T | | | Z-SNP2 | | M04 | | | M12 | | |
| SNP ID | rs1800497 | | | rs6277 | | | rs12364283 | | rs879606 | | | rs907094 | | |
| allele | A2/A2 | A2/A1 | A1/A1 | T/T | C/T | C/C | T/T | C/T | G/G | A/G | A/A | A/A | A/G | G/G |
| Phenotype | ↑↑* | ↑↓* | ↓↓* | ↓↓* | ↑↓* | ↑↑* | ↓↓ | ↑↓ | ↑↑ | ↑↓ | ↓↓ | ↑↑ | ↑↓ | ↓↓ |
| Gene | COMT | | | DRD4 | | | | | | | | | | |
| SNP | Val158Met | | | C-521T | | | VNTR | | Indel | | | | | |
| SNP ID | rs4680 | | | rs1800955 | | | | | rs12720364 | | | | | |
| allele | M/M | M/V | V/V | C/C | C/T | T/T | short | long | G/G | -/G | -/- | | | |
| Phenotype | ↓↓ | ↑↓ | ↑↑ | ↑↑ | ↑↓ | ↓↓ | ↑↑ | ↓↓ | ** | ** | ** | | | |

SNP: Single Nucleotide Polymorphism
↑↓: denotes an increase or decrease in dopaminergic expression (i.e. D2/D4 density, COMT enzyme, DARPP-32 protein)
*: denotes controvery in the literature, please refere to discussion
**: phenotype currently unknown

**Table 1. Genotype characteristics of selected dopamine-related genes**

Importantly, I adopted the intermediate phenotype (IP) approach to link these nine dopamine-related genetic polymorphisms with substance dependence (Table 1). It has been suggested that IP candidates should be based on (i) functional polymorphisms known to affect the coding of the protein of interest (here, proteins underlying the expression of the DA system); (ii) theoretical or conceptual models for how that protein in the brain region(s) of interest plays a role in the associated IP (here, theories relating DA to reinforcement learning, cognitive control, and individual personality traits); and (iii) a suitable task (or inventory) that probes the specific computations of that IP (here, an electrophysiological measure of a cortical mechanism for dopamine-dependent reward processing and cognitive control (the reward-positivity), a behavioral index of a

subcortical mechanism for dopamine-dependent reinforcement learning (PST performance), and four personality risk factors associated with drug addiction (impulsivity, novelty seeking, depression proneness and anxiety sensitivity)[2] (Conrod & Woicik, 2002).

## Specific Aim 1

*To investigate whether cognitive and behavioral impairments associated with substance abuse result from the impact of disrupted dopamine signals on cortical and subcortical brain areas involved in cognitive control and decision making.*

First, do substance dependent individuals produce abnormal dopamine-related reward signals in the ACC? According to the Reinforcement Learning Theory of the ACC, the reward-positivity reflects the impact of positive RPE signals on the ACC for the purpose of reinforcement learning and cognitive control (Holroyd & Coles, 2002). Based on this idea, I predicted that if a loss of cognitive control results in part from the impact of disrupted positive RPE signals on ACC, then the reward-positivity should be abnormal in Dependent but not Non-dependent individuals. Specifically, I hypothesized that the DA system compensates for drug induced changes to the reward circuitry by discounting the motivational value of natural rewards and punishments, reducing the magnitude of their associated RPE signals, thereby leading to cognitive control and decision making impairments, hence abnormal reward-positivity. This finding would indicate that individuals suffering from substance dependence are impaired at using normal rewards and

[2] Personality risk factors were measured using the following inventories: 1) the Addiction-Prone Personality (APP) Scale, a 21-item scale which assays the role of personality in the development of addiction (Anderson, Barnes, Patton, & Perkins, 1999), 2) the Substance Use Risk Profile Scale (SURPS), a 23-item assessment tool that measures levels of several specific personality risk factors for substance abuse/dependence including Impulsivity, Anxiety, Hopelessness, and Sensation Seeking (Conrod & Woicik, 2002). These measures were scored according to their guidelines (see appendix).

punishment to develop neural representations of action value, and thus are impaired at using these action values for the purpose of cognitive control.

Second, do substance dependent individuals produce abnormal dopamine-related reward signals in the basal ganglia? According to the Basal Ganglia Go/NoGo model, performance in the PST reflects dopaminergic signaling in a "Go" pathway via D1 receptors, and "No-go" pathway via D2 receptors for the purpose of reinforcement learning and decision making (Frank et al., 2004). Based on this idea, I predicted that if impaired decision making results in part from the impact of disrupted dopaminergic RPE signals on the Go and NoGo pathway of the basal ganglia, then performance in this task should be abnormal in Dependent but not Non-dependent individuals. This finding would suggest that chronic drug abuse may ultimately drive the decision making system to withdraw control over behaviors that it should inhibit (impaired avoidance learning) and facilitate behaviors that it should not (impaired reward learning).

## Specific Aim 2

*To investigate whether the cognitive and behavioral impairments associated with substance abuse result in part from genetic abnormalities that render the DA system vulnerable to the potentiating effects of addictive drugs*

Can our genetic makeup predispose us to addiction? One strategy for addressing this question depends on the concept of *intermediate phenotypes*: biological and psychological factors that are relatively proximal to genetic influence and confer vulnerability to (rather than determine) psychopathology (Meyer-Lindenberg & Weinberger, 2006). Based on this concept, I adopted the intermediate phenotype approach to link nine dopamine-related genetic polymorphisms with substance dependence (Table

X). In particular, I explored the viability of five candidate IPs: the reward-positivity (Holroyd & Yeung, 2012; Holroyd & Coles, 2002), the PST (Frank et al., 2004), and four personality risk factors associated with drug addiction (impulsivity, novelty seeking, depression proneness and anxiety sensitivity) (Conrod & Woicik, 2002). I hypothesized that if cognitive control, decision making, and personality risk factors mediate the relationship between dopamine-related genetic polymorphisms and substance dependence, then this would be evident in the relationship between the genes and the IPs, and between the IP and substance dependence, but not between the genes and substance dependence. Evidence of a dopamine-related genetic link to abnormalities in these IPs would provide support for the hypothesis that such maladaptive behavior seen in substance dependent individual results from the impact of DA RPE signals on genetically vulnerable brain mechanisms for cognitive control and decision making, and would provide insight into how dopamine-related genes predispose individuals to drug addiction.

### Specific Aim 3

*To assess whether the cognitive and behavioral impairments associated with substance abuse can be rehabilitated over time with addiction therapy*

Although the specific aims of this research were to assess important individual differences associated with the neural and cognitive mechanisms underlying substance dependence, a link between this study and prevention or therapy is not immediately obvious. Thus, to assess the impact of addiction therapy on DA mechanisms of decision making, which are believed to constitute the primary neurobiological cause of substance dependence, I used the PST and tested a substance dependent population before and after treatment, as well as a control population comprised of undergraduate students tested over

two sessions expanding a 7-8 week time window. The success of this investigation depended both on the Go/NoGo theory and on the utility of the PST for testing the theory. Critically, the extensive empirical support that the PST has provided for the Go/NoGo model of the basal ganglia strongly suggests that PST performance should be stable over time, but to my knowledge this prediction has never been explicitly tested (Ragland et al., 2012; Ragland et al., 2009). Thus as a subgoal of the study I examined whether various measures of PST performance were consistent within individuals over time.

To foreshadow my results: the PST data failed to demonstrate adequate test–retest reliability in the student sample. Nevertheless, I reasoned that the PST measures might be stable within subpopulations of individuals characterized by particular individual traits related to the DA system and learning style. For this reason, I utilized the PST to investigate the relative contribution of multiple dopamine-related genetic polymorphisms, personality traits and drug use history on individual differences in decision making. Thus, if reinforcement learning signals carried by the midbrain DA system are instrumental to the decision making function implemented by the basal ganglia, are modulated by particular genetic polymorphisms, and appear to contribute to individual differences associated with personality and substance dependence, then the PST should be sensitive to the relative contribution of each of these factors and their interactions to decision making.

## Summary Statement

In sum, the present thesis combined the allelic association method of behavioural genetics with the methods of modern cognitive neuroscience and examined the relationship between brain structures involved in cognitive control, decision making and reinforcement learning on the one hand, and the impairment of these functions in substance

abuse on the other hand. It is my hope that this thesis will motivate future investigations of a hitherto virtually ignored factor in current addiction research and treatment, that is, the important individual variability observed in the propensity to self-administer drugs, the sensitivity to drug-associated cues, the severity of the withdrawal state, and the ability to quit. Success in these efforts would represent an important step toward the creation of a unified theoretical model of substance abuse that spans multiple levels of analysis, including its biological, behavioral and cognitive manifestations. Such a step would appear to be critical for furthering the development of new therapeutic treatments and clinical management for the disorder.

# Experiment One[3]

*Abstract*

Recent theories of drug dependence propose that the transition from occasional recreational substance use to harmful use and dependence results from the impact of disrupted midbrain dopamine signals for reinforcement learning on frontal brain areas that implement cognitive control and decision making. I investigated this hypothesis in humans using electrophysiological and behavioral measures believed to assay the integrity of midbrain dopamine system and its neural targets. This investigation revealed two groups of dependent individuals, one characterized by disrupted dopamine-dependent reward learning and the other by disrupted error learning associated with depression-proneness. These results highlight important neurobiological and behavioral differences between two classes of dependent users that can inform the development of individually-tailored treatment programs.

[3] This experiment has been published: Baker, T. E., Stockwell, T., Barnes, G., and Holroyd, C. B. (2011). Individual Differences in Substance Dependence: At the Intersection of Brain, Behaviour, and Cognition. *Addiction Biology, 16*, 458-466. (note the term feedback error-related negativity was used in this study instead of the reward-positivity).

# Individual Differences in Substance Dependence: At the Intersection of Brain, Behaviour, and Cognition

Are we in control of our own decisions? Most of us feel in control, but individuals who suffer from severe drug dependence exhibit impaired control over their substance use despite often catastrophic consequences on personal health, finances, and social relationships. Yet, despite the widespread availability and prevalence of addictive substances in most societies (Anderson, 2006), only some drug users ultimately become dependent (Kessler et al., 2005). Over the last several decades, multidisciplinary efforts in addictions research have indicated that substance dependence results from a confluence of risk factors related to biology, cognition and learning, personality, genetics and the social environment, but there is as yet little direct evidence in humans of the neuroadaptive mechanisms that mediate the transition from occasional, controlled drug use to the impaired control that characterizes severe dependence (Hyman, 2007).

Notably, all addictive drugs stimulate the midbrain dopamine system (MDS) (Di Chiara G. & Imperato, 1988), which projects to and regulates brain structures underlying cognitive control and decision making, namely prefrontal cortex (Cohen et al., 2002), ACC (Holroyd & Coles, 2002) and the BG (Cohen & Frank, 2008). MDS neurons distribute information about rewarding events such that phasic bursts and dips in dopamine neuron activity are elicited when events are respectively "better than expected" (positive reward prediction error [RPE]) and "worse than expected" (negative RPE) (Schultz, 1998). In keeping with formal models of reinforcement learning, these RPEs "propagate back in time" in trial-and-error learning tasks from reward delivery to the earliest predictive indicator of reward. Accordingly, it has been suggested that the dopamine RPEs serve as

reinforcement learning signals, gradually optimizing behavior by associating predictive cues and behaviors with forthcoming rewards (Schultz, 1998). In this way the dopamine RPE signals appear to increase the "incentive salience" or "wanting" of rewards, that is, the motivation to work for the reward in a given behavioral context, as distinct from the affective enjoyment or "liking" of the reward when consumed (McClure et al., 2003).

In view of the role played by the MDS in reinforcement learning, addiction has recently been hypothesized to be fundamentally a problem of learning and memory (Hyman, 2005). According to this view, drugs of abuse effectively increase the magnitude of the positive RPEs carried by the MDS by raising extracellular dopamine levels either directly or indirectly (Di Chiara G. & Imperato, 1988). Whereas natural rewards and external cues associated with reward produce transient increases in dopamine neuron activity only when these events are unexpected, addictive drugs and drug-related cues increase dopamine levels even when these events are expected, thereby augmenting the size of the elicited positive RPE signals (Rice & Cragg, 2004). In turn, these exaggerated signals induce changes to synaptic connectivity (Hyman et al., 2006) that rewire and disrupt the neural targets of the MDS in ACC, BG and orbitofrontal cortex (OFC) (Robinson & Kolb, 2004; Homayoun & Moghaddam, 2006), causing the motivational value of states that precede drug consumption to grow without bound (Redish, 2004). Because these brain areas implement neural processes that are central to cognitive control and decision making—including goal-directed action selection, response activation and inhibition, performance monitoring, and reward-based learning (Holroyd & Coles, 2002; Miller & Cohen, 2001; Cohen & Frank, 2008; Cohen et al., 2002)—addictive drugs are sometimes said to "usurp" the cognitive control system (Hyman, 2007).

Here, I hypothesized that the impact of disrupted RPEs on brain networks involved in cognitive control and decision making precipitate the compulsive drug use that defines severe dependence. To investigate this hypothesis, I indirectly assayed the integrity of the dopamine system and frontal brain areas involved in cognitive control and decision making in young adults using a combination of electrophysiological and behavioral measures together with surveys of substance use and personality.

Specifically, to assess the neural integrity of the MDS and its projections to frontal cortex, event-related brain potentials (ERPs) were recorded from participants as they navigated a "virtual T-maze" to find rewards (Baker & Holroyd, 2009). It is believed that the impact of dopamine RPEs on motor-related areas in ACC modulate the amplitude of a component of the ERP called the feedback error-related negativity (fERN) (Holroyd & Coles, 2002; Baker & Holroyd, 2009). Like the dopamine RPE signals, the fERN is sensitive to events that first indicate when events are better or worse than expected (Holroyd & Coles, 2002; Holroyd & Krigolson, 2007; Baker & Holroyd, 2009; Holroyd et al., 2009). Further, genetic (Marco-Pallares et al., 2009), pharmacological and neuropsychological (Overbeek et al., 2005) evidence implicates dopamine in fERN production, although the specific mechanism is debated (Jocham & Ullsperger, 2009). I predicted that if substance dependence results in part from the impact of disrupted dopamine RPE signals on frontal brain structures involved in cognitive control, then the fERN should be abnormal in Dependent but not Non-dependent individuals.

In addition, immediately following the T-maze participants engaged in the Probabilistic Selection Task (PST) (Frank et al., 2004), a trial-and-error learning task that is believed to be sensitive to dopamine dysfunction. The PST has provided insight into

individual differences related to Parkinson's disease, attention-deficit hyperactivity disorder, schizophrenia, normal aging, genetic makeup, the effect of dopaminergic agonists and antagonists, and "top-down" modulation of the BG by OFC and ACC (Cohen & Frank, 2008). According to an influential neurocomputational theory of the BG-MDS, positive dopamine RPEs facilitate approach learning in this task by reinforcing a BG "Go" pathway via D1 receptors, whereas negative dopamine RPEs facilitate avoidance learning by reinforcing a BG "No-go" pathway via D2 receptors (Cohen & Frank, 2008). For example, prior studies revealed that people with Parkinson's disease, who have low striatal dopamine levels, were better at avoidance learning than approach learning; dopamine medications reversed this bias as predicted by the models (Frank et al. 2004). I predicted that if substance dependence results in part from the impact of disrupted dopamine RPE signals on brain structures involved in decision making, then performance in this task should be abnormal in Dependent but not Non-dependent individuals.

## MATERIALS AND METHODS

### Participants

I first collected survey data (substance use history, personality risk factors associated with addiction, and family history) from 412 first- and second-year undergraduate students. Of these participants, 70 agreed to return to participate in an electrophysiological and behavioral experiment on a subsequent day (two additional participants were excluded due to a reported head injury). The computer-based survey was comprised of several separate inventories, namely, the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (Humeniuk & Ali, 2006), a validated screening test developed by the World Health Organization for identifying the degree of problematic

substance use (i.e. tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants, sedatives, hallucinogens, inhalants, opioids and "other drugs"); the Severity of Alcohol Dependence Questionnaire, which assesses the severity of alcohol abuse and dependence (Stockwell, Murphy, & Hodgson, 1983); the Addiction-Prone Personality (APP) Scale (Anderson et al., 1999), a 21-item self-report questionnaire that assesses the role of personality in the susceptibility to addiction; and the Substance Use Risk Profile Scale (SURPS) (Conrod & Woicik, 2002), a 23-item self report questionnaire that provides a measure on four dimensions of personality traits—depression-proneness, anxiety-sensitivity, impulsivity, and sensation seeking—that are risk factors for substance use.

For the purpose of this study, participants were classified as either Dependent or Non-dependent substance users according to their scores on the Global Continuum of Substance Risk (GCR) scale of the ASSIST. Specifically, participants with GCR scores falling within the bottom (score < 16) and top (score > 41) quartiles of this sample were classified as Non-dependent (18 participants) and Dependent (18 participants) users, respectively. These scores are comparable to the cut-offs established in previous validation studies of the ASSIST for non-dependence (score < 15) and dependence (score > 39.5) (Newcombe et al., 2005). The Dependent Group tended to abuse alcohol, cannabis and tobacco, but some individuals also reported taking amphetamines, cocaine, sedatives and/or hallucinogens (see Appendix A, Experiment 1). The study was conducted in accordance with the ethical standards prescribed in the 1964 Declaration of Helsinki.

**Procedure**

*ERP Task – Virtual T-Maze*

The Virtual T-Maze is a guessing/reinforcement learning task that elicits robust

fERNs (Baker & Holroyd, 2009). Participants navigated the virtual T-Maze by pressing left and right buttons corresponding to images of a left and right alley presented on a computer screen. After each response an image of the chosen alley appeared, followed by a feedback stimulus (apple or orange) indicating whether the participant received 0 or 5 cents on that trial; unbeknownst to the participants, the feedback was random and equiprobable. The experiment consisted of 4 blocks of 50 trials each separated by rest periods. ERPs were created for each electrode and subject by averaging the single-trial EEG according to feedback type (for a complete description of EEG Data Acquisition and Analysis methods, please see Appendix A, Experiment 1).

For each participant, the fERN was measured at channel FCz, where it reaches maximum amplitude (Holroyd & Krigolson, 2007; Miltner, Braun, & Coles, 1997). To isolate the fERN from other overlapping ERP components, the fERN was evaluated for each participant as a difference wave by subtracting the Reward feedback ERPs from the corresponding No-reward feedback ERPs (Miltner et al., 1997; Holroyd & Krigolson, 2007). The mean amplitude of this difference wave was obtained by averaging the difference wave within a 200–320 ms window following feedback onset. The P2 and P3 components were also measured for the purpose of comparison. The P2 was measured base-to-peak at a frontal-central channel (FCz) for the Reward and No-reward ERPs. The P3 amplitude was measured by identifying the maximum positive-going value of the Reward and No-reward ERPs recorded at electrode site Pz, within a window extending from 300 to 600 ms following the presentation of the feedback stimulus (see Appendix A Experiment 1 for further details).

*Behavioral Task - The Probabilistic Selection Task*

Consistent with standard practice the feedback stimuli in the T-maze task were delivered at random, providing a means to identify the fERN using the difference wave approach (Holroyd & Coles, 2002; Holroyd & Krigolson, 2007; Baker & Holroyd, 2009; Holroyd et al., 2009), but for this reason the task did not provide a meaningful performance measure. Hence, immediately after participants completed the T-maze I asked them to engage in the PST, a task designed to identify individual biases to learning from positive or negative feedback (Frank et al., 2004). In brief, during an initial Learning Phase participants were exposed to three pairs of stimuli presented in random order (for more details, please see Appendix A, Experiment 1). The response mappings were probabilistic such that one stimulus in each of the three pairs was rewarded on 80%, 70%, and 60% of the trials, respectively, with the remaining stimulus in each pair rewarded on the complementary percentage of trials. Given that these stimulus probabilities are not optimal for extracting the fERN using the difference wave approach, EEG data were not recorded during this task (Holroyd & Krigolson, 2007; Holroyd et al., 2009). Participants learned by trial-and-error to choose the more frequently rewarded stimulus over the alternative in each pair. Critically, they could do so either by learning that particular stimuli were associated with relatively more reward, by learning that particular stimuli were associated with relatively more punishment, or both. During the Test Phase participants were exposed to all possible combinations of these stimuli in a random order and were required to select the symbol in each pair that they believed to be correct, but without receiving any feedback about their choices. If participants learned more from positive feedback during the Learning Phase, then they should reliably choose the Good

Stimulus in all novel test pairs in which it is present. On the other hand, if they learned more from negative feedback during the Learning Phase, then they should reliably avoid the Bad Stimulus in all novel test pairs in which it is present. Participants who did not perform better than chance on Test Phase trials consisting of the easiest stimulus pair were eliminated from further analysis. In total, the data of six participants were discarded.

As in previous studies I identified two subgroups of participants (Frank et al. 2005, Frank et al. 2007). Participants who tended to pick the stimulus that was most frequently rewarded during the Learning Phase (the "Good Stimulus"), which depends on learning from positive reinforcement, were classified as "Positive Learners", whereas participants who tended to avoid the stimulus that was most frequently punished during the Learning Phase (the "Bad Stimulus"), which depends on learning from negative reinforcement, were classified as "Negative Learners". Six subjects displayed equally good performance in choosing the Good Stimulus and avoiding the Bad Stimulus and were not included in either group (but were included in a continuous measure of relative learning biases; see below). Group comparisons confirmed that Positive Learners (n=32) were better than Negative Learners (n=27) at choosing the Good Stimulus, $t(57) = 6.28$, $p < .001$, whereas Negative Learners were better than Positive Learners at avoiding the Bad Stimulus, $t(57) = -4.7$, $p < .001$ (for more details, see Appendix A, Experiment 1).

## RESULTS

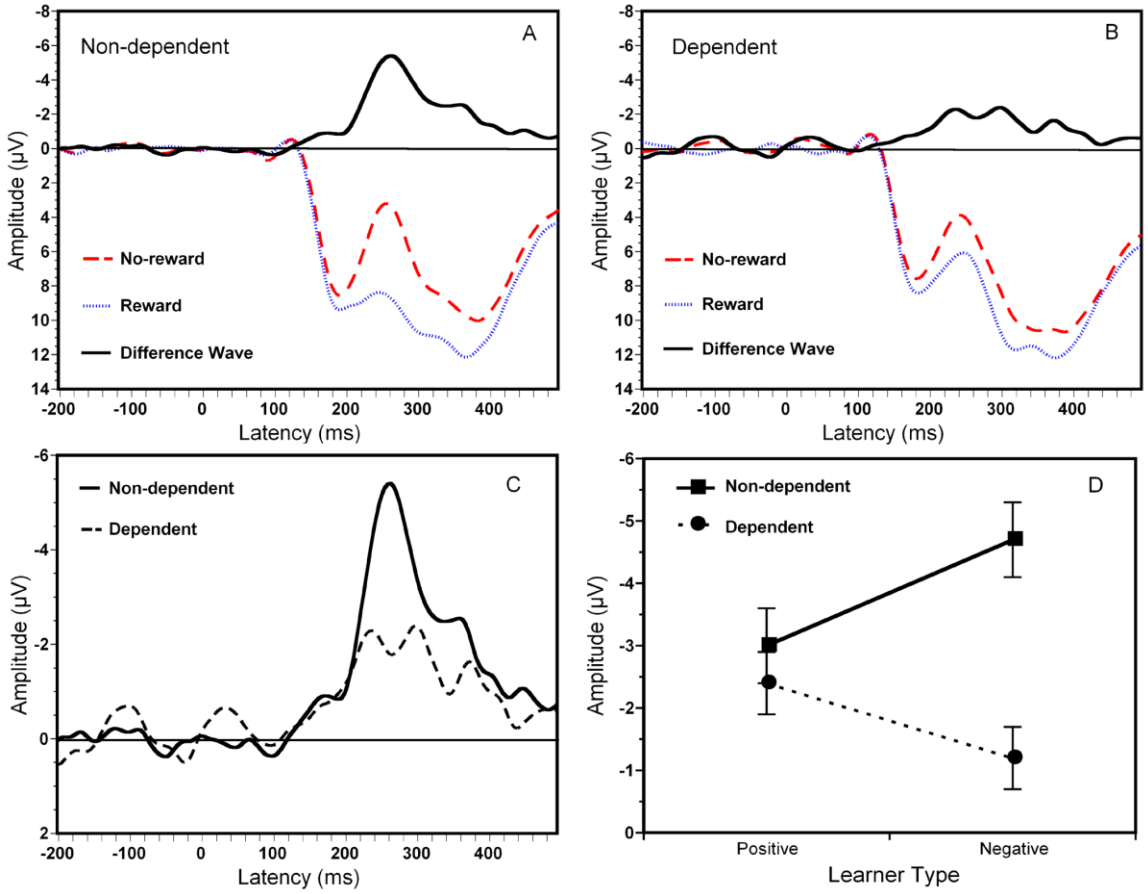


**Figure 7. ERP data associated with frontal-central electrode channel FCz. Grand-average ERPs associated with Reward (blue dotted lines) and No-reward (red dashed lines) outcomes and associated difference waves (black solid lines) for the (A) Non-dependent Group and the (B) Dependent Group. (C) fERN Difference waves for the Non-dependent Group (solid lines) and Dependent Group (dashed lines). In A-C, 0 ms corresponds to time of feedback delivery. (D) fERN amplitude as a function of Learner Type (Positive and Negative) derived from performance on the Probabilistic Selection Task, for the Non-dependent Group (solid line) and the Dependent Group (dashed line). Bars indicate the standard error of the mean. Negative voltages are plotted up by convention.**

## Electrophysiological Results

Figure. 7 (A and B) illustrates the ERPs elicited by the Reward and No-reward feedback and the associated difference waves, averaged across participants separately for the Non-dependent and Dependent Groups. The ERPs for the Non-dependent Group

revealed a typical fERN occurring at about 250 ms following feedback presentation (Holroyd & Coles, 2002) (Figure. 7A), whereas the ERPs for the Dependent Group were nearly identical, exhibiting little difference between conditions (Figure. 7B). Figure. 7C presents the associated difference waves together, revealing a truncated fERN in the Dependent Group (M= -1.9 μV, SE = $\pm$.4) relative to the Non-dependent Group (M= -3.6 μV, SE = $\pm$.5), $t(34) = -2.34$, $p < .05$. Further analysis indicated that the amplitudes of the P200 and the P300 were about the same for the two groups ($p>.05$), confirming that the effect of interest was isolated to the predicted ERP component–the fERN–and thus did not reflect an overall processing difference between the groups. Moreover, this effect remained statistically significant when variability associated with personality-related risk factors for substance use (i.e., depression-proneness, anxiety, impulsivity, and sensation seeking), as measured by the SURPS and APP, was controlled for using ANCOVA, $F(1, 36) = 3.9$, $p < .05$. Hence the degree of substance use appears to have affected fERN amplitude independently of the personality traits that precipitated the substance use in the first place.

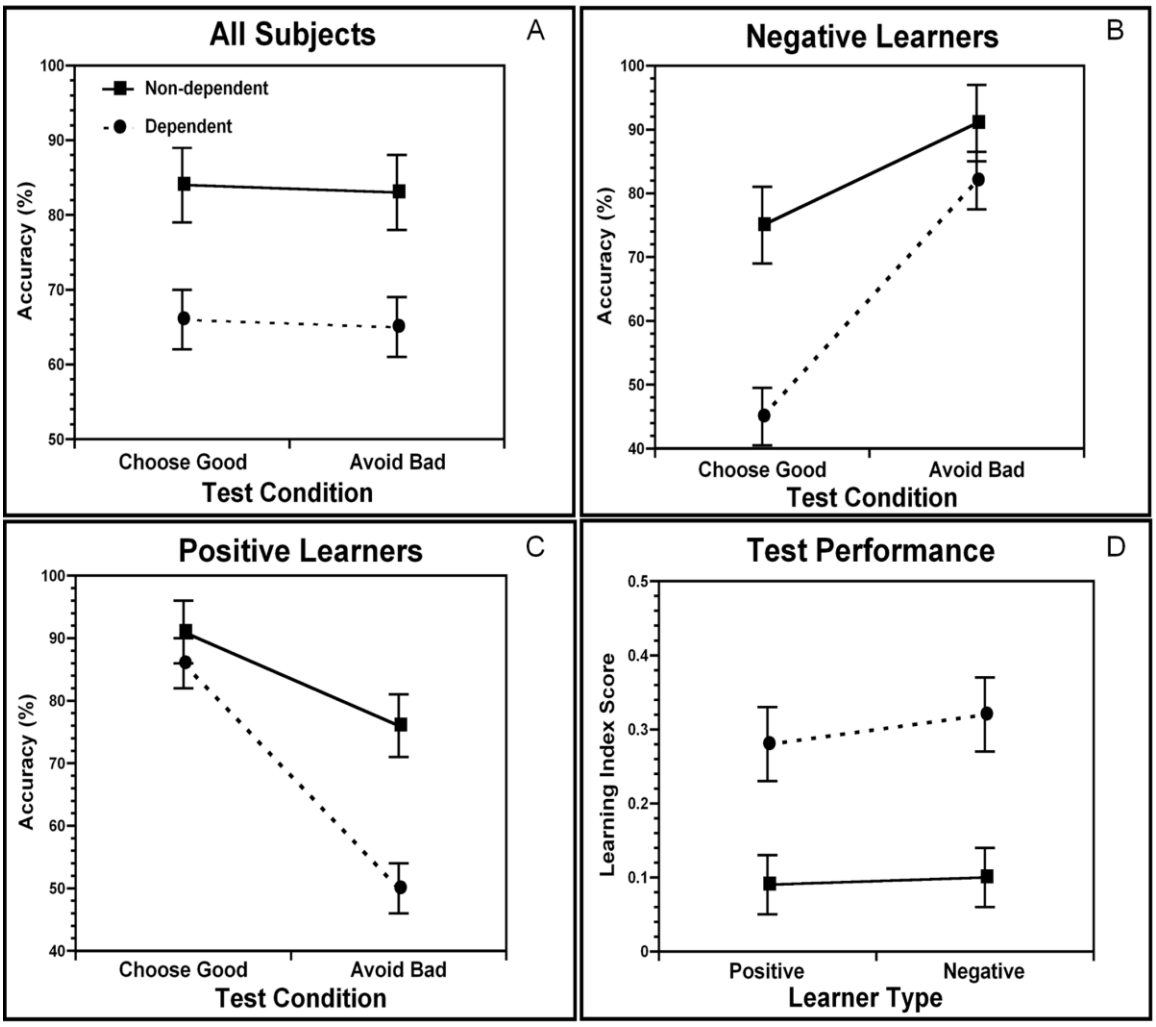


**Figure 8. Performance on the Probabilistic Selection Task (PST). Accuracy in the Test Phase of the PST for the Dependent and Non-dependent Groups, separately for the Choose Good and Avoid Bad conditions, for (A) all participants, (B) Negative Learners only, and (C) Positive Learners only. Note that chance accuracy is 50%. (D) Learning Index Scores derived from the PST accuracy data, separately for Positive and Negative Learners. Dependent Group data are indicated by circles and dotted lines and Non-dependent Group data are indicated by squares and solid lines. Bars indicate standard errors of the mean.**

## Behavioral Results

Overall, a two-way ANOVA on Test Phase accuracy with Group (Non-dependent, Dependent) and Stimulus type (Positive, Negative) as factors revealed a main effect of

Group, indicating that the Non-dependent Group performed more accurately (83%) than the Dependent Group (66%) did, $F(1,31) = 9.2$, $p < .005$, ES=.23 (Figure. 8A). Specifically, Non-dependent participants avoided choosing the Bad Stimulus more often (84%) than Dependent participants did (65%), $t(28) = 2.7$, $p < .01$, and there was a trend such that the Non-dependent participants chose the Good Stimulus (84%) more often than the Dependent participants did (66%), $t(28) = 1.8$, $p < .08$. No between-group differences in performance were found during the Learning Phase of the task (see Appendix A, Experiment 1).

I examined this between-group difference in Test Phase accuracy by classifying the Dependent and Non-dependent participants as either Negative or Positive Learners. For Negative Learners, both groups tended to avoid choosing the Bad Stimulus about equally often, $t(12) = 1.2$, $p > .05$, but the Non-dependent participants (n=7) tended to chose the Good Stimulus more often (75%) than the Dependent participants (n=7) did (44%), $t(12) = 2.7$, $p < .05$ (Figure. 8B). Likewise, for Positive Learners, both groups tended to chose the Good Stimulus about equally often, $t(14) = 0.92$, $p > .05$, but the Non-dependent participants (n=7) tended to avoid choosing the Bad Stimulus more often (76%) than the Dependent participants (n=9) did (50%), $t(14) = 2.8$, $p < .01$ (Figure. 8C).

I investigated this issue further by determining for each subject the degree to which they used their preferred strategy relative to their non-preferred strategy. For each subject, I computed the Learning Index Score (LIS), defined as LIS = (preferred accuracy - nonpreferred accuracy)/(preferred accuracy + nonpreferred accuracy); higher LIS scores indicate a greater preference for one strategy over the other. The LIS scores for Dependent and Non-dependent participants are shown separately for Positive and Negative Learners

in Figure. 8D. A two-way ANOVA on LIS as a function of Group (Non-dependent, Dependent), and learner type (Positive, Negative) revealed a main effect of Group, $F(1, 28) = 14.46$, $p < .001$, ES = .35, indicating that Dependent participants exhibited a larger learning bias (Mean = .30) compared to Non-dependent participants (Mean = .10); all other main effects and interactions were not significant, $p > .05$. Taken together, these results indicate that the Dependent and Non-dependent participants performed the task about equally well when allowed to use their preferred strategies, but that the Dependent participants were severely impaired relative to the Non-dependent participants when required to use their non-preferred strategies. Thus, the overall performance difference across groups illustrated in Figure. 8A resulted mainly from the Dependent participants responding at chance accuracy when forced to rely on their less favored methods for response selection. Note that this finding argues against a general cognitive or learning impairment in the Dependent participants, which would be expected to impact both strategies equally.

**Interaction between fERN and PST Results**

Given that the reward processing system that produces the fERN might be sensitive to learning style, I examined fERN amplitude as a function of both Group and Learner Type. A two-way ANOVA on fERN amplitude with Group (Non-dependent, Dependent) and Learner Type (Positive, Negative) as factors revealed a significant interaction between Group and Learner Type, $F(1, 28) = 4.3$, $p < .05$, ES = .13 (Figure. 7D). Post-hoc analysis revealed that the ERP effect of interest was mainly driven by a reduced fERN in Dependent Negative Learners (M = -1.2 μV, SE = $\pm$ .5) relative to Non-dependent Negative Learners (M = -4.7 μV, SE = $\pm$ .4), $p < 0.01$; all other paired comparisons were

nonsignificant (p >.05, corrected for multiple comparisons using Bonferonni correction). In other words, the reduced fERN in the Dependent Group relative to the Non-dependent Group was associated with the participants who were better in the PST at avoiding the Bad Stimulus than at choosing the Good Stimulus. Further, a two-way ANOVA on each of the personality trait scores as a function of Learner Type and Group revealed that none of these were related to Learner Type or Group (p > .05) except for Depression-proneness (Conrod & Woicik, 2002). Specifically, Dependent Positive Learners scored higher on the Depression-proneness scale (M = 14, SE = $\pm$ 1.1) than did Dependent Negative Learners (M = 10, SE = $\pm$ .6), $t(14) = 2.4$, $p < 0.05$. In other words, Dependent participants who scored high on the Depression-proneness scale were relatively successful in the PST at choosing the Good Stimulus but relatively impaired at avoiding the Bad Stimulus. Further analysis indicated that scores on the Depression-proneness were about the same for the Non-dependent Positive Learner compared to the Non-Dependent Negative Learner Group (p>.05), confirming that the effect of interest was isolated to Dependent Group and thus did not reflect an overall difference in Depression-proneness between learning strategies. Taken together, these results indicate that Dependent individuals who fail to learn from reward feedback produce a truncated neural response to feedback, whereas Dependent individuals who fail to learn from error feedback exhibit higher levels of Depression-proneness.

## DISCUSSION

These findings are indicative of two separate groups of dependent drug users, one characterized by impaired reward learning and the other characterized by impaired error learning. According to a neurocomputational theory of the fERN, this electrophysiological

signal is argued to be elicited by the impact of RPEs carried by the MDS onto motor areas in ACC, where they are utilized for the adaptive modification of behavior according to principles of reinforcement learning (Holroyd & Coles, 2002). Importantly, the difference in the ERPs elicited by positive and negative feedback has recently been shown to result mainly from reward processing induced by positive feedback (Holroyd, Pakzad-Vaezi, & Krigolson, 2008; Cohen, Elger, & Ranganath, 2007). In line with this observation, I found that for the dependent individuals who were impaired at reward learning, a negative-going deflection in the ERP following Reward trials mirrored the negative-going deflection in the ERP following No-reward trials. In other words, reward feedback failed to induce dopamine-dependent reward processing in these individuals. Further, computational simulations of the BG-MDS have indicated that disrupted positive dopamine RPEs tend to upset reward learning while sparing error learning (Cohen & Frank, 2008) as I observed (Figure. 8B). These findings are consistent with the proposal that substance dependence is associated with the impact of impaired dopamine-mediated reinforcement learning signals on neural areas for cognitive control and decision making.

It remains to be determined whether the drug use was a consequence or the cause of this reward processing impairment. On the one hand, the findings survived statistical control of several important personality-related risk factors for drug use. Further, the results are consistent with the observation that all drugs of abuse stimulate the dopamine system (Di Chiara G. & Imperato, 1988), resulting in maladaptive synaptic changes (Hyman et al., 2006) that disrupt neural networks in ACC, OFC, and BG (Robinson & Kolb, 2004; Homayoun & Moghaddam, 2006), which in turn desensitizes the system to non-drug rewards (Koob & Le Moal, 2005) like the small monetary incentives used here

(Volkow, Fowler, Wang, Baler, & Telang, 2009). These considerations suggest that heavy drug use may have modified the midbrain dopamine system and its neural targets in this population. On the other hand, it is also possible that abnormal dopamine signals resulted directly from dopamine-related genetic polymorphisms associated with addiction-proneness (Kreek et al., 2005), impaired reward learning and spared error learning (Cohen & Frank, 2008), and reduced fERN amplitudes (Marco-Pallares et al., 2009). In fact, I suspect that both factors may be involved, such that in dependence-prone individuals the reinforcing properties of addictive drugs exploit genetic vulnerabilities to the dopamine system.

By contrast, I found that the dependent individuals who were impaired at error learning scored high on the depression proneness scale when compared to dependent individual who were not impaired at error learning. It is interesting to note that depression and drug dependence are highly comorbid, both because depressed individuals tend to take drugs of abuse for the purpose of self-medication (Markou, Kosten, & Koob, 1998), but also because substance use can lead to depression (Rehm et al., 2006). Further, depressed individuals sometimes rely on the analgesic properties of alcohol and other drugs to ameliorate negative affect (Conrod & Woicik, 2002), which directs their thought processes away from negative self-rumination toward-positive self-reflection (Stephens & Curtin, 1995). In this way the analgesic properties of drugs can reinforce behaviors that protect against negative, self-relevant information (Markou et al., 1998). Hence, I suggest that the depression-prone dependent individuals in this study tended to ignore error feedback in favor of positive feedback during the Training phase of the PST, leading to better performance on the "Choose Good" trials relative to the "Avoid Bad" trials during the Test

Phase of the PST. Consistent with this view, substance use could impair error learning directly by altering OFC structure and function (Robinson & Kolb, 2004; Homayoun & Moghaddam, 2006), thereby disrupting "top-down" regulation of the BG Go and No-go pathways (Cohen & Frank, 2008). The transition of these individuals from a propensity to use addictive substances to dependence could also be facilitated by dopamine-related genetic vulnerabilities associated with addiction-proneness (Kreek et al., 2005), impaired negative learning and spared positive learning (Cohen & Frank, 2008; Klein et al., 2007), and reduced error-related brain activation in ACC (Klein et al., 2007).

Although the participants were not screened for the presence of comorbid disorders, such as attention deficit hyperactivity disorder and major depression, the experimental results remained robust even when the effects of personality traits related to anxiety, depression-proneness, impulsivity, and sensation seeking were controlled for statistically. Nevertheless, future studies should examine this possible confounding factor. It was also the case that the participants were not screened for acute drug use before starting the experimental session. Aside from the fact that they did not display any obvious signs of recent drug or alcohol use while being tested, I believe that these results are uncontaminated by acute drug use for the following reasons. First, dopamine agonists such as caffeine, nicotine and amphetamine increase error-related negativity amplitude (Overbeek et al., 2005; Jocham & Ullsperger, 2009), but the dependent individuals in this study exhibited decreased, rather than increased, fERNs. Second, depressants such as alcohol tend to depress other ERP components such as the P300 in addition to the ERN (Holroyd & Yeung, 2003; Polich & Criado, 2006). By contrast, despite the large reduction in fERN amplitude in the dependent participants in this study, the P200 and P300

components appeared entirely normal—indicating that the effects of drug use were in fact limited to the fERN.

Given that substance users bring with them diverse life histories, personalities, biological/genetic profiles and drug preferences, substance dependence has proven extremely challenging to treat. An obvious next step would be the inclusion of neurobiological markers of substance dependence in individually tailored treatment programs. For instance, combined assessment of electrophysiological, cognitive and genetic profiles could potentially improve upon current therapeutic approaches and better predict vulnerability to relapse. By highlighting important neurobiological and behavioral differences between two classes of dependent users, this research may represent an important step in this promising direction.

# Experiment Two[4]

*Abstract*

The development and expression of the midbrain dopamine system is determined in part by genetic factors that vary across individuals such that dopamine-related genes are partly responsible for addiction vulnerability. However, a complete account of how dopamine-related genes predispose individuals to drug addiction remains to be developed. Adopting an intermediate phenotype approach, I investigated whether behavioral and electrophysiological measures of reinforcement learning and cognitive control as well as personality risk factors for drug addiction mediate the influence of multiple dopamine-related genetic polymorphisms over substance use. These results bridge the gap between genes and behavior by revealing several dopamine-related neural pathways underlying individual differences in substance dependence and illustrate how future interventions might be individually tailored for specific genetic, cognitive and personality profiles.

[4] This experiment has been submitted for publication: Baker, T. E., Stockwell, T., Barnes, G., Haesevoets , R., and Holroyd, C. B. Top-down vs. bottoms-up! Intermediate phenotypes for cognitive control and personality mediate the expression of dopamine genes in addiction.

# Top-down vs. bottoms-up! Intermediate phenotypes for cognitive control and personality mediate the expression of dopamine genes in addiction

Can our genetic makeup predispose us to addiction? Rapid advances in molecular genetics have inspired optimism that answers to such intractable psychiatric questions, together with novel therapeutics, may be on the horizon. But unlike disorders that result from a single gene mutation, substance dependence appears to have a polygenic origin mediated by a confluence of vulnerabilities related to neurobiology, behavior, cognition, personality and the environment (Goldman, Oroszi, & Ducci, 2005). Thus, despite the fact that substance dependence is partly heritable (Uhl et al., 2008), compelling evidence linking individual genes with the disorder remains elusive.

One strategy for addressing complex gene-disease relationships depends on the concept of *intermediate phenotypes*: biological and psychological factors that are relatively proximal to genetic influence and confer vulnerability to (rather than determine) psychopathology (Meyer-Lindenberg & Weinberger, 2006). In the case of substance abuse, all addictive drugs potentiate the activity of the midbrain dopamine system (Di & Imperato, 1988), which acts as the linchpin of a neural mechanism for reinforcement learning and decision making (Glimcher, 2011), so individual variability in dopamine expression may present a core vulnerability to addiction (Sweitzer, Donny, & Hariri, 2012). For instance, two recent studies proposed that the relationship between a dopaminergic receptor variant of the DRD4 gene and heavy drinking is mediated by the personality trait of *novelty seeking* (Ray et al., 2009; Laucht, Becker, Blomeyer, & Schmidt, 2007). Yet because several other dopamine-related genes have also been associated with substance abuse (Gorwood et al., 2012) and with various personality traits

(Kreek, Nielsen, Butelman, & LaForge, 2005), a complete account of how dopamine-related genes predispose individuals to drug addiction remains to be developed.

Here I adopted the intermediate phenotype (IP) approach[5] to link nine dopamine-related genetic polymorphisms with substance dependence (Table 2). In particular, I explored the viability of six candidate IPs: an electrophysiological measure of a cortical mechanism for dopamine-dependent reward processing and cognitive control (Holroyd & Coles, 2002; Holroyd & Yeung, 2012), a behavioral index of a subcortical mechanism for dopamine-dependent reinforcement learning (Frank et al., 2004), and four personality risk factors associated with drug addiction (impulsivity, novelty seeking, depression proneness and anxiety sensitivity) (Conrod & Woicik, 2002). Key to my approach is the application of statistical modeling procedures more commonly utilized in the social sciences (mediation analysis and structural equation modeling) to elucidate causal relationships across complex multivariate data sets (see also Ray et al., 2009; Laucht et al., 2007).

Substance dependence was defined as *patterns of drug use* that impose a significant cost on the individual, are difficult to interrupt, are likely to recur following interruption, and are characterized by tolerance and withdrawal symptoms as measured by the Global Continuum of Substance Risk score (GCRs) of the WHO ASSIST (Humeniuk & Ali, 2006). GCRs data, together with data associated with personality risk factors and family history, were collected from 812 undergraduate students at the University of Victoria. Of these subjects, 196 returned on a subsequent day to participate in an

[5] It has been suggested that IP candidates should be based on (i) functional polymorphisms known to affect the coding of the protein of interest (here, proteins underlying the expression of the dopamine system); (ii) theoretical or conceptual models for how that protein in the brain region(s) of interest plays a role in the associated IP (here, theories relating dopamine to reinforcement learning, cognitive control, and individual personality traits); and (iii) a suitable task (or inventory) that probes the specific computations of that IP (here, the reward positivity, the Probabilistic Selection Task, and SURPS) (*3, 11*).

electrophysiological and behavioral experiment and to provide saliva samples for DNA analysis (Table 2). 42 individuals met criteria for substance dependence (GCRs>41) (see Appendix A, Experiment 2), 43% of whom were dependent on alcohol, 24% on cannabis, 12% on tobacco, and 9.6% on at least one controlled substance. As expected, a partial regression analysis indicated that the genotypes as a group did not reliably predict participants' GCRs, $F(9, 194) = 1.7$, $p = .08$ − motivating the IP approach − but the promoter C-521T polymorphism (rs1800955) of the DRD4 gene uniquely predicted GCRs both within this model (Beta = .194, $t = 2.7$, $p = .008$) and on its own, $F(1, 194) = 4.9$, $p = .02$. An allele comparison revealed that C carriers (CC, GCRs=32; CT, GCRs=29) displayed a higher degree of substance dependence compared to homozygous T carriers (GCRs=22), $p < .01$, $p < .05$, respectively.

**Table 2. Genotype characteristics of the research sample population**

| Gene | DRD2 | | | | | | | | PPP1R1B (DARPP-32 protein) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SNP | Taq1A | | | C957T | | | SNP2 | | M04 | | | M12 | | |
| SNP ID | rs1800497 | | | rs6277 | | | rs12364283 | | rs879606 | | | rs907094 | | |
| allele | A2/A2 | A2/A1 | A1/A1 | T/T | C/T | C/C | T/T | C/T | G/G | A/G | A/A | A/G | A/G | G/G |
| Phenotype | ↑↑ | ↑↓ | ↓↓ | ↑↑ | ↑↓ | ↓↓ | ↑↑ | ↑↓ | ↑↑ | ↑↓ | ↓↓ | ↑↑ | ↑↓ | ↓↓ |
| Sample | 109 | 76 | 10 | 52 | 107 | 36 | 160 | 35 | 136 | 47 | 12 | 117 | 61 | 17 |
| Frequency | 56% | 39% | 5% | 27% | 55% | 18% | 82% | 18% | 70% | 24% | 6% | 60% | 31% | 9% |
| Gene | COMT | | | DRD4 | | | | | | | | | | |
| SNP | Val158Met | | | C-521T | | | VNTR | | Indel | | | | | |
| SNP ID | rs4680 | | | rs1800955 | | | | | rs12720364 | | | | | |
| allele | M/M | M/V | V/V | C/C | C/T | T/T | short | long | G/G | -/G | -/- | | | |
| Phenotype | ↓↓ | ↑↓ | ↑↑ | ↑↑ | ↑↓ | ↓↓ | ↑↑ | ↓↓ | unknown | | | | | |
| Sample | 54 | 101 | 40 | 43 | 107 | 45 | 108 | 87 | 75 | 89 | 29 | | | |
| Frequency | 28% | 52% | 20% | 22% | 55% | 23% | 55% | 44% | 38% | 46% | 15% | | | |

SNP: Single Nucleotide Polymorphism

↑↓: denotes an increase or decrease in dopaminergic expression (i.e. D2/D4 density, COMT enzyme, DARPP-32 protein)

I first investigated whether the reward-positivity, a component of the event-related brain potential (ERP) said to index the impact of dopamine signals for reinforcement learning on anterior cingulate cortex (ACC) (Holroyd & Yeung, 2012; Holroyd & Coles,

2002), could serve as an IP for substance dependence. A previous study indicated that the reward-positivity is selectively disrupted in substance-dependent users, consistent with impaired reward processing and cognitive control in this population (Baker, Stockwell, Barnes, & Holroyd, 2011; Experiment 1). I recorded the electroencephalogram from participants as they navigated a virtual T-Maze with button presses (see Appendix A, Experiment 2). After each response an image of the chosen alley appeared followed by a feedback stimulus (apple or orange) indicating whether the participant received a reward (5 cents) or punishment (0 cents) on that trial; unbeknownst to the participants, the feedback was random and equiprobable. The single-trial EEG data were averaged for each electrode and subject according to feedback type to create Reward and No-reward ERPs. Following convention, the size of the reward-positivity was then determined by identifying the peak amplitude of the difference between the Reward and No-reward ERPs within a 200-400 ms window following feedback onset (Baker & Holroyd, 2009; see Appendix A, Experiment 2). The analysis was restricted to the electrode channel where the signal was maximal (FCz).

A regression analysis indicated that the reward-positivity reliably predicted participants' GCRs, $F(1, 194) = 16.1$, $p < .001$, accounting for 8% of the variance. To investigate this further, participants were classified as either Dependent (n = 43 subjects; GCRs > 42), Moderate Users (n = 96; GCRs = 40−17) or Non-dependent (n = 58; GCRs < 16) (see Appendix A, Experiment 2). For the dependent individuals, the ERP to the Reward feedback produced a negative-going deflection that mirrored the ERP to No-reward feedback, indicating a reduction of the reward-positivity to positive feedback (Figure. 9a); the reward-positivity was severely reduced for the Dependent group (M= -3.0

μV, SE = ±.5) relative to the Non-dependent Group (M= -5.7 μV, SE = ±.4), and the Moderate Group (M= -5.6 μV, SE = ±.3), $F(2, 196) = 9.7$, $p < .001$, replicating the previous finding (Baker et al., 2011). Importantly, the amplitudes of other prominent ERP components (N100, P200, P300) were equivalent for the three groups ($p>.05$), confirming that the effect of interest was isolated to the reward-positivity and did not reflect an overall processing difference across the participants. These findings survived statistical control of personality risk factors for drug use ($p < .001$), suggesting that this abnormality in reward processing is unrelated to individual differences in personality.

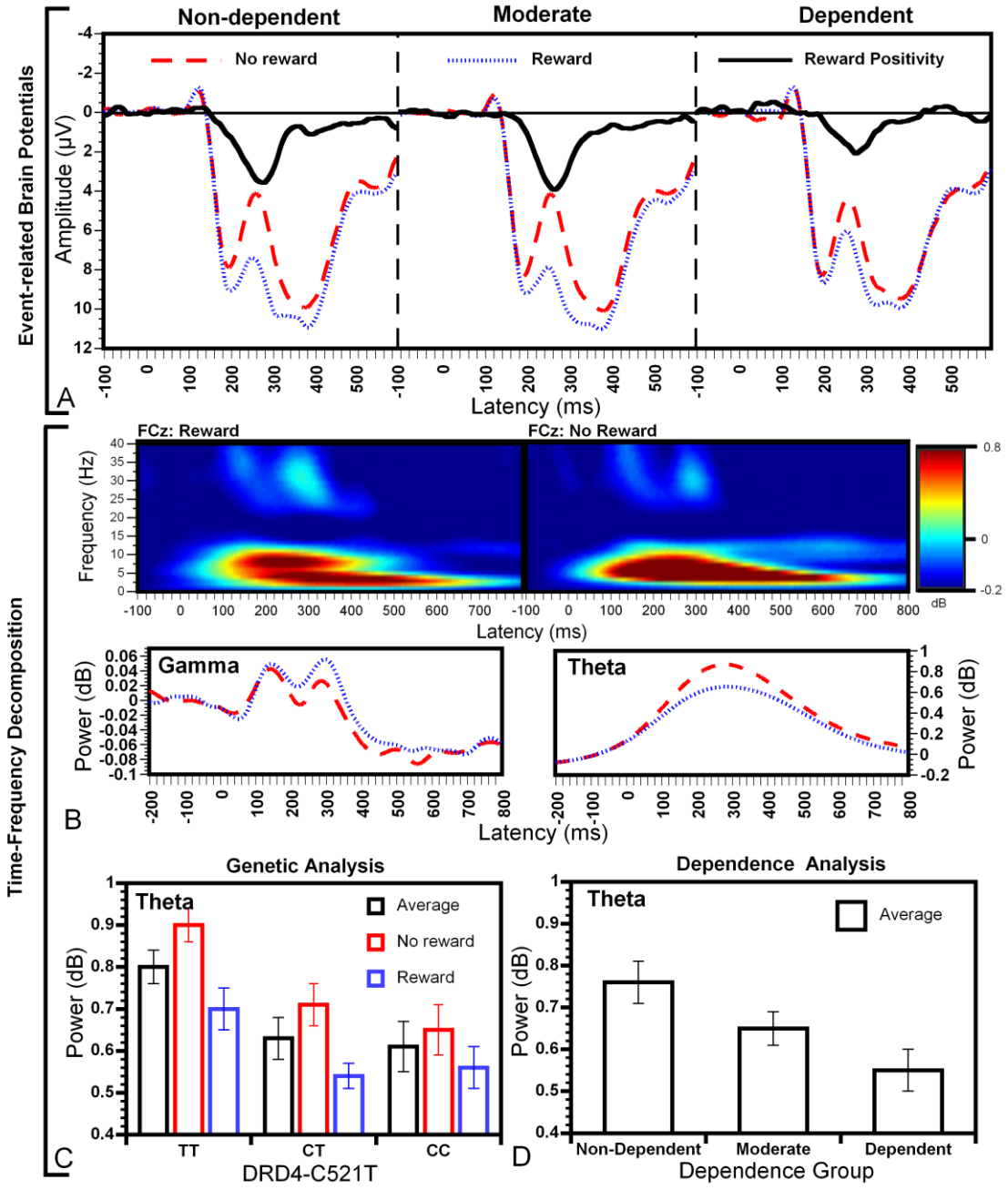


**Figure 9. ERP, time-frequency, and genetic analysis associated with frontal-central electrode channel FCz. [A] Grand-average ERPs associated with Reward (blue dotted lines) and No-reward (red dashed lines) outcomes and reward-positivity (black solid lines) for the (left) Non-dependent, (middle) Moderate, and (right) Dependent Group. Negative voltages are plotted up by convention. [B] Time-frequency analysis of the EEG associated with outcome processing. (Top) Panels indicate changes in power for each frequency band with respect to baseline elicited by Reward (left) and No-reward (right) outcomes. (Bottom) The time course**

**of the change in gamma (left) and theta (right) power associated with Reward (blue dotted lines) and No-reward (red dashed lines) outcomes. Note, only gamma and theta displayed significant differences in power between outcomes. [C] Genetic analysis on time-frequency data. Bar graph depicting average (Black), Reward (Blue) and No-reward (Red) theta for DRD4-521 allele groups. [D] Bar graph depicting average theta for the (left) Non-dependent, (middle) Moderate, and (right) Dependent Groups. Bars indicate the standard error of the mean. All data recorded at channel FCz.**

Although the reward-positivity has been previously linked to dopamine related genes (i.e., DRD4, COMT) (Marco-Pallares et al., 2009; Kramer et al., 2007), in the present study none of the genotypes significantly predicted reward-positivity amplitude ($p > .05$). The data averaging process underlying the ERP approach can obscure information contained in the ongoing EEG (Tallon-Baudry & Bertrand, 1999), so I reasoned that time-frequency analysis might better reveal gene-dependent electrophysiological effects. My analysis focused on frequency bands previously associated with reinforcement learning and the reward-positivity, namely, gamma [20-40 Hz] (Hajihosseini, Rodriguez-Fornells, & Marco-Pallares, 2012; Marco-Pallares et al., 2008) and theta [4-8 Hz] (Cavanagh, Frank, Klein, & Allen, 2010). Single-trial EEG data were segmented in 2000 ms epochs centered on feedback presentation and convoluted with a complex Morlet wavelet for frequencies from 1Hz to 40 Hz (linear increase) relative to a 100 ms pre-stimulus baseline. For each subject and feedback type, the peak power and latency of each frequency band were obtained by detecting the maximum power within a 1000 ms window following the onset of the feedback stimulus (see Appendix A, Experiment 2). The analysis was restricted to the electrode channel where the reward-positivity was maximal (FCz).

A regression analysis confirmed that theta (Beta = -.261, $t = -3.9$, $p < .001$) and gamma (Beta = -.294, $t = -4.4$, $p < .001$) band energy contributed significantly to the

amplitude of the reward-positivity, F(2, 195) = 30.1, p = .001, accounting for 19% of the variance. Consistent with previous reports, theta (p<.001) and gamma (p<.01) band power differed between the Reward and No-Reward trials during the time period (200-400 ms post-feedback) and at the spatial location (frontal-central) associated with the reward-positivity (see Appendix A, Experiment 2)[6]. Because theta and gamma appear to interact to produce the reward-positivity[7], I examined whether power in these frequency bands also predicted GCRs. Overall, a regression model reliably predicted participants' GCRs, F(5, 195) = 2.5, p = .03, accounting for 6% of the total variance, with mainly theta power rather than gamma power underlying this relationship (Beta = -.251, *t* = -2.8, p < .005): theta power was reduced for the Dependent group (M= .55 dB, SE = $\pm$.06) relative to the Non-dependent Group (M= .76 dB, SE = $\pm$.05) and the Moderate Group (M= .65 dB, SE = $\pm$.04), F(2, 196) = 3.5, p < .05 (Figure. 9D). As with the reward-positivity, this finding survived statistical control of personality risk factors for drug use, F(2, 196) = 3.2, p = .04 (see Appendix A, Experiment 2). Moreover, when the contribution of the reward-positivity was controlled for statistically, the effect disappeared (p>.05), suggesting that the reward-positivity may mediate the effect of theta on GCRs. The meditation hypothesis requires

[6]A repeated measures ANOVA on band power as a function of Frequency (theta, gamma) and Feedback (Reward, No Reward) confirmed this observation, revealing a main effect of Frequency, *F*(1, 195) = 551.7, p < .001, a main effect of Feedback, *F*(1, 195) = 16.6, p < .001, and an interaction between Frequency and Feedback, *F*(1, 195) = 36.2, p < .001. Post-hoc analyses indicated the EEG was characterized by greater power in the theta band (M = .66 dB, *SE* = $\pm$ .03) than gamma (M = .02 dB, *SE* = $\pm$ .01), p < .001, and that overall band power was greater for no reward (M = .38 dB, *SE* = $\pm$ .02) compared to reward feedback (M = .30 dB, *SE* = $\pm$ .02), p < .01. In regards to the interaction, gamma and theta power were inversely related: reward trials were characterized by decreased theta power (M = .58 dB, *SE* = $\pm$ .02) and increased gamma power (M = .04 dB, *SE* = $\pm$ .013), whereas No-reward trials were characterized by increased theta power (M = .74 dB, *SE* = $\pm$ .04) and decreased gamma power (M = .01 dB, *SE* = $\pm$ .014) (Figure. 1B, bottom panels). As a check, test results for all other frequency bands were non-significant for this comparison (p>.05).

[7] A recent proposal suggests that unexpected task-relevant events elicit a burst of theta in the ACC, one half-cycle of which describes the N200 ERP component. Further, unexpected rewards elicit a phasic increase in dopamine (possibly reflected by an increase in gamma) that inhibits the N200 and reduces theta activity (*17*)

that theta be significantly related to both the reward-positivity and GCRs (conditions that were satisfied; see above), that the reward-positivity be related to GCRs (also satisfied), and that the relation of theta with GCRs be reduced in the presence of the reward-positivity while the indirect effect remains statistically significant (Baron & Kenny, 1986). A reduction in the size of the direct effect from theta to GCRs in the presence of the reward-positivity, p = .20, together with a significant test of the indirect effect (p =.003), satisfies the third requirement, indicating that the reward-positivity mediates the contribution of theta to the GCRs.

Next, I investigated whether any of the nine dopamine-related polymorphisms predicted theta[8]. Although the genotypes together did not reliably predict theta, F(9, 194) = .92, p = .50, the promoter C-521T polymorphism of the DRD4 gene uniquely predicted theta both in this model (Beta = -.148, t = -2.0, p = .03) and on its own, F(1, 194) = 4.9, p = .02, consistent with previous findings (Marco-Pallares et al., 2009). An ANOVA with repeated measures on theta activity (Reward, No-reward) as a function of DRD4-521 allele group (TT, CT, CC) revealed a main effect of feedback, F(1, 192) = 21.2, p <.001, such that more theta was associated with No-reward trials relative to Reward trials (Figure. 9) and a main effect of DRD4-521, F(1, 192) = 3.4, p =.03, indicating a reduced theta response for homozygous C carriers (M = .61 dB, *SE* = $\pm$ .05) and heterozygous carriers (M = .62 dB, *SE* = $\pm$ .03) as compared to homozygous T carriers (M = .80 dB, *SE* = $\pm$ .05), p = .02, p = .01, respectively (Figure. 9). No interaction was detected (p>.05)[9]. Together,

[8] Differences in gamma power between reinforcing events were significantly larger for homozygous DRD4-521 T carriers (M = .07 dB, SE = + .02), compared to homozygous C carriers (M = .009 dB, SE = + .02), t(86) =¬ 1.9, p < .05, and a trend for CT carriers was observed (M = .024 dB, SE = + .03), p = .056 (Figure. S4).

[9]Previous research has suggested an interaction on theta power between the Val158Met polymorphism (rs4680) of the Catechol-O-methyltransferase (COMT) gene−with the Met allele accounting for a four-fold decrease

these finding suggest the relationship between the DRD4-521 and substance dependence was mediated by reward-related electrophysiological signals produced in ACC (Figure. 10) (see Appendix A, Experiment 2).

Both the reward-positivity (Baker & Holroyd, 2011a) and frontal midline theta (Cavanagh et al., 2010) are believed to be produced in medial frontal cortex, probably within caudal ACC. The function of this brain region is controversial, but a recent theory holds that caudal ACC is responsible for learning the value of extended, context-specific sequences of behavior directed toward particular goals, and further, that the reward-positivity reflects the impact of dopamine reinforcement learning signals on ACC for this purpose (Holroyd & Yeung, 2012). Viewed in this context, the mediation effect indicates that D4 receptors play a pivotal role in decision making over extended behaviors. D4 receptors, which are highly expressed in frontal regions involved in cognitive control (e.g., cingulate gyrus, middle frontal gyrus, frontal lobe, and amygdala) (Mulcrone & Kerwin, 1997), appear to inhibit pyramidal neurons (Rubinstein et al., 2001; Wang, Zhong, & Yan, 2002; Wang, Zhong, Gu, & Yan, 2003) in response to tonic dopamine activity (Onn, Wang, Lin, & Grace, 2006). Notably, application of a D4 agonist in medial frontal cortex impairs shifting between alternative task strategies, whereas blockade of D4 receptors improves this function (Floresco, Magyar, Ghods-Sharifi, Vexelman, & Tse, 2006). This

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in dopamine catabolism leading to increased tonic activity and decreased phasic activity− and the DRD4-521(*27*). For this reason I explored this possibility in the present data set. Separate ANOVAs on theta activity (reward and no-reward) as a function of DRD4 allele group and COMT allele group (Val/Val, Val/Met, Met/Met) revealed an interaction of genotypes on reward related theta activity, $F(4, 195) = 2.5$, $p = .02$, indicating greater theta activity of the CT allele group in the presence of fewer Val alleles compared to the CC allele ($p<.05$), and greater theta activity for the CC allele group in the presence of more Val alleles compared to the CT allele ($p<.05$). Although no main effects were observed, post hoc tests did reveal a significant difference in reward related theta power between heterozygous C carriers (M = .54 dB, *SE* = $\pm$ .04) and homozygous T carriers (M = .67 dB, *SE* = $\pm$ .05), $t(150) = -2.3$, $p < .05$, but no differences were observed for the homozygous C carriers ($p=.07$).

evidence suggests that D4 receptor activation may antagonize event-related phasic activity underlying behavioral flexibility (Floresco & Magyar, 2006).

I speculate that low D4 density may enable the ACC to respond dynamically to event-related activity whereas increased D4 density and/or tonic dopamine activity would have the converse effect. Consistent with this possibility, I found that individuals carrying the T allele of the DRD4-521−which accounts for a 40% reduction in D4 transcriptional efficiency (Okuyama, Ishiguro, Toru, & Arinami, 1999)−displayed a relatively strong medial frontal theta response to salient events, evidently by releasing the ACC from tonic inhibition of the dopamine system. By contrast, C allele carriers displayed a suppressed medial frontal theta response to salient events and showed elevated levels of substance dependence. Whereas too much D4 inhibition might disrupt the normal reinforcement learning function of ACC, the dopamine-potentiating effects of addictive substances might compound this problem, resulting in unstable reward valuation as revealed by the electrophysiological measures.

I next investigated whether four personality traits—anxiety, depression, impulsivity, and novelty seeking, as measured by the Substance Use Risk Profile Scale (SURPS) (Conrod & Woicik, 2002)−could serve as IPs for a contribution of dopamine-related genes to substance dependence. These traits have been previously associated with substance dependence (Conrod & Woicik, 2002), dopamine related genes (e.g. DRD4, and DRD2) (Kotyuk et al., 2009; Hamidovic, Dlugos, Skol, Palmer, & de, 2009) and reinforcement learning (Cavanagh, Bismark, Frank, & Allen, 2011). Consistent with previous findings, the SURPS measures provided a good overall predictor of GCRs, $F(1, 194) = 10.4$, $p < .001$, accounting for 16% of the total variance. In particular, GCRs were

most strongly predicted by novelty seeking ($p < .001$), followed by impulsivity ($p < .001$), and depression-proneness ($p < .05$). The effect of anxiety was not statistically significant ($p = .09$) in this model, but was a modest predictor on its own, $F(1, 194) = -6.1$, $p < .01$. Separate regressions of each personality trait on all genotypes together did not yield a predictive model but did reveal several unique predictors.

Notably, DRD4-521 − which also predicted GCRs and theta activity; see above − best predicted depression ($p < .05$): CC ($M=13$) and CT ($M=12.5$) carriers displayed higher depression scores compared to TT carriers ($M=11.2$), ($p < .01$, $p < .05$, respectively). Further, depression mediated the relationship between the DRD4-521 and GCRs: when the effect of DRD4-521 and GCRs was controlled for by the mediator, the relationship was reduced ($p = .07$) and the indirect effect was significant, *(*$p = 0.02$). Thus although the main effect of the DRD4 gene on substance dependence was mediated by medial frontal electrophysiological activity related to reward processing, a secondary effect was mediated by depression-proneness (Figure. 10). Functional neuroimaging studies have revealed a reduced neural response to negative feedback and abnormalities in ACC-mediated performance monitoring in depression (Elliott, Sahakian, Michael, Paykel, & Dolan, 1998; Kumar et al., 2008; Steele, Kumar, & Ebmeier, 2007), individual differences that might reflect excessive D4-dependent inhibition of frontal cortex. Insensitivity to error information appears to impair the ability to learn response-outcome contingencies and can contribute to learned helplessness by reducing the perception of control over external events (Elliott et al., 1998). Further, depression-prone individuals are often characterized by high neuroticism−a tendency to focus primarily on the self and to maintain self-focused attention on negative affect (Conrod & Woicik, 2002). Provided this evidence, excessive

D4-inhibition of ACC may render individuals incapable of switching from negative to more positive affective states. Conversely, drugs of abuse that potentiate the reinforcing effects of dopamine may provide depressed individual with the opportunity to switch thought processes while concomitantly reinforcing this maladaptive behavior.

Next, the Val158Met polymorphism (rs4680) of the Catechol-O-methyltransferase (COMT) gene exclusively predicted anxiety; ($p < .03$): carriers of the Val/Val ($M=13.7$) and Met/Val ($M=13.3$) allele displayed higher scores on the anxiety personality scale compared to Met/Met carriers ($M=12.5$), $p<.05$. The Val allele accounts for a four-fold increase in catecholamine (dopamine, norepinephrine, and epinephrine) catabolism in frontal cortex, which has been hypothesized to augment phasic signaling in that region (Bilder et al., 2004). Norepinephrine in particular plays an important role in vigilance, attention and learning by putatively serving as a neural alert signal, and is implicated in the etiology of anxiety-related disorders (Goddard et al., 2010). By extension, an increase in COMT activity may lead to heightened phasic activations of the "alert" function, evoking unnecessary feelings of arousal and anxiety. Individuals with this polymorphism might therefore be especially sensitive to the anxiolytic and reinforcing properties of alcohol.

The personality trait of impulsivity was best predicted by the M12 polymorphism (rs907094) of the PPP1R1B gene, which codes for the DARPP-32 protein ($p < .05$): individuals homozygous for the G allele ($M=11.8$) displayed higher scores on the impulsivity scale compared to both A/G ($M=9.7$) and A/A carriers ($M=9.7$), $F(2, 195)$, $5.1$, $p<.01$. The DARPP-32 protein regulates the sensitivity of striatal neurons to glutamtergic excitation and dopaminergic modulation (Svenningsson et al., 2004), facilitating the functional connectivity between brain regions including the projection from

dorsal lateral prefrontal cortex to the striatum (Meyer-Lindenberg et al., 2007). DARPP-32 also plays an important role in the actions of drugs of abuse (Svenningsson, Nairn, & Greengard, 2005). The frontal-striatal system implements control functions such as impulse regulation (Fineberg et al., 2010), so it is natural that decreased DARPP-32 availability might be associated with higher levels of impulsivity, as I observed here. Individuals displaying impaired inhibitory control due to frontal-striatal dysregulation may thus be particularly vulnerable to drug-related potentiation of the midbrain dopamine system.

Although the DRD2-Taq1A predicted novelty seeking ($p < .05$), a subsequent ANOVA revealed only a marginal difference between the allele groups, $F(2, 195)$, 1.8 $p<.10$. This result is perhaps surprising given that of all the known dopamine-related polymorphisms, the A1 allele of the Taq1A polymorphism (rs1800497) of the DRD2 gene, which is characterized by reduced striatal D2 density, is strongly implicated in substance abuse, novelty seeking(Noble, 1998) and, recently, reinforcement learning (Klein et al., 2007). Previous studies have suggested that low D2 expression may be indicative of poor decision making, a hallmark of substance dependence (Klein et al., 2007), and may also drive maladaptive behaviors that compensate for a chronically low "reward state" (Blum et al., 2000). Here, individuals homozygous for the A2 allele (M=17.2) displayed higher scores on the novelty seeking scale compared to both A1/A2 (M=16.6) and A1/A1 carriers (M=16.3), contrasting with previous reports. How low striatal D2 densities expressed by the DRD2 variants (TaqA1, C957T, SNP2) translate into a vulnerability to addiction warrants continued research.

Finally, a potential IP associated with the impact of dopamine signals for reinforcement learning on the basal ganglia was assessed using the probabilistic selection task (PST) (Frank et al., 2004). In the present study, however, PST performance did not reliably predict GCRs and for this reason will not be considered here further; results related to genetic influence over task performance will be discussed in the next chapter. Taken together, these findings suggest that the dopaminergic contribution to addiction may play out most strongly via control mechanisms in medial frontal cortex (as revealed by the reward-positivity) compared to striatal mechanism for reinforcement learning (as revealed by PST performance).

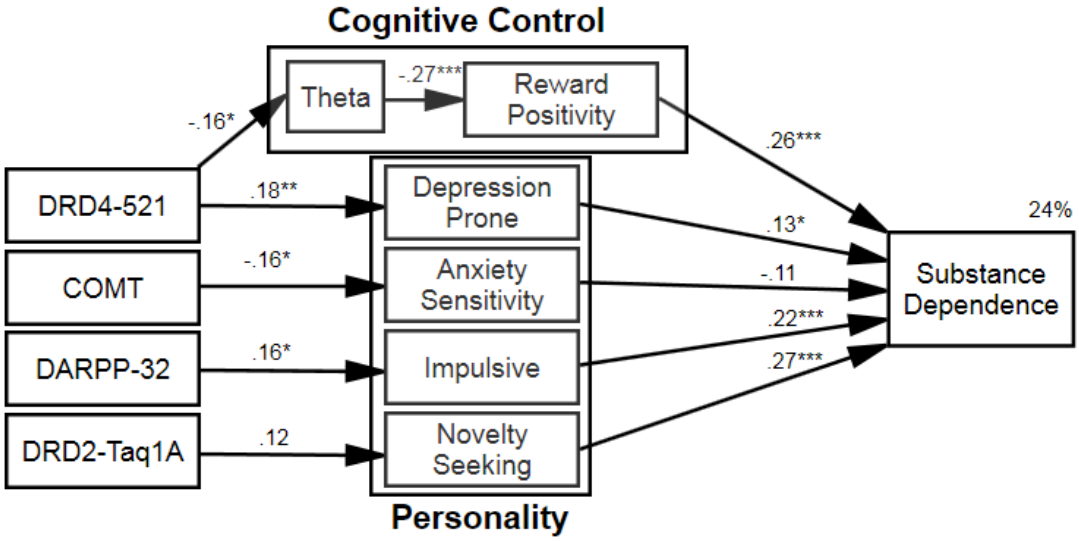


**Figure 10. Top. Structural equation model with standardized regression coefficients representing the influence of IPs on level of substance dependence. *p<.05, **p<.005, ***p<.001. Dotted lines indicate mediation pathways. Results indicate an overall strong fit as per conventional criteria (APPENDIX A) [$\chi 2$ = 48.3, *df* = *44*, p = .304, CFI = .96, GFI = .96, RMSEA = .02, 90% CI [0.001 to 0.05], $\chi 2/df$ ratio=1.1], explaining approximately 24% of individual variance in substance dependence.**

I investigated the relative contribution of each of these factors to substance dependence by creating a structural equation model based on the results of the regression analyses (Figure. 10). Paths connecting genes to IPs were selected according to the unique genotype predictor of each IP. Because the contribution of theta to GCRs was mediated by the reward-positivity, I included the reward-positivity as a mediating variable on this pathway. The model provided a strong fit of the data, attesting to the appropriateness of the IP approach (Figure. 10). While these findings are consistent with the proposal that genetics factors play an important part in determining vulnerability to drug-seeking and addictive behavior (Goldman et al., 2005), an alternative model would highlight bidirectional effects between symptoms, in that each disorder has independent origins, but its course and severity is exacerbated by the other disorder over time (Mackie et al., 2011). For example, whereas depression is often shown to predict alcohol abuse and dependence, evidence has also shown that heavy alcohol use increase an individual's vulnerability for depression (Mackie et al., 2011). In fact, I suspect that both factors may be involved, but will only be resolved by investigating genetic-related developmental trajectories within the addiction process. Finally, I utilized the model to identify different populations of substance dependent users. Cluster analysis indicated two groups of substance dependent individuals (see Appendix A, Experiment 2), the first of which accounted for 43% of the substance dependent sample, characterized by reduced reward-positivity amplitudes (M= -1.8 μV) and high depression-proneness scores (M= 15.2), and the second of which accounted for 54% of the substance dependent sample, characterized by high novelty seeking scores (M= 19.2) and relatively normal reward-positivity amplitudes (M= -4.1 μV). Although exploratory, the cluster analysis converges on several vulnerabilities related

to decision making as specified within a unified theoretical framework for addiction (Redish et al., 2008). For example, the severely reduced reward-positivity can be understood in terms of an altered allostatic set points due to overvaluation of drug-related rewards in the planning and habit system (vulnerabilities 2, 4, 7 in *53*), whereas depression-proneness can be understood by an inability to switch responses in the face of failures and losses (vulnerability 6).

By highlighting several dopamine-related neural pathways underlying individual differences in substance dependence, the model suggests a theoretical framework for bridging the gap between genes and behavior in drug addiction. These findings illustrate how future interventions might be individually tailored for specific genetic, cognitive and personality profiles. For instance, depression-prone individuals with a reduced reward-positivity might be treated with behavioral therapy and pharmaceuticals (e.g. D4 antagonists), whereas individuals prone to novelty seeking might be treated with behavioral therapy alone. By identifying how brain and personality link genes to addiction, novel treatments for substance dependence may finally be on the horizon.

# Experiment Three[10]

*Abstract*

To what degree are our actions truly free vs. predetermined? An influential neurocomputational theory of the biological mechanisms of decision making, the "Basal Ganglia Go/NoGo model", holds that individual variability in decision making is determined by differences in the makeup of a striatal system for approach and avoidance learning. According to this model, an individuals' ability to learn from positive and negative reinforcement can be predicted by genetic, psychiatric, and trait factors related to the dopamine system. The model has been tested empirically with the Probabilistic Selection Task (PST), which determines whether individuals learn better from positive or negative feedback. Here I utilized the PST to investigate the relative contribution of multiple dopamine-related genetic polymorphisms, personality traits and drug use history on individual differences in decision making. Although I found characteristics that predicted individual differences in approach vs. avoidance learning, these observations were qualified by additional findings that appear inconsistent with the predictions of the Go/NoGo Model, including a failure to demonstrate test–retest reliability of any PST performance measures over a 7-8 weeks interval. The present results point to several individual traits related to the dopamine system and learning style that may modulate decision making across individuals but future research is needed to confirm the validity of these and previous PST findings.

[10] This experiment has been submitted for publication: Baker, T. E., Stockwell, T., and Holroyd, C. B. Constraints on Decision Making: Implications from Genetics, Personality, and Addiction.

Constraints on Decision Making: Implications from Genetics, Personality, and Addiction

Neuroimaging studies reveal that normal performance on decision making tasks is associated with widespread activations of the basal ganglia, midbrain dopamine system, and connected structures. These neural pathways are integral components of complex functional neuroanatomical loops underlying reinforcement learning and decision-making that appear critical for several cognitive, motor, and emotional functions (Packard & Knowlton, 2002). Individual variability related to genetics (Frank et al., 2009; Frank & Hutchison, 2009; Klein et al., 2007), personality traits (DeYoung et al., 2010; Simon et al., 2010; Bornovalova et al., 2009; Zermatten, Van der Linden, d'Acremont, Jermann, & Bechara, 2005; Jentsch & Taylor, 1999) and complex psychiatric disorders (Waltz, Frank, Wiecki, & Gold, 2011; Wiecki & Frank, 2010; Moustafa, Cohen, Sherman, & Frank, 2008; Moustafa, Sherman, & Frank, 2008; Frank, Samanta, Moustafa, & Sherman, 2007; Frank, Scheres, & Sherman, 2007; Waltz, Frank, Robinson, & Gold, 2007; Steele et al., 2007; Beste, Saft, Andrich, Gold, & Falkenstein, 2006; Frank et al., 2004; Solomon, Smith, Frank, Ly, & Carter, 2011; Maia & Frank, 2011) are associated with biases in basal ganglia function in such tasks, reflecting idiosyncratic differences in our abilities to learn and make choices. Yet the neural mechanisms that underlie individual differences in decision making remain poorly understood.

According to an influential neurocomputational model of decision making, "the Basal Ganglia Go/NoGo model", dopaminergic signaling in the basal ganglia facilitates or suppresses action representations during reinforcement learning tasks: phasic bursts of dopamine activity facilitate reward learning by reinforcing striatal connections that express D1 receptors (the "Go/Approach" pathway), whereas phasic dips in dopamine activity

facilitate avoidance learning by reinforcing striatal connections that express D2 receptors (the "NoGo/Avoidance" pathway) (Frank et al., 2004). Empirically, the model predictions are typically tested with the Probabilistic Selection Task (PST), a trial-and-error learning task in which subjects are required to learn three concurrent discriminations (stimulus pairs AB, CD and EF), rewarded with schedules of 80%/20%, 70%/30% and 60%/40%, respectively. In a subsequent Test Phase, the subjects are asked to select between novel combinations of the original stimuli without receiving feedback. Subjects who are more accurate at picking the stimulus that was most frequently rewarded (the "Good Stimulus") are classified as "Positive Learners" whereas subjects who are more accurate at avoiding the stimulus that was most frequently punished (the "Bad Stimulus") are classified as "Negative Learners" (Frank et al., 2007).

The PST has provided insight into individual differences related to reinforcement learning (Cohen & Frank, 2008), genetics (Frank et al., 2009; Frank & Hutchison, 2009; Frank et al., 2007; Frank et al., 2007), normal aging (Frank & Kong, 2008), "top-down" modulation by orbital frontal cortex and anterior cingulate cortex (Paulus & Frank, 2006; Frank & Claus, 2006), pharmaceutical manipulations (Frank & O'reilly, 2006), and psychiatric conditions (especially, Parkinson's disease, attention-deficit hyperactivity disorder, and schizophrenia; for review, see Maia & Frank, 2011). For example, genetic studies show that the ability to learn from positive or negative reinforcement can be predicted by variability related to single nucleotide polymorphisms (SNPs) affecting D1 and D2 gene expression in the Go/Approach and NoGo/Avoid pathways . The Go/NoGo model predicts that reduced striatal D2 density should be associated with impaired accuracy on Avoid trials together with spared accuracy on Approach trials in the PST

(Frank et al., 2009; Frank & Hutchison, 2009; Frank et al., 2007; Frank et al., 2007). Consistent with this prediction, Klein and colleagues (2007) demonstrated that male carriers of the A1 allele (A1/A1 and A2/A1 combined) of the Taq1A SNP of the DRD2 gene, which is associated with reduced D2 expression (Thompson et al., 1997; but see Zhang et al., 2007), were selectively impaired at avoiding the Bad Stimulus during the Test Phase. Frank and Hutchison (2007) initially reported similar results but found that effects of the Taq1A polymorphism on accuracy on Avoid trials were due to indirect association with the C957T SNP of the DRD2 gene; participants carrying the C allele of the C957T SNP, which has also been identified to cause a reduction in striatal D2 receptor expression and binding potential (Hirvonen et al., 2009; Hirvonen et al., 2009; Hirvonen et al., 2004; but see Duan et al., 2003), were relatively inaccurate on Avoid trials but performed about normally on Approach trials (Frank & Hutchison, 2009; Frank et al., 2007). On the other hand, Frank and Hutchison (2009) revealed that carriers of the C allele (minor) of promoter SNP (C/T) (rs12364283) were selectively inaccurate on Avoid trials. Because this polymorphism is associated with greater D2 expression (Zhang et al., 2007), this finding appears inconsistent with the Go/No-go model.

The Go/NoGo Model further predicts that good performance on Approach trials should be associated with enhanced efficacy of striatal D1 receptors, as for example modulated by the PPP1R1B gene (Frank et al., 2007). The M12 polymorphism (rs907094) of the PPP1R1B gene codes for the DARPP-32 protein, which is highly concentrated in the striatum, regulates the sensitivity of D1 striatal neurons to glutaminergic excitation and dopaminergic modulation, and is required for D1-receptor mediated synaptic plasticity and reward learning (Meyer-Lindenberg et al., 2007; Svenningsson et al., 2004). A previous

study found that A/A compared to G carriers of this polymorphism were relatively better at choosing the Good Stimulus compared to avoiding the Bad Stimulus in the PST Test Phase, a result that implicates striatal D1 receptors in reward learning (Frank et al., 2007).

The Go/NoGo model is also being utilized to investigate psychiatric and neurological disorders that involve disturbances of the midbrain dopamine system and basal ganglia, in particular, Parkinson's disease, attention-deficit hyperactivity disorder, and schizophrenia. The model predicts that disruption in dopaminergic signaling in the basal ganglia Go and NoGo pathways can selectively impair approach and avoidance learning on the PST (Maia & Frank, 2011). For example, the model predicts that people with Parkinson's disease will be more accurate on Avoid than Approach trials of the PST while off medication due to a diminished dopamine signal, and more accurate on Approach than Avoid trials while on medication due to an enhanced dopamine signal, findings that have been confirmed empirically (Frank et al., 2004). Further, Maia and Frank (2011) have recently proposed that the Go/NoGo model can provide important insights into addiction. Because all addictive drugs potentiate the reinforcing effects of the midbrain dopamine system (Di Chiara G. & Imperato, 1988) and upset the normal function of its neural targets (Hyman et al., 2006), addiction is a natural candidate for investigating the Go/NoGo model using the PST (Maia & Frank, 2011). Consistent with this proposal, undergraduate participants classified as Positive Learners who were substance dependent displayed reduced accuracy on Avoid trials together with normal accuracy on Approach trials, relative to Positive Learners who were not dependent (Baker, Stockwell, Barnes, & Holroyd, 2011). By contrast, substance dependent Negative Learners showed the reverse effect. These initial findings suggest two pathways to addiction, one characterized by

impaired approach learning and another by impaired avoidance learning. However, these findings failed to replicate in a follow-up study (Experiment 3).

Though less explored, the Go/NoGo model is also proving useful for understanding individual differences in personality. For example, a recent study attributed enhanced accuracy on Avoid trials of the PST by depressed individuals to hypersensitivity to punishment (Cavanagh et al., 2011). Further, Frank and colleagues (2007) attributed impulsive decision-making to an inability to self-modulate decision times as a function of conflict, a consequence of a reduced coupling between cognitive control regions (i.e. anterior cingulate cortex) and basal ganglia output. Other personality traits associated with different styles of reinforcement learning would also appear promising for investigation using the PST. For instance, individuals high in sensation seeking are less sensitive to the negative consequences of their actions, make relatively more risky choices, and perform poorly on decision making tasks (Bechara, Damasio, & Damasio, 2000; Bechara, 2003; Noel et al., 2011; Zermatten et al., 2005; Zuckerman, 1988; Zuckerman & Kuhlman, 2000). As well, anxious individuals appear to be hypersensitive to negative consequences following their actions and are risk-averse (Raghunathan & Pham, 1999; Maner & Schmidt, 2006; Mitte, 2008; Meyer-Lindenberg, 2010). Although these personality traits might appear to have little in common, in fact they have all been associated with individual differences in dopamine expression (Montag et al., 2008; Hamidovic et al., 2009; Laine, Ahonen, Rasanen, & Tiihonen, 2001; Lawford, Young, Noble, Kann, & Ritchie, 2006), reinforcement sensitivity (Bechara, 2001; Maner & Schmidt, 2006), and vulnerability to addiction (Conrod & Woicik, 2002). The PST might therefore elucidate the neural

mechanisms of decision making associated with these personality traits, providing particular insight into substance abuse.

Here I utilized the PST to investigate individual differences related to genetics, substance use and personality, as well as the interaction between these factors. First, I sought to replicate and extend previous findings on the effects of genetic polymorphisms related to the expression of dopamine D1 and D2 receptors over PST performance. I also considered three genetic polymorphisms that regulate dopaminergic modulation of cognitive control mechanisms in frontal cortex that, to my knowledge, heretofore have not been investigated utilizing the PST, specifically the *promoter -521 (C/T) SNP (rs1800955)*, the *indel -1217G ins/del (-/G) (rs12720364)*, and the *variable number of tandem repeats (VNTR) polymorphism (long/short) in exon III* (Table 1). Although the T allele of the promoter -521 and the VNTR short have been associated with reduced D4 expression (Okuyama et al., 1999; Oak et al., 2000; McGeary, Esposito-Smythers, Spirito, & Monti, 2007), the specific effects of the DRD4-1217G on D4 expression is not known. However, a fMRI study by Fan and colleagues (2003) found that individuals homozygous for the G allele of the DRD4-1217G displayed a relatively strong BOLD response in the anterior cingulate cortex to task conflict. Based on this finding, I propose that carriers of the G allele of the DRD4-1217G should perform better in high conflict trials in the PST.

I also examined a gene that regulate the expression of the Catechol-O-methyltransferase (COMT) enzyme, the primary mechanism for dopamine inactivation in prefrontal cortex: the Val158Met polymorphism (rs4680) of the COMT gene accounts for a four-fold variation in dopamine catabolism, with the Met allele underlying decreased dopamine catabolism and increased dopamine concentrations in frontal cortex (Chen et al.,

2004; Meyer-Lindenberg et al., 2005; Matsumoto et al., 2003). Although the prevailing idea about the function of COMT highlights its important role in regulating dopamine levels in prefrontal cortex, an influential hypothesis also points to its effect over tonic and phasic dopamine activity in the basal ganglia: It has been proposed that lower COMT levels associated with the Met allele cause increased tonic dopamine that in turn activates D2 autoreceptors, together with a concomitant decrease in phasic dopamine signals subcortically (Bilder et al., 2004). In view of the Go/NoGo model, this proposal suggests that Met carriers should demonstrate a negative learning bias due to a blunted phasic reward response.

Because substance dependence has only recently been investigated using the PST (Baker et al., 2011), with mixed results (Baker et al. 2012), I also aimed to re-examine this issue by integrating data gathered over three experiments (see methods) and by testing a clinical population before and after treatment following a 7-8 week interval. In addition, I examined several personality traits associated with the dopamine system, reinforcement learning, and addiction, namely, impulsivity, novelty seeking, depression and anxiety. Finally, I looked for interactions on PST performance across all of these characteristics related to genetics, personality, and substance abuse, as a complete account of the neural mechanisms of decision making likely depends on the complex interaction of all of these factors.

The success of this investigation depends both on the Go/NoGo theory and on the utility of the PST for testing the theory. Critically, the extensive empirical support that the PST has provided for the Go/NoGo model of the basal ganglia strongly suggests that individual differences in PST performance should be stable over time, but to my

knowledge this prediction has never been explicitly tested (Ragland et al., 2012; Ragland et al., 2009). Thus as a subgoal of the study I examined whether various measures of PST performance were consistent within individuals over time.

In sum, reinforcement learning signals carried by the midbrain dopamine system are instrumental to the decision making function implemented by the basal ganglia, are modulated by particular genetic polymorphisms, and appear to contribute to individual differences associated with personality and addiction. Here I used the PST to assess the relative contribution of each of these factors and their interactions to decision making.

## MATERIALS AND METHODS

### Participants

Across three experiments, I collected survey data (substance use history, personality risk factors associated with addiction, and family history) and PST data from 499 subjects. Of these, 378 were undergraduate students at the University of Victoria, 70 of whom were part of a previous addiction study (Experiment 1) and 196 participated as part of a genetics study on the neural mechanisms of reward processing and substance use (Experiment 2), the data of which are reanalyzed here. The remaining participants were involved in a third study wherein I collected survey and PST data over two sessions from undergraduate students (n=112) and from individuals who were currently seeking treatment at a local treatment center (n=121) (Experiment 3) PST procedures across these three studies were identical, except for Experiment 3 in which PST data were collected for all groups at two different times (Time 1 and Time 2). Further, subjects in Experiment 1 and 2 but not in Experiment 3 had EEG recorded during a separate reward task. For Experiment 3, the treatment population was recruited from individuals currently seeking addiction treatment at Edgewood Addiction Treatment center in Nanaimo, British Columbia, Canada (http://www.edgewood.ca/). Edgewood is a private abstinence-based detox and drug rehab center, oriented on a 12 Step Foundation with an average length of treatment of 7-8 weeks. Inclusion criteria for this study did not involve any particular demographic group; the mix of subjects was expected to reflect the age, sex, and ethnic composition of the general population of first and second year undergraduate students at the University of Victoria and patients at Edgewood. All participants provided informed consent as approved by the Office of the Vice-President of Human Research, University of

Victoria, and the ethics board at Edgewood. The study was conducted in accordance with the ethical standards prescribed in the 1964 Declaration of Helsinki.

*Questionnaire*

The computer-based survey was comprised of several separate inventories (Baker et al. 2011), but for the purpose of this study, I focused on the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (Humeniuk et al., 2008), a validated screening test developed by the World Health Organization for identifying the degree of problematic substance use (i.e., tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants, sedatives, hallucinogens, inhalants, opioids and "other drugs"), and the Substance Use Risk Profile Scale (SURPS) (Conrod & Woicik, 2002), a 23-item self report questionnaire that provides measures on four dimensions of personality—depression-proneness, anxiety-sensitivity, impulsivity, and sensation seeking—that are risk factors for substance use. Both inventories were scored according to their guidelines; the scores served as continuous variables and were used for group identification (see below).

*Substance dependence*. Participants were classified according to their scores on the Global Continuum of Substance Risk (GCR) scale of the ASSIST. The GCR scores (GCRs) provide a measure of *patterns of drug use* that impose a significant cost on the individual, are difficult to interrupt, and are likely to recur following interruption. Specifically, participants with GCR scores falling within the bottom (GCRs < 15), middle (GCRs = 38−16), and top (GCRs > 39) quartiles of the undergraduate student sample (collapsed across studies, N=396) were classified as non-dependent (ND), moderately dependent (MD), and substance dependent (SD), respectively. These scores are comparable to the cut-offs established in previous validation studies of the ASSIST for

non-dependence (score < 15) and dependence (score > 39.5) (Newcombe et al., 2005). Further, a substance-dependent treatment group (SDTx) was composed of the individuals seeking treatment, all but 6 of whom scored higher than the top cut-off. Because these 6 individuals were under treatment for non-substance related addictions (e.g., gambling, sex), their data were excluded from the treatment group (SDTx).

*Personality*. Individuals were assigned to personality groups corresponding to each of the four SURPs subscales−depression-proneness (DPR), anxiety-sensitivity (ANX), impulsivity (IMP), and novelty seeking (NS)−according to whether their scores on that subscale exceeded one standard deviation above the mean; if they scored high on more than one subscale then they were assigned to the personality group in which they showed the greatest statistical deviance as reflected in their z-scores (Conrod & Woicik, 2002). Participants whose scores did not exceed the cut-offs on any of the dimensions were categorized as "unspecified" (USP). Because the undergraduate and treatment groups were categorically different in terms of their demographics and other traits, personality means and standard deviations were calculated and analyzed separately for the two groups.

*Behavioral Task - The Probabilistic Selection Task*

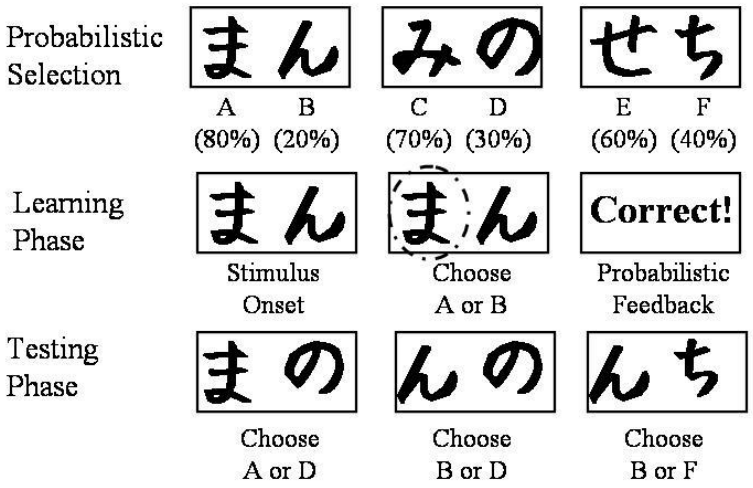


**Figure 11. Probabilistic Learning Task. Top row: Stimuli and reward probabilities (percent positive feedback). Middle row: Schematic of an example trial during the Learning Phase. Bottom row: Schematic of an example trial during the Test Phase.**

Participants were asked to position their hand and forearms so that both fingertips of the index fingers rested on buttons 1 and 0 of a standard computer keyboard placed in front of them, and were provided with written and verbal instructions explaining the procedure. On each trial of the task they viewed a fixation cross (green circle, 1 s) followed by a pair of visual stimuli that are not easily verbalized by most English speakers (i.e., Japanese Hiragana characters) presented in black on a white background in 72 pt font (Figure.11). They then pressed the key corresponding to the stimulus that they believed to be correct. Visual feedback was provided following each choice: the word "Correct!" printed in blue or "Incorrect" printed in red (1 s). If no response was made within 6 s then the words "no response detected" were displayed in red (1 s). During an initial Learning Phase participants were exposed to three pairs of stimuli presented in random order (AB, CD, EF; Figure. 11, top). The response mappings were probabilistic such that one stimulus in each of the three pairs was rewarded on 80%, 70%, and 60% of the trials, respectively,

with the remaining stimulus in each pair rewarded on the complementary percentage of trials (see Figure 11, top). Stimulus-probability assignments were counterbalanced across subjects.

Participants learned by trial-and-error to choose the more frequently rewarded stimulus over the alternative in each pair, namely, by selecting stimuli A, C and E more often than B, D, and F. Critically, they could do so either by learning that stimuli A, C and E were associated with relatively more positive feedback, by learning that stimuli B, D and F were associated with relatively more negative feedback, or both. Participants advanced to the Test Phase of the task if after any block of 60 trials they satisfied performance criteria for the three stimulus pairs (65% A in AB, 60% C in CD, 50% E in EF), or after six blocks (360 trials) of training if these criteria were not met. During the Test Phase participants were exposed to all possible combinations of these stimuli (i.e., AB, CD, EF, AC, AD, AE, AF, BC, BD, BE, BF, CE, DF) in a random order. As before, subjects were required to select the symbol in each pair that they believed to be correct, but without receiving any feedback about their choices. They were told to use "gut instinct" whenever they did not know how to respond. Each test pair was presented 6 times. Importantly, to minimize potential learning effects between sessions, different stimuli were used in the two sessions.

For the purpose of this study, behavioral measures of interest consisted mainly of Test Phase accuracy and reaction time. Participants were also classified as either "Positive Learners" (learning from positive feedback) or "Negative Learners" (learning from negative feedback) according to their performance in the Test Phase on "Approach trials" that involved the A stimulus (the "Good Stimulus"; AC, AD, AE, AF) relative to "Avoid trials" that involved the B stimulus (the "Bad Stimulus", BC, BD, BE, BF). In addition, I

also explored a measure of response conflict by comparing accuracy and reaction times for test pairs with similar reinforcement values (e.g., 80 vs. 70%, High Conflict) with those of pairs having more easily discriminable values (e.g., 80 vs. 30%, Low Conflict). Further, I analyzed performance separately for High Conflict Approach trials (AC, AE, CE) trials and High Conflict Avoid trials (BD, BF, DF), called "Win–win" (Approach) and "Lose–lose" (Avoid) trials, respectively (Frank et al., 2007; Cavanagh, Frank, Klein, & Allen, 2010). The data of participants who could speak, read and/or write Japanese were eliminated from further analysis (2 participants).

**Procedure**.

All participants were asked to complete the computer-based questionnaire followed by the PST in one session. In addition, for Study 3, individuals were asked to complete these tasks over two sessions (Time 1 and Time 2) spanning a 7-8 week interval. For the treatment group, session one began within three days following intake assessment. An Edgewood staff nurse provided the description of the experimental procedure and presented the consent form to each subject. Individuals who provided their consent were asked to complete the computer based questionnaire, followed by the PST. Session two commenced 7-8 weeks following initial intake and procedures were identical to the first. Following the completion of the second session, participants were provided with a debriefing form. For both sessions an Edgewood staff nurse was on hand to go through the procedures, consent and debriefing instructions, and answered any questions from the participating individuals. For the undergraduate individuals all procedures were identical to that of the treatment group, with the exception of environment, treatment provided, and study administrator (research assistant vs. Edgewood staff nurse). In all cases, the

participants' privacy was ensured via a numbering system. All analysis calculations were made using the statistical analysis program SPSS (Version 18) (SPSS Corp, 2003).

## RESULTS

### Participants

Within the student population, data of 7 participants containing coding errors and of 2 participants who could read, write, and/or speak Japanese were excluded, leaving 369 participants. Of the 121 individuals currently seeking treatment, 60 returned to complete the questionnaire, while only 25 agreed to complete the PST. Of those individuals who did not complete Session 2, 9 individuals left treatment, 44 completed treatment but did not agree to participate after session 1, and 8 were not reported. Notably, the GCRs for those individuals who left treatment (mean GCRs = 108.6, SE = 24) were relatively high compared to those of the individuals who completed treatment (mean GCR score = 83.6, SE = 4), $t(111) = -1.8$, $p < .05$.

A two-way ANOVA with repeated measures on GCRs of the Study 3 participants with Time (Time 1, Time 2) and Dependent Group (SDTx, SD, MD, ND) as factors revealed a main effect of Group, $F(2, 149) = 76.2$, $p < .001$, indicating that GCRs were significantly different from one another, $p<.001$, and a significant interaction between Time and Dependent Group, $F(3,149) = 3.1$, $p<.05$. Post hoc tests indicated that for the SDTx group, GCRs were reduced at Time 2 (mean GSR score = 76.1, SE = 5) compared to Time 1 (mean GSR score = 86.1, SE = 5), t(56), 2.5, $p<.01$. All other groups displayed similar GCRs between Time 1 and Time 2 ($p>.05$). This result was evidently driven by the portion of the GCR scale that measures the frequency of substance use, given that the

treatment facility is abstinence-based with an average length of treatment of 7-8 weeks (Figure 12).

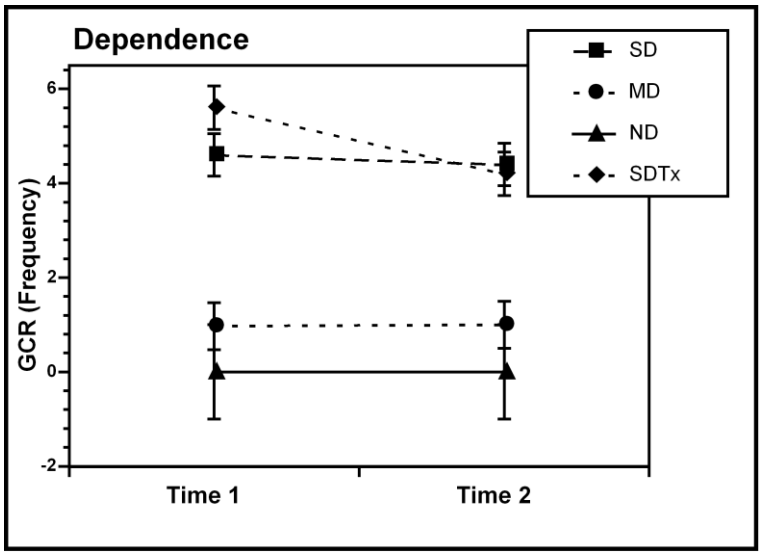


**Figure 12. Substance use frequency for Non-dependent (ND: blue bars), Moderately Dependent (MD: circle), Substance Dependent (SD: square), and Substance Dependent Treatment (SDTx: diamond) groups for Time 1 and Time 2 as measured by the ASSIST v3. Bars indicate the standard error of the mean.**

## PST and Learning Bias

| Learner Type | Positive | Negative | Neutral | Total |
|---|---|---|---|---|
| Sample | 159 | 163 | 47 | 369 |
| age | 20 | 21 | 19 | 20.1 |
| sex (f) | 124 | 125 | 33 | 282 |
| PST | | | | |
| Choose Good | mean | | | |
| Accuracy (mean) | 83% | 58% | 75% | 72% |
| (SE) | 1% | 2% | 3% | 1% |
| Reaction Time (mean) | 1132 | 1277 | 1148 | 1186 |
| (SE) | 33 | 40 | 67 | 24 |
| Avoid Bad | | | | |
| Accuracy (mean) | 58% | 82% | 75% | 72% |
| (SE) | 2% | 1% | 3% | 1% |
| Reaction Time (mean) | 1379 | 1302 | 1278 | 1320 |
| (SE) | 40 | 37 | 78 | 26 |

**Table 3. Undergraduate student accuracy and reaction time (mean and standard error) on the PST in the Choose Good and Avoid Bad conditions of the Test Phase averaged according to Learner Type and group total.**

The initial analyses focused on the data of the undergraduate student sample grouped across the three studies (at Time 1 for Study 3; n=369). A two-way ANOVA with repeated measures on Accuracy with Learner Type (Positive, Negative, Neutral) and Stimulus Type (Approach, Avoid) as factors revealed a significant interaction, $F(2,366) = 307.81$, $p<.001$ (Table XX), as expected. No main effects were observed. Next, a two-way ANOVA on reaction time with Learner Type (Positive, Negative, Neutral) and Stimulus Type (Approach, Avoid) as factors revealed a main effect of Stimulus Type, $F(1, 366) = 55.2$, $p<.001$), indicating that reaction time for Avoid trials was slower (mean = 1315.8 ms, SE =30) compared to Approach trials (mean = 1178.9 ms, SE =28), $p<.001$). A significant interaction was also revealed between Learner Type and Stimulus Type, $F(2,366) = 18.5$,

$p<.001$. Post hoc analysis indicated that both Positive and Neutral Learners responded faster for Approach trials compared to Avoid trials ($p<.01$), whereas the reaction times of Negative Learners were nearly identical, $p>.05$ (Table 1).

For the 96 undergraduate students who completed the PST at both Time 1 and Time 2 in Study 3 (over a 7-8 week interval), a three-way ANOVA with repeated measures on PST accuracy with Time (Time 1, Time 2), Stimulus Type (Approach, Avoid), and Learner Type (Positive, Neutral, Negative) as a factors revealed a significant interaction between Stimulus Type and Learner type, $F(2,95) = 9.6$, $p<.001$ (see above), and a three-way interaction, $F(2,95) = 21.8$, $p<.001$. Post hoc tests indicated that the Positive Learners were more accurate on Approach compared to Avoid trials at Time 1, $p<.001$, but not at Time 2, $p>.05$. Similarly, Negative Learners were more accurate on Avoid compared to Approach trials at Time 1, $p<.001$, but not at Time 2, $p>.05$. For the Neutral Learners, accuracy on Approach and Avoid trials were about equal at Time 1 and Time 2, $p<.05$ (Figure 13). No other main effects nor interactions were observed.

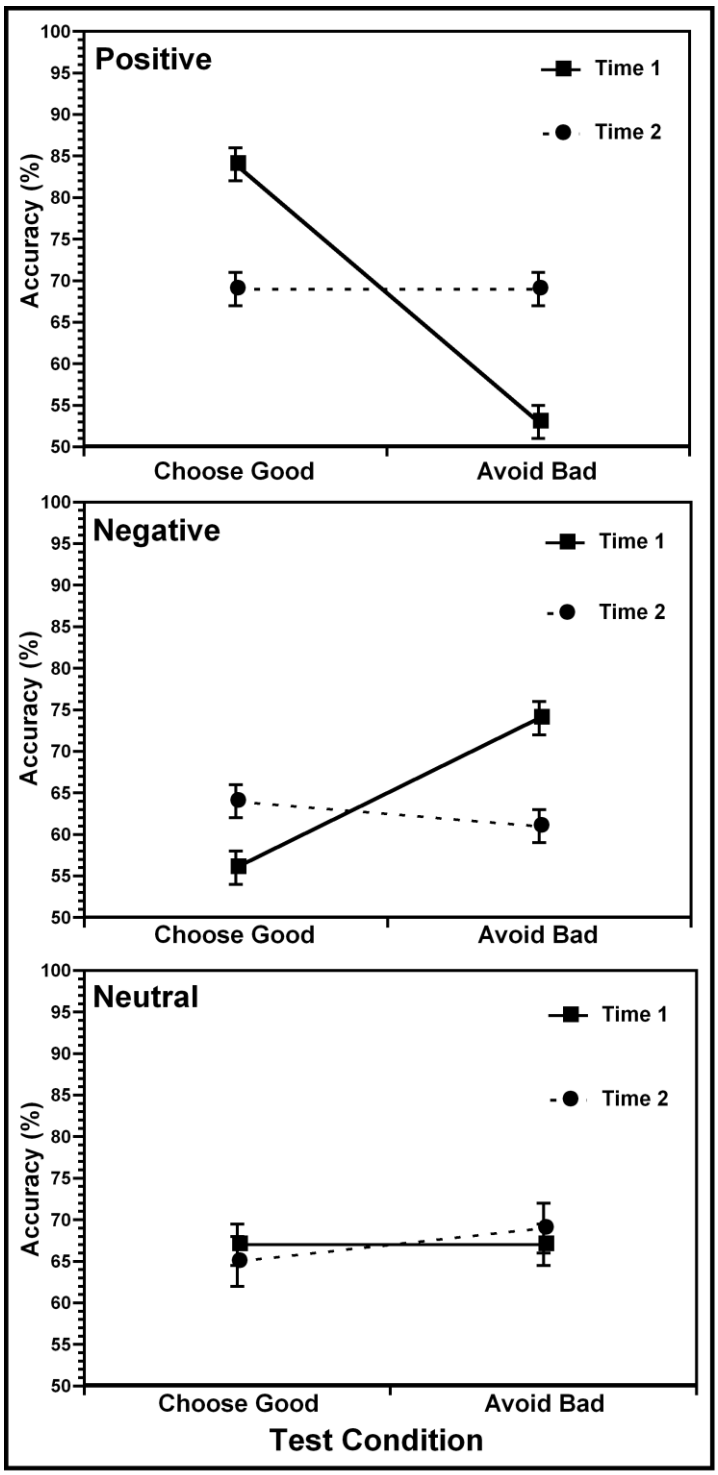


**Figure 13. Undergraduate student Test Phase accuracy on the PST for Time 1 (solid line) and Time 2 (dotted line) separately for the Choose Good and Avoid Bad trials and for Positive Learners (top, n=39), Negative Learners (middle, n=41) and Neutral Learners (bottom, n=16). Note that chance accuracy is 50%.**

To investigate this result further, I conducted a test–retest reliability analysis on PST performance. First, Pearson correlation coefficients were computed to quantify the reliability of task performance. An acceptable reliability was determined as $r > 0.6$ (McGraw & Wong, 1996). Accuracy on Approach and Avoid trials failed to demonstrate adequate test–retest reliability, ($r = .02$, $p=.85$, and $r = -.05$, $p = .67$, respectively). Similar results were obtained when a partial correlation was computed controlling for age, gender, GCRs, and personality traits: Approach ($r = .028$, $p=.79$), and Avoid ($r = -.073$, $p = .54$). As well, reaction time for Approach and Avoid trials displayed poor test–retest reliability ($r = .287$, $p<.005$, and $r = .257$, $p < .01$, respectively). Similar results were reported with the partial correlation, Approach ($r = .287$, $p<. 005$), and Avoid ($r = .257$, $p < .01$). All other PST measures failed to demonstrate adequate test–retest reliability ($r < .4$). As a check, I conducted a test-retest analysis on other variables: GCRs ($r = .91$, $p<. 001$), Depression-proneness ($r = .721$, $p<. 001$), Anxiety ($r = .675$, $p<. 001$), Impulsivity ($r = .791$, $p<. 001$), and Novelty Seeking ($r = .862$, $p<. 001$) all demonstrated good test-retest reliability, in agreement with the range prescribed by Kuntsi and colleagues (2001) (Figure 14).

Next, I computed the kappa coefficient to examine the consistency in which individuals were classified as Positive, Neutral, and Negative Learners across time. Values of Kappa from 0.40 to 0.59 are considered moderate, 0.60 to 0.79 substantial, and 0.80 outstanding (Landis & Koch, 1977). The reliability for the Learner Type was found to be Kappa = -.02 ($p = .801$), indicating inconsistency in learning bias across time. As a check, I removed individuals classified as Neutral Learners at Time 1 or at Time 2. Again, the reliability for the Learner Type was found to be poor, Kappa = -.02 ($p = .851$) (Figure 14).

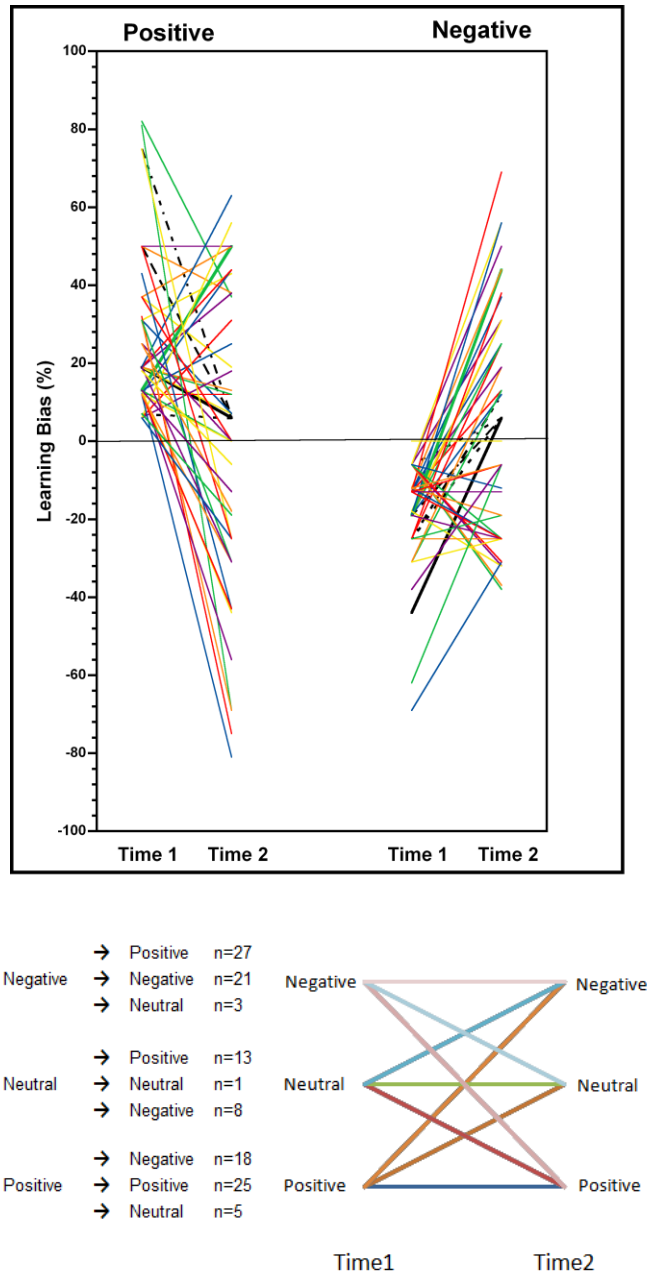


**Figure 14. Learning bias across Time. Learning bias (positive accuracy, negative accuracy) derived from the undergraduate student PST accuracy data, separately for Positive and Negative Learners across Time 1 and Time 2 (Top). Classification of learner type across Time 1 and Time 2 (bottom). Notably, an individuals learning bias between Time 1 and Time 2 was not consistent.**

## PST and Genetics

| Gene | DRD2 | | | | | | | | PPP1R1B (DARPP-32 protein) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SNP | Taq1A | | | C957T | | | SNP2 | | M04 | | | M12 | | |
| SNP ID | rs1800497 | | | rs6277 | | | rs12364283 | | rs879606 | | | rs907094 | | |
| allele | A2/A2 | A2/A1 | A1/A1 | T/T | C/T | C/C | T/T | C/T | G/G | A/G | A/A | A/A | A/G | G/G |
| Sample | 109 | 76 | 10 | 52 | 107 | 36 | 160 | 35 | 136 | 47 | 12 | 117 | 61 | 17 |
| Phenotype | ↑↑* | ↑↓* | ↓↓* | ↓↓* | ↑↓* | ↑↑* | ↓↓ | ↑↓ | ↑↑ | ↑↓ | ↓↓ | ↑↑ | ↑↓ | ↓↓ |
| Choose Good | | | | | | | | | | | | | | |
| Accuracy (mean) | 73% | 69% | 58% | 74% | 70% | 68% | 70% | 75% | 70% | 72% | 77% | 71% | 70% | 74% |
| (SE) | 2% | 3% | 6% | 3% | 2% | 4% | 2% | 3% | 2% | 3% | 6% | 2% | 3% | 6% |
| Reaction Time (mean) | 1204 | 1213 | 1308 | 1142 | 1240 | 1234 | 1260 | 997 | 1232 | 1146 | 1255 | 1216 | 1189 | 1275 |
| (SE) | 43 | 51 | 88 | 63 | 45 | 56 | 35 | 58 | 37 | 71 | 79 | 38 | 64 | 103 |
| Avoid Bad | | | | | | | | | | | | | | |
| Accuracy (mean) | 72% | 72% | 52% | 77% | 69% | 69% | 73% | 61% | 70% | 77% | 67% | 71% | 71% | 71% |
| (SE) | 2% | 3% | 7% | 3% | 2% | 4% | 2% | 4% | 2% | 3% | 7% | 2% | 3% | 6% |
| Reaction Time (mean) | 1324 | 1313 | 1322 | 1260 | 1364 | 1271 | 1347 | 1193 | 1315 | 1395 | 1461 | 1308 | 1299 | 1473 |
| (SE) | 45 | 56 | 83 | 63 | 49 | 50 | 25 | 90 | 41 | 68 | 117 | 41 | 65 | 109 |

| Gene | COMT | | | DRD4 | | | VNTR | | Indel | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| SNP | Val158Met | | | C-521T | | | VNTR | | Indel | | |
| SNP ID | rs4680 | | | rs1800955 | | | | | rs12720364 | | |
| allele | M/M | M/V | V/V | C/C | C/T | T/T | short | long | G/G | -/G | -/- |
| Sample | 54 | 101 | 40 | 43 | 107 | 45 | 108 | 87 | 75 | 89 | 29 |
| Phenotype | ↓↓ | ↑↓ | ↑↑ | ↑↑ | ↑↓ | ↓↓ | ↑↑ | ↓↓ | ** | ** | ** |
| Choose Good | | | | | | | | | | | |
| Accuracy (mean) | 68% | 74% | 67% | 74% | 69% | 73% | 71% | 72% | 66% | 73% | 68% |
| (SE) | 4% | 2% | 4% | 3% | 2% | 3% | 2% | 2% | 3% | 2% | 4% |
| Reaction Time (mean) | 1178 | 1238 | 1195 | 1136 | 1240 | 1221 | 1178 | 1261 | 1160 | 1170 | 1266 |
| (SE) | 54 | 45 | 71 | 55 | 47 | 56 | 38 | 52 | 47 | 51 | 72 |
| Avoid Bad | | | | | | | | | | | |
| Accuracy (mean) | 75% | 70% | 70% | 75% | 69% | 73% | 75% | 69% | 68% | 71% | 72% |
| (SE) | 3% | 2% | 4% | 3% | 3% | 3% | 2% | 3% | 3% | 3% | 4% |
| Reaction Time (mean) | 1267 | 1358 | 1292 | 1287 | 1318 | 1353 | 1305 | 1363 | 1228 | 1280 | 1369 |
| (SE) | 47 | 52 | 68 | 61 | 50 | 58 | 37 | 58 | 48 | 48 | 83 |

SNP: Single Nucleotide Polymorphism

↑↓: denotes an increase or decrease in dopaminergic expression (i.e. D2/D4 density, COMT enzyme, DARPP-32 protein)

*: denotes controvery in the literature, please refere to discussion

**: phenotype currently unknown

**Table 4. Genotype characteristics of the research sample population with PST accuracy and reaction time data.**

The above results indicate that PST Learner Type constitutes an unstable individual differences measure of decision making, at least for a typical undergraduate student population. Nevertheless, I reasoned that PST performance might be relatively more consistent across time for particular subpopulations of participants. In particular,

previous findings that dopamine-related genetic polymorphisms contribute to individual differences in PST performance (Frank et al., 2007; Frank et al., 2007; Frank et al., 2009; Frank & Hutchison, 2009; Klein et al., 2007) should be replicable, suggesting that PST performance is stable within those subpopulations. For this reason, I examined whether genetic determinants of D1 and D2 receptor expression in the striatum differentially modulate the ability to learn from negative and positive feedback in the PST. For exploratory purposes, I also examined the effects of genes that regulate the expression of the D4 receptor and the COMT enzyme−which both mediate dopaminergic modulation of the control functions of prefrontal cortex (Bilder et al., 2004; Oak et al., 2000)−on PST performance.

*DRD2.* The Go/NoGo model predicts that reduced striatal D2 density should be associated with impaired accuracy on Avoid trials together with spared accuracy on Approach trials in the PST (Frank & Hutchison, 2009). Accordingly, I examined whether decreased D2 expression as coded by several DRD2-related genetic polymorphisms (Table 2) would replicate previous findings of relatively poor avoidance learning in these individuals. Specifically, I focused on three genetic polymorphisms that affect D2 expression: 1) the *Taq1A (A1/A2) SNP (rs1800497)*, 2) the *C957T (C/T) SNP (rs6277)*, and 3) the *promoter SNP (C/T) (rs12364283)* ("promoter $SNP_2$", Zhang et al., 2007). Age, sex, and GCRs were statistically controlled throughout these analyses. A regression analysis indicated that the DRD2 SNPs together reliably predicted participants' accuracy on Avoid trials, $F(3, 194) = 3.4$, $p < .01$. In this model, accuracy on Avoid trials was uniquely predicted by the promoter $SNP_2$, Beta = -.180, $t = -2.5$, $p < .01$, and on its own, $F(1, 195) = 6.8$, $p < .01$, indicating that increased D2 receptor density is associated with relatively

worse accuracy on Avoid trials. The DRD2 genes did not have any effect on reaction time on Avoid trials. Next, a regression analysis on accuracy on Approach trials did not yield a predictive model (p=.104). However, the Taq1A uniquely predicted accuracy on Approach trials both within this model, Beta = .145, t = 1.9, $p < .05$, and on its own, $F(1, 194) = 4.4$, $p < .05$. These results suggest that individuals with low D2 availability, a characteristic of the A1 allele, were less accurate on Approach trials. Next, a regression analysis on Approach reaction time yielded a predictive model, $F(1, 194) = 4.1$, $p < .01$. Notably, the promoter $SNP_2$ uniquely contributed to the prediction of Approach reaction time both within this model, Beta = -.233, t = -3.3, $p < .001$, and on its own, $F(1, 194) = 10.8$, $p < .001$.

To confirm these gene-dose effects (DRD2 SNP2 →Avoid accuracy/reaction time; DRD2 Taq1A→Approach accuracy), I conducted a two-way ANOVA with repeated measures on accuracy and reaction time with Stimulus Type (Approach, Avoid) and Allele (aa, ab, bb) as factors separately for each DRD2 SNP (Figure 15). In regards to accuracy, this analysis revealed a main effect of Taq1A Allele, $F(2, 192) = 4.5$, $p < .01$. Post hoc tests indicated that individuals homozygous for the A1 allele (55%) were relatively inaccurate compared to homozygous A2 (73%, $p<.005$) and heterozygous (71%, $p<.01$) carriers. However, in contrast to the model predictions, their performance was worse for *both* Approach and Avoid trials ($p>.05$)[11]. For the promoter $SNP_2$, this analysis revealed an interaction, $F(1, 193) = 8.5$, $p < .005$. Post hoc analysis indicated that C allele carriers (enhanced D2 expression) were significantly worse at avoiding the Bad Stimuli on Avoid trials (61%) compared to choosing the good stimuli on Approach trials (75%), $p<.05$, while

[11] Following Klein et al. 2007, when A1A1 and A1A2 were combined and tested against A2A2, the results were non-significant, even when the data of female participants were excluded as in that study ($p>.05$).

T allele carriers (reduced D2 expression) were about the same between trial conditions (p=.158), also in apparent contradiction to the Go-No/go model. In regards to reaction time, this analysis revealed a main effect of Stimulus Type (see results above), a main effect of promoter $SNP_2$ Allele, $F(1, 193) = 7.1$, $p < .01$, which indicated that individual homozygous for the T allele (mean = 1303.1 ms, SE =33) were significantly slower compared to C carriers (mean = 1094.7 ms, SE =70), p<.01, and a trend toward an interaction between Stimulus Type and promoter $SNP_2$, $F(1, 193) = 3.2$, $p = .07$[12]. The DRD2 SNPs did not show any effects on the conflict measures (p>.05).

[12] Although the C957T SNP (rs6277) of the DRD2 gene did not reliably predict accuracy on Avoid trials within the combined DRD2 regression model (p=.166) nor on its own, (p=.08), a follow-up allele comparison indicated that accuracy on Avoid trials was significantly different between CT (68%) and TT (78%) carriers, t(157), -2.2, p<.05. Further, when CC and CT allele groups were combined, following Frank et al. (2007), a significant difference between the CT/CC (69%) and TT (78%) allele groups was revealed, $F(1, 194) = 4.5$, $p < .05$, and a regression analysis indicated that C957T (CT/CC combined) predicted accuracy on Avoid trials (p=.04).

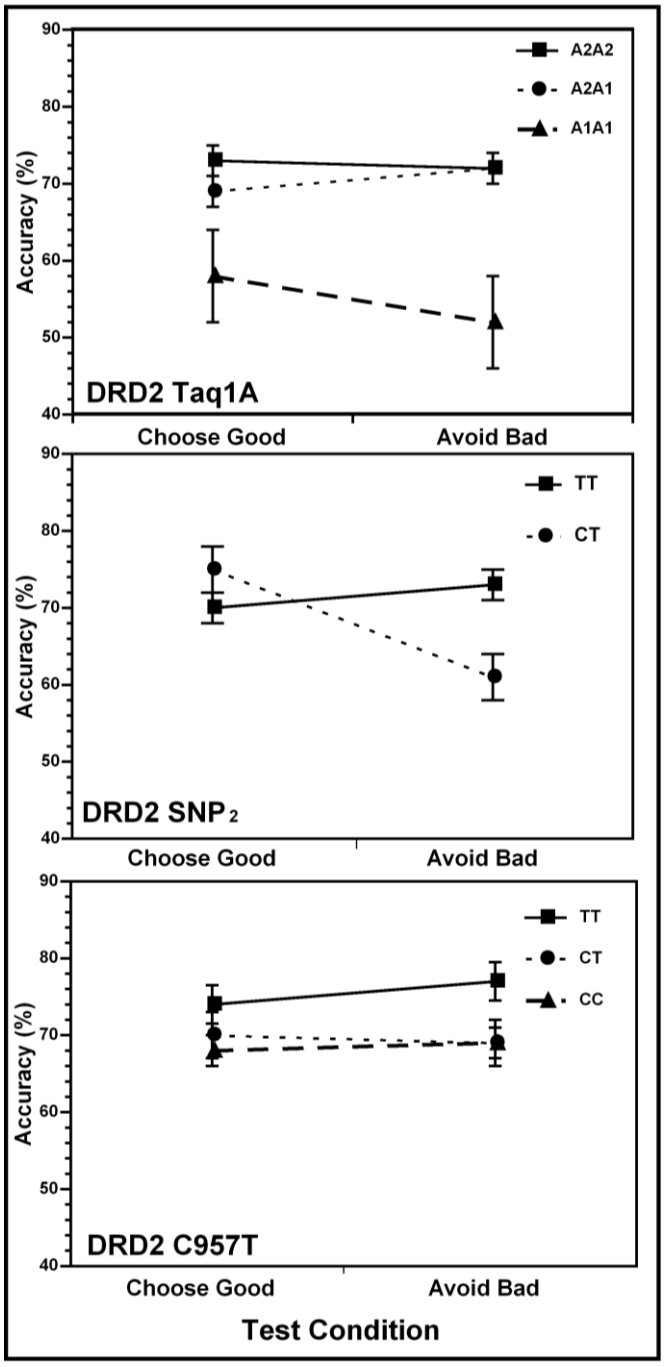


**Figure 15. Undergraduate student accuracy on the Probabilistic Selection Task (PST) in Study 2 according to DRD2 SNPs Taq1A (Top panel), promotor $SNP_2$ (Middle Panel), and C957T (Bottom Panel) separately for the Choose Good and Avoid Bad trials. Bars indicate standard errors of the mean.**

*PPP1R1B (gene coding for the DARPP-32 protein).* The Go/NoGo model predicts that good Approach performance would be associated with enhanced striatal D1 efficacy, as coded for example by the PPP1R1B gene (Frank et al., 2007). However, when I examined the effects of two polymorphisms associated with the PPP1R1B gene--the M12 (rs907094) SNP and the M04 (rs879606) SNP—on accuracy on Approach trials, both M04 and M12 did not affect any of the PST performance measures, even when low frequency allele groups were combined following Frank and colleagues (2007).

*DRD4.* To my knowledge the D4 receptor has yet to be investigated using the PST task, and the Go/NoGo model does not make any explicit predictions about its impact on PST performance (Frank & Fossella, 2011). Nonetheless, because D4 receptor expression in the frontal cortex is implicated in cognitive control function, including top down control over the basal ganglia and other motor structures (Frank & Claus, 2006), I examined whether three SNPs related to the DRD4 gene predict PST performance: 1) the *promoter -521 (C/T) SNP (rs1800955)*, 2) the *indel -1217G ins/del (-/G) (rs12720364)*, and 3) the *variable number of tandem repeats (VNTR) polymorphism (long/short) in exon III* (Table 1). A regression analysis indicated the DRD4 SNPs modestly predicted accuracy on High Conflict trials, $F(3, 194) = 2.3$, $p = .07$, together with normal accuracy and reaction times on Approach and Avoid trials. Specifically, accuracy on High Conflict trials was most strongly predicted by DRD4-1217G, Beta = .195, $t = 2.4$, $p < .01$. The DRD4 SNPs also reliably predicted accuracy on Lose−lose trials, $F(3, 194) = 2.8$, $p < .05$, which was strongly predicted by the DRD4-1217G, Beta = .233, $t = 2.8$, $p < .005$. A one-way ANOVA on High Conflict accuracy on DRD4-1217G Allele (GG, G/-, -/-) as between-subject factors revealed a main effect of group, $F(2, 194) = 3.6$, $p < .05$. Post hoc analysis

indicated that individuals homozygous for the G allele (66%) were significantly more accurate during the High Conflict conditions compared to -/G (60%), and -/- (57%) carriers, $p < .05$. A comparable ANOVA was computed for Lose-lose accuracy, which also revealed a main effect of group, $F(2, 194) = 2.9$, $p < .05$. Post-hoc tests indicated that individuals homozygous for the G allele (66%) were significantly better during the Lose conditions compared to -/G (58%), and -/- (54%) carriers, $p < .05$. All results remained significant while controlling for all other SNPs (Figure 16).

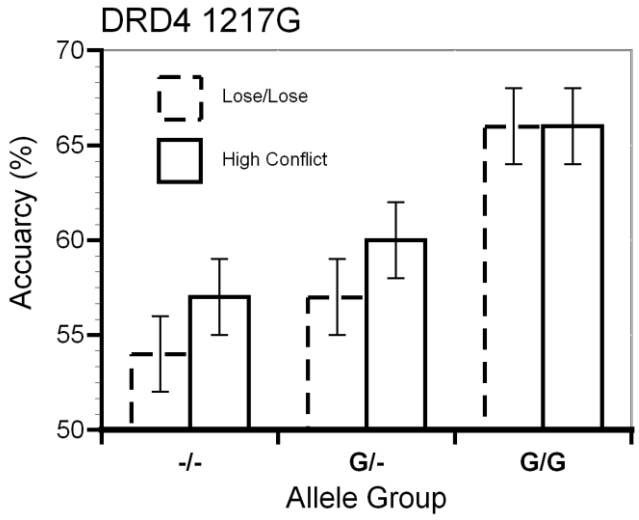


**Figure 16. PST Test Phase Accuracy associated with the DRD4-1217G gene in Study 3. Data are shown for the --/ G/- and G/G allele groups, separately for the High Conflict and Lose-lose conditions. Bars indicate standard errors of the mean.**

*COMT*. According to the Go/NoGo model, the COMT enzyme can enhance avoidance learning during the Learning Phase by facilitating the maintenance of negative outcomes in working memory in prefrontal cortex (Frank et al., 2007). This prediction was confirmed in Frank et al. (2007). For the purpose of this study, I focused primarily on COMT effects on Test Phase performance given that, according to Bilder and colleagues

(2004), COMT can also impact dopamine tonic and phasic signaling subcortically. However, the COMT gene did not reliably predict any PST measure during the Test Phase.

**Substance Dependence and PST**

| Dependent Group | SD | | | | MD | | | | ND | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Learner Type | Positive | Negative | Neutral | Total | Positive | Negative | Neutral | Total | Positive | Negative | Neutral | Total |
| Sample | 36 | 35 | 11 | 82 | 83 | 82 | 27 | 192 | 40 | 46 | 9 | 95 |
| GCR | 60 | 60 | 63 | 61 | 28 | 27 | 29 | 28 | 10 | 10 | 7 | 9 |
| PST | | | | | | | | | | | | |
| Choose Good ACC | 82% | 58% | 80% | 73% | 83% | 59% | 72% | 72% | 83% | 57% | 74% | 72% |
| RT | 1114 | 1289 | 1198 | 1200 | 1165 | 1219 | 1087 | 1157 | 1116 | 1324 | 1159 | 1200 |
| Avoid Bad ACC | 55% | 84% | 80% | 73% | 53% | 80% | 72% | 68% | 65% | 82% | 74% | 74% |
| RT | 1377 | 1314 | 1343 | 1345 | 1368 | 1283 | 1251 | 1301 | 1393 | 1308 | 1241 | 1314 |

**Table 5. Undergraduate student accuracy and reaction time (mean and standard error) on the PST in the Choose Good and Avoid Bad conditions of the Test Phase averaged according to Learner Type and Dependent group total.**

PST performance might also be replicable in other specific populations such as in people with disorders that directly impact the midbrain dopamine system. For example, two previous studies found that Positive vs. Negative Learner type can be driven by dopaminergic medication in people with Parkinson's disease (Frank et al., 2004; Frank, 2005; Frank et al., 2007): Evidently in these individuals the non-medicated disease state (characterized by dopamine system deterioration) and the medicated state (characterized by dopamine system over-activation) overwhelm other sources of variability in dopamine system expression. I reasoned that chronic drug use might have similar consequences, as all drugs of abuse exert their addictive properties by acting directly on the midbrain dopamine system, which in turn induces functional and structural changes in important brain regions for reinforcement learning including the cortical-striatal loops. This

dysregulation should be evident in PST performance but the specific directions of the effects are less clear.

Here I re-examined my previous findings (Baker et al., 2011) to see whether decision making impairments in substance dependent individuals are reflected in PST performance. A regression analysis indicated that undergraduate GCRs did not reliably predict PST performance, $p>.05$. A two-way ANOVA on accuracy and reaction time with Dependent Group (SD, MD, ND) and Stimulus Type (Approach, Avoid) as factors also failed to reveal any main effects and interactions, $p>.05$, confirming the results of the regression analysis. As a check, I conducted a test-retest reliability analysis on each of the three undergraduate student substance dependent groups in Study 3. The ND group displayed adequate test-retest reliability for reaction times on both Approach and Avoid trials ($r = .54$, $p=.006$, and $r = .68$, $p < .001$, respectively). Further, the SD group showed adequate test-retest reliability for accuracy on Approach trials ($r = .45$, $p = .03$). All other groups presented poor test-retest reliability for accuracy on Approach and Avoid trials when analyzed separately, $r<.20$.

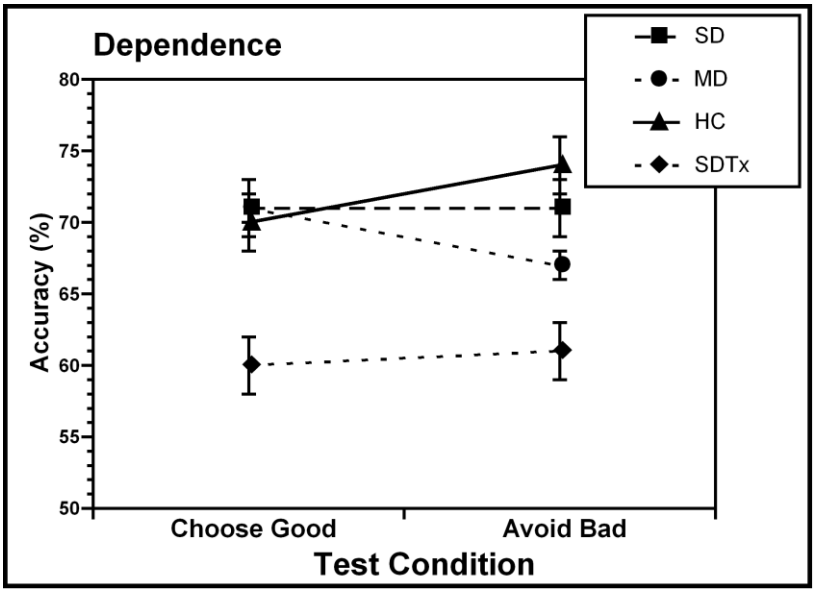

**Figure 17. Performance on the Probabilistic Selection Task (PST). Accuracy in the Test Phase of the PST for the Substance-dependent [SD] (Square), Moderately-dependent [MD] (Circle), Non-dependent [ND] (Triangle), and Substance-dependent in Treatment [SDTx] (Diamond) groups, separately for the Choose Good and Avoid Bad conditions. Student participants were grouped across all three studies (Time 1 for Study 3) and SDTx participants were grouped at time 1 for study 3. Note that chance accuracy is 50%. Bars indicate standard errors of the mean.**

To explore these results further, I examined between-group differences in Test Phase accuracy according to Learner type (i.e., Negative, Neutral, or Positive Learners) (Table 3). This analysis yielded one predictive model such that GCRs reliably predicted accuracy on Avoid trials in Positive Learners, $F(1, 158) = 4.9$, $p < .05$. Follow-up one-way ANOVA with repeated measures on accuracy with Stimulus Type (Approach, Avoid) as factors on Positive Learners indicated a main effect of stimulus, $F(1,182) = 245.8$, $p<.001$, indicating that Positive Learners were more accurate at choosing the Good Stimulus (81%) compared to avoiding the Bad Stimulus (55%), and a trend for a main effect of group, $F(2,156) = 2.5$, $p=.09$. Post hoc tests indicated that Positive Learner ND participants performed slightly better (n=40, 74%) compared to MD (n=84, 68%, $p<.05$) and the SD participants (n=36, 69%, $p<.10$). Further, a significant interaction was detected, $F(2,156) = 7.2$, $p<.01$. Post hoc analysis indicated that Positive Learners tended to choose the Good Stimulus about equally often across groups, $p> .05$. Critically, the Positive Learner ND participants tended to avoid choosing the Bad Stimulus more often (65%) than the SD (55%, $p<.05$), and MD (52%, $p<.005$) participants did (Figure. 18). Note that when the data from Study 1 were excluded from this analysis, this interaction remained statistically significant ($p<.05$). No differences were found for reaction time. As a check, I conducted a test-retest reliability analysis on each substance dependent learner type group in Study 3. Only ND positive learners displayed adequate test-retest reliability for both Approach and

Avoid reaction time, (r = .70, p=.07) and (r = .84, p = .01), respectively. Further, the Positive Learner SD group showed marginal test-retest reliability for Accuracy on Avoid trials, (r = .60, p=.14). All other tests for accuracy and reaction time remained relatively poor across groups, r<.20.

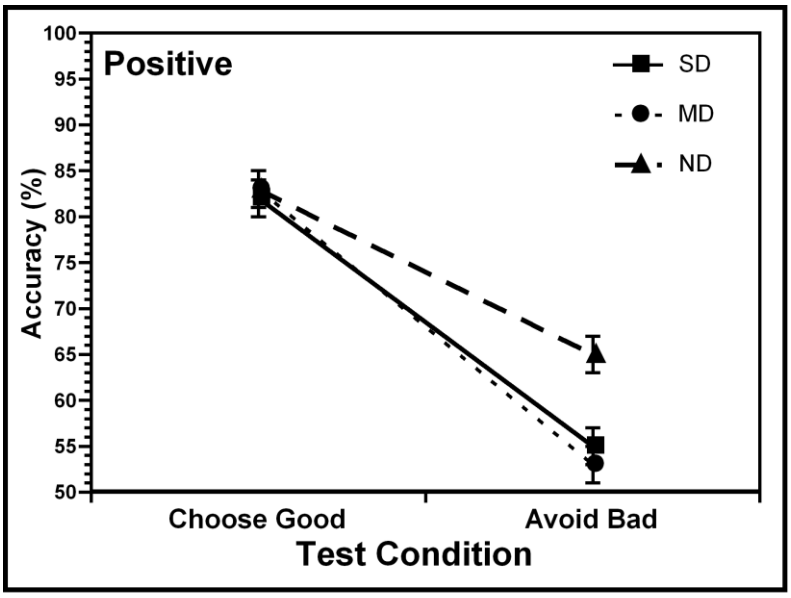


**Figure 18. Undergraduate student performance on the Probabilistic Selection Task (PST) for Positive Learners according to degree of substance dependence. Accuracy in the Test Phase of the PST for the Substance-dependent [SD] (Square), Moderately-dependent [MD] (Circle), Non-dependent [ND] (Triangle) separately for the Approach and Avoid conditions, for Positive Learners only. Note that chance accuracy is 50%. Bars indicate standard errors of the mean.**

### PST and Personality

PST performance might also be affected by differences in personality. Some personality traits have been associated with behavioral differences in learning and decision making on the one hand, and with differences in the expression of the dopamine system on

the other hand. For example, a recent study demonstrated that enhanced sensitivity to punishment in depressed individuals contributes to better performance on Avoid trials of the PST (Cavanagh et al., 2011). Hence, it is reasonable to suppose that PST performance may be more consistent in subpopulations characterized by particular personality traits. Here I focused on personality traits associated with biases in learning and decision making on the one hand, and with addiction on the other: impulsivity, novelty seeking, depression and anxiety, and unspecified. Overall, a regression analysis indicated that the SURPs measures together reliably predicted participants' accuracy on Avoid trials, $F(1, 370) = 2.6$, $p < .05$. Within this model, only novelty seeking, Beta = .139, $t = 2.4$, $p < .01$, and impulsivity, Beta = -.111, $t = -2.1$, $p < .05$, predicted accuracy on Avoid trials, whereas depression and anxiety were not statistically significant. Accuracy for Approach trials and reaction time for Approach and Avoid trials were not reliably predicted by the SURPs, $p>.05$.[13]

Follow-up pairwise t-tests comparing accuracy between test conditions (Approach, Avoid) of the high impulsive individuals IMP [n=40] indicated that IMP participants were more accurate at choosing the Good Stimulus (75%) compared to avoiding the Bad Stimulus (63%), $t(39) = 4.1$, $p < .05$. However, a similar t-test analysis did not reveal any differences between test conditions in high novelty seeking individuals (NS [n=48]) (Figure. 19). Interestingly, NS individuals displayed a good test-retest reliability for accuracy on Approach trials ($r = .80$, $p=.01$); reliability on Approach and Avoid trials across time was relatively poor for all other groups, $r<.20$.

[13] It is interesting to note that the reaction times for Approach (mean = 1279.9 ms, SE =72) and Avoid (mean = 1329.4 ms, SE =78) trials were nearly identical, $p>.05$, for high Novelty Seekers, whereas all other groups displayed significantly faster reaction times for Approach trials compared to Avoid trials ($p<.001$).

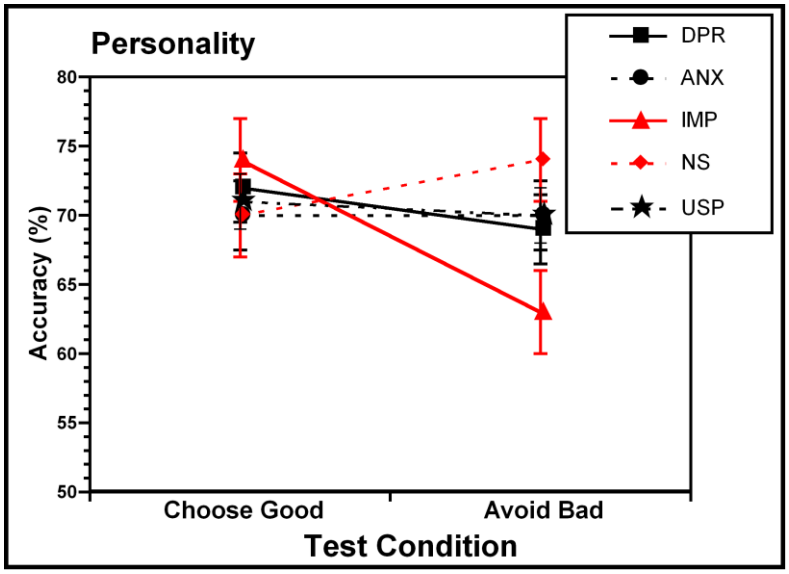


**Figure 19. Performance on the Probabilistic Selection Task (PST) as reflected in personality traits. Accuracy in the Test Phase of the PST for undergraduate participants for the Depression-proneness [DPR] (Black Square), Anxiety-sensitivity [ANX] (Black Circle), Impulsivity [IMP] (Red Triangle), novelty seeking [NS] (Red Diamond) and unspecified [USP] (Black Star) groups, separately for the Choose Good and Avoid Bad conditions. Note that chance accuracy is 50%. Bars indicate standard errors of the mean.**

**Intersecting Genetics, Substance Dependence, and Personality with PST.**

To examine the interacting effects of these individual differences on decision making, as an exploratory analysis I conducted a series of multiple ANOVAs on PST accuracy and reaction time for Approach and Avoid trials, using as factors: 1) substance dependence (SD, MD, ND) and learner type (Positive, Negative, Neutral), 2) substance dependence and personality trait (DPR, ANX, IMP, NS, USP), 3) substance dependence and genotype, separately for each SNP (allele: aa, ab, bb), 4) personality and learner type, and 5) personality and genotype, separately for each SNP. For example, to look at the interaction between the SNP C957T for the DRD2 gene and substance dependence, I

conducted a three-way ANOVA on accuracy with Dependent Group (SD, MD, ND) and C957T Allele (TT, CT, CC) and Stimulus Type (Approach, Avoid) as factors. Overall, this analysis yielded only a trend towards an interaction between substance dependent group and the DRD4- 127G allele group on Approach and Avoidance accuracy, $F(2, 191) = 3.2$, $p = .07$. Post hoc tests indicated that the SD [-/G(-/-)] group were relatively worse at Test Phase accuracy (65%), compared to SD GG group (78%), $p<.01$. No interactions were observed between Genetic and Personality groups, $p>.05$, or between substance dependence and personality groups, $p>.05$.

**Treatment Population Results**

*PST performance*. A series of regression analyses indicated that the GCRs did not reliably predict accuracy or reaction time on Approach, Avoid, and High Conflict trials in the SDTx group, even when the analyses were conducted separately on each Learner Type. Nevertheless, when the undergraduate student data combined across the three studies (Time one for Study 3) were included in the analysis, a two-way ANOVA on accuracy with Dependent Group (SDTx, SD, MD, ND), and Stimulus Type (Approach, Avoid) as factors revealed a main effect of Dependent Group, $F(3,430) = 5.7$, $p<.001$ (Figure. 12), even when controlling for age and sex, $F(3,430) = 3.2$, $p<.05$. Post-hoc tests indicated that SDTx individuals were less accurate overall (60%) compared to the SD (71%, $p<.001$), MD (69%, $p<.001$), and ND (73%, $p<.001$) individuals (Figure. 17). A two-way ANOVA with repeated measures on PST accuracy and reaction time with Time (Time 1, Time 2) and Test Condition (Approach, Avoid) as factors did not reveal any main effects and interactions. Including Learning Type as a between-group factor also yielded non-

significant results. Lastly, all measures of the PST failed to demonstrate adequate test–retest reliability within the SDTx sample.

*Personality.* A regression analysis indicated that the SURPs measures together did not reliably predict PST accuracy or reaction time for the treatment population, p>.05. However, the depression-proneness scale uniquely predicted both accuracy on Avoid, Beta = .261, t = 1.9, p <.05, and Lose-lose, Beta = .299, t = 2.3, p <.05, trials within the group model. A follow-up ANOVA on accuracy and reaction time with Personality group (DPR[n=8], ANX[n=11], IMP[n=8], NS[n=10], USP[28]) and Test Conditions (Approach, Avoid) as factors did not reveal any main effects and interactions. An ANOVA on accuracy and reaction time with Personality group and Test Conditions (Win-win, Lose-lose) as factors also did not reveal any main effects and interactions. However, a follow up pairwise t-test comparing the accuracy data (Approach, Avoid) for the DPR group indicated a trend showing DPR participants were more accurate on Avoid trials (72%) compared to Approach trials (61%), t(7) = 3.6, p = .07. No other personality groups displayed this pattern of results. Furthermore, a pairwise t-test comparing accuracy conflict data (Win-win, Lose-lose) also revealed a trend showing DPR participants were more accurate on Lose-lose trials (68%) compared to Win-win trials (56%), t(7) = 3.7, p = .08. No other personality groups displayed this pattern of results.

Next, separate two-way ANOVAs with repeated measures conducted on each of the SURPs measures in Study 3 with Time (Time 1, Time 2) and Dependent Group (SDTx, SD, MD, ND) as factors revealed a main effect of Group for Depression-proneness, F(2, 149) = 19.3, p < .001, indicating that depression scores were significantly larger for SDTx group compared to all other groups (p<.001), and a significant interaction between Time

and Group, $F(3,149) = 3.2$, $p<.05$. Post hoc tests indicated that for the SDTx groups, depression scores were reduced at Time 2 (mean = 15.6, SE = 3) compared to Time 1 (mean = 16.6, SE = 3), t(56), 2.4, $p<.01$, while all other groups depression scores were nearly identical between sessions, $p>.05$. A comparable two-way ANOVA also revealed a significant interaction for anxiety, $F(3,149) = 7.4$, $p<.01$, indicating that for the SDTx group, anxiety scores were reduced at Time 2 (mean = 13.4, SE = 3) compared to Time 1 (mean = 14.4, SE = 3), t(56), 3.3, $p<.005$; all other groups displayed similar scores between sessions. In regards to impulsivity, an ANOVA revealed a main effect of group $F(2,149) = 19.8$, $p<.001$, indicating that SDTx impulsivity scores were significantly larger than all other groups ($p<.001$), and SD and ND displayed significant differences between each other ($p< .005$). For novelty seeking, an ANOVA analysis revealed a main effect of Group, $F(2,149) = 2.8$, $p<.05$, such that novelty seeking scores were larger for the SD group compared to all other groups ($p<.001$).

Finally, for each SURP group, a two-way ANOVAs with repeated measures on PST accuracy with Time (Time 1, Time 2) and Test Condition (Approach, Avoid) as factors revealed a trend toward an interaction between Time and PST accuracy for the Depression-proneness group, $F(1,8) = 3.2$, $p=.07$.[14] Further, a two-way ANOVA with repeated measures on the Depression-proneness group with Time (Time 1, Time 2) and Test Condition (Win-win, Lose-Lose, Avoid) as factors also revealed a trend towards an interaction, $F(1,8) = 3.0$, $p=.10$.[15]

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[14] For accuracy on approach and avoid trials the effect size value (partial $eta^2 = .45$) drew my attention to a notable interaction, despite it not being statistically significant: At Time 1, the DPN group were more accurate on Avoid (71%) compared to Approach (61%) trials, whereas at Time 2, this pattern reversed, such that DPN individuals were more accurate on Approach (71%) compared to Avoid (50%) trials.

[15] For accuracy on Lose-lose and Win-win trials, at Time 1, the DPN group were more accurate on Lose-lose (70%) compared to Win-win (55%) trials, whereas at Time 2, this pattern reversed, such that Depression-

# Discussion

The Go/NoGo neurocomputational model of the basal ganglia has been extremely influential, providing insight into the neural mechanisms of a host of individual differences and psychiatric disorders related to the function of the midbrain dopamine system (Frank & Fossella, 2011). The model has been validated largely with the PST, which provides a means for differentiating between individuals who learn better from positive or negative feedback (Frank, Loughry, & O'reilly, 2001; Frank et al., 2007; Maia & Frank, 2011). Yet despite the fact that the PST has been widely adopted for this purpose, to my knowledge its reliability has heretofore not been determined—as is the case for many widely used measures of cognitive function (Kunsti, et al., 2001). I addressed this issue by examining the test–retest reliability of the PST data in Study 3 wherein the participants completed the task twice across a 7-8 week timespan. To my surprise, the PST data failed to demonstrate adequate test–retest reliability in this sample.

Nevertheless, I reasoned that the PST measures might be stable within subpopulations of individuals characterized by particular individual traits related to the dopamine system and learning style. Although I found evidence of such differences, which I discuss below, the test-retest reliabilities of these differences in the Study 3 participants were also low, except for a few exceptions. Notably, healthy individuals who were classified as Positive Learners, relative to those who use substances, displayed adequate test-retest reliability for reaction time on Approach and Avoidance trials. This findings suggests that the ability to modulate decision times appears relatively stable across time,

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prone individuals were more accurate on Win-win (70%) compared to Lose-lose (58%) trials. I used a regression analysis to test whether any change in SURPs (e.g. change in levels of depression, as shown above) would predict change in PST performance (Time 2 – Time 1), however, no associations were observed.

but substance use can cause variability in this dynamic control. Further, I did not collect genetics data in Study 3 so the reliability of the genetics findings remain unconfirmed, which may be especially concerning given that several of the genetics observations did not replicate previous findings. These results strongly suggest that PST performance measures – both in this study and others – should be evaluated with caution when used to characterize individual differences. Nonetheless, I also note that whereas the overall reliability test in Study 3 involved nearly 100 subjects—the results of which therefore appear valid—the tests on the Study 3 subgroups involved relatively fewer participants. For this reason, I cautiously suggest that future studies involving greater numbers of participants, which I recommend, will demonstrate the reliability of many of the findings here.

Bearing these caveats in mind, these results elucidate previous observations on the genetics of reinforcement learning and decision making. To begin with, the Go/NoGo model holds that striatal D2 receptors with high dopamine affinity are inhibited by baseline levels of dopamine (Frank et al., 2004). According to this account, pauses in firing of midbrain dopamine neurons elicited by negative outcomes disinhibit striato-pallidal neurons via release of D2 receptor-mediated inhibition. Hence the greater the D2 receptor density, the more likely these neurons are inhibited by tonic dopamine signaling and therefore the greater learning signal that arises when dopamine levels drop, enhancing the ability to avoid bad events (Frank and Hutchison, 2009). By extension, impaired performance on Avoid trials of the PST Test Phase is proposed to result from a diminished negative reinforcement learning signal, either directly from reduced phasic dips in dopamine or indirectly from a reduction in striatal D2 receptors. Consistent with this idea,

Klein and colleagues (2007) demonstrated that male carriers of the A1 allele (A1/A1 and A2/A1 combined) of the Taq1A SNP of the DRD2 gene, in which the A1 allele is associated with reduced D2 expression (Thompson et al., 1997; but see Zhang et al., 2007), were selectively impaired at avoiding the bad stimuli during the Test Phase. However, these findings failed to replicate this Taq1A effect: homozygous and heterozygous A1 carriers combined performed nearly identically to homozygous A2 carriers. Note that due to the small prevalence of the A1A1 genotype (3-5% of healthy Caucasians), A1/A1 and A1/A2 subjects are commonly grouped as A1+ subjects, as in Klein and colleagues (2007). By contrast, the relatively large sample size here allowed for comparing the A1/A1 (n=10), A2/A1 (n=76), and A2/A2 (n=109) alleles separately, but participants with the A1/A2 and A2/A2 alleles nevertheless performed nearly identically. Notably, participants with the A1/A1 alleles were relatively inaccurate at *both* Avoid and Approach trials of the PST task (see below), which appears inconsistent with the Go/NoGo model.

These negative results are perhaps not surprising given that several studies have failed to find an association between the Taq1A SNPs and D2 density (Zhang et al., 2007; Laruelle, Gelernter, & Innis, 1998; Lucht & Rosskopf, 2008), and the Taq1A effects on avoidance learning have been proposed to be a result of an indirect association with C957T SNP of the DRD2 gene (Frank & Hutchison, 2009). In regards to the latter, Frank and Hutchison (2007) initially reported similar results to Klein and colleagues (2007) but later found that when both the Taq1A and C957T were analyzed together, the effect of Taq1A vanished. Specifically, carriers of the C allele of the C957T SNP—which according to Hirvonen and colleagues (2004, 2009) are associated with reduced striatal D2 receptor binding potential and expression—performed relatively worse at avoiding the Bad

Stimulus but performed normally at choosing the Good Stimulus (Frank et al., 2007; Frank & Hutchison, 2009). In the present study, I also found that C carriers (CT/CC allele combined) of this gene were relatively poor at avoiding the bad stimuli relative to TT carriers. Further, when the CT and CC group data were analyzed separately, the CC group displayed comparable accuracy on Avoid trials to that of both allele groups. This may be surprising given that the CC allele group expresses the fewest D2 receptors and thus would be expected to perform the worst on Avoid trials, an idea inconsistent with the Go/NoGo model.

Conversely, Frank and Hutchison (2009) demonstrated that carriers of the C allele of DRD2 promoter $SNP_2$ (Zhang et al., 2007) were selectively impaired at avoidance learning, even when the effects of other DRD2 SNPs were statistically controlled. I replicated these findings here such that CT carriers, compared to TT carriers, performed significantly worse on Avoid trials, displaying a bias toward choosing the Good stimulus during the Test Phase. On the other hand, contrary to the Go/NoGo model, a seminal study that analyzed 23 polymorphisms within the DRD2 gene in terms of their effects on D2 receptor mRNA expression in postmortem brain tissue demonstrated that the C allele enhances promoter activity over the T allele. In other words, the C allele is associated with more D2 receptors, even though participants carrying the C allele are relatively inaccurate on Avoid trials in the PST.

In sum, the Go/NoGo model predicts that the greater the D2 receptor density, the greater learning signal that arises when dopamine levels drop, promoting good performance on Avoid trials (Frank and Hutchison, 2009). Here I found that participants carrying the C allele of the C957T SNP, which is associated with reduced D2 expression

(Hirvonen et al., 2004, 2009), performed relatively worse at avoiding the bad stimulus with no effect on choosing the good stimulus, replicating previous work (Frank et al, 2007; Frank and Hutchison, 2009) and consistent with the model's prediction. By contrast, participants carrying the C allele of DRD2 promoter $SNP_{2,}$ corresponding to increased D2 expression (Zhang et al. 2007), were selectively impaired at avoidance learning, which replicates the results of Frank and Hutchison (2009) but which appears inconsistent with the predictions of the Go/NoGo model. Finally, individuals carrying the A1 allele of the Taq1A SNP, which is associated with reduced D2 expression, performed nearly identically to homozygous A2 carriers—a result that fails to replicate Klein et al. (2007) and that may be inconsistent with the predictions of the Go/NoGo model. Moreover, homozygous A1 carriers performed worse overall, being less accurate on both Avoid and Approach trials (see below).

An obvious question is why do *both* enhanced D2 expression as coded by the promoter $SNP_2$ and reduced D2 expression as coded by the C957T SNP result in impaired accuracy on Avoid trials? In regards to the latter observation, the impact of the C957T gene on D2 expression is still a matter of contention. On the one hand, positron emission tomography studies have revealed that the C allele is associated with reduced striatal D2 receptor binding potential (Hirvonen et al., 2004, 2009), which would be consistent with the predictions of the Go/NoGo model, i.e., poor avoidance learning in participants expressing the C allele. On the other hand, an *in vitro* study by Duan and colleagues (2003) found the opposite pattern of results: the T allele was associated with reduced mRNA translation and stability whereas the C allele was not associated with such changes in mRNA structure, leading to increased DRD2 expression in C allele carriers. Furthermore,

Zhang and colleagues (2007) demonstrated that the C957T polymorphism is not in fact directly responsible for changes in D2 receptor expression. Until these questions are resolved, it is difficult to make any inferences as to why the C allele is consistently associated with poor accuracy on Avoid trials, though the result appears reliable.

Although the effect of the C957T gene on D2 expression remains inconclusive, such that the PST results associated with this gene are difficult to interpret, the present findings with respect to the promoter $SNP_2$ appear to contradict the Go/No-go theory, at least as the theory is normally interpreted. Instead, I propose an alternative account of this finding: Greater numbers of D2 receptors may allow for greater inhibition of the No-go pathway. According to this proposal, larger numbers of D2 receptors would require longer pauses in dopamine neuron firing following negative feedback to disinhibit the system sufficiently to facilitate avoidance learning. In other words, the greater the D2 receptor density, the less sensitive the D2 system is to transient dips in dopamine. This mechanism would result in a diminished negative learning signal following negative feedback and ultimately to impaired accuracy on Avoid trials, as I observed here. This proposal provides a consistent account of these PST findings together with the previous observations of the C allele of promoter $SNP_2$ by Zhang and colleagues (2007) and the C allele of C957T by Duan and colleagues (2003): impaired accuracy on Avoid trials associated with increased striatal D2 receptor expression.

In addition, the Go/NoGo model predicts that good performance on Approach trials of the PST should be associated with enhanced striatal D1 receptor efficacy (Frank et al., 2007). Because striatal D1 receptors have relatively low dopamine affinity their stimulation is hypothesized to depend on phasic dopamine bursts, with larger bursts

producing greater neural plasticity, thereby promoting good performance on Approach trials of the PST Test Phase. By extension, impairments on these trials are proposed to result from a diminished positive reinforcement learning signal, either directly from reduced phasic bursts in dopamine as seen in people with Parkinson's disease or indirectly from reduced D1 efficacy as modulated by the PPP1R1B gene (Frank et al., 2007). This gene codes for variation of the DARPP-32 protein, which is partly responsible for regulating the sensitivity of D1 striatal neurons to glutaminergic excitation and dopaminergic modulation (Meyer-Lindenberg et al., 2007; Svenningsson et al., 2004). Here I investigated the M12 (rs907094) and M04 (rs879606) polymorphisms of the PPP1R1B gene. However, the present results did not reveal any allelic effects on accuracy or reaction time on Approach trials, nor on any other PST measure, failing to replicate the results of a previous study in which A/A compared to G carriers of the M12 SNP were shown to be relatively better at choosing the Good Stimulus compared to avoiding the Bad Stimulus during the PST Test Phase (Frank et al., 2007).

This result is disconcerting given the straightforward predictions of the Go/NoGo model together with the previous PST findings. Perhaps the role of DARPP-32 in reward learning is more complex than previously thought. The DARPP-32 protein was initially described as a major integrator of glutamate and dopamine signaling underlying synaptic plasticity for reinforcement learning (Lindskog et al., 2006). However, recent findings indicate that DARPP-32 may function to integrate information processing in multiple brain regions via a variety of neurotransmitters, neuromodulators, neuropeptides, and steroid hormones (Svenningsson et al., 2004). Further, DARPP-32 also mediates effects of D2 receptor stimulation and plays a crucial role in the induction of both long-term depression

and long-term potentiation (Calabresi et al., 2000). For these reasons, I suggest that evidence linking the PPP1R1B gene variants, DARPP-32 expression, and PST performance should be interpreted with caution. Future genetic studies should select candidate genes that are more tightly linked to D1 receptor function such as the DRD1 SNP (rs686).

In fact, the Taq1A of the DRD2 gene was actually the best and only predictor of Approach learning, even when statistically controlling for the effects of other DRD2 genes. In particular, a regression analysis indicated that increasing numbers of A1 alleles were associated with worse accuracy on Approach trials. This was not observed for accuracy on Avoid trials. However, this gene-dose effect was not apparent in the follow-up ANOVA analysis, where heterozygous A1 carriers compared to homozygous A2 carriers displayed similar accuracy on Approach and Avoid trials. Further, individuals homozygous for the A1 allele were relatively impaired at choosing the Good Stimulus as well as avoiding the Bad Stimulus, so the impairment was not restricted to Approach trials *per se.*

These results are also difficult to interpret. On the one hand, the Go/NoGo model predicts that individuals with fewer striatal D2 receptors should demonstrate a positive learning bias, such that negative feedback has a smaller influence on behavior than positive feedback (Frank & Hutchison, 2009). On the other hand, the associations between the A1 allele of the Taq1A and reward deficiency syndrome (Blum et al., 2000) and smaller reward-induced cortical and subcortical activations observed in fMRI studies, (Kirsch et al., 2006; Cohen, Krohn-Grimberghe, Elger, & Weber, 2007) support the converse prediction, a negative bias, such that positive feedback should have a smaller influence on behavior than negative feedback. I observed an overall blunting effect of

reinforcement−both positive and negative−in individuals homozygous for the A1 allele, providing a potential link between this genotype and several impulsive, addictive and compulsive disorders (e.g., polysubstance abuse, smoking, ADHD, obesity, and Tourette's syndrome) previously associated with this allele (Blum et al., 1991; Lawford et al., 2006; Noble, 2003; Noble, 2000b; Noble, 2000a). Consistent with this idea, the low frequency of homozygous A1 individuals in the population would suggest that two A1 alleles together may present a strong evolutionary liability. Future studies of this gene should utilize large sample sizes to separate the effects of one vs. two A1 alleles on basal ganglia activation and on task performance.

It has been proposed that the Go/NoGo pathways are regulated by top-down control from prefrontal cortex and anterior cingulate cortex (Frank & Claus, 2006; Frank et al., 2007; Frank et al., 2007). For this reason, the D4 receptor and the COMT enzyme—which are preferentially expressed in frontal cortex—should be associated with PST performance. Of the three D4 SNPs I analyzed, only the DRD4-1217G polymorphism uniquely predicted PST performance. Specifically, homozygous G carriers were more accurate compared to -/G and -/- carriers on High Conflict trials, particularly on Lose-lose trials. Although the exact mechanism by which this SNP affects D4 expression is still unknown, it is interesting to note that an fMRI study found that variation in the G allele of the DRD4-1217G correlated with anterior cingulate cortex activation to response conflict (Fossella et al., 2002; Fan et al., 2003). Consistent with this idea, a previous study found that deep brain stimulation of the subthalamic nucleus in people with Parkinson's disease reduces coupling between cognitive control regions in the frontal midline and basal ganglia output nuclei, resulting in impulsive decision making (Frank et al. 2007). Taken together,

these findings provide further support for a functional link between conflict-related activity in the anterior cingulate cortex and top down control over the basal ganglia during decision making (Cockburn and Frank, 2011).

The Go/NoGo model also predicts that disruption of the midbrain dopamine system and its neural targets in the basal ganglia can selectively impair approach and avoidance learning on the PST (Maia & Frank, 2011; Frank & Fossella, 2011). For example, people with Parkinson's disease exhibit poor performance on Approach and Avoid Trials while off vs. on medication, respectively (Frank et al., 2004; Frank et al., 2007). The functional and structural changes to the Go/No-go pathways and their cortical connections induced by chronic drug use should also be evident in PST performance. In fact, I previously found that substance dependent individuals classified as Positive Learners were less accurate at Avoid trials while exhibiting normal accuracy on Approach trials in comparison to non-dependent participants, whereas substance dependent Negative Learners showed the opposite pattern (Baker et al., 2011; Experiment 1). However, in a follow-up genetic study (Experiment 2) using a larger cohort of subjects, these findings failed to replicate. Here I re-examined these findings by grouping data across the first two studies with data collected in a third study, including that of a clinical population before and after treatment as well as an undergraduate control population before and after a 7-8 week interval. Although no associations were found between substance dependence and overall PST performance in the undergraduate student sample, substance dependent and moderately dependent Positive Learners were impaired on Avoid trials relative to non-dependent Positive Learners. Importantly, this finding remained statistically significant

even when the subjects from Study 1 were excluded from the analysis, confirming that the following two studies replicated the original finding.

I propose that substance use impairs learning from negative feedback by altering the structure and function of the orbital frontal cortex, thereby disrupting "top-down" regulation of the basal ganglia Avoid pathway (Baker et al. 2011). Several observations support this proposal. First, substance use alters orbital frontal structure and function (Robinson & Kolb, 2004; Homayoun & Moghaddam, 2006), which would be expected to disrupt the "top-down" regulation of the NoGo pathways (Frank & Claus, 2006). Second, a recent study showed that orbital frontal damage selectively disrupts the ability to learn from negative feedback in the PST (Wheeler & Fellows, 2008), elucidating why such individuals repeatedly engage in actions that have negative consequences (Bechara, Tranel, & Damasio, 2000). Third, substance abuse is also associated with impaired performance on the Iowa Gambling Task (Bechara & Damasio, 2002; Bechara et al., 2002), which is characteristic of orbital frontal cortex damage (Bechara et al., 2000). Understood in this context, the present results suggest that the dopaminergic contribution to addiction may play out most strongly via control mechanisms in frontal cortex (Baker et al. 2012), indirectly impacting the basal ganglia mechanism for avoidance learning in this subgroup of individuals (Kalivas & Volkow, 2005).

I also observed impaired accuracy on Avoid and Approach trials by the individuals undergoing treatment relative to the student groups, even when controlling for group differences in age and sex. Further, this deficit in PST performance did not change over time in the treatment individuals, indicating that it did not reflect an acute effect of drug use. Although a number of explanations could account for these findings, I tentatively

suggest that chronic drug abuse over an extended period of time may ultimately drive the decision making system to withdraw control over behaviors that it should inhibit (impaired avoidance learning) and facilitate behaviors that it should not (impaired reward learning).

Although to my knowledge the Go/NoGo model has not been utilized to predict individual differences in PST performance related to personality *per se*, previous research has demonstrated how traits such as depression, impulsivity, anxiety, and novelty seeking are reflected in decision making. Further clues to the relationship between personality traits and PST performance are supported by a clinical study on depression, which showed that depressed individuals are better able to avoid the Bad Stimuli than approach the Good Stimuli during the Test Phase of the PST (Cavanagh et al., 2011; but see Chase et al., 2010). Here I found a statistical trend indicating that SDTx individuals who were relatively prone to depression displayed better accuracy on Avoid compared to Approach trials, as well as better accuracy on Lose-lose compared to Win-win trials, results that appear consistent with the clinical study[16]. Given these observations one might expect that people with anxiety, who are also characterized by hypersensitivity to punishment, would behave similarly but here this trait was not associated with any PST measure.

Previous work also supports the prediction that impulsive individuals should demonstrate a positive bias in which negative feedback has a smaller influence on behavior than positive feedback. For example, individuals with orbital frontal damage, who are often described as impulsive (Antonucci et al., 2006), show impaired ability to learn from negative feedback in the PST (Wheeler & Fellows, 2008), suggesting a dysregulation of

[16] Interestingly, depression-prone individuals in treatment showed a decrease in depression-proneness scores following treatment and, although only a trend, exhibited a reversed pattern of Approach and Avoid learning before and after treatment. However, provided the small sample size and poor test-retest reliability of the PST, this findings should be evaluated with caution.

top-down control over basal ganglia NoGo pathway. Indeed, high impulsivity was associated with poor accuracy on Avoid trials in the present study. This finding appears compatible with the present findings that high levels of impulsivity are associated with decreased DARPP-32 protein expression, which facilitates the functional connectivity between brain regions including the projection from prefrontal cortex to the striatum (Meyer-Lindenberg et al., 2007; Curcic-Blake et al., 2012). Further, deep brain stimulation of the subthalamic nucleus, which reduces coupling between cognitive control regions (anterior cingulate cortex) and basal ganglia output, results in impulsive decision making (Frank et al., 2007). Given that the frontal system implements control functions related to impulse regulation and top-down control over the NoGo pathway, individuals displaying impaired inhibitory control may thus perform particularly worse on Avoid trials of the PST.

Previous work has indicated that novelty seekers demonstrate a negative bias in which positive feedback relative to negative feedback exerts a smaller influence over behavior (Krebs, Schott, & Duzel, 2009). For instance, novelty seeking has been conceptualized as a dopamine-mediated heritable tendency towards exploration and excitement in response to novel stimuli (Cloninger, Svrakic, & Przybeck, 1993): individuals high in Novelty Seeking show a heightened dopaminergic response to novel events relative to rewarding events, possibly indicating that these individuals may be relatively insensitive to natural rewards and more sensitive to highly novel or stimulating rewards (Krebs et al., 2009). Here I found that high Novelty Seeking predicted better accuracy at Avoid trials relative to Approach trials. Perhaps in these participants, positive feedback failed to elicit a sufficiently positive reward signal to bias performance in favor

of Approach trials. In support of this idea, Approach and Avoid reaction times were nearly identical in novelty seekers, suggesting that these conditions were processed indifferently, whereas all of the other personality groups displayed a relative decrease in Approach reaction time. Furthermore, Novelty Seekers also displayed relatively good test-retest reliability on Approach trial accuracy, consistent with the idea that the underlying mechanism contributing to this trait is stable. In addition, animal studies indicate that rats selectively bred for high reactivity to novelty are characterized by elevated levels of extracellular dopamine in the striatum (Hooks et al., 1994; Piazza et al., 1991). Given that increased tonic activity can contribute to decreased phasic activity of the dopamine system in subcortical regions (Bilder et al. 2004), the increased tonic dopamine activity may contribute to a smaller reward signal in individuals characterized by high Novelty Seeking.

Finally, a moderate interaction between substance dependence group and DRD4-127G allele group on PST Test Phase accuracy was revealed. Specifically, substance dependent individuals carrying the allele associated with a reduced anterior cingulate cortex BOLD response to conflict (Fan et al., 2003; Fossella et al., 2002) displayed relatively poor accuracy on both Approach and Avoid trials, compared to substance dependent individuals who carry the allele associated with a strong anterior cingulate cortex response to conflict. These findings suggest that individuals who display a relatively weak cognitive control system may be more susceptible to the negative consequence of drugs of abuse on the decision making system, possibly reflecting susceptibility to addiction, whereas the genotype associated with stronger cognitive control may act as a protective mechanism, an idea consistent with my previous work (Experiment 1 and 2; Baker et al. 2011, 2012).

**Limitations**

This study has several limitations. First, of the 121 treatment group subjects who initially participated in session 1 of Study 3, half agreed to complete the questionnaire in session 2, and of these, half agreed to engage in the PST. As is not uncommon for studies of clinical populations, the response and participation rates in this study were not ideal. Various institutional (e.g. scheduling problems, treatment commitments, etc.) and individual (e.g. lack of interest) factors may have contributed to nonparticipation. Second, although a primary goal of this study was to identify interactions between the variables of interest − dopamine-related genetic polymorphisms, personality traits and drug use history – the present results revealed little evidence of this. These factors may in fact be relatively independent of each other, but a more likely possibility is that the myriad of individual variables examined in this study may demand larger sample sizes. Further, the lack of interactions could be partly due to the definition of the personality groups, which were based on the most extreme scores within each individual even when the scores were extreme on more than one measure.

As discussed above, the test-retest analysis revealed that the PST performance measures were unreliable in the undergraduate sample. This negative finding could have obtained because most undergraduate students are not in fact biased toward either positive or negative learning, but it may also be because the task sensitivity to such differences could be further optimized. For example, if subjects were given the opportunity to engage in a Practice Phase that included both a block of the Learning Phase followed by a block of the Test-Phase, this could enable subjects to better understand the purpose of the task, thereby increasing the stability of Test Phase performance across sessions. Providing a

monetary incentive during learning might also increase participant engagement and performance stability (Hakyemez, Dagher, Smith, & Zald, 2008; Savine & Braver, 2010; Chiew & Braver, 2011; Savine, Beck, Edwards, Chiew, & Braver, 2010). Additionally, because the Test Phase typically utilizes only a few testing pairs (each pair being tested 6 times), future studies could identify an optimal number of Test Phase trials that would decrease individual variability and avoid ceiling effects. And finally, it is recommended that future PST studies sample behavior at two separate times in order to verify the test–retest reliability of the data at hand.

## Conclusion

Advances in computational cognitive neuroscience have substantially furthered understanding of the neural mechanisms of decision making. At the forefront of this research, the Basal Ganglia Go/NoGo model proposed by Frank and colleagues (2004) has demonstrated considerable explanatory power with respect to the role of dopamine and basal ganglia circuitry in reinforcement learning. In the present study, I utilized this theoretical framework to investigate individual differences in decision making as determined by factors related to genetics, personality, and substance use. Contrary to the standard interpretation of the theory, the present results suggest that individuals expressing enhanced D2 expression are impaired on Avoid trials of the PST due to stronger D2-mediated inhibition of the No-go pathway. The present results also highlight the role of the frontal D4 system in top-down control during high conflict situations. Substance abuse history and personality traits were also associated with constraints in decision making, providing a key for understanding the underlying cognitive control and decision making problems associated with these traits. At the same time, and in contradiction to the

Go/NoGo model, I found that homozygous A1 carriers of the TaqI (A1/A2) genetic polymorphism, which is associated with reduced dopamine D2 receptor expression, displayed global blunting to positive and negative reinforcement rather than a specific inability to learn from negative feedback, and further, that two polymorphisms associated with enhanced D1 efficacy were not associated with enhanced approach learning. Of greatest concern, the present data failed to show adequate test-retest reliability on any measure of PST performance for a sample of nearly 100 undergraduate student participants. Although the PST as a means for investigating the Go/No-go model of decision making is supported by sound theoretical and empirical work, these findings highlight the need for future studies that establish the validity of the task and that replicate the positive findings here.

# General Discussion

The ultimate aim of the present thesis was to further the understanding of cognitive control and decision-making in relation to substance dependence, with a primary focus on the relative contribution of individual differences and the neurobiological aspects of these complex cognitive processes. Rooted in a cognitive neuroscience perspective on substance dependence, the studies included in the current thesis are based on three theoretical proposals. First, contemporary theories of substance dependence propose that the transition from occasional recreational substance use to harmful use and dependence results from the impact of disrupted midbrain DA signals for reinforcement learning on frontal brain areas that implement cognitive control and decision making (Redish et al., 2008; Berke & Hyman, 2000; Hyman, 2007; Hyman et al., 2006; Hyman, 2005). Second, according to an influential neurocomputational model of reinforcement learning and cognitive control proposed by Holroyd and Coles (2002), the reward-positivity is hypothesized to be elicited by the impact of reinforcement learning signals carried by the midbrain DA system onto motor areas in ACC, where they are utilized for the adaptive modification of behavior according to principles of reinforcement learning (Holroyd & Coles, 2002). Third, according to an influential neurocomputational model of decision making, "the Basal Ganglia Go/NoGo model" proposed by Frank and colleagues (2004), dopaminergic signaling in the basal ganglia facilitates or suppresses action representations during reinforcement learning tasks (e.g., the PST): phasic bursts of dopamine activity facilitate reward learning by reinforcing striatal connections that express D1 receptors (the "Go/Approach" pathway), whereas phasic dips in dopamine activity facilitate avoidance

learning by reinforcing striatal connections that express D2 receptors (the "NoGo/Avoidance" pathway) (Frank et al., 2004).

Using the two neurocomputational models as conceptual framework, I tested the hypothesis that the neuroadaptive mechanisms that mediate the transition from occasional, controlled drug use to the impaired control that characterizes severe dependence is facilitated by the impact of disrupted DA signals on brain networks involved in cognitive control and decision making: By acting on the abnormal reinforcement learning system of the genetically vulnerable, addictive drugs hijack the control system to reinforce maladaptive drug-taking behaviors. The hypothesis was tested empirically using a combination of electrophysiological and behavioral assays of the integrity of midbrain DA system in humans, combined with assessments of dopamine-related genetic polymorphisms associated with the DRD2, DRD4, COMT, and PPP1R1B gene, and surveys of substance use and personality. In brief, Experiment 1 revealed two groups of dependent individuals, one characterized by disrupted dopamine-dependent reward learning and the other by disrupted error learning associated with depression-proneness. Experiment 2 revealed several dopamine-related neural pathways underlying individual differences in substance dependence, and proposed a theoretical model for bridging the gap between genes and behavior in drug addiction. The results of Experiment 3 revealed that individuals undergoing treatment displayed global blunting to positive and negative reinforcement that did not change over time, indicating that the impairment did not reflect an acute effect of drug use. In addition to this main finding, Experiment 3 also pointed to several individual traits (e.g. gene, personality, and substance use history) related to the dopamine system and learning style that may modulate decision making across

individuals, but revealed additional findings that appear inconsistent with the predictions of the Go/NoGo model, including a failure to demonstrate test–retest reliability of any PST performance measures.

The general discussion begins with a summary of rationales and main findings of the current thesis. Thereafter, the results regarding cognitive control and decision making will be discussed in relation to central contemporary theories of substance dependence. And finally, I discuss future directions of the current research program, as well as provide a unified theoretical model of substance dependence that spans multiple levels of analysis, including its biological, behavioral and cognitive manifestations, and highlight its importance for furthering the development of new therapeutic treatments and clinical management for the disorder.

## Neural Correlates of Cognitive Control in Substance Dependence

Multiple lines of evidence have revealed that many of the control and decision making functions associated with ACC are impaired in people who abuse substances (Peoples, 2002). These findings support the hypothesis that addictive drugs drive maladaptive behaviors through pharmacological interactions with neural mechanisms evolved for cognitive control and reinforcement leaning (Redish, 2004; Redish et al., 2008). However, the neuroadaptive mechanisms that underlie such aberrant changes in the ACC remains a key, unanswered question. As a starting point of my research, I wished to address this issue directly by identifying the cognitive control dysfunction in substance dependent individuals using a conceptual framework that specifies how motor-related areas in ACC use dopaminergic RPE signals carried by the DA system for the purpose of

cognitive control according to principles of reinforcement learning. This theory holds that the impact of negative and positive RPE signals carried by the midbrain DA system modulates activity of the ACC, alternatively disinhibiting and inhibiting the ACC following unpredicted error and reward events, respectively. Accordingly, unexpected task-relevant events in general, including unexpected positive feedback, evoke activity that is intrinsic to the ACC, producing a component of the ERP called the N200. But following unpredicted rewards, the N200 is suppressed by extrinsically applied positive RPE signals carried by the midbrain dopamine system, resulting in an ERP component called the reward-positivity (Holroyd, Pakzad-Vaezi, & Krigolson, 2008; Baker & Holroyd, 2011b). Thus, by using the reward-positivity, I examined whether the impact of RPE signals on ACC networks are in fact disrupted in individuals who suffer from substance dependence. Specifically, I predicted that if substance dependence results in part from the impact of disrupted dopamine RPE signals on ACC, then the reward-positivity should be abnormal in Dependent but not Non-dependent individuals.

Indeed, the results of Experiment 1 and 2 both indicated that the reward-positivity was disrupted in substance dependent individuals, confirming my hypothesis. Importantly, several key observations were observed. First, the ERPs elicited by the Reward and No-reward feedback were nearly identical, exhibiting little difference between conditions. Because the N200 on reward trials were just as large on no reward trials, this observations suggests that following unpredicted rewards the N200 was not suppressed by extrinsically applied positive DA RPE signals, resulting in a blunted reward-positivity. In other words, reward feedback failed to induce dopamine-dependent reward processing in these individuals. Second, the amplitudes of the P200 and the P300 were about the same

between groups, confirming that the effect of interest was isolated to the predicted ERP component–the reward-positivity–and thus did not reflect an overall processing difference between the groups. Third, this effect remained statistically significant even when variability associated with personality-related risk factors for substance use (i.e., depression-proneness, anxiety, impulsivity, and sensation seeking) was controlled for. Finally, the reward-positivity was the second strongest predictor of substance dependence, next to the personality trait of novelty seeking. These findings are consistent with the proposal that substance dependence is associated with the impact of impaired DA-mediated reinforcement learning signals on neural areas for cognitive control and decision making.

In general, the results from Experiment 1 and 2 support the view that the cognitive control function of the ACC is severely disrupted in substance dependent individuals. To be more precise, all drugs of abuse stimulate the DA system (Di Chiara G. & Imperato, 1988), thereby increasing the magnitude of dopaminergic RPE signals. These RL signals are conveyed to the neural targets of the DA system, including the ACC, where their impact reorganizes synaptic connectivity in a way that biases the control system to engage in drug-seeking behavior (Hyman et al., 2006; Robinson & Kolb, 2004; Homayoun & Moghaddam, 2006). Thus, the cognitive control system compensates for these changes by discounting the motivational value of natural rewards, reducing the magnitude of their associated RPEs, which in turn desensitizes the system to non-drug rewards (Koob & Le Moal, 2005) like the small monetary incentives used here (Volkow et al., 2009). Consistent with this idea, a recent finding indicated that following overnight abstinence from smoking, feedback indicating potential opportunities to puff on a cigarette elicited a

relatively large reward-positivity (puff-positivity) in heavy smokers compared to light smokers, and showed a reduced reward-positivity to earning money (Wood, Baker, & Holroyd, 2012). This finding would indicate that the reward processing system in these individuals are not insensitive to rewards per se, but rather that the system is particularly sensitive to drug-related rewards relative to non-drug-related rewards. Importantly, previous research has indicted that environmental cues associated with nicotine delivery become conditioned reinforcers with powerful incentive properties that motivate continued nicotine self-administration (Caggiula et al., 2002; Caggiula et al., 2001). Such cue-reward associations are evidently learned via the phasic reward signals carried by the midbrain DA system (Redish, 2004). In combination with the results of Experiment 1, these findings would suggest that abnormal dopamine-dependent reinforcement signals cause substance dependent individuals to pursue cues that predict drug intake while ignoring cues that predict normal rewards. Further, individuals suffering from substance dependence are impaired at using normal rewards and punishment to develop neural representations of action value, and thus are impaired at using these action values for the purpose of cognitive control. The functional consequence of this maladaptive control process is that drug rewards become overvalued at the expense of other natural rewards, contributing to compulsion and to a marked narrowing of life goals to obtaining and using drugs (Hyman et al., 2006).

From a practical point of view, these findings highlight the utility of the reward-positivity in the study of substance dependence. Although other ERP components (e.g., P300: Iacono & Malone, 2011; Ehlers, Gilder, & Phillips, 2008) have been used to investigate substance dependence in the past , to my knowledge this is the first example of

an ERP component that provides a biological plausible theory of its functional origin, which has been highly influential and supported from a variety of methodological domains including neuropsychological and pharmacological studies (for review see Overbeek, Nieuwenhuis, & Ridderinkhof, 2005) genetic studies (Marco-Pallares et al., 2009; Beste, Saft, Andrich, Gold, & Falkenstein, 2006), and animal studies (e.g., Vezoli & Procyk, 2009). Further, several studies have shown that the reward-positivity component indexes a dopamine-like reward prediction error signal (e.g., Baker & Holroyd, 2009) and displays good test-retest reliability and substantial heritability (Olvet & Hajcak, 2008; Olvet & Hajcak, 2009; Weinberg & Hajcak, 2011; Anokhin et al., 2008). Importantly, because the theoretical and empirical work presented here are consistent with contemporary theories of addiction that emphasize deficits in reward-related learning, cognitive control, and decision making (Hyman, 2005; Redish et al., 2008; George & Koob, 2010), future clinical, electrophysiological, and genetic investigations of psychopathology associated with abnormal regulation of the DA and cognitive control system (i.e. substance dependence) are warranted.

## Neural Correlates of Decision Making in Substance Dependence

It has been proposed that the disruption of dopaminergic RPE signals by addictive drugs upset the normal function of basal ganglia and may precipitate the abnormal decision-making processes that are characteristic of substance dependence (Kalivas & Volkow, 2005). For example, insensitivity to positive and/or negative consequences of an action, a function of the basal ganglia Go/NoGo pathways, may be indicative of poor decision making, a hallmark of substance dependence (Klein et al., 2007). Yet, how drugs

of abuse lead to decision making impairments in the basal ganglia Go and NoGo pathways remain unclear. A specific aim of my research was to address this issue directly by identifying decision making impairments in substance dependent individuals using a conceptual framework (Basal Ganglia Go/NoGo model) explaining how dopaminergic signaling in the basal ganglia facilitate or suppress action representations during the PST according to principles of reinforcement learning: phasic bursts of dopamine activity facilitate reward learning by reinforcing striatal connections that express D1 receptors (the "Go/Approach" pathway), whereas phasic dips in dopamine activity facilitate avoidance learning by reinforcing striatal connections that express D2 receptors (the "NoGo/Avoidance" pathway) (Frank et al., 2004). Importantly, the model has been tested empirically with the PST, which determines whether individuals learn better from positive or negative feedback. Thus, by using the behavioural measures of the PST (e.g. accuracy on Approach and Avoid trials during the Test Phase) and the Go/NoGo model as conceptual framework, I examined whether the impact of RPE signals on basal-ganglia networks involved in decision making are in fact disrupted in individuals who suffer from substance dependence. Specifically, I predicted that if substance dependence results in part from the impact of disrupted dopamine RPE signals on brain structures involved in decision making, then performance in this task should be abnormal in Dependent but not Non-dependent individuals.

Consistent with my prediction, the results of Experiment 1 revealed that Dependent individuals were relatively worse at selecting the Good Stimulus and avoiding the Bad Stimulus compared to Non-dependent individuals. Interestingly, when these subjects were classified according to their learning bias (Positive vs. Negative Leaner Types), a different

pattern of results emerged. First, substance dependent individuals classified as Positive Learners were less accurate at Avoid trials while exhibiting normal accuracy on Approach trials in comparison to non-dependent participants. Importantly, when this effect was re-examined using subjects combined across all three studies, both substance dependent and moderately dependent Positive Learners were impaired on Avoid trials relative to non-dependent Positive Learners. This finding remained statistically significant even when the subjects from Study 1 were excluded from the analysis, confirming that the following two studies replicated the original finding. Yet, as shown in Study 1, depression-proneness score were significantly higher for this group, but this result did not replicate.

Nevertheless, this significant effect on Avoid accuracy in this subgroup of dependent individual is intriguing, given the consistency across studies. I speculate that continued drug use exacerbates the natural bias of the basal ganglia system to rely on one strategy over the other, possibly by a disruption of orbital frontal cortex "top-down" regulation of the basal ganglia Avoid pathway. Several observations support this proposal. First, substance use alters orbital frontal structure and function (Robinson & Kolb, 2004; Homayoun & Moghaddam, 2006), which would be expected to disrupt the "top-down" regulation of the NoGo pathways (Frank & Claus, 2006). Second, orbital frontal damage selectively disrupts the ability to learn from negative feedback in the PST (Wheeler & Fellows, 2008). Third, substance abuse is also associated with impaired performance on the Iowa Gambling Task (Bechara & Damasio, 2002; Bechara et al., 2002), which is characteristic of orbital frontal cortex damage (Bechara et al., 2000). Understood in this context, the present result suggest that the decision making impairment in addiction may play out most strongly via deficits in orbital frontal cortex functioning, indirectly

impacting the basal ganglia mechanism for avoidance learning in this subgroup of dependent individuals (Kalivas & Volkow, 2005). In support of this idea, it is suggested that lateral orbital areas respond to negative events and are predictive of a switch in behavior, supporting the possibility that this region mediates avoidance learning (Frank & Claus, 2006). More so, negative reinforcement information maintained in lateral orbital frontal cortex working memory representations can exert top-down control over decision-making processes, particularly the striatal No/Go system, thus preventing the execution of responses that would lead to negative outcomes (Frank & Claus, 2006). Thus, drugs of abuse may impair this specific function of the orbital frontal cortex, accounting for the decision making deficits in avoidance learning in the PST or it is also possible that abnormal avoidance learning resulted directly from dopamine-related genetic polymorphisms associated with addiction-proneness (Kreek et al., 2005), impaired error learning (Cohen & Frank, 2008), and reduced error-related brain activation in frontal cortex (Klein et al., 2007).

Finally, impaired accuracy on Avoid and Approach trials was observed in individuals undergoing treatment relative to the student groups, even when controlling for group differences in age and sex. Although a number of explanations could account for these findings, I tentatively suggested that chronic drug abuse over an extended period of time may have ultimately drove the decision making system to withdraw control over behaviors that it should inhibit (impaired avoidance learning) and facilitate behaviors that it should not (impaired reward learning). Further, this deficit in PST performance did not change over time in the treatment individuals, indicating that it did not reflect an acute effect of drug use. However, this portion of the study lacked sufficient statistical power,

given that of the 121 treatment group subjects who initially participated in session 1 of Experiment 3, only 26 agreed to engage in the PST at session 2. As it is not uncommon for studies of clinical populations, the response and participation rates in this study were not ideal. Various institutional (e.g., scheduling problems, treatment commitments) and individual (e.g., lack of interest) factors may have contributed to nonparticipation. Future research is needed to confirm the validity of these results.

To my knowledge, this is the first set of experiments utilizing the PST and the Go/NoGo theory as conceptual framework to investigate substance dependence. The PST was selected for this investigation based on its sound theoretical and empirical work, which has provided insight into individual differences related to reinforcement learning (Cohen & Frank, 2008), genetics (Frank et al., 2009; Frank & Hutchison, 2009; Frank et al., 2007; Frank et al., 2007), normal aging (Frank & Kong, 2008), "top-down" modulation by orbital frontal cortex and anterior cingulate cortex (Paulus & Frank, 2006; Frank & Claus, 2006), pharmaceutical manipulations (Frank & O'reilly, 2006), and psychiatric conditions (especially, Parkinson's disease, attention-deficit hyperactivity disorder, and schizophrenia; for review, see Maia & Frank, 2011). Although the present results highlighted important neurobiological and behavioral differences between dependent users that could potentially inform the development of individually-tailored treatment programs, these observations were qualified by additional findings that appear inconsistent with the predictions of the Go/NoGo Model, including a failure to demonstrate test–retest reliability of any PST performance measures over a 7-8 weeks interval. It is recommended that future research is needed to confirm the validity of these and previous PST findings, as indicated in Experiment 3.

Nevertheless, I reasoned that the PST measures might be stable within subpopulations of individuals characterized by particular individual traits related to the dopamine system and learning style. Thus, for Experiment 3, I utilized the PST to investigate the relative contribution of multiple dopamine-related genetic polymorphisms, personality traits and drug use history on individual differences in decision making. These results point to several individual traits related to the dopamine system and learning style that may modulate decision making across individuals, revealing potential vulnerabilities related to substance dependence.

Foremost, the genetic results indicated that individuals expressing enhanced D2 expression as coded by the promoter $SNP_2$ (Zhang et al., 2007) and the C957T (Duan et al., 2003) SNP result in impaired accuracy on Avoid trials, observations that appear inconsistent with the predictions of the Go/NoGo Model. According to the Basal Ganglia Go/NoGo model, impaired performance on Avoid trials is proposed to result from a diminished negative reinforcement learning signal, either directly from reduced phasic dips in dopamine or indirectly from a reduction in striatal D2 receptors. Alternately, I proposed that individuals expressing enhanced D2 expression are impaired on Avoid trials of the PST due to stronger D2-mediated inhibition of the No-go pathway. In other words, the greater the D2 receptor density, the less sensitive the D2 system is to transient dips in dopamine. This mechanism would result in a diminished negative learning signal following negative feedback and ultimately to impaired accuracy on Avoid trials, as I observed here. These results also highlight the role of the frontal D4 system in top-down control during high conflict situations. In addition, substance dependent individuals carrying the D4 allele associated with a reduced anterior cingulate cortex BOLD response

to conflict (Fan et al., 2003; Fossella et al., 2002) displayed relatively poor accuracy on both Approach and Avoid trials, compared to substance dependent individuals who carry the allele associated with a strong anterior cingulate cortex response to conflict. These findings suggest that individuals who display a relatively weak cognitive control system may be more susceptible to the negative consequence of drugs of abuse on the decision making system, possibly reflecting susceptibility to addiction, whereas the genotype associated with stronger cognitive control may act as a protective mechanism. Taken together, these findings support the idea that decision making processes are partly constrained by our genetic make-up, and may possibly reflect differential vulnerability to substance dependence in one or more of the subcomponents of the decision making system.

Furthermore, several personality traits influenced performance on the PST, consistent with several lines of research implicating maladaptive affective factors in decision making (Bechara et al., 2000; Bechara, 2003; Noel et al., 2011; Zermatten et al., 2005; Zuckerman, 1988; Zuckerman & Kuhlman, 2000; Raghunathan & Pham, 1999; Maner & Schmidt, 2006; Mitte, 2008; Meyer-Lindenberg, 2010). First, a statistical trend was revealed indicating that individuals currently seeking treatment and who were relatively prone to depression displayed better accuracy on Avoid compared to Approach trials, as well as better accuracy on Lose-lose compared to Win-win trials. These results are consistent with a recent study which attributed enhanced accuracy on Avoid trials of the PST by depressed individuals to hypersensitivity to punishment (Cavanagh et al., 2011). Furthermore, high impulsivity in undergraduate students was associated with poor accuracy on Avoid trials. This finding appears compatible with the genetic findings of

Experiment 2 that high levels of impulsivity are associated with decreased DARPP-32 protein expression, which facilitates the functional connectivity between brain regions including the projection from prefrontal cortex to the striatum (Meyer-Lindenberg et al., 2007; Curcic-Blake et al., 2012). Given that the frontal system implements control functions related to impulse regulation and top-down control over the NoGo pathway, individuals displaying impaired inhibitory control may thus perform particularly worse on Avoid trials of the PST. Finally, high Novelty Seeking predicted better accuracy at Avoid trials relative to Approach trials. Perhaps in these participants, positive feedback failed to elicit a sufficiently positive reward signal to bias performance in favor of Approach trials. In support of this idea, Approach and Avoid reaction times were nearly identical in novelty seekers, suggesting that these conditions were processed indifferently, whereas all of the other personality groups displayed a relative decrease in Approach reaction time. Furthermore, Novelty Seekers also displayed good test-retest reliability on Approach trial accuracy, consistent with the idea that the underlying mechanism contributing to this trait is stable. Taken together, these findings highlight the important role our personality structures play in decision making and in the development and maintenance of several forms of psychopathology associated with susceptibility to drug abuse.

Although I found characteristics that predicted individual differences in approach vs. avoidance learning, these observations were qualified by additional findings that appear inconsistent with the predictions of the Go/NoGo Model. For example, Klein and colleagues (2007) demonstrated that male carriers of the A1 allele (A1/A1 and A2/A1 combined) of the Taq1A SNP of the DRD2 gene, in which the A1 allele is associated with reduced D2 expression (Thompson et al., 1997; but see Zhang et al., 2007), were

selectively impaired at avoiding the bad stimuli during the Test Phase. However, the present findings failed to replicate this Taq1A effect: homozygous and heterozygous A1 carriers together performed nearly identically to homozygous A2 carriers. Notably, an overall blunting effect of reinforcement−both positive and negative−was observed in individuals homozygous for the A1 allele, providing a potential link between this genotype and several impulsive, addictive and compulsive disorders (e.g., polysubstance abuse, smoking, ADHD, obesity, and Tourette's syndrome) previously associated with this allele (Blum et al., 1991; Lawford et al., 2006; Noble, 2003; Noble, 2000b; Noble, 2000a). Consistent with this idea, the low frequency of homozygous A1 individuals in the population would suggest that two A1 alleles together may present a strong evolutionary liability. Future studies of this gene should utilize large sample sizes to separate the effects of one vs. two A1 alleles on basal ganglia activation and on task performance.

More so, the Go/NoGo model predicts that poor performance on Approach trials of the PST should be associated with reduced striatal D1 receptor efficacy (Frank et al., 2007). In particular, impairments on Approach trials are proposed to result from a diminished positive reinforcement learning signal, either directly from reduced phasic bursts in dopamine as seen in people with Parkinson's disease or indirectly from reduced D1 efficacy as modulated by the PPP1R1B gene (Frank et al., 2007), which codes for variation of a protein responsible for regulating the sensitivity of D1 striatal neurons to glutaminergic excitation and dopaminergic modulation (Meyer-Lindenberg et al., 2007; Svenningsson et al., 2004). However, the results did not reveal any allelic effects on accuracy or reaction time on Approach trials, nor on any other PST measure, inconsistent with the predictions of the Go/NoGo model (Frank et al., 2007).

Taken together, the results of Experiment 3 indicate that individual differences related to genetics, substance abuse history, and personality bias the basal ganglia system during reinforcement learning and decision making, and are undoubtedly a major influence on our ability to learn and make choices. Yet, the data failed to show adequate test-retest reliability on any measure of PST performance for a sample of nearly 100 undergraduate student participants. Although the PST has been used substantially to investigate a basal ganglia mechanism involved in decision making, as described by the Go/No-go model, the findings highlight the need for future studies that establish the validity of the task and that replicate these findings here.

## Genetics, Drugs, and Cognitive Control

Like most studies that find an association between brain function, behavior, cognitive impairment and substance abuse, the findings of Experiment 1 raise the question of causality: Do the observed cognitive control impairments stem from chronic drug use itself, or from factors related to genetics, such that the reinforcing properties of addictive drugs exploit genetic vulnerabilities of the dopamine system. In respect to the DA system, the development and expression of the DA system is determined in part by genetic factors that vary across individuals such that dopamine-related genes are partly responsible for addiction-proneness. Thus, people who abuse substances may be characterized in part by genetic abnormalities that render the DA system vulnerable to the potentiating effects of addictive drugs. Consistent with this idea, several lines of research have established the importance of particular neural networks and genes specifically implicated in addiction

liability, addictions-related phenotypes (e.g. personality risk factors), reward processing, and cognitive control (reviewed in Goldman et al., 2005).

To investigate this idea, I adopted an intermediate phenotype (IP) approach to link several dopamine-related genetic polymorphisms with substance dependence. In particular, I explored the viability of five candidate IPs: the reward-positivity, an electrophysiological measure of a cortical mechanism for dopamine-dependent reward processing and cognitive control (Holroyd & Coles, 2002; Holroyd & Yeung, 2012), the PST, a behavioral index of a subcortical mechanism for dopamine-dependent reinforcement learning (Frank et al., 2004), and four personality risk factors associated with drug addiction (impulsivity, novelty seeking, depression proneness and anxiety sensitivity) (Conrod & Woicik, 2002). Key to this approach is the application of statistical modeling procedures more commonly utilized in the social sciences (mediation analysis and structural equation modeling) to elucidate causal relationships across complex multivariate data sets (see also Ray et al., 2009; Laucht et al., 2007).

By adopting an IP approach, this study successfully modelled several dopamine-related neural pathways underlying individual differences in substance dependence, including its biological, cognitive, and personality manifestations. It is important to note that all the aforementioned IPs predicted substance dependence in this model, except for the PST measures. First, the relationship between the variations in D4 expression and substance dependence was mediated by reward-related electrophysiological signals produced in ACC, the reward-positivity and frontal midline theta. The mediation effect indicated that D4 receptors play a pivotal role in reward processing function of the cognitive control network in ACC. In particular, D4 receptors, which are highly expressed

in frontal regions involved in cognitive control (Mulcrone & Kerwin, 1997), appear to inhibit pyramidal neurons (Rubinstein et al., 2001; Wang et al., 2002; Wang et al., 2003) in response to tonic dopamine activity (Onn et al., 2006). Notably, application of a D4 agonist in medial frontal cortex in the rat impairs shifting between alternative task strategies, whereas blockade of D4 receptors improves this function (Floresco et al., 2006). This evidence suggests that D4 receptor activation may antagonize event-related phasic activity underlying behavioral flexibility (Floresco & Magyar, 2006). Given these observations, low D4 density may enable the ACC to respond dynamically to event-related activity whereas increased D4 density and/or tonic dopamine activity would have the converse effect. Consistent with this possibility, individuals with reduced D4 expression displayed a relatively strong medial frontal theta response to salient events, evidently by releasing the ACC from tonic inhibition of the dopamine system. By contrast, individual with enhanced D4 expression displayed a suppressed medial frontal theta response to salient events and showed elevated levels of substance dependence. Whereas too much D4 inhibition might disrupt the normal reinforcement learning function of ACC, the dopamine-potentiating effects of addictive substances might compound this problem, resulting in unstable reward valuation as revealed by the electrophysiological measures.

Interestingly, although the main effect of D4 expression on substance dependence was mediated by medial frontal electrophysiological activity related to reward processing, a secondary effect was mediated by depression-proneness. Functional neuroimaging studies have revealed a reduced neural response to negative feedback and abnormalities in ACC-mediated performance monitoring in depression (Elliott et al., 1998; Kumar et al., 2008; Steele et al., 2007), individual differences that might reflect excessive D4-dependent

inhibition of frontal cortex. Further, depression-prone individuals are often characterized by a tendency to focus primarily on the self and to maintain self-focused attention on negative affect (Conrod & Woicik, 2002). Provided this evidence, excessive D4-inhibition of ACC may render individuals incapable of switching from negative to more positive affective states. Conversely, drugs of abuse that potentiate the reinforcing effects of dopamine may provide depressed individual with the opportunity to switch thought processes while concomitantly reinforcing this maladaptive behavior.

An increase in COMT enzyme expression exclusively predicted high anxiety. Specifically, the Val allele of the COMT gene accounts for a four-fold increase in catecholamine (dopamine, norepinephrine, and epinephrine) catabolism in frontal cortex, and has been hypothesized to augment phasic signaling in that region (Bilder et al., 2004). Norepinephrine in particular plays an important role in vigilance, attention and learning by putatively serving as a neural alert signal, and is implicated in the etiology of anxiety-related disorders (Goddard et al., 2010). By extension, an increase in COMT activity may lead to heightened phasic activations of the "alert" function, evoking unnecessary feelings of arousal and anxiety. Individuals with this polymorphism might therefore be especially sensitive to the anxiolytic and reinforcing properties of alcohol.

The personality trait of impulsivity was best predicted by expression of the DARPP-32 protein, as reflected by the PPP1R1B gene. As described above, the DARPP-32 protein regulates the sensitivity of striatal neurons to glutamtergic excitation and dopaminergic modulation (Svenningsson et al., 2004), facilitating the functional connectivity between brain regions including the projection from dorsal lateral prefrontal cortex to the striatum (Meyer-Lindenberg et al., 2007). DARPP-32 also plays an important

role in the actions of drugs of abuse (Svenningsson et al., 2005). The frontal-striatal system implements control functions such as impulse regulation (Fineberg et al., 2010), so it is natural that decreased DARPP-32 availability might be associated with higher levels of impulsivity, as I observed here. Individuals displaying impaired inhibitory control due to frontal-striatal dysregulation may thus be particularly vulnerable to drug-related potentiation of the midbrain dopamine system.

Although novelty seeking was one the strongest predictors of substance dependence, there was a lack of a genetic association with this personality traits. Yet, there was an slight association between DRD2-Taq1A and novelty seeking, and is perhaps surprising given that of all the known dopamine-related polymorphisms, the A1 allele of the Taq1A polymorphism of the DRD2 gene, which is characterized by reduced striatal D2 density, is strongly implicated in substance abuse, novelty seeking (Noble, 1998) and, recently, reinforcement learning (Klein et al., 2007). Here, individuals homozygous for the A2 allele displayed higher scores on the novelty seeking scale compared to both A1/A2 and A1/A1 carriers, contrasting with previous reports. How low striatal D2 densities expressed by the DRD2 variants (TaqA1, C957T, SNP2) translate into a vulnerability to addiction warrants continued research.

I then utilized the model to identify different populations of substance dependent users. Cluster analysis indicated two groups of substance dependent individuals. The first group of Experiment 2 was characterized by reduced reward-positivity amplitudes and high depression-proneness scores. The second group was characterized by high novelty seeking scores and relatively normal reward-positivity amplitudes. Although exploratory, the cluster analysis converges on several vulnerabilities related to decision making as

specified within a unified theoretical framework for addiction (Redish et al., 2008). For example, the severely reduced reward-positivity can be understood in terms of an altered allostatic set points due to overvaluation of drug-related rewards in the planning and habit system (vulnerabilities 2, 4, 7 in Redish et al., 2008), whereas depression-proneness can be understood by an inability to switch responses in the face of failures and losses (vulnerability 6) (see section below). In sum, the model presented in Experiment 2 suggests a theoretical framework for bridging the gap between genes and behavior in drug addiction and illustrates how future interventions might be individually tailored for specific genetic, cognitive and personality profiles.

## Integrating General Theories of Addiction with the Reward-positivity

Over the last 30 years, a number of theories have been proposed attempting to explain how disruptions in learning and decision making systems lead to substance dependence. According to Redish and colleagues (2008), these theories can be grouped into the following primary categories:

(1) Opponent processes: based on changes in homeostatic and allostatic levels that change the needs of the individual
(2) Reward-based processes and hedonic components: based on pharmacological access to hedonically positive signals in the brain.
(3) Incentive salience: based on a sensitization of motivational signals in the brain
(4) Non-compensable DA: based on a role of dopamine as signaling an error in the prediction of the value of taking an action, leading to an overvaluation of drug-seeking
(5) Impulsivity: in which users make rash choices, without taking into account later costs
(6) Situation recognition and categorization: based on a misclassification of situations that produce both gains and losses
(7) Shifting balances: based on deficiencies in the balance between executive and habit systems, in which it becomes particularly difficult to break habits through cognitive mechanisms either through over-performance of the habit system or

> under-performance of flexible, executive, inhibitory systems or a change in the balance between them

All these perspectives have explanatory power as to the causes of addiction, and all provide suggested methods of investigation and treatment of addiction. However, Redish and colleagues (2008, pg. 416) argue that each theory explains "a different vulnerability in the decision-process system, capable of driving an individual to make an addictive choice. Thus, the set of theories provides a constellation of potential causes for addictive choice behavior. Importantly, the identification of addiction as vulnerabilities in the biological decision-making system means that understanding addiction will require an understanding of how animals (including humans) make decisions". Based on this argument, Redish and collegues (2008) reconciled these theories on substance dependence into a unified theory of addiction and identified 10 key vulnerabilities in the decision making system: (1) moving away from homeostasis, (2) changing allostatic set points, (3) euphorigenic "reward-like" signals, (4) overvaluation in the planning system, (5) incorrect search of situation-action-outcome relationships, (6) misclassification of situations, (7) overvaluation in the habit system, (8) a mismatch in the balance of the two decision systems, (9) over-fast discounting processes, and (10) changed learning rates.

I was impressed by the theoretical sophistication and depth, and by the paradigm laid out in this unified theory (taking a basic cognitive neuroscience understanding of action-selection and decision making and identifying failures in these system), and strongly believe this type of an approach is essential if we are to fulfill the promise of a neuroscience-based, mechanistically detailed approach to the understanding, diagnosis and treatment of addiction, which many agree should characterize the psychiatry and

neurology of the future (Maia & Frank, 2011). However, there still remains several unresolved issues within this theory: (1) a specific method or clinical instrument with which to identify the presence or absence of each vulnerability within an individual is greatly lacking, (2) key parameters that underlie individual differences are still unknown, including whether those key parameters are genetic, environmental, or some combination thereof; and (3) a complete account of how the control system and habit system interact to produce addictive behaviour is still unknown (Redish et al. 2008). Here, I propose that the theoretical approach and empirical support in this thesis holds promise for integrating experimental, computational, and theoretical analyses of human cognitive control and decision making functions within the context of the unified theory of addiction proposed by Redish and colleagues (2008). In what follows, I attempt to construct a bridge between the unified theory of addiction and the present thesis work.

*Vulnerability 1 (deviations from homeostasis) and Vulnerability 2 (changes in allostatic set-points).* Based on the conceptual framework of the *opponent processes theory* (Koob, Caine, Parsons, Markou, & Weiss, 1997; Koob & Le, 1997; Ahmed & Koob, 1998; Koob & Le, 2001), Redish and colleagues (2008) propose these vulnerabilities result from changes in homeostatic and allostatic levels that change the needs of the individual. In particular, the *opponent processes theory* states that two opposing processes control affect and the motivational changes observed after chronic drug use (Koob et al., 1997). For instance the rewarding effect of the drug (a-process) will trigger a delayed aversive effect (b-process) that gets larger with chronic drug use, and will counteract the (a-process) to maintain homeostasis. In regards to allostasis−the process of maintaining reward function stability through changes in brain reward and stress

mechanisms− not only the b-process gets larger with chronic drug use but the reward set point from which the a-process and b-process are anchored progressively shifts downward, creating an allostatis state (George & Koob, 2010). Further, because opioid and alcohol addictions are characterized by an intense withdrawal/negative affect stage (b-process), it represents one of the main driving forces for drug seeking behaviour. Within this framework, drugs can change the needs of an organism either by moving the system away from the homeostatic set-point itself (a withdrawal state after drug use), requiring drugs to return the system to homeostasis (vulnerability 1), or by changing the system's desired set-point itself, thus requiring drugs to achieve the new inappropriate set-point (vulnerability 2). Accordingly, Redish et al. (2008) proposed that in either case, these changes will modify the perceived needs of the organisms, and will thus change the evaluated value of expected outcomes.

The reinforcement theory of the ACC provides a theoretical framework in which to test the presence or absence of vulnerability 1 and 2 within an individual. In the context of the opponent processes theory of addiction, initial drug use may induce changes to synaptic connectivity that can potentially rewire and 'usurp' the ACC, progressively shifting the 'natural' reward set point downward, and contribute to possible abnormalities of the cognitive control system, as revealed by a blunted reward-positivity. The reward-positivity reflects revisions of an ongoing probabilistic estimate of future reward (the RPE), where the reward itself indicates whether or not a goal is achieved (a binary outcome indicating the "set point") (Holroyd and Yeung, 2012). Thus, if the evaluated value of expected outcomes is changed in an individual following chronic substance use, then it would be evident in the reward-positivity, as shown in Experiment 1 and 2.

Consistent with this idea, the reward-positivity can be used as a measure of the a-process following allostatisic shift, or shift in the evaluation of expected outcome during withdrawal (vulnerability 2). For instance, following overnight abstinence from smoking, feedback indicating potential opportunities to puff on a cigarette elicited a relatively large reward-positivity in heavy smokers compared to light smokers, and showed a reduced reward-positivity to earning money (Wood et al., 2012). This finding would indicate a change in the evaluation of expected outcomes of drug-taking following abstinence, thus reflecting a motivating factor in the initiation of drug use behaviour in order to return the system to homeostasis (vulnerability 1). Taken together, the reinforcement learning theory of the ACC may provide a means to test the ideas proposed by the opponent processes theory, and identify vulnerabilities 1 and 2 in humans.

*Vulnerability 3 (overvaluation of the expected value of a predicted outcome-mimicking reward), Vulnerability 4 (overvaluation in the planning system), and Vulnerability 5 (Incorrect search of stimulus→action→outcome relationships).* First, the idea behind vulnerability 3 is that drugs mimic the reward signal and trick the decision making system into believing that it just received a strong reward. This reward signal will be stored in stimulus-response and stimulus-outcome mappings in decision making system, which would lead to the recall of these exaggerated signals and associated mappings when the decision making systems is triggered by a cue predicting these reward-mimicking drugs. This vulnerability is recognizable by strong craving effects following the drug-related cue. Additionally, a fundamental vulnerability of the stimulus-response and stimulus-outcome mappings is in the valuation of the outcome (vulnerability 4). In particular, the overvaluation of the planning systems occurs when the level of "wanting"

and the "value" of the outcome satisfying that perceived want is exaggerated, presumably over learned through drugs impact on DA signaling projecting to the striatum and frontal cortex (Robinson & Berridge, 2008; Robinson & Berridge, 1993). Further, the central idea behind vulnerability 5 is that if a drug were to increase the likelihood of retrieving a specific stimulus→action→outcome relationship, then one would expect this to limit the set of possibilities explored, which would appear as a cognitive blinding to alternatives, thus leading to an increase in attention to drug-related cues (Redish & Johnson, 2007). Taken together, these vulnerabilities represent an overvaluation of expected drug outcomes (craving) and an increased likelihood of taking actions leading to those expected drug outcomes (Redish, 2004; Redish & Johnson, 2007; Redish et al., 2008). The functional consequence of this maladaptive learning process is that drug rewards become overvalued at the expense of other natural rewards, contributing to compulsion and to a marked narrowing of life goals to obtaining and using drugs (Hyman et al., 2006).

Central to the neural mechanisms underlying these vulnerabilities proposed by Redish and colleagues (2008) is the *incentive salience theory of addiction* (Robinson & Berridge, 2008; Robinson & Berridge, 1993). For this reason, vulnerabilities 3-5 were grouped together in this section. According to the incentive salience theory of addiction, repeated exposure to potentially addictive drugs can persistently change brain circuits that normally regulate the attribution of incentive salience to stimuli, a psychological process involved in motivated "wanting" behaviour (Robinson & Berridge, 2008; Robinson & Berridge, 1993). The nature of these 'neuroadaptations' is to render these brain circuits hypersensitive ('sensitized') in a way that results in pathological levels of incentive salience being attributed to drugs and drug-associated cues, and the motivation to work

towards drug related-goals in a given behavioural context (Robinson & Berridge, 2008; Robinson & Berridge, 1993). Based on this idea, addiction has been conceptualized as a "learning disorder" (Hyman, 2005). For example, it has been shown that treatment with drugs facilitates the development of stimulus-response habits in animals (Miles, Everitt, Dalley, & Dickinson, 2004; Miles, Everitt, & Dickinson, 2003; Nelson & Killcross, 2006) possibly via recruitment of the dorsal striatum (Everitt, Dickinson, & Robbins, 2001). However, Robison and Berridge (2008) argue that complex and flexible behaviour observed in addicts indicates pathological motivation for drugs that cannot be explained by learning simple stimulus-response type habits, whereas these habits are more likely to contribute to the automatized behaviours and rituals involved in consuming drugs once obtained. Robison and Berridge (2008) propose that 'addicts in the real world are not stimulus response automatons; they are, if nothing else, quite resourceful' (Robinson & Berridge 2008, pp. 1338).

In line with this argument, Holroyd and Yeung (2012) proposed a theory that the function of the ACC is responsible for selecting and maintaining high-level "options" that map sequences of relatively primitive actions from initial states to goal states. In particular, options represent action policies comprised of sequences of simple, primitive actions and can be defined by their associated goal states and the set of initiation states that trigger the options. Further, other systems execute those options (dorsal lateral prefrontal cortex and dorsal striatum), and evaluate progress toward the options' goal-states (orbital frontal cortex, ventral striatum), which is consistent with the existing concepts about the computational function of these cognitive control systems, with which the ACC interacts. Building on this theoretical concept, and in line with Robison and Berridge (2008)

argument , I propose that abnormal RPE signal carried by the DA system on ACC may increase the incentive salience of cues or states that motivate high level options, rather than primitive low-level actions. Specifically, the ACC implements a high-level decision-making mechanism that uses the RPE signals to choose between action plans or options, rather than just learning of simple stimulus-response associations, a function attributed to the basal ganglia (Holroyd & Yeung, 2012). This is a critical point. Under this framework, repeated exposure to addictive drugs may persistently alter ACC circuits that normally regulate the attribution of incentive salience to cues or states that motivate *goal-directed temporally extended sequences of actions* rather than simple actions. This maladaptive process may render the ACC hypersensitive ('sensitized') or amplify the "incentive salience" or "wanting" of drug related rewards, thereby increasing the frequency and intensity of options that lead to the acquisition of drugs. By this definition, it may explain the complex behaviours or 'options' addicts engage in, such as scamming, stealing and negotiating, that cannot be explained by stimulus-response habits. For instance, the results of Experiment 1 and 2, which indicate that dependent individuals display an abnormal reward-positivity to monetary rewards, and the results of the previous discussed smoking study (Wood et al., 2012), where heavy smokers show a normal reward-positivity to drug-related rewards (such as earning cigarette puffs) relative to other "natural" awards (such as earning money) would suggest that in substance dependent individuals' *goal-directed temporally extended sequences of actions* are shaped more by the heightened reward value of the drugs, as indexed by the reward-positivity, than by the natural rewards. Thus, given the choice between options, one would expect that the ACC would more likely select the drug option more often than alternatives in a given behavioural context.

Further, this conceptualization may provide insight into the findings from Experiment 2 and 3 suggesting that the dopaminergic contribution to addiction may play out most strongly via control mechanisms in ACC (as revealed by an abnormal reward-positivity) compared to striatal mechanism for reinforcement learning (as revealed by normal PST performance). More importantly, vulnerability 3-5 should in theory be extended to explain more complex, high levels behaviours, rather than simple stimulus-response type mappings. This can be accomplished by adopting the reward-positivity and hierarchical theory of the ACC (Holroyd & Yeung, 2012) to access whether or not these vulnerabilities in option selection exist in humans. Furthermore, the present research also indicates that susceptibility to these vulnerabilities may arise through an interaction among the genetics (D4 expression), and the cognitive control mechanism of the individual (theta oscillations).

*Vulnerability 6 (the illusion of control).* This vulnerability is based within the context of cognitive biases involved in gambling behaviour. Problem gamblers are often characterized by cognitive distortions such as misclassification of situations, illusion of control, and hindsight bias (for review, see Griffiths, 1994; Griffiths, 1996). Misclassification of situations is defined as incorrectly identifying a statistically unlikely sequence of wins as a separate situation from more-commonly experienced losses. Illusion of control is defined as an expectancy of success higher than the objective probability would warrant. And hindsight bias refers to the tendency of problem gamblers to "explain away" losses by post-hoc identification of differences in cues between the losses and memories of wins (Griffiths, 1994). In essence, the basic assumption is that in some probabilistic setting, those conditions which involved factors of choice, familiarity, and

competition stimulate the illusion of control to produce ‘false’ skill orientations (e.g. Henslin (1967) reported that craps players rolled the dice softly if they wanted low numbers and harder if they wanted higher numbers (Henslin, 1967)). Together, this vulnerability reflects the false belief that gambling has an element of skill such that the time taken to lose all one’s money can be lengthened by skillful playing (Griffiths, 1994).

According to Redish and colleagues (2008), the relationship between these cognitive biases can be understood by a vulnerability to over-categorize and over-generalize events. In regards to the former, over-categorization occurs if gambling losses are not recognized as occurring in the same situation as previous gambling wins, a individual can potentially (incorrectly) learn two stimulus→action→outcome relationships, one leading to a winning outcome, one leading to a losing outcome. Under this condition, it is possible that an individual may incorrectly predict that they can know when they will achieve a winning outcome (the illusion of control). In regards to the latter, over-generalization refers to the inability to re-categorize situations (by recognizing actual changes) can lead to the perseveration of responses and an inability to switch responses in the face of failure and losses. As this vulnerability implies, these stimulus→action→outcome relations probably contribute to the automatized behaviours and rituals involved in problem gambling, perhaps via dysregulation of the basal ganglia and orbital frontal circuitry.

Consistent with this idea, Frank and Claus (2006) adapted the Basal Ganglia Go/NoGo model to explain the relationship between orbital frontal cortex and the basal ganglia during decision making. They argue that the orbital frontal cortex is specialized to maintain recent gain–loss information in working memory and can have a top-down

biasing effect on the more primitive basal ganglia system. In particular, medial orbital frontal cortex tends to be activated by positive outcomes and maintenance of current strategies, and have a top-down biasing effect on approach responding via the Go pathway within the basal ganglia. Conversely, lateral orbital frontal cortex responds to negative events and is predictive of a switch in behavior, supporting the possibility that this region supports avoidance responding via the NoGo pathway. This division of labor between the Go and NoGo pathways systems could explain the cognitive biases described in vulnerability 6.

Specifically, disruption to the lateral orbital frontal areas may lead to impairments in the maintenance of negative events in working memory, thereby resulting in the inability to switch behavior following losses. Thus pathological gambling could arise from the inability to create a negative reinforcement history in orbital frontal cortex, thereby contributing to the individual incorrectly identifying a statistically unlikely sequence of wins compared to the more-commonly experienced losses. Such a deficit may contribute to over-generalization of the situation, as described by vulnerability 6. Consistent with this idea, Dependent users who were classified as Positive learners were impaired at avoidance learning in the PST, possibly a result of a drug induced disruption of top-down control of the orbital frontal cortex on the basal ganglia NoGo pathway. Further, orbital frontal damage selectively disrupts the ability to learn from negative feedback in the PST (Wheeler & Fellows, 2008), and orbital frontal damage has been shown to impair learning in the Iowa Gambling Task (Bechara & Damasio, 2002; Bechara et al., 2002). Frank and Claus (2006) also demonstrated that by lesioning the orbital frontal cortex in the Go/NoGo model, the model was unable to adequately weigh the magnitudes of rewards and

punishments when making decisions, leading to poor performance in the Iowa Gambing Task.

Taken together, I propose that the Basal Ganglia Go/NoGo model could provide important insights into pathological gambling in the context of vulnerability 6. For instance, DA medication can block negative RPE signals in Parkison's patients leading to impairments in avoidance learning (Frank et al. 2004). This may also disrupt representations in lateral orbital frontal cortex, which in the model would prevent the encoding of loss information while enhancing gain representations (Frank and Claus, 2006). Frank and Claus (2006) proposed that such actions could potentially explain the documented effects of medication on inducing pathological gambling in Parkison's patients (Dodd et al, 2005). In relation, a diminished negative reinforcement learning signal can also result from enhanced D2 expression in the NoGo pathway, leading to impairments in avoidance learning. This could also reduce lateral orbital cortex representations as well, possibly representing a genetic vulnerability to pathological gambling. The straightforward predictions of the Go/NoGo model would be that problem gamblers should display impairments in avoidance learning. In sum, the Basal Ganglia Go/NoGo model using the PST would be a natural candidate for investigating vulnerability 6, and may provide important information about the regulation of cognitive biases in gambling addicts, and possibly the development of drug-related habits.

*Vulnerability 7 (overvaluaiton of actions).* Vulnerability 7 refers to the idea that addictive substances increase the size of phasic DA signals by raising extracellular DA levels (Di Chiara G. & Imperato, 1988), effectively increasing the magnitude of positive RPEs (Rice & Cragg, 2004). In turn, the augmented RPEs cause the motivational value of

states/actions that precede drug consumption to increase without bound, biasing the action-selection mechanism to favor behaviors that ultimately converge on drug use (Redish, 2004; Redish et al., 2008). These changes are mediated by synaptic modification at the molecular level that result in the rewiring of underlying neural networks (Robinson & Kolb, 2004; Homayoun & Moghaddam, 2006) . Critically, these exaggerated RPE signals are conveyed by the DA system to the orbital frontal cortex, basal ganglia and ACC, (Allman et al., 2001; Seamans & Yang, 2004; Gorelova et al., 2002; Schultz, Tremblay, & Hollerman, 1998; Schultz, Tremblay, & Hollerman, 2000) where they result in the development of misshapen and bulbous neurons (Robinson, Gorny, Mitton, & Kolb, 2001). It is important to note that vulnerabilities 7 is described only in the context of RPE signaling in the basal ganglia, but in actual fact these signals are also conveyed to the orbital frontal cortex and ACC for the purpose of cognitive control and reinforcement learning (Holroyd & Coles, 2002; Schultz et al., 1998; Schultz et al., 2000). Provided the main finding of this thesis, I will discuss vulnerability 7 in the context of cognitive control.

In particular, a central claim of the reinforcement learning theory of the ACC (Holroyd and Coles, 2002), and the basis of this thesis, is that the reward-positivity reflects the impact of dopaminergic RPE signals on motor areas of the ACC for the purpose of cognitive control. Under this context, vulnerability 7 has already been tested in humans. In particular, across two experiments, the reward-positivity was observed to be severely disrupted in substance dependent individuals. In particular, because the impact of the exaggerated RPE signals reorganizes synaptic connectivity in a way that biases the control system to engage in drug-seeking behavior, the cognitive control system compensates for these changes by discounting the motivational value of natural rewards, reducing the

magnitude of their associated RPEs, which in turn desensitizes the system to non-drug rewards (Koob & Le Moal, 2005) like the small monetary incentives used here (i.e. a blunted reward-positivity). Further, this study also demonstrated how D4 expression can impact reward-related oscillations in ACC, providing a genetic basis in which this vulnerability can be explored further.

*Vulnerability 8 (Selective inhibition of the planning system).* Core to vulnerability 8 is the balance between a control (or planning) system and the primitive habit system. Redish and colleagues (2008) propose that frontal control systems are involved in the shift between habit and planning systems, and exposure to drugs can shift the normal balance between systems, emphasizing one over the other. For example, alcohol can impair hippocampus (Givens & McMahon, 1995; Givens, 1995) and frontal cortex (Oscar-Berman, Kirkley, Gansler, & Couture, 2004; Oscar-Berman et al., 2009; Oscar-Berman, 2012) function, which would shift the normal balance from the planning to the habit system (Redish et al., 2008). Such deficits can be accounted for by the hierarchical reinforcement learning theory of the ACC proposed by Holroyd and Yeung (2012). For instance, this theory proposes a division of labor between the ACC, dorsal lateral prefrontal cortex  and dorsal striatum. In particular, the ACC selects and maintains options, and that dorsolateral prefrontal cortex (higher levels actions) and motor structures in the dorsal striatum (primitive actions) execute those options. In this way, the ACC decides what task to perform and then directs dorsolateral prefrontal cortex to implement that task, which in turn provides top-down biasing signals to the dorsal striatum to facilitate execution of the actions to take (Holroyd and Yeung, 2012). Thus, deficits in the ACC and/or even the dorsal lateral prefrontal cortex that prevents these systems to

function optimally (e.g. excessive alcohol use, Korsakoff's syndrome), would result in enhanced function in the habit system and encourage the automation of behaviours. In line with this idea, an impaired shifting system (vulnerability 8) would make it difficult for the planning system to correct a misguided habit system, possibly contributing to a cue-dependent uncontrolled relapse, and possibly independent of explicitly identified craving (Redish et al. 2008). Under the conceptual framework of the theory proposed by Holroyd and Yeung (2012), investigation into this vulnerability is possible.

*Vulnerability 9 (Over-fast discounting processes).* Core to vulnerability 9 is temporal discounting of rewards, such that addicts discount faster than non-addicts (Redish et al. 2008). Temporal discounting refers to the tendency of people to discount rewards as they approach a temporal horizon in the future or past (i.e. rewards become so distant in time that they cease to be valuable). To put it another way, it is a tendency to give greater value to rewards as they move away from their temporal horizon and towards the "now". For example, a nicotine deprived smoker may highly value a cigarette available anytime in the next 6 hours but assign little or no value to a cigarette available in 6 months (Odum, Madden, & Bickel, 2002). Interestingly, the trait of impulsivity has been strongly linked to both steeper discounting rates (Rubia, Halari, Christakou, & Taylor, 2009; Kayser, Allen, Navarro-Cebrian, Mitchell, & Fields, 2012) and addiction susceptibility (Verdejo-Garcia et al., 2008; Arce & Santisteban, 2006; Kreek et al., 2005). Further, animal studies and indirect evidence in humans suggest that lower DA in the frontal cortex contributes to steeper discounting by impairing corticostriatal function (Kayser et al., 2012). In fact, Experiment 2 demonstrated that the personality trait of impulsivity was best predicted by DARPP-32 protein expression, a protein that regulates the sensitivity of

striatal neurons to glutamtergic excitation and dopaminergic modulation (Svenningsson et al., 2004), facilitating the functional connectivity between brain regions including the projection from dorsal lateral prefrontal cortex to the striatum (Meyer-Lindenberg et al., 2007). DARPP-32 also plays an important role in the actions of drugs of abuse (Svenningsson et al., 2005). This finding indicated that individuals displaying impaired inhibitory control due to frontal-striatal dysregulation may thus be particularly vulnerable to drug-related potentiation of the midbrain dopamine system, and could possibly account for their temporal discounting vulnerability. Thus, the PPP1R1B could be a potential genetic link between impulsivity and vulnerability 9. In addition, a recent study indicated that individual differences in temporal discounting were reflected in reward-positivity magnitudes with high discounters having larger immediate reward-positivities than low discounters (Cherniawsky & Holroyd, 2012). These results highlight the role of the reward-positivity in exploring the relationship between the DARPP-32 expression, impulsivity, temporal discounting, and addiction (i.e. vulnerability 9).

*Vulnerability 10 (changes in learning rates).* This vulnerability depends on specific learning rate. For example, nicotine enhances the presence of already available phasic dopaminergic signals in vitro (Rice & Cragg, 2004). Following the hypothesized role of phasic RPE signals in learning, this would predict that nicotine would enhance small learning signals, further increasing the likelihood of making cue-related associations. As noted by Redish and colleagues (2008), if nicotine did generally enhance learning signals, this would make smokers particularly susceptible to cue-driven associations (Chiamulera 2005). In fact, the previously mentioned smoking study found partial evidence for this idea (Wood, Baker, and Holroyd, 2012). In particular, following overnight abstinence from

smoking, feedback indicating potential opportunities to puff on a cigarette elicited a relatively large reward-positivity in heavy smokers, but a smaller reward-positivity to monetary rewards, indicating that the system is particularly sensitive to drug-related rewards relative to non-drug-related rewards.

The next question would be whether or not this heightened reward-positivity can predict learning rate. I propose this can be simply investigated using the reward-positivity and the reinforcement learning theory of the ACC as a conceptual framework. For instance, in a previous study, I used a pseudo-reinforcement learning task where a predictive cue (i.e. reward, no-reward, neutral) was presented before the corresponding feedback stimulus. Participants were informed that if a 'reward' predictive cue appeared, it would indicate that they would receive a reward at the end of the trial; a 'no-reward' predictive cue appeared would indicate no reward at the end of the trial; and a 'neutral' predictive cue was uninformative and did not predict the outcome at the end of the trial. The results showed that a reward-positivity was elicited to the cues predicting their outcome, and not to the presentation of the feedback itself. Further, when a neutral predictive cue was presented (containing no predictive information), the reward-positivity was only elicited at the presentation of the feedback cue. Using this paradigm, one could include a predictive cue indicating that they would receive a drug related reward (e.g. puff of a cigarette), and compare the reward-positivity across the predictive cues and feedback cues. If nicotine does have an effect on learning rate, then a straight forward prediction would be that the predictive cue indicating a drug reward should show a larger reward-positivity at the feedback cue early in learning, and at the predictive cue later in learning, relative to the reward cue and feedback. In theory, this drug related reward-positivity

should show evidence of an earlier propagation from the feedback to the predictive cue. In sum, the reward-positivity and the virtual TF-maze paradigm are amenable to the study of vulnerability 10.

## Future Directions

*Treatment.* In sum, this thesis revealed important individual differences associated with the neural and cognitive mechanisms underlying substance dependence. Yet, a link between this study and prevention or therapy is not immediately obvious. Given that addicts bring with them different life histories, personalities, genetic vulnerabilities and drug preferences, a "one-treatment-fits-all" approach to addiction would seem naive. Unfortunately, the current therapeutic paradigm more or less follows this one-model approach. Ultimately, I envision that treatment programs could be tailored to meet the needs of individual users. For example, Redish and colleagues (2008) proposed that each vulnerability outlined in their unified model drives the decision making process towards the addictive choice and provides a potential access-point for the addiction to relapse, but each vulnerability is a different failure point of the decision making process and leads to error through a different mechanism. Thus, each vulnerability is likely to require a different treatment regimen (Redish et al. 2008). But first, there needs to be a tool in which a particular vulnerability can be identified, and used to access the impact of a particular treatment regimen to determine whether or not the therapy is effective. Importantly, this tool needs to identify the state of the neural process underlying the vulnerability, whether this neural process changes over the course of treatment, and whether it can predict treatment success or relapse vulnerability.

An ultimate goal of this study was to potentially create such a tool. I believe that by assaying the integrity of the dopamine system and its neural targets involved in cognitive control and decision using a combination of electrophysiological (reward-positivity), behavioral (PST), and genetic assays (DRD2, DRD4, COMT, PPP1R1B) together with surveys of substance use and personality risk factors, one can use these measures as a tool for investigation . For example, in Experiment 2, I was able to utilize the model to identify different populations of substance dependent users. Cluster analysis indicated two groups of substance dependent individuals, the first of which accounted for 43% of the substance dependent sample, characterized by reduced reward-positivity amplitudes and high depression-proneness scores, and the second of which accounted for 54% of the substance dependent sample, characterized by high novelty seeking scores and relatively normal reward-positivity amplitudes. Interestingly, the cluster analysis converges on several vulnerabilities related to decision making as specified within a unified theoretical framework for addiction (Redish et al., 2008). For example, the severely reduced reward-positivity can be understood in terms of an altered allostatic set point due to overvaluation of drug-related rewards in the planning and habit system (vulnerabilities 2, 4, 7 ), whereas depression-proneness can be understood by an inability to switch responses in the face of failures and losses (vulnerability 6).

More so, these findings illustrate how future interventions might be individually tailored for specific genetic, cognitive and personality profiles. For instance, depression-prone individuals with a reduced reward-positivity and enhanced D4 expression might be treated with cognitive behavioral therapy and pharmaceuticals (e.g. D4 antagonists), whereas a cocaine addict with a reduced reward-positivity who carries the Met/Met allele

might be given a different regime, behavioural theory and a COMT agonist. Further, novelty seekers carrying the A1+ allele and exhibiting a normal reward-positivity might be assigned to behavioral therapy alone. By identifying how brain and personality link genes to addiction, novel treatments for substance dependence may finally be on the horizon.

*Sex and Gender analysis.* The purpose of statistically controlling for biological sex throughout this thesis was not intended to ignore the fact that sex differences were irrelevant, but rather by the need to understand better how important individual variables underlying substance abuse conspire to make that person addicted in the first place. On the contrary, I agree with the idea that sex and gender play important roles in vulnerability to substance dependence and should be investigated in the future. In particular, I believe that the theoretical and empirical framework of this thesis will give me such an opportunity.

For instance, concerning the susceptibility to addiction, an important underlying biochemical difference between sex-and gender is strongly associated with the interaction between hormone modulation and the dopaminergic reward system (Anker & Carroll, 2011). For example, animal studies have demonstrated that the gonadal steroid hormones estrogen and progesterone modulate DA activity and thereby induce variation in behavioral and neurochemical responses to psychomotor stimulant drugs, such as cocaine (Carroll & Anker, 2010). Interestingly, a recent human study has shown that in females, the response of the dopaminergic reward system to reward depends on the phase of the menstrual cycle (Dreher et al., 2007). In particular, when women anticipate uncertain rewards, they activate the brain regions involved in processing emotions, particularly the amygdala and the orbitofrontal cortex, to a greater extent during the follicular phase (4 to 8 days after the start of the period) than during the luteal phase (6 to 10 after the hormone

surge). Furthermore, when men anticipate rewards, they mainly activate a different region involved in motivation for obtaining rewards (the ventral striatum). This study suggests that the increase in activity of certain regions of the female brain during the follicular phase would modulate behavior linked to obtaining rewards, such as approach behavior during reward anticipation and hedonistic behavior when the reward is received. These effects of gonadal hormones on the DA-related reward system are postulated to have important implications for gender differences in susceptibility to addiction. Drawing on this evidence and on recent biologically inspired models of addiction, I propose to use the reward-positivity and PST in combination with hormone assays to investigate how males and females differ in response to rewards and decision making in the tasks proposed, and whether such differences depend on the female menstrual cycle. In so doing, I hope to identify sex-based factors underlying the susceptibility to addiction that will be amenable to novel therapies for drug addiction.

*The salient network and addiction.* Understanding important individual differences observed in the development and maintenance of addiction, including hedonic allostasis, incentive salience, and motivation, remains largely unexplored (Koob, 2010). For instance, whereas human functional neuroimaging studies point to particular brain structures related to sensing, predicting, and valuing rewards,  complex reward representations (i.e. effort, saliency, motivation, and risk) are not supported by any one of these areas in isolation, but are crucially dependent on their functional connectivity and interactions. For example, a recent hypothesis suggests that the ability to encode whether or not an action is worth taking in view of the expected goal and the effort of performing the action depends on a "salience network"(Ullsperger, Harsay, Wessel, & Ridderinkhof, 2010), encompassing the

Anterior Insula Cortex (AIC), important for integrating personally and motivationally important ‘‘salient’’ information in the broad spectrum of nociceptive, emotional and social, cognitive, homeostatic and sympathetic efferent and interoceptive autonomic domains with cognitive processes (Ullsperger et al., 2010); and the ACC, implicated in allocating cognitive and physical resources, or “effort” during cognitive tasks (Walton et al., 2002; Walton et al., 2003; Walton, Croxson, Rushworth, & Bannerman, 2005). Although this network appears to be involved in salient–effort calculations, the exact causal interactions between the AIC and ACC in the service of decision making and the development and maintenance of addiction remains to be explored. To address this issue, I propose to develop novel multi-modal neuroimaging approaches in order to accelerate the momentum towards a fuller understanding of complex cognitive function and dysfunction.

*Psychometric properties of the PST.* As discussed in Experiment 3, the test-retest analysis revealed that the PST performance measures were unreliable in the undergraduate sample. This negative finding could have obtained because most undergraduate students are not in fact biased toward either positive or negative learning, but it may also be because the task sensitivity to such differences could be further optimized. Thus, before using this task in future studies, it psychometric properties need to be identified, and improved upon. In Experiment 3, I provide some examples of how the stability of this task may be improved. For example, if subjects were given the opportunity to engage in a Practice Phase that included both a block of the Learning Phase followed by a block of the Test-Phase, this could enable subjects to better understand the purpose of the task, thereby increasing the stability of Test Phase performance across sessions. Providing a monetary incentive during learning might also increase participant engagement and performance

stability (Hakyemez et al., 2008; Savine & Braver, 2010; Chiew & Braver, 2011; Savine et al., 2010). Additionally, because the Test Phase typically utilizes only a few testing pairs (each pair being tested 6 times), future studies could identify an optimal number of Test Phase trials that would decrease individual variability and avoid ceiling effects. And finally, it is recommended that future PST studies sample behavior at two separate times in order to verify the test–retest reliability of the data at hand. I believe once these issues are addressed, research programs using this task can continue.

## The Dynamic Equilibrium Model of Addiction

> "Any intelligent fool can make things bigger, more complex, and more violent. It takes a touch of genius — and a lot of courage to move in the opposite direction." E.F. Schumacher.

One of the goals of my thesis was to develop a unified theoretical model of addiction that spans multiple levels of analysis, including its biological, behavioral and cognitive manifestations. The model to be proposed is biologically plausible, can account for the state of the cognitive control system (ACC) and decision making system (basal ganglia), and includes a process for the internal regulation of their functioning via feedback (midbrain DA system). Furthermore, the model can account for the electrophysiological (e.g. reward-positivity, theta), behavioural (e.g., approach and avoidance learning in the PST), and genetic (e.g., DRD4-521) findings observed in the experiments which comprise the present research. The structure of this model is based on a simple model called "Daisy World" or non-linear dynamic model, that was developed in the 1980s to model states of dynamic equilibrium−the states of natural system that oscillate around a mean condition−of Earth systems (e.g., how the rise and fall of Earth's

temperature impacts glacial periods, ocean currents, and vegetation growth (Watson & Lovelock, 1983).

According to the framework of Daisy World, a **natural system** is an organized group of related objects or components that work independently and interact to create a whole. A system consists of three basic elements: (1) a functioning set of components, (2) a flow of energy which powers them, and (3) a process for the internal regulation of their functioning called feedback. In particular, outputs generated by the functioning of a system's components either encourages change in the system **(positive feedback)** or discourages change and acts to regulate the system to keep it in a state of equilibrium **(negative feedback)**. Thus, the state of the system is a result of feedback mechanisms between system components. Further, all systems have **leverage points**, points of vulnerability where imposed stress yields maximum change. A **trigger** (fire, species invasion) can also set off an environmental change, and once a change is initiated, the system responds by adjusting exchanges of energy and mass. If the stress is released, a period of recovery to its previous state occurs. Should the system be stressed beyond its threshold, it will seek a new state of equilibrium.

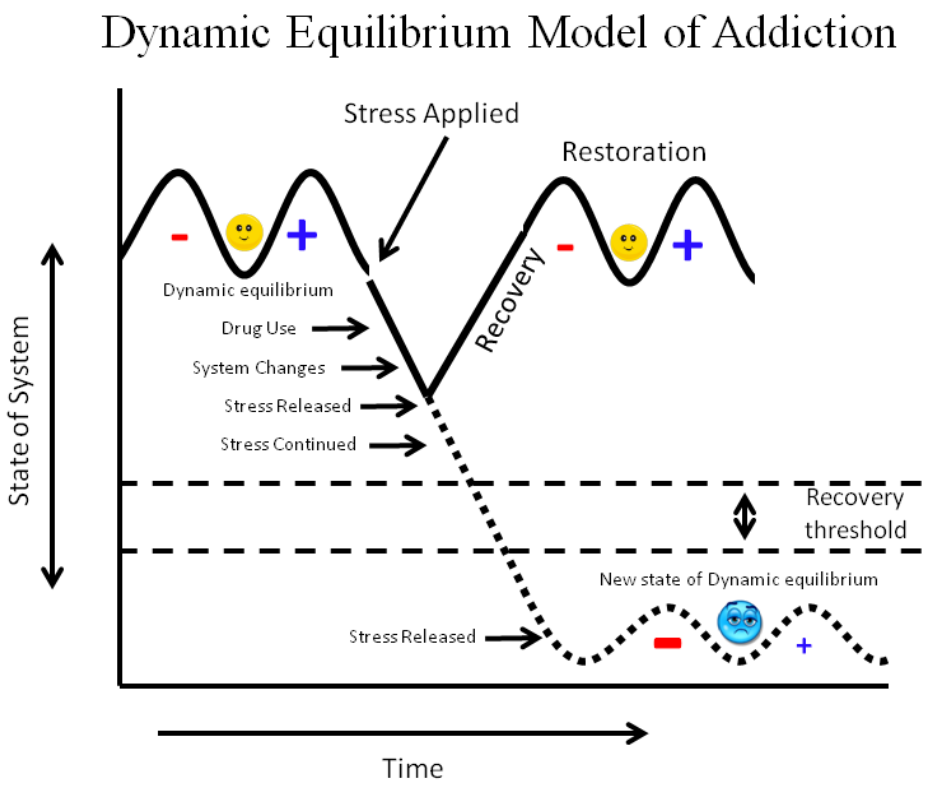


**Figure 20. An abstract representation of the Dynamic Equilibrium Model of Addiction based on Daisy World**

Utilizing the simple structure of the Daisy World model, I propose a model to account for the cognitive and behavioral impairments associated with substance dependence observed in the present research. The proposed model, termed the "Dynamic Equilibrium Model of Addiction" (Figure 20), builds of the theoretical foundation of the reinforcement learning model of the ACC (Holroyd and Coles, 2002), the Basal Ganglia Go/NoGo model (Frank et al. 2004), and the unified model of addiction (Redish et al. 2007), and the empirical work described in this thesis. The system in which this model describes is the **cognitive control system,** which is comprised of the ACC, dorsal lateral prefrontal cortex, orbital frontal cortex, and basal ganglia. Each of these components work independently and interact to create a whole. In particular, the components of this system

are organized hierarchically, which builds on the principles of the hierarchical reinforcement learning theory of the ACC (Holroyd & Yeung, 2012). Specifically, the ACC selects and maintains options, that dorsolateral prefrontal cortex and motor structures in the dorsal striatum execute those options, and that orbitofrontal cortex and the ventral striatum evaluate progress toward the options' goal-states. Further, ACC learns to associate values with different options and chooses the appropriate option for the current environmental state according to standard reinforcement learning principles (Holroyd and Yeung, 2012; Holroyd and Coles, 2002). In this way, ACC decides what task to perform and then directs dorsal lateral prefrontal cortex to implement that task, which in turn provides top-down biasing signals to the basal ganglia to facilitate execution of the chosen policy (Holroyd and Yeung, 2012).

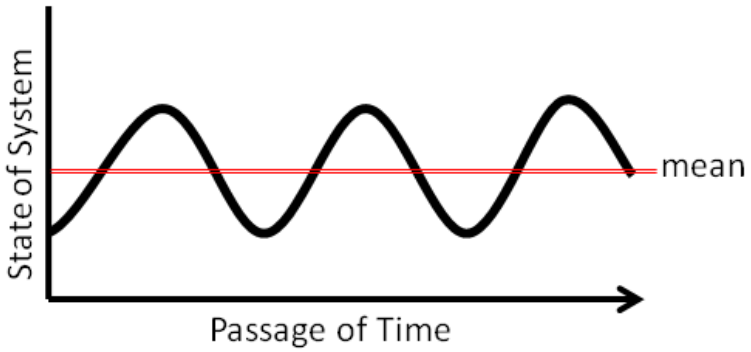


**Figure 21. System equilibrium over time**

Importantly, in order to function optimally, the cognitive control system tends towards a state of dynamic equilibrium where the system inputs are balanced by system outputs. In particular, the state of the natural system oscillates around a mean condition, a state known as **dynamic equilibrium** (Figure 21), and it's this mean condition that determines the functioning of the system. This idea follows the same relationship between cognitive performance and DA levels, where both too little and too much DA impairs

cognitive performance (Cools & D'Esposito, 2011). In particular, the relationship between cognitive control functioning (e.g., motivated behavior, working memory, and reward-related learning) and DA levels (e.g., DA concentration, DA receptor availability) follow an U-shaped function whereby the optimum level of behavior exists at a certain level of dopaminergic stimulation (trough), and moving out of the trough towards either peak by excessive or low levels of dopamine can lead to worsened cognitive performance. Thus, in order to function optimally, the cognitive control system would need to maintain a steady-state equilibrium at the optimal condition and remain constant over time. For instance, the level of DA availability (tonic and phasic activity) and density of DA type receptors in the ACC may fluctuate over a time period, but the overall range must remain constant in order for all components of the system to adapt and function optimally. In other words, the equilibrium state of the cognitive control system can be represented as peaks (unstable) and valleys (stable) and the goal of the cognitive control system would be to maintain optimal performance by keeping a stable equilibrium state.

Further, because cognitive control is a multifactorial phenomenon, requiring a dynamic balance between cognitive stability and flexibility, the existence of an optimum DA level for cognitive function implicates the need to take into account baseline levels of DA when isolating the effects of DA on the equilibrium state of the system. In particular, DA levels regulate the balance of D1 and D2/D4 receptor-dependent synaptic activity in frontal cortex: D1 receptor activation, promoted by high levels of DA, favors stable working memory representations (Wall et al., 2011); in contrast, D2/D4 receptor activation, promoted by lower levels of DA, favors response flexibility and task switching (Floresco & Magyar, 2006; Floresco et al., 2006). These network dynamics may constitute

a mechanism for maintaining the state of dynamic equilibrium. By extension, variability in gene expression may determine the DA baseline and thereby contribute to the stability and flexibility of the system. For example, several studies have noted the effect of COMT activity (variations in DA catabolism) on the U-shaped relation between DA and prefrontal cortex function (Cools & D'Esposito, 2011). In particular, at a normative baseline, COMT activity in Val homozygotes (decreased DA levels) is associated with suboptimal prefrontal DA, Met homozygotes (enhanced DA levels) have superoptimal prefrontal DA levels, and heterozygotes have near optimal prefrontal DA levels. Thus, Val or Met homozygotes can be pushed nearer to the peak (unstable state) as a result of increased or decreased frontal DA transmission (e.g., drug of abuse, withdrawal), further impairing the stability and/or flexibility of the system.

Likewise, variation in D4 expression, which normally acts as a neural inhibitor in frontal cortex and are highly sensitive to tonic signaling, can also effect the U-shaped function, or state of dynamic equilibrium. For example, too much D4 expression can lead to superoptimal levels of inhibition of neuronal activity in frontal cortex, impairing cognitive flexibility, whereas too little can lead to suboptimal levels of inhibition of neuronal activity in frontal cortex, impairing cognitive stability. Thus, too little or too much inhibition via D4 expression can push an individual nearer to the peak (unstable state). In sum, too achieve an optimal level of cognitive flexibility and stability, optimal levels of neural inhibition of frontal cortex need to be maintained and regulated.

In addition, outputs generated by the functioning of the cognitive control system either encourages change in the system by positive feedback (positive RPE signals carried by the midbrain DA system), which can facilitate long-term potentiation, or discourage

change by negative feedback (negative RPE signals), which can facilitate long-term depression. Negative feedback acts to regulate the system to keep it in a state of equilibrium. Thus, a balance of positive and negative feedback, and optimal levels of phasic and tonic DA activity will allow the system to maintain balance and regulate optimal cognitive control functioning. The dynamics between positive and negative feedback are similar to the processes described in vulnerability 1 and 2 in the unified model of addiction (Redish et al. 2008). Taken together, the expression of the DA system can have either beneficial or detrimental effects on the equilibrium states of the cognitive control system. Critically, upon disturbance (e.g., increased DA transmission by drug use), genetic factors can determine the ability of the system to move towards an unstable equilibrium state, and following the disturbance, return back to its natural stable equilibrium state. Thus manipulating DA will have paradoxical consequences for distinct cognitive control processes, depending on the optimal levels of DA in different components of the cognitive control system.

As described by the Daisy Model, all systems have **leverage points,** points of vulnerability where an imposed stress yields maximum change. In regards to the cognitive control system, these leverage points can be considered vulnerabilities 1-10. For instance, repeated exposure to potentially addictive drugs (enhanced positive feedback: vulnerability 7) can persistently disrupt the component of cognitive control system that normally regulates the state of equilibrium (vulnerability 1 and 2), thereby gradually pushing the system away from a stable state (trough) to an unstable state (peak). Further, a **trigger** (incentive salient cues: vulnerability 3,4,5) can also set off a system change (i.e. increasing the frequency and intensity of behaviour that leads to the acquisition of drugs). Once the

change is initiated, the system responds by adjusting the DA exchanges (up or down regulating DA receptor expression or DA tonic levels). If the stress is released (abstinence), a period of recovery to its previous state occurs. This could take anywhere from one day to several weeks. However, if drug use continues or commences shortly afterwards, and should the cognitive control system be stressed beyond its threshold, it will seek a new state of equilibrium (vulnerability 7). Within this framework, drugs can change the needs of a cognitive control systems either by moving the system away from the initial equilibrium state itself (a withdrawal state after drug use), requiring drugs to return the system to a stable equilibrium state (vulnerability 1), or by changing the system's desired set-point itself, thus requiring drugs to achieve the new inappropriate equilibrium state (vulnerability 2).

Once the cognitive control system is set in this new equilibrium state, the system will now have to maintain optimal cognitive control functioning, and stability of the new dynamic equilibrium state by inclusion of drug use. Without drug use, the system will be driven into an unstable state (peak), possibly inducing negative feedback or triggers (i.e. craving, withdraw state, anxiety, depression), and driving the cognitive control system to respond to this change by seeking out drugs. In other words, this is the new equilibrium state of addiction.

By extension, I believe the reward-positivity and PST will be useful in testing the Dynamic Equilibrium Model of Addiction. For instance, an important feature of this model is determining the cognitive control system state of dynamic equilibrium over time. In particular, the existence of an optimum DA level for cognitive function implicates the need to take into account baseline levels of DA when isolating the effects of DA on the

equilibrium state of the system. To test this idea, I believe the PST would be an appropriate method to identify the balance between positive and negative feedback, (i.e. optimal levels of positive and negative RPE signaling in the striatum). Ideally, one would expect if the DA baseline is at an optimal level, then an individual should not display a significant bias in learning from either positive and negative feedback. Alternatively, a bias in reinforcement learning could be an indication of abnormalities in an individual's baseline. This could indicate where an imposed stress (e.g., drug use) may yield maximal change. For example, a positive bias driven by a genetic determinant (DRD2 $SNP_2$) may represent a vulnerability to the potentiating effect of DA and thus a higher risk of the system to move towards an unstable state, and harder for the system to return to a stable state.

Further, to function optimally, the cognitive control system requires a dynamic balance between cognitive stability and flexibility. In this regard, the reward-positivity and oscillatory dynamics of theta activity may provide an indication of the state the cognitive control system is in, particularly the ACC component of the system. For example, an individual expressing enhanced D4 expression may display superoptimal levels of inhibition leading to impairments in cognitive flexibility. Initial drug use may release inhibition temporarily, allowing an individual to switch states (e.g., negative to positive state), but may be particularly slow to return to their initial stable state following drug use. This may result in prolonged periods of drug use behaviours. Thus, repeated drug use can easily push the system beyond threshold within a shorter period of time, and rapidly transverse to a new equilibrium state.

Further, by indexing how the system responds to natural vs. drug- related rewards, the reward-positivity could provide an indication of the type of equilibrium state the cognitive control system is presently in (addictive or non-addictive). This would be very beneficial in treatment management. For example, if the goal of the treatment is to return an individual to their previous equilibrium state before drug use and improve cognitive function, then using the reward-positivity to monitor their transition from one state to the other may be beneficial. Further, if an individual cannot be removed from this addictive state, a harm reduction type therapy can potentially use the reward-positivity to determine an optimal balance between the system's response to normal vs. drug rewards. Finally, the Dynamic Equilibrium Model of Addiction can also account for personality risk factors. For example, some personality traits may show differences in the slope between a stable and unstable state or the level of recovery threshold, and possibly predict how fast or slow an individual can seek a new state of equilibrium or recover to an initial state.

In sum, I believe this is a good starting point to simplify and unify the risk factors associated with substance dependence that can ultimately benefit an individual suffering from an addiction. Nevertheless, this model in still in its infancy, and I acknowledge that it is not perfect and more work needs to be done in the future in regards to its conceptual framework, making specific predictions using the reward-positivity and PST, and how this model can be implemented into treatment.

## Concluding Remarks

By highlighting several dopamine-related neural pathways underlying individual differences in substance dependence, this thesis presents a theoretical framework for

bridging the gap between genes, cognition, personality, and behavior in substance dependence. Importantly, these findings illustrate how future interventions might be individually tailored for specific genetic, cognitive and personality profiles. For instance, utilizing the reward-positivity and the reinforcement learning theory of the ACC as conceptual framework, as well as the PST and the Basal Ganglia Go/NoGo model, to investigate the vulnerabilities outlined in the unified theory of addiction proposed by Redish and colleagues (2008) seems like an obvious next stage of addiction research, and holds promise for integrating experimental, computational, and theoretical analyses of cognitive control and decision making impairments in substance dependence within the field of cognitive neuroscience research. In particular, this approach may provide a better understanding how cognitive control and reward- related processing can be broken down into distinct computational functions of brain structures, and thus provide an anatomical/functional framework within which to understand and make specific predictions regarding the dysfunctions underlying complex behaviors observed in substance dependence. Such an approach would appear to be critical for furthering the development of new therapeutic treatments and clinical management for addiction.

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# Appendix A

## Supplementary Material

### Experiment 1

### Material and Methods

#### ERP Task – Virtual T-Maze.

Participants were seated comfortably in an electromagnetically shielded room under dim lighting and were asked to position their hand and forearm so that both fingertips of the index fingers would rest on a standard E-prime SRX Button Box placed in front of them. They were provided with written and verbal instructions that explained the procedure and stressed that they should maintain correct posture and minimize head movement and eye blinks. The Virtual T-Maze is a guessing/reinforcement learning task that has been shown to elicit robust fERNs (Baker and Holroyd 2009). In brief, at the start of each block of trials participants were shown 3 different aerial views of the maze, each for 3 seconds, to familiarize themselves with its virtual dimensions (see Baker and Holroyd, 2009). On each trial participants were presented with an image of the base arm of a T-Maze showing the length of the arm and two alleys projecting to the left and to the right from its far end (1000 msec). Next, a green double arrow appeared at the intersection of the base arm and participants were instructed to choose one of the two arms by pressing either a left or a right button. Following their button press, the green double disappeared and the image of the base arm was again displayed (500 msec) before they were shown a view of the alley that they selected (1000 msec). The image of the alley was followed by an image of either an apple or an orange appearing against the far wall of that alley (1000 msec), followed by a blank screen (500 msec) and then the next trial began. Participants

were told that presentation of one type of fruit indicated that the alley they selected contained 5 cents (Reward feedback), and that the presentation of the other fruit indicated that the alley they selected was empty (No-reward feedback); the mappings between feedback stimuli and reward types were counterbalanced across participants. Participants were also informed that at the end of the experiment they would be rewarded all the money they found, and that they were to respond in a way that maximized the total amount of money earned. Unbeknownst to the participants, on each trial the type of feedback stimulus was selected at random (50% probability for each feedback type, which is a standard probability used to elicit a robust fERN). The experiment consisted of 4 blocks of 50 trials each separated by rest periods. At the end of the experiment, participants were informed about the probabilities and were given a $10 performance bonus.

*Data Acquisition.* The electroencephalogram (EEG) was recorded using a montage of 36 electrodes placed according to the extended international 10-20 system (Jasper 1958). Signals were acquired using Ag/AgCl ring electrodes mounted in a nylon electrode cap with a conductive gel (Falk Minow Services, Herrsching). Signals were amplified by low-noise electrode differential amplifiers with a frequency response of DC 0.017 – 67.5 Hz (90dB octave roll off) and digitized at a rate of 250 samples per second. Digitized signals were recorded to disk using Brain Vision Recorder software (Brain Products GmbH, Munich). Inter-electrode impedances were maintained below 10 KΩ. Two electrodes were also placed on the left and right mastoids. The EEG was recorded using the average reference. For the purpose of artifact correction the horizontal electroocculogram (EOG) was recorded from the external canthi of both eyes, and vertical EOG was recorded from the sub-orbit of the right eye and electrode channel Fp2.

*Data Analysis.* Post-processing and data visualization were performed using Brain Vision Analyzer software (Brain Products GmbH, Munich). The digitized signals were filtered using a 4-th order digital Butterworth filter with a passband of .10 – 20 Hz. An 800 ms epoch of data extending from 200 ms prior to 600 ms following the onset of each feedback stimulus was extracted from the continuous data file for analysis. Ocular artifacts were corrected using the eye movement correction algorithm described by Gratton et al. (1983). The EEG data were re-referenced to linked mastoids electrodes. The data were baseline corrected by subtracting from each sample the mean voltage associated with that electrode during the 200 ms interval preceding stimulus onset. Muscular and other artifacts were removed using a ±150 μV level threshold and a ±35 μV step threshold as rejection criteria. ERPs were then created for each electrode and participant by averaging the single-trial EEG according to feedback type (Reward, No-reward).

**ERP analysis**

*fERN.* The fERN was measured at channel FCz, where it reaches maximum amplitude (Holroyd, Larsen, & Cohen, 2004). To isolate the fERN from other overlapping ERP components, the fERN was evaluated for each participant as a difference wave by subtracting the Reward feedback ERPs from the corresponding No-reward feedback ERPs (Holroyd & Coles, 2002). The mean amplitude of this difference wave was obtained by averaging the difference wave within a 200–320 ms window following feedback onset.

*P2.* The P2 was measured base-to-peak at a frontal-central channel (FCz) by first identifying the most negative value of the ERP within a 50-150 ms window following the presentation of the feedback, the latency of which was taken as the time of onset of the P2. Next, the maximum positive value of the ERP within a window extending from P2 onset

to 250 ms following the presentation of the feedback was identified, the time of which was taken as the peak latency of the P2. The difference in voltage between peak onset and peak maximum was defined as P2 amplitude. This algorithm was applied to the Reward and No-reward ERPs associated with electrode site FCz.

*P3.* P3 amplitude was measured by identifying the maximum positive-going value of the Reward and No-reward ERPs recorded at electrode site Pz, within a window extending from 300 to 600 ms following the presentation of the feedback stimulus. The time of peak amplitude was defined as P3 latency.

**Behavioral Task - The Probabilistic Selection Task.**

Following the ERP task, participants remained seated in the electromagnetically shielded room and were asked to engage in the Probabilistic Selection Task (PLT) (Frank et al., 2004). Participants were asked to position their hand and forearms so that both fingertips of the index fingers rested on buttons 1 and 0 of a standard computer keyboard placed in front of them, and were provided with written and verbal instructions explaining the procedure. On each trial of the task they viewed a fixation cross (green circle, 1 s) followed by a pair of visual stimuli that are not easily verbalized by most English speakers (i.e., Japanese Hiragana characters) presented in black on a white background in 72 pt font (Figure 22). They then pressed the key corresponding to the stimulus that they believed to be correct. Visual feedback was provided following each choice (the word "Correct!" printed in blue or "Incorrect" printed in red, 1 s). If no response was made within 6 s then the words "no response detected" were displayed in red (1 s). During an initial Learning Phase participants were exposed to three pairs of stimuli presented in random order (AB, CD, EF; see Figure 22 [top]). The response mappings were probabilistic such that one

stimulus in each of the three pairs was rewarded on 80%, 70%, and 60% of the trials, respectively, with the remaining stimulus in each pair rewarded on the complementary percentage of trials (Figure 22, [top]). Stimulus-probability assignments were counterbalanced across subjects.

Participants learned by trial-and-error to choose the more frequently rewarded stimulus over the alternative in each pair, namely, by selecting stimuli A, C and E more often than B, D, and F. Critically, they could do so either by learning

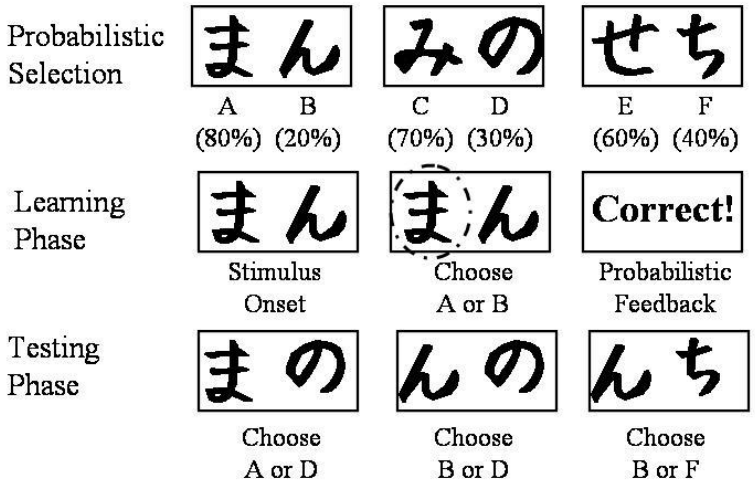


**Figure 22. Probabilistic Learning Task. Top row: Stimuli and reward probabilities (percent positive feedback). Middle row: Schematic of an example trial during the learning phase. Bottom row: Schematic of an example trial during the test phase.**

that stimuli A, C and E were associated with relatively more Reward, by learning that stimuli B, D and F were associated with relatively more punishment, or both. Participants advanced to the Test Phase of the task if after any block of 60 trials they satisfied performance criteria for the three stimulus pairs (65% A in AB, 60% C in CD, 50% E in EF), or after six blocks (360 trials) of training if these criteria were not met.

During the Test Phase participants were exposed to all possible combinations of these stimuli (i.e., AB, AC, AD, AE, AF, BC, BD, BE, BF, CE, DF, CD, EF) in a random order. As before, subjects were required to select the symbol in each pair that they believed to be correct, but without receiving any feedback about their choices. They were told to use "gut instinct" whenever they did not know how to respond. Each test pair was presented 6 times, for a total of 60 trials. Participants were later classified as either "Positive Learners" (learning from reinforcement) or "Negative Learners" (learning from errors) according to their relative performance on trials involving either A (the "Good Stimulus", i.e., AC, AD, AE, AF) or B (the "Bad Stimulus", i.e., BC, BD, BE, BF) stimuli (Figure 22, bottom) (Frank et al., 2007). The data of participants who did not perform better than chance on AB trials (consisting of the easiest stimulus pair) during the test phase were eliminated from further analysis. In total, the data of six participants were discarded, two of whom were from the Non-dependent Group and the remainder of whom were unclassified participants with intermediate ASSIST scores. In addition, four subjects displayed equally good performance in choosing the good stimulus and avoiding the bad stimulus and were not included in either group (but are included in the continuous measure of relative learning biases).

**Additional Analysis**

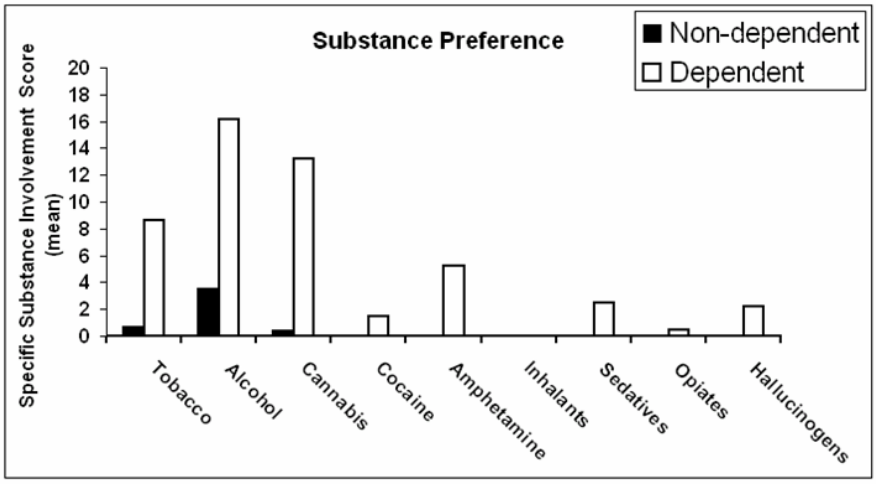


**Figure 23. Substance Preference. Substance preferences for Non-dependent (white bars) and Dependent (black bars) groups as measured by the Specific Substance Involvement Score of the ASSIST v3. Please note that the Dependent group tended to abuse alcohol, cannabis and tobacco, but some individuals also reported taking amphetamines, cocaine, sedatives and/or hallucinogens.**

*Performance during the Learning Phase*

In the Learning Phase of the task, no main effects of group (Dependent vs. Non-dependent) were found for several measures of performance ($p>.05$). Specifically, there was no difference in accuracy during the Learning Phase between the Dependent (67% +/- 2% correct) vs. Non-dependent (71% +/- 2% correct) groups ($p > 0.5$). Further, there was no difference in reaction time during the Learning Phase between the Dependent (1197 ms +/- 101 ms) vs. Non-dependent (1232 ms +/- 77 ms) groups ($p > 0.5$). No differences in the number of training trials to reach criterion before advancing to the Test Phase were also found between the Dependent (167 trials +/- 26 trials) vs. Non-dependent (141 trials +/- 30 trials) groups ($p > 0.5$).

## Experiment 2

### Introduction

Intermediate Phenotype: It has been suggested that IP candidates should be based on (i) functional polymorphisms known to affect the coding of the protein of interest (here, proteins underlying the expression of the dopamine system); (ii) theoretical or conceptual models for how that protein in the brain region(s) of interest plays a role in the associated IP (here, theories relating dopamine to reinforcement learning, cognitive control, and individual personality traits); and (iii) a suitable task (or inventory) that probes the specific computations of that IP (here, the reward-positivity, the Probabilistic Selection Task, and SURPS).

### Material and Methods

#### Participants

I collected questionnaire data from 812 undergraduate students recruited from the University of Victoria, each of whom received course credit in a psychology course for their participation. Of these, 196 participants returned to complete the behavioral and ERP experiment and received a monetary bonus as described below. One subject was excluded due to DNA sequencing error. All remaining participants had normal or corrected-to-normal vision and all participants gave informed consent. The study was approved by the local research ethics committee and was conducted in accordance with the ethical standards prescribed in the 1964 Declaration of Helsinki.

#### Group Screening and Assignment

All participants completed a computer-based questionnaire comprised of several separate inventories that assess problematic drug use, the degree of addiction vulnerability, and personality risk factors for substance abuse, namely, the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (Humeniuk & Ali, 2006), a validated screening test developed by the World Health Organization (WHO) for identifying the degree of problematic substance use (i.e. tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants, sedatives, hallucinogens, inhalants, opioids and "other drugs"), especially in individuals who use multiple substances; the Severity of Alcohol Dependence Questionnaire, which assesses the severity of alcohol abuse and dependence; the Addiction-Prone Personality (APP) Scale (Anderson et al., 1999), a 21-item self-report questionnaire that assesses the role of personality in the susceptibility to addiction; and the Substance Use Risk Profile Scale (SURPS) (Conrod & Woicik, 2002), a 23-item self report questionnaire that provides a measure on four dimensions of personality traits—depression-proneness, anxiety-sensitivity, impulsivity, and sensation seeking—that are risk factors for substance use (see Appendix B). All information obtained was kept strictly confidential and stored in a locked filing cabinet. Participants were allowed 60 minutes to complete the questionnaire in a computer lab at the University of Victoria. Up to 20 participants completed it at a time. Participants were provided with both written and verbal instructions that explained the procedure and stressed that they should answer each of the questions truthfully and to the best of their knowledge.

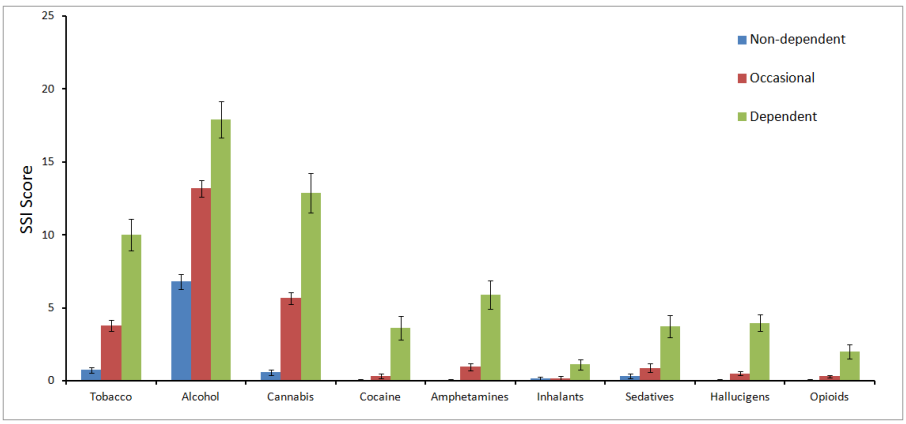


**Figure 24. Substance preferences for Non-dependent (blue bars), Occasional (red bars) and Dependent (green bars) groups as measured by the Specific Substance Involvement Score of the ASSIST v3. Bars indicate the standard error of the mean**

For the purpose of this study, participants were classified as either Dependent, Occasional users or Non-dependent substance users according to their scores on the Global Continuum of Substance Risk (GCR) scale of the ASSIST (Newcombe et al., 2005; Humeniuk et al., 2008; Humeniuk & Ali, 2006). Specifically, participants with GCR scores falling within the bottom (score < 16) and top (score > 41) quartiles of the sample were classified as Non-dependent and Dependent users, respectively. These scores are comparable to the cut-offs established in previous validation studies of the ASSIST v3 for non-dependence (score < 15) and dependence (score > 39.5) (Newcombe et al., 2005). The Dependent group tended to abuse alcohol, cannabis and tobacco, but some individuals also reported taking amphetamines, cocaine, sedatives and/or hallucinogens (Figure. 24).

**Genotyping**

I genotyped for 9 different polymorphisms that appear to influence dopaminergic expression and functioning (COMT Val156Met, rs4680; DRD4 C-521T, rs1800955; DRD4 VNTR, and DRD4 -127 Indel; DRD2 Taq$^{\alpha}$1, rs1800497; DRD2 C957T, rs6277;

DRD2 rs12364283; PPP1R1B rs879606; and PPP1R1B rs907094). Following the T-maze and PST, purified DNA was obtained from participants by collecting and processing saliva samples using Oragene OG-500 DNA Collection Kits (DNA Genotek, Ottawa, Canada), as per manufacturer's instructions. Each participant's sample was processed at the Center for Biomedical Research DNA Sequencing Facility, University of Victoria. Nine separate regions of genomic DNA, each containing a polymorphism of interest, were amplified by polymerase chain reaction (PCR), and purified. Genotyping of the DRD2 $Taq^{\alpha}1$, PPP1R1B rs879606, PPP1R1B rs907094, DRD4 C-521T, and DRD4 -127 Indel single nucleotide polymorphisms (SNPs) was accomplished by digestion with a restriction endonuclease appropriate to each polymorphism ($Taq^{\alpha}1$, AvaII, MseI, FspI, and BstEII, respectively), and subsequent separation by agarose gel electrophoresis. Genotyping of the COMT Val156Met, DRD2 C957T, and DRD2 rs12364283 polymorphisms was accomplished by tetra-primer amplification refractory mutation system-polymerase chain reaction (tetra-primer ARMS-PCR), and subsequent separation by agarose gel electrophoresis. Genotyping of the DRD4 VNTR polymorphism was accomplished by separation of the amplification fragment by agarose gel electrophoresis. Each genotyping method for each SNP target was verified by performing DNA sequence analysis (LI-COR 4200 Genetic Analyzer, Lincoln, NE) on a representative subset of samples.

*DRD2*. The *A1 allele of the TaqI (A1/A2) SNP (rs1800497),* (Thompson et al., 1997), the *C allele of the C957T (C/T) SNP (rs6277)* (Hirvonen et al., 2004; Hirvonen et al., 2009; but see Duan et al., 2003), and the *T allele of the promoter Zhang_SNP-2 (C/T) (rs12364283)* (Zhang et al., 2007) of the DRD2 gene, have been identified to cause a reduction in striatal D2 receptor expression and binding potential.

*DRD4*. The T allele of the promoter -521 (C/T) SNP (rs1800955) (Okuyama et al., 1999) of the DRD4 gene have been identified to cause a reduction in D4 expression. The 'long' allele (VNTR-L = 7 or more repeats, VNTR-S =6 or less repeats) of the variable number of tandem repeats (VNTR) polymorphism in exon III has been shown to cause a blunted intracellular response to dopamine, does not appear to bind dopamine antagonists and agonists with great affinity, and are associated with attenuated inhibition of intracellular signal transduction (Oak, Oldenhof, & Van Tol, 2000). The DRD4 (-1217G ins/del) polymorphism has been shown to modulate the conflict monitoring function of ACC (Fan, Fossella, Sommer, Wu, & Posner, 2003) but its effects on D4 expression is currently unknown.

*COMT*. A number of studies indicate the val158met polymorphism (rs4680) of the Catechol-O-methyltransferase (COMT) gene accounts for a four-fold variation in catecholamine (dopamine, norepinephrine, and epinephrine) catabolism −with the Met allele accounting for a four-fold decrease in catabolism leading to increased tonic activity and decreased phasic activity (Matsumoto et al., 2003; Chen et al., 2004; Meyer-Lindenberg et al., 2005; Grace, 1991; Bilder et al., 2004).

*DARPP-32 (PPP1R1B haplotype)*: DARPP-32 is a phosphoprotein that is stimulated by D1 receptor activation and that modulates dopamine-dependent synaptic plasticity (Svenningsson et al., 2002; Svenningsson et al., 2004; Svenningsson et al., 2005), and a 7-SNP haplotype of the PPP1R1B gene affects DARPP-32 expression levels (Meyer-Lindenberg et al., 2007).

**General Statistics**

Most calculations, including linear regression analyses, were made using the statistical analysis program SPSS (Version 18) (SPSS Corp, 2003). Between-group (ie, sex, ethnicity) differences in means are tested using Student's t-test; 95% confidence intervals (CIS) for the differences between groups are also provided. Deviation from the genotype counts predicted by Hardy–Weinberg (HW) equilibrium expectations was computed (Rodriguez, Gaunt, & Day, 2009). I performed three sets of analyses. For the first order of analysis, simple regression models were computed to determine any unique relationships between the variables of interest (i.e. genetic data, electrophysiological data, PST data, personality risk factors, and substance dependence measures). All tests of significance were two-tailed. Analysis of variance was also used to compare the variable scores by genotype, in order to demonstrate the existence of gene dose–response relationships.

Whenever a relationship was found between these variables, a second order of analysis investigated whether or not the relationship was mediated as prescribed by Baron and Kenny (1986). As noted in the main text, this approach has been used to demonstrate that the effects of a dopamine-related genetic polymorphism on substance abuse are mediated by the personality trait of novelty seeking (Ray et al., 2009; Laucht et al., 2007). In brief, a mediational hypothesis can be accepted if three conditions are satisfied: 1) the independent variable (e.g., genotype) is significantly related to the mediator (e.g., personality risk factors); 2) the independent variable is significantly related to the dependent variable (e.g., substance dependence); and 3) the mediator is significantly associated with the dependent variable when regressed on both the mediator and the independent variable, and the effect of the independent variable is reduced compared with

that in the second regression. Therefore, for each combination of independent variable, dependent variable, and potential mediator, I estimated three regression equations: 1) the mediator was regressed on the independent variable, 2) the dependent variable was regressed on the independent variable, and 3) the dependent variable was regressed on both the independent variable and the mediator. Mediational analyses were conducted using a structural equational modeling framework.

For the third level of analysis, I explored causal pathways that associated the genes and the selected intermediate phenotypes with substance dependence. To do so, a recursive path modeling strategy was conducted using a structural equational modeling framework. In particular, a unified structural equational model was calculated employing maximum likelihood estimation specifically examining the interrelationships among the aforementioned variables. The performance of the hypothesized model (see Figure. 10) was assessed with various fit criteria, including the chi-square test, comparative fit index (CFI) (Bentler, 1990), goodness-of-fit test (GFI) (Tabachnick & Fidell, 2007), and the root mean square error of approximation (RMSEA; (Browne & Cudeck, 1993). The CFI and the RMSEA are sensitive to model misspecification and are minimally affected by sample size (Hu & Bentler, 1995). The CFI ranges from 0 to 1, with 0.90 indicating acceptable fit (Bentler, 1990). The RMSEA fit values less than 0.05 indicating close fit and values less than 0.10 indicating reasonable fit (Steiger, 1990). The GFI explains what the proportion of the variance/covariance patterns in the sample variance is accounted for by the model matrix. GFI values should exceed .9 for a reasonable model, and .95 for an impressive model (Tabachnick & Fidell, 2007). All analysis procedures were conducted in AMOS Version 18 for SPSS program.

Finally, a k-means clustering analysis was used to generate intermediate phenotype profiles within the substance dependent sample. The number of clusters was determined by a hierarchical clustering method, as suggested by Milligan (Milligan, 1980), and then followed by a K-means cluster analysis to optimize the results. First, Ward's (Ward, 1963) hierarchical clustering procedure was employed, which uses the squared Euclidian distance to determine the similarity between subjects' profiles on the variables. The optimal number of clusters was determined empirically when there was a marked discontinuity in the fusion coefficient value associated with merger and reduction to a smaller number of clusters. Based on the hierarchical analysis results, a two cluster solution was chosen for the K-mean cluster analysis. Next, a K-means relocation cluster analysis was conducted to evaluate the stability of the clusters and to iteratively relocate subjects into the cluster with the closest centroid. The K-means clustering is terminated when each subject has been placed in the cluster containing the closest centroid. Discriminant analyses were then performed to confirm cluster separation. Multivariate analyses of variance were performed to determine the significance of the overall group differences.

**ERP Task – Virtual T-Maze.**

Participants were seated comfortably in an electromagnetically shielded room under dim lighting and were asked to position their hand and forearm so that both fingertips of the index fingers would rest on a standard E-prime SRX Button Box placed in front of them. They were provided with written and verbal instructions that explained the procedure and stressed that they should maintain correct posture and minimize head movement and eye blinks. The Virtual T-Maze is a guessing/reinforcement learning task

that has been shown to elicit a robust reward-positivity (Baker & Holroyd, 2009). In brief, at the start of each block of trials participants were shown 3 different aerial views of the maze, each for 3 seconds, to familiarize themselves with its virtual dimensions (Figure. 25, top row). On each trial participants were presented with an image of the base arm of a T-Maze showing the length of the arm and two alleys projecting to the left and to the right from its far end (Figure. 25, bottom). Participants were instructed to choose one of the two arms by pressing either a left or a right button. Then, they were shown a view of the alley that they selected, followed by an image of either an apple or an orange appearing against the far wall of that alley. Participants were told that presentation of one type of fruit indicated that the alley they selected contained 5 cents (Reward feedback), and that the presentation of the other fruit indicated that the alley they selected was empty (No-reward feedback); the mappings between feedback stimuli and reward types were counterbalanced across participants. Participants were also informed that at the end of the experiment they would be rewarded all the money they found, and that they were to respond in a way that maximized the total amount of money earned. Unbeknownst to the participants, on each trial the type of feedback stimulus was selected at random (50% probability for each feedback type, which is a standard probability used to elicit a robust Rew-P). The experiment consisted of 4 blocks of 100 trials each separated by rest periods. At the end of the experiment, participants were informed about the probabilities and were given a $10 performance bonus.

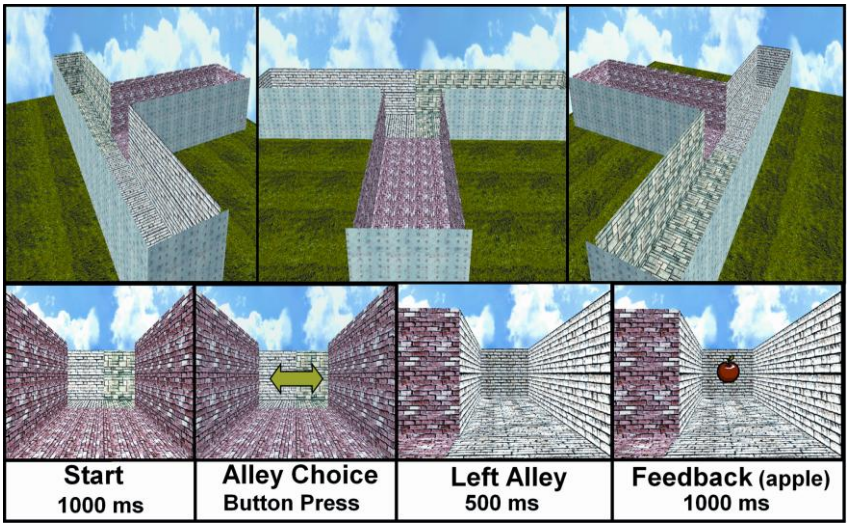


**Figure 25. The Virtual T-Maze task. Top: Three views of T-Maze from above. Bottom: Sequence of events comprising an example trial of the T-maze Task; stimulus durations are indicated at the bottom of each panel. The double arrow remained visible until the button press. Please note that the size of the arrow was magnified in this figure for the purpose of exposition.**

*Data Acquisition.* The electroencephalogram (EEG) was recorded using a montage of 36 electrodes placed according to the extended international 10-20 system (Jasper, 1958). Signals were acquired using Ag/AgCl ring electrodes mounted in a nylon electrode cap with a conductive gel (Falk Minow Services, Herrsching). Signals were amplified by low-noise electrode differential amplifiers with a frequency response of DC 0.017 – 67.5 Hz (90dB octave roll off) and digitized at a rate of 250 samples per second. Digitized signals were recorded to disk using Brain Vision Recorder software (Brain Products GmbH, Munich). Inter-electrode impedances were maintained below 10 KΩ. Two electrodes were also placed on the left and right mastoids. The EEG was recorded using the average reference. For the purpose of artifact correction the horizontal electroocculogram (EOG) was recorded from the external canthi of both eyes, and vertical EOG was recorded from the sub-orbit of the right eye and electrode channel Fp2.

*Data Analysis.* Post-processing and data visualization were performed using Brain Vision Analyzer software (Brain Products GmbH, Munich). The digitized signals were filtered using a 4-th order digital Butterworth filter with a passband of .10 – 20 Hz. An 800 ms epoch of data extending from 200 ms prior to 600 ms following the onset of each feedback stimulus was extracted from the continuous data file for analysis. Ocular artifacts were corrected using the eye movement correction algorithm described by (Gratton, Coles, & Donchin, 1983). The EEG data were re-referenced to linked mastoids electrodes. The data were baseline corrected by subtracting from each sample the mean voltage associated with that electrode during the 200 ms interval preceding stimulus onset. Muscular and other artifacts were removed using a ±150 μV level threshold and a ±35 μV step threshold as rejection criteria. ERPs were then created for each electrode and participant by averaging the single-trial EEG according to feedback type (Reward, No-reward).

*Reward-positivity.* The reward-positivity was measured at channel FCz, where it reaches maximum amplitude (Holroyd et al., 2004). To isolate the reward-positivity from other overlapping ERP components, the reward-positivity was evaluated for each participant as a difference wave by subtracting the Reward feedback ERPs from the corresponding No-reward feedback ERPs (Holroyd & Coles, 2002). The size of the reward-positivity was then determined by identifying the peak amplitude of the difference between the reward and non-reward ERPs within a 200-400 ms window following feedback onset

*P200.* The P200 was measured base-to-peak at a frontal-central channel (FCz) by first identifying the most negative value of the ERP within a 50-150 ms window following the presentation of the feedback, the latency of which was taken as the time of onset of the

P200. Next, the maximum positive value of the ERP within a window extending from P200 onset to 250 ms following the presentation of the feedback was identified, the time of which was taken as the peak latency of the P200. The difference in voltage between peak onset and peak maximum was defined as P200 amplitude. This algorithm was applied to the Reward and No-reward ERPs associated with electrode site FCz.

*P300.* P300 amplitude was measured by identifying the maximum positive-going value of the Reward and No-reward ERPs recorded at electrode site Pz, within a window extending from 300 to 600 ms following the presentation of the feedback stimulus. The time of peak amplitude was defined as P300 latency.

*Time-Frequency analysis.* I computed a single trial wavelet-based time-frequency analysis using custom-written Matlab routines that implement the method described by(Lachaux, Rodriguez, Martinerie, & Varela, 1999). The continuous EEG data were segmented in epochs from 500 preceding to 1000 ms following feedback presentation and filtered using a $4^{th}$ order digital Butterworth filter with a passband from 0.1 to 40 Hz. Single-trial EEG data were convoluted with a complex Morlet wavelet in the studied frequencies (from 1Hz to 40 Hz; linear increase) with respect to baseline were computed for each trial and averaged for each subject before performing a grand average (for a complete description of the analysis procedure see Marco-Pallares et al., 2008). For each subject and feedback location, I identified the maximum mean increase in power for delta [1-4 Hz], theta [4-8 Hz], alpha [8-13 Hz], beta [13-20 Hz] and gamma [20-40 Hz] within a temporal window extending from -500 to 1000 ms post-stimulus relative to a 100 ms pre-stimulus baseline. The peak power and latency of each frequency band were obtained by detecting the maximum power within a 600 ms window following the onset of feedback

stimulus, separately for rewards and no rewards. This analysis was restricted to channel FCz where theta and gamma power are found to be maximal.

**Behavioral Task - The Probabilistic Selection Task.**

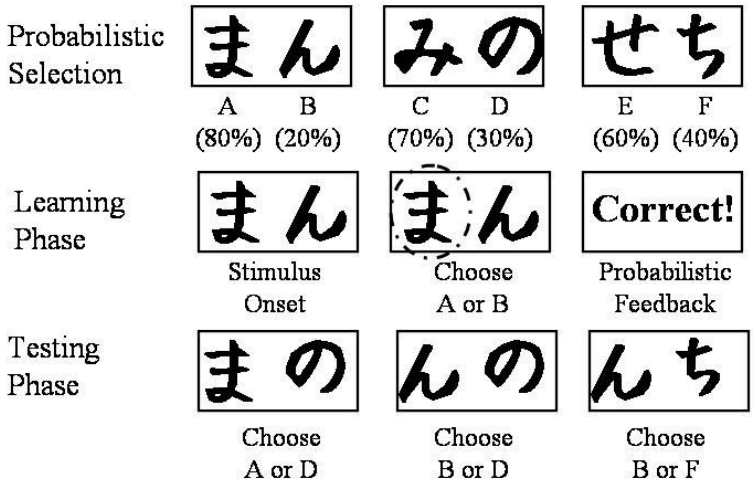


**Figure 26. Probabilistic Learning Task. Top row: Stimuli and reward probabilities (percent positive feedback). Middle row: Schematic of an example trial during the learning phase. Bottom row: Schematic of an example trial during the test phase.**

Following the ERP task, participants remained seated in the electromagnetically shielded room and were asked to engage in the Probabilistic Selection Task (PST) (Frank et al., 2004). Participants were asked to position their hand and forearms so that both fingertips of the index fingers rested on buttons 1 and 0 of a standard computer keyboard placed in front of them, and were provided with written and verbal instructions explaining the procedure. On each trial of the task they viewed a fixation cross (green circle, 1 s) followed by a pair of visual stimuli that are not easily verbalized by most English speakers (i.e., Japanese Hiragana characters) presented in black on a white background in 72 pt font (Figure 26). They then pressed the key corresponding to the stimulus that they believed to be correct. Visual feedback was provided following each choice (the word “Correct!”

printed in blue or “Incorrect” printed in red, 1 s). If no response was made within 6 s then the words “no response detected” were displayed in red (1 s). During an initial Learning Phase participants were exposed to three pairs of stimuli presented in random order (AB, CD, EF; see Figure 26 [top]). The response mappings were probabilistic such that one stimulus in each of the three pairs was rewarded on 80%, 70%, and 60% of the trials, respectively, with the remaining stimulus in each pair rewarded on the complementary percentage of trials (Figure 26, [top]). Stimulus-probability assignments were counterbalanced across subjects.

Participants learned by trial-and-error to choose the more frequently rewarded stimulus over the alternative in each pair, namely, by selecting stimuli A, C and E more often than B, D, and F. Critically, they could do so either by learning that stimuli A, C and E were associated with relatively more Reward, by learning that stimuli B, D and F were associated with relatively more punishment, or both. Participants advanced to the Test Phase of the task if after any block of 60 trials they satisfied performance criteria for the three stimulus pairs (65% A in AB, 60% C in CD, 50% E in EF), or after six blocks (360 trials) of training if these criteria were not met. During the Test Phase participants were exposed to all possible combinations of these stimuli (i.e., AB, CD, EF, AC, AD, AE, AF, BC, BD, BE, BF, CE, DF) in a random order. As before, subjects were required to select the symbol in each pair that they believed to be correct, but without receiving any feedback about their choices. They were told to use “gut instinct” whenever they did not know how to respond. Each test pair was presented 6 times.

## RESULTS

### Participants

Participants (148 female, 48 males) were 20.4 (SD = 4.1; range = 18–51) years of age on average, and 91% of the sample was Caucasian. Genotype groups did not differ with regard to gender, age or ethnicity (P > 0.05); therefore, it is unlikely that population stratification confounded the analyses presented herein. Further, with the exception of the PPP1R1B polymorphisms (p<0.05), the sample showed no deviation from Hardy–Weinberg equilibrium (Hardy, 1908; Weinberg, 1908) at any of the selected loci for the overall sample (p>.05), suggesting that the observed genotype frequencies are consistent with previous studies of primarily Caucasian and unselected samples.

**Time-Frequency X Genetic results**

*Consistent with previous reports, theta (p<.001) and gamma (p<.01) band power differed between the Reward and No-Reward trials during the time period (200-400 ms post-feedback) and at the spatial location (frontal-central) associated with the reward-positivity (Supplementary Material).* A repeated measures ANOVA on band power as a function of Frequency (theta, gamma) and Feedback (Reward, No-reward) confirmed this observation, revealing a main effect of Frequency, $F(1, 195) = 551.7$, $p < .001$, a main effect of Feedback, $F(1, 195) = 16.6$, $p < .001$, and an interaction between Frequency and Feedback, $F(1, 195) = 36.2$, $p < .001$. Post-hoc analyses indicated the EEG was characterized by greater power in the theta band (M = .66 dB, SE = + .03) than gamma band (M = .02 dB, SE = + .01), $p < .001$, and that overall band power was greater for No-reward (M = .38 dB, SE = + .02) compared to reward feedback (M = .30 dB, SE = + .02), $p < .01$. In regards to the interaction, gamma and theta power were inversely related: reward trials were characterized by decreased theta power (M = .58 dB, SE = + .02) and increased gamma power (M = .04 dB, SE = + .013), whereas No-reward trials were

characterized by increased theta power (M = .74 dB, SE = + .04) and decreased gamma power (M = .01 dB, SE = + .014). As a check, test results for all other frequency bands were non-significant for this comparison (p>.05).

**Reward-positivity and the interaction between Theta, and Gamma**

*Because theta and gamma appear to interact to produce the reward-positivity (Supplementary Material).* A recent formulation of the reinforcement learning theory of the error-related negativity holds that activity intrinsic to the ACC produces the N200, and that on trials following unpredicted rewards, the N200 is suppressed by the reward-positivity (Holroyd, Pakzad-Vaezi, & Krigolson, 2008; Baker & Holroyd, 2011b). By extension, unexpected task-relevant events elicit a burst of theta in the ACC, one half-cycle of which describes the N200 ERP component. Further, unexpected rewards elicit a phasic increase in dopamine (possibly reflected by an increase in gamma) that inhibits the N200 and reduces theta activity (Holroyd, Hajihosseini, & Baker, 2012; Baker & Holroyd, 2011a; Hajihosseini et al., 2012; Hosseini & Holroyd, 2011).

**Gamma Power and DRD4-C521T**

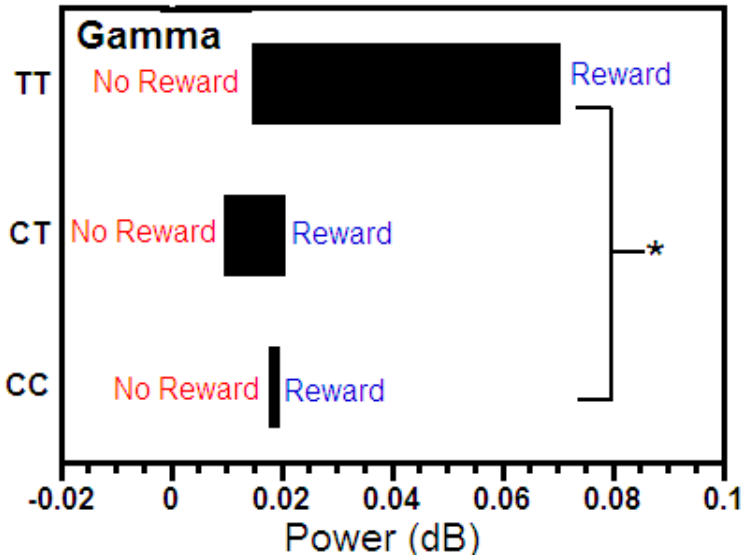

**Figure 27. Floating bar graph depicting gamma mean differences between Reward and No-reward outcomes for DRD4-C521T allele groups. Note highest difference in power between outcomes for TT group.**

*Next, I investigated whether any of the nine dopamine-related polymorphisms predicted theta* (Supplementary Material) Differences in gamma power between reinforcing events were significantly larger for homozygous DRD4-521 T carriers (M = .07 dB, SE = + .02), compared to homozygous C carriers (M = .009 dB, SE = + .02), t(86) =¬ 1.9, p < .05, and a trend for CT carriers was observed (M = .024 dB, SE = + .03), p = .056 (Figure. 27).

**Interaction between COMT, DRD4, and Theta power**

*No interaction was detected (p>.05) (*Supplementary Material*)* Previous research has suggested an interaction on theta power between the val158met polymorphism (rs4680) of the Catechol-O-methyltransferase (COMT) gene−with the Met allele accounting for a four-fold decrease in dopamine catabolism leading to increased tonic activity and decreased phasic activity− and the DRD4-521(27). For this reason I explored this possibility in my own data. Separate ANOVAs on theta activity (reward and no-reward) as a function of DRD4 allele group and COMT allele group (val/val, val/met, met/met) revealed an interaction of genotypes on reward related theta activity, F(4, 195) = 2.5, p = .02, indicating greater theta activity of the CT allele group in the presence of fewer Val alleles compared to the CC allele (p<.05), and greater theta activity for the CC allele group in the presence of more Val alleles compared to the CT allele (p<.05). Although no main effects were observed, post hoc tests did reveal a significant difference in reward related theta power between heterozygous C carriers (M = .54 dB, SE = + .04) and

homozygous T carriers (M = .67 dB, SE = + .05), t(150) =¬ -2.3, p < .05, but no differences were observed for the homozygous C carriers (p=.07).

**PST results**

I followed the analysis approach outlined above to explore the associations between substance dependence, personality risk factors, dopamine related polymorphisms, and performance on the PST (i.e. positive and negative learning). No associations were observed between GCR and PST performance, nor personality risk factors and PST performance (p>.05). Results will be presented elsewhere.

**Path Analysis results**

**Standardized Regression Weights**

| | | | Estimate | S.E. | C.R. | P |
|---|---|---|---|---|---|---|
| Theta | ← | DRD4_521 | -0.158 | 0.041 | -2.23 | 0.026 |
| Anxiety | ← | COMT | -0.163 | 0.262 | -2.303 | 0.021 |
| Impulsive | ← | DARPP-32 | 0.158 | 0.264 | 2.227 | 0.026 |
| Novelty Seeking | ← | DRD2_TaqA1 | 0.120 | 0.357 | 1.679 | 0.093 |
| Depression | ← | DRD4_521 | 0.180 | 0.324 | 2.546 | 0.011 |
| Reward positivity | ← | Theta | -0.332 | 0.614 | -4.898 | <.001 |
| Substance dependence | ← | Impulsive | 0.218 | 0.589 | 3.424 | <.001 |
| Substance dependence | ← | Depression | 0.125 | 0.424 | 1.959 | 0.05 |
| Substance dependence | ← | Reward positivity | 0.258 | 0.371 | 4.043 | <.001 |
| Substance dependence | ← | Anxiety | -0.109 | 0.512 | -1.716 | 0.086 |
| Substance dependence | ← | Novelty Seeking | 0.265 | 0.439 | 4.164 | <.001 |

**Table 6. Standardized regression weights for direct path in proposed model**

**Standardized Indirect Effects**

| | | | P-value |
|---|---|---|---|
| Reward positivity | ← | DRD4_521 | 0.034 |
| Substance dependence | ← | Theta | 0.002 |
| Substance dependence | ← | DARPP-32 | 0.054 |
| Substance dependence | ← | DRD2_TaqA1 | 0.075 |
| Substance dependence | ← | DRD4_521 | 0.008 |
| Substance dependence | ← | COMT | 0.072 |

**Table 7. Standardized effects for indirect paths in proposed model**

**Cluster Results**

The application of Ward's hierarchical cluster analysis resulted in two clusters of substance dependent individuals. The K-means relocation procedure using two clusters terminated in a small number of iterations indicating that stable cluster solutions had been found. Table 8 presents for each cluster the mean standardized scores for the five separate intermediate phenotypes employed in the cluster analysis. Cluster 1 (43%) is notable for its elevation on Depression proneness scores (M= 15.2) and reduced reward-positivity amplitude (M= -1.8 μV). Cluster 2 is distinguished by its elevated values on novelty seeking (M= 19.2) and the reward-positivity amplitude (M= -4.1 μV)

To verify these clusters, a discriminant analysis was conducted to predict whether an individual was in cluster 1 or cluster 2. Predictor variables were reward-positivity, depression proneness, anxiety, impulsivity, and sensation seeking. The log determinants were quite similar, and Box's M indicated that the assumption of equality of covariance matrices was not violated. The discriminate function revealed a significant association between groups and all predictors, accounting for 62.32% of between group variability. Overall, the discriminant analysis yielded functions correctly classifying 100% and 91.3% of the substance dependent individuals into Clusters 1 and 2, respectively, for the original

sample. In the cross-validation sample, 100%, and 91.3% of the substance dependent individual for Clusters 1 and 2, respectively, were correctly classified. MANOVA results are present in Table 8).

| | Cluster 1 | Cluster 2 | F-value | df | *P* |
|---|---|---|---|---|---|
| Sample | 19 | 23 | | | |
| Reward Positivity | -1.80 | -4.10 | 6.10 | (1, 42) | p=.01 |
| SURPS | | | | | |
| Depression | 15.20 | 10.30 | 38.70 | (1, 42) | p=.001 |
| Anxiety | 12.70 | 11.10 | 5.10 | (1, 42) | p=.03 |
| Impulsivity | 11.10 | 9.90 | 2.80 | (1, 42) | p=.10 |
| Novelty Seeking | 16.70 | 19.60 | 10.20 | (1, 42) | p=.003 |

**Table 8. Cluster and Means for Intermediate Phenotypes, and MANOVA results.**

# Appendix B

## Substance Use Risk Profile Scale (SURPS)

Please indicate the extent to which you agree with the following statements by circling the appropriate response statement using the following scale:

**1 = Strongly disagree 2 = Disagree 3 = Agree 4 = Strongly Agree**

| | | | | | |
|---|---|---|---|---|---|
| **1.** | I am content. | **1** | **2** | **3** | **4** |
| **2.** | I often don't think things through before I speak. | **1** | **2** | **3** | **4** |
| **3.** | I would like to skydive. | **1** | **2** | **3** | **4** |
| **4.** | I am happy. | **1** | **2** | **3** | **4** |
| **5.** | I often involve myself in situations that I later regret being involved in. | **1** | **2** | **3** | **4** |
| **6.** | I enjoy new and exciting experiences even if they are unconventional. | **1** | **2** | **3** | **4** |
| **7.** | I have faith that my future holds great promise. | **1** | **2** | **3** | **4** |
| **8.** | It's frightening to feel dizzy or faint. | **1** | **2** | **3** | **4** |
| **9.** | I like doing things that frighten me a little. | **1** | **2** | **3** | **4** |
| **10.** | It frightens me when I feel my heart beat change. | **1** | **2** | **3** | **4** |
| **11.** | I usually act without stopping to think. | **1** | **2** | **3** | **4** |
| **12.** | I would like to learn how to drive a motorcycle. | **1** | **2** | **3** | **4** |
| **13.** | I feel proud of my accomplishments. | **1** | **2** | **3** | **4** |
| **14.** | I get scared when I'm too nervous. | **1** | **2** | **3** | **4** |
| **15.** | Generally, I am an impulsive person. | **1** | **2** | **3** | **4** |
| **16.** | I am interested in experience for its own sake even if it is illegal. | **1** | **2** | **3** | **4** |
| **17.** | I feel that I'm a failure. | **1** | **2** | **3** | **4** |
| **18.** | I get scared when I experience unusual body sensations. | **1** | **2** | **3** | **4** |
| **19.** | I would enjoy hiking long distances in wild and uninhabited territory. | **1** | **2** | **3** | **4** |
| **20.** | I feel pleasant. | **1** | **2** | **3** | **4** |
| **21.** | It scares me when I'm unable to focus on a task. | **1** | **2** | **3** | **4** |
| **22.** | I feel I have to be manipulative to get what I want. | **1** | **2** | **3** | **4** |
| **23.** | I am very enthusiastic about my future. | **1** | **2** | **3** | **4** |

# Scoring the SURPS

The SURPS

The SURPS consists of 23 items measuring four dimensions of personality risk for substance abuse. The scale was designed using a multiple response structure. Items have been reduced to the following four subscales:

| *Introversion/Hopelessness Dimension* | *Anxiety Sensitivity Dimension* |
|---|---|
| Item 1 | Item 8 |
| Item 4 | Item 10 |
| Item 7 | Item 14 |
| Item 13 | Item 18 |
| Item 17 | Item 21 |
| Item 20 | |
| Item 23 | |

| *Impulsivity Dimension* | *Sensation Seeking Dimension* |
|---|---|
| Item 2 | Item 3 |
| Item 5 | Item 6 |
| Item 11 | Item 9 |
| Item 15 | Item 12 |
| Item 22 | Item 16 |
| | Item 19 |

***Note:*** **Items 1, 4, 7, 13, 20 and 23 require an inversion of respondent's score**.