THE INTERACTION BETWEEN EXTERNALIZING PRONENESS AND STRIATAL DOPAMINE ON DISTINCT ASPECTS OF REWARD PROCESSING

A Dissertation

by

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Submitted to the Office of Graduate and Professional Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

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August 2017

Major Subject: Psychology

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ABSTRACT

Externalizing proneness, or impulse control and substance abuse problems, has been broadly associated with dysregulation in reward sensitivity. The goal of this investigation was to systematically determine the effects of distinct manifestations of externalizing proneness, namely disinhibition and substance abuse, on specific aspects of reward processing using a Research Domain Criteria approach. Additionally, this investigation examined whether striatal dopamine moderates the impact of externalizing proneness on reward processing. Striatal tonic dopamine levels were operationalized using spontaneous eyeblink rate. Participants completed disinhibition and substance abuse subscales of the brief form Externalizing Spectrum Inventory, and then performed assessments of reward wanting and learning, devaluation sensitivity, effort expenditure for rewards, and reward-incentivized cognitive control. Results revealed that disinhibition and substance abuse exerted unique effects on reward processing, which were moderated by variation in striatal dopamine levels. High-disinhibited individuals with low striatal dopamine showed greater reward wanting and preferred less physically effortful, smaller rewards. Individuals with substance abuse problems and high striatal dopamine showed enhanced long-term reward learning, while high substance users with low dopamine showed enhanced learning of immediately rewarding options, exerted greater cognitive effort to obtain rewards, and showed deficits in reward-incentivized cognitive control. Substance abuse, independent of striatal dopamine, was associated with reduced reward devaluation sensitivity. Collectively, these results suggest that in individuals with externalizing proneness, low striatal dopamine may represent a risk factor for addiction or elevated impulse control problems.

CONTRIBUTORS AND FUNDING SOURCES

I would like to thank my committee members, Lisa Geraci, Jessica A. Bernard, and Steven Woltering, for their invaluable feedback to the design and framing of this dissertation. I would also like to especially thank my faculty chair and advisor, Darrell A. Worthy, for feedback and support throughout all stages of this dissertation. I would also like to thank Christopher Patrick, Ross Otto, and Bo Pang for their instrumental contributions to Studies 1 and 2. This work was supported by an NIA Grant AG043425 to Darrell A. Worthy.

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1. INTRODUCTION

Externalizing, or impulse control, problems are pervasive and can have substantial consequences. Research from the National Comorbidity Survey shows the incidence rate of impulse control disorders, including substance abuse conditions, in the United States to be approximately 8% to 9% (Insel & Fenton, 2005; Kessler et al., 1994; Wang et al., 2005). In addition, many more individuals exhibit subclinical manifestations of disinhibition and substance abuse that also have adverse effects. One prominent domain in which externalizing tendencies can engender negative consequences is decision making. In particular, externalizing behavior has been linked to impairments in reward-based decisions that contrast short-term versus long-term consequences (Bechara & Damasio, 2002).

Despite the prevalence of externalizing proneness and the important consequences of reward-based decision-making, research aimed at examining the effects of externalizing proneness on specific aspects of reward processing is limited. One way to systematically address this issue is to utilize the Research Domain Criteria (RDoC) framework. The RDoC characterizes reward processing as the Positive Valence Systems domain and includes eight unique constructs or sub-constructs of reward processing, such as reward learning, reward valuation (reward "wanting"), effort valuation, habit learning, and long-term responsiveness to reward (Cuthbert & Kozak, 2013; Insel et al., 2010). Reward wanting, learning, effort valuation, and habit learning all depend on ventral striatum dopaminergic functioning (Berridge & Robinson, 1998; Hyman, Malenka, & Nestler, 2006; Treadway et al., 2012). While work with sustained responsiveness to reward shows that this construct depends on dopamine, limited research has been conducted with this construct and involvement of striatal dopamine specifically. Instead, most work has been focused on the role of the

orbitofrontal cortex (OFC) and hypothalamus in long-term responsiveness to reward (Elliott, Dolan, & Frith, 2000; Weiss, 2005). Thus, the current investigation was aimed at investigating (1) the effects of externalizing proneness on reward processing using the RDoC framework, and (2) the role of striatal dopamine in moderating these effects. This not only provides a systematic approach to test the proposed research questions, but also contributes to the RDoC conceptualization of externalizing behavior.

1.1 Substance Abuse, Trait Disinhibition, and Dopaminergic Function

A clear problem with current research on externalizing proneness and reward-based decision-making is that the unique manifestations of externalizing tendencies, namely disinhibition and substance abuse, are often conflated (Moeller & Dougherty, 2002). While these two constructs are highly comorbid, they nevertheless represent phenotypically distinctive phenomena (Armstrong & Costello, 2002; Finn et al., 2009; Krueger et al., 2007; Waldman & Slutske, 2000). Substance abuse entails recreational or problematic use of drugs and alcohol, whereas disinhibition reflects broader tendencies toward nonplanfulness, impulsive risk taking, irresponsibility, and alienation from others (Patrick, Kramer, Krueger, & Markon, 2013). Thus, a second goal of the current proposal is to test for individual contributions of disinhibition and substance abuse on specific aspects of reward processing.

Molecular genetic research demonstrates that allelic variation in dopaminergic genes, including DRD2 and DRD3, is related both to disinhibitory traits and to substance abuse problems (Comings, Muhleman, Ahn, Gysin, & Flanagan, 1994; Derringer et al., 2010; Kreek, Nielsen, Butelman, & LaForge, 2005). Moreover, extensive research has demonstrated that dopamine plays a critical role in the neural circuitry underlying reward learning and wanting (e.g., Berridge & Robinson, 1998; Ikemoto, 2007; Robinson &

Berridge, 2000; Wise, 2004). A recent review demonstrated that discrete dopamine-dependent neurobiological systems underlie wanting and learning aspects of reward processing (Baskin-Sommers & Foti, 2015). Taken together, findings from human behavioral and molecular genetic research along with neuroscientific evidence indicate a role for genetically based variation in striatal dopaminergic function in general proneness to externalizing problems. Although research demonstrates that dopaminergic variation is associated with externalizing problems, the exact nature of this relationship for specific facets of externalizing problems, such as trait disinhibition and substance abuse (Krueger et al., 2007; Patrick et al., 2013), is unclear. One possibility is that the distinction between disinhibition and substance abuse corresponds to differences in striatal dopaminergic function.

1.2 Dopamine and Distinct Aspects of Reward Processing

According to incentive-sensitization theory, associative learning mechanisms determine the dopaminergic sensitization to incentive salience, a process by which stimuli become rewarding and wanted. Extensive research has demonstrated that dopamine plays a critical role in the neural circuitry underlying reward learning and wanting (e.g., Berridge & Robinson, 1998; Ikemoto, 2007; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006; Robinson & Berridge, 2000; Wise, 2004). Specifically, a recent review demonstrated that discrete dopamine-dependent neurobiological processes underlie wanting and learning aspects of reward responding (Baskin-Sommers & Foti, 2015). The distinction between reward wanting and learning processes is crucial to understanding the role of externalizing behavior in reward-based decision making. Physiological reward wanting drives approach toward reward and enhances reward motivation. Dopamine signals in the ventral striatum

connect incentive value to a reward stimulus (Baskin-Sommers & Foti, 2015). Learning, on the other hand, involves dopamine signaling from the ventral striatum to the prefrontal cortex, which updates goal representations and associations between a stimulus and its outcome (Baskin-Sommers & Foti, 2015; Everitt & Robbins, 2005; Ma et al., 2010; Motzkin, Baskin-Sommers, Newman, Kiehl, & Koenigs, 2014). Dopaminergic neurons in the mesolimbic system encode predictions about a reward and update that prediction based on feedback from prediction errors, thus signaling the reward value of stimuli in reinforcement learning contexts (Berridge, Robinson, & Aldridge, 2009; Flagel et al., 2011; Glimcher, 2011; Hollerman & Schultz, 1998). However, it is unclear whether tonic or phasic striatal dopamine is the basis for the effects of wanting and learning processes.

Tonic dopamine refers to the baseline level of extrasynaptic dopamine in the brain, whereas phasic dopamine refers to the spiking activity of dopamine neurons in response to a stimulus, such as a reward signal (Schultz, 1998). Trait impulsivity has been associated with decreased D2/D3 autoreceptor availability and increased amphetamine-induced dopamine release in the ventral striatum (Buckholtz et al., 2010). Drug or alcohol addiction alters the balance between the tonic and phasic dopamine system. Frequent drug use increases tonic dopamine levels, which inhibits phasic dopamine release (Grace, 1995). Thus, the dopamine system is altered in substance abusers such that tonic striatal dopamine levels are elevated and the phasic dopamine system becomes desensitized and weakened in its reactivity (Grace, 1995). As a function of this, individuals may use substances to restore the tonic-phasic dopamine system to equilibrium (Grace, 1995, 2000).

This disequilibrium between tonic and phasic dopamine makes it especially important to examine how tonic dopamine interacts with substance abuse tendencies to affect reward-

based behavior. In regard to reward processing, phasic dopamine activity, in particular, has been shown to encode reward prediction errors in the striatum (Ljungberg, Apicella, & Schultz, 1992; Niv, Daw, Joel, & Dayan, 2007; Schultz, 1998;Waelti, Dickinson, & Schultz, 2001). On the other hand, tonic dopamine levels encode the average reward rate (Niv et al., 2007). Given the distinct role of striatal tonic and phasic dopamine in reward processing and the association between externalizing proneness and dopaminergic gene variation, it is possible that differences in dopaminergic function moderate the relationship between externalizing proneness aspects of reward processing. Thus, a final goal of the proposed research is to investigate how striatal dopamine interacts with trait disinhibition and substance abuse to affect reward processing.

1.3 Current Studies

The current investigation entailed four studies to assess the interaction between striatal dopamine and externalizing proneness on specific aspects of reward processing. The first study was designed to assess the interaction between externalizing proneness and striatal dopamine on reward wanting and learning. Previous research with substance abuse and reward-based decision-making shows mixed findings with some studies observing that substance abuse predicts poorer associative learning, and thus poorer reward-based decision-making, on the Iowa Gambling Task (IGT; Bechara, 2003; Bechara & Damasio, 2002). However, other studies find no such deficits (Bolla et al., 2003; Ernst et al., 2003). Additionally, research on impulsivity, though quite limited, shows no association between trait disinhibition and IGT performance (Upton, Bishara, Ahn, & Stout, 2011). With regard to reward wanting, a recent review demonstrates that substance abuse has been associated with increased preference for immediate hypothetical monetary and drug rewards over delayed

reward using the delay discounting paradigm (Yi, Mitchell, & Bickel, 2010). However, for trait disinhibition, only one study has tested for an effect on reward-based decision making separate from its association with substance abuse. This study, by de Wit et al. (2007), demonstrated that nonplanful impulsivity predicted preference for immediate rewards, or enhanced "wanting", but overall composite impulsivity reports were not significantly predictive of delay discounting preferences. Although research shows that substance abuse predicts poorer associative reward learning and nonplanful impulsiveness is associated with increased preference for immediate rewards, work on this topic has been somewhat mixed and is quite limited in scope. Consequently, Study 1 examined the interaction between externalizing proneness and striatal dopamine on reward wanting (using the delay discounting paradigm) and reward learning (using a reinforcement learning task).

Study 2 assessed interactions between externalizing proneness and striatal dopamine on reward disengagement. While enhanced learning of action-reward contingencies may be beneficial in some situations, such as academic or job-related contexts where increased studying or working may lead to better grades and promotions, this is not always the case. For example, when action-reward associations are learned between a drug and its rewarding properties, then enhanced reward learning may serve as a risk factor for transitioning from recreational drug use to addiction (Hogarth et al., 2013). Thus, Study 2 used a reinforcement learning task with a devaluation component, whereby one option becomes devalued, to test both reward learning and disengagement, or "devaluation".

The purpose of Study 3 was to investigate the possible interaction between externalizing proneness and striatal dopamine on a reward-based decision-making task in which one must expend effort to receive rewards. This tests the "effort valuation" construct

in the RDoC framework. Because the delay discounting paradigm does not entail effort-based decision-making, one remaining question is whether striatal dopamine alters reward wanting in individuals with higher externalizing behaviors when one has to expend effort to receive rewards. Previous work on effort expenditure demonstrates that ventral striatal tonic dopamine depletion reduces willingness to expend effort to obtain rewards in rats (Treadway et al., 2009). The discrepancy in these findings, in which diminished tonic dopamine leads to enhanced encoding of reward prediction errors but also reduces effort expenditure for such rewards, emphasizes the need to understand how tonic DA interacts with trait disinhibition to predict effort-based decision-making.

Using the RDoC framework, substance use disorders have been characterized as dysregulation of the positive valence systems and cognitive control domains (Sanchez & Cruz-Fuentes, 2016). Therefore, Study 4 was designed to compare reward wanting and inhibitory control demands and their relationship with externalizing proneness. Although by name trait disinhibition encompasses behaviors characterized by a lack of inhibitory control, research on stop signal task performance, a cognitive control task that assesses behavioral inhibitory control, finds no significant associations with overall trait impulsiveness; instead, only the motor impulsiveness subscale correlates with poorer stop signal task inhibitory control (Enticott, Ogloff, & Bradshaw, 2006; Shen, Lee, & Chen, 2014). In contrast, a considerable amount of work has shown that substance abuse is associated with poorer inhibitory control on the stop signal task (e.g., Ersche et al., 2011; Goudriaan et al., 2005; Li et al., 2006; Monterosso et al., 2005; Moreno et al., 2012). The purpose of Study 4 was to determine how inhibitory control is affected by reward valuation by providing an immediate reward for correct inhibition.

2. STUDY 1: REWARD WANTING AND LEARNING

Study 1[1] was designed to assess the influences of general externalizing proneness and its specific manifestation in the form of substance abuse on reward learning and behavioral choices, and the role of variations in striatal dopamine levels (as indexed by spontaneous eyeblink rate) in moderating this relationship. Previous research shows that substance abuse is related to poorer associative learning on the Iowa Gambling Task (Bechara, 2003; Bechara & Damasio, 2002). In contrast, however, superior associative learning for drug stimuli and reward outcomes is a proposed mechanism for transitioning from recreational drug use to addiction (Hogarth, Balleine, Corbit, & Killcross, 2013). Thus, the current research on the relationship between substance abuse and reward learning appears mixed.

Because tonic dopamine encodes the average reward rate, while phasic dopamine encodes reward prediction errors (Ljungberg et al., 1992; Niv et al., 2007; Schultz, 1998; Waelti et al., 2001), dopamine may interact with substance abuse to affect reward-based associative learning. In particular, elevated tonic dopamine levels may enhance learning of the long-term average rewards associated with each reward option. Low tonic dopamine levels may lead to larger phasic spikes in response to reward prediction errors, and thus enhanced associations of the immediate action-reward contingencies (Daw, 2003; Niv et al., 2007). Thus, high tonic dopamine levels may operate to enhance updating of reward values and thereby facilitate learning of the long-term average reward rates of differing options. In contrast, low tonic dopamine may result in poorer associative learning due to over-reliance on immediate action-reward contingencies at the expense of long-term action-reward contingencies.

[1] *Reprinted with permission from "Striatal Dopamine, Externalizing Proneness, and Substance Abuse Effects on Wanting and Learning during Reward-Based Decision-Making" by K. A. Byrne, C. J. Patrick, and D. A. Worthy, 2016. *Clinical Psych Science*, 4, 760-774. Copyright 2016 by SAGE Publishing.

Given that nonplanful impulsivity is associated with enhanced preference for immediate rewards, trait disinhibition appears to be associated with increased reward wanting. Based on this limited research, I predicted that individuals with more disinhibitory tendencies and low tonic dopamine levels (larger phasic spikes in response to reward stimuli) would show enhanced reward wanting preferences.

For all studies, a power analysis was conducted using G*Power to determine the appropriate sample size. The results revealed that a sample of 91 would be needed to have 80% power and a medium effect size to detect an effect with a regression with five predictors (eyeblink rate index of striatal dopamine, Disinhibition, Substance Abuse, EBR X Disinhibition, and EBR X Substance Abuse); thus, a sample size of at least 91 participants was obtained for each study.

2.1 Participants

A total of 93 undergraduate students (48 females; age range = 18–22) completed the delay discounting task for partial course credit in their introduction to psychology course. Of these, 67 (36 females) also performed the reward learning task.

2.2 Materials and Design

Externalizing Spectrum Inventory–Brief Form. To assess disinhibitory/externalizing tendencies, I administered the Disinhibition and Substance Abuse subscales from the Externalizing Spectrum Inventory–Brief Form (ESI-BF; Patrick et al., 2013). The Disinhibition subscale consisted of 20 items that assess general externalizing proneness (i.e., proclivities toward reckless-impulsive behavior, and affiliated traits; Krueger et al., 2007), and includes questions about problematic impulsivity, irresponsibility, theft, impatient urgency, fraud, alienation, planful control, and boredom proneness. The Substance Abuse subscale contained 18 items pertaining to use of and problems with alcohol and other drugs.

For each scale, item responses were made using a 4-point Likert-type scale (*true, somewhat true, somewhat false,* or *false*). Both the Disinhibition and Substance Abuse subscales show strong validity in relation to relevant criterion measures (Patrick & Drislane, 2015; Venables & Patrick, 2012), and both exhibited very high internal consistency within the current sample (αs = .94 and .95). It is important that the ESI-BF Disinhibition scale is a measure of an individual's general proclivity for externalizing problems, whereas the ESI-BF Substance Abuse scale indexes a distinct manifestation of this broad disinhibitory liability—namely, problematic use of alcohol/drugs.

Spontaneous Eyeblink Rate (Tonic Dopamine Index). Spontaneous eyeblink rate (EBR) was used as an index of striatal tonic dopamine (Karson, 1983). Specifically, previous research demonstrates that faster spontaneous EBR is indicative of elevated dopamine levels in the striatum (Colzato, Slagter, van den Wildenberg, & Hommel, 2009; Karson, 1983; Taylor et al., 1999). More recently, spontaneous eyeblink rate has been shown to have a strong correlation with dopamine D2 receptor density, which mediates tonic dopamine levels, in the ventral striatum and caudate nucleus (Groman et al., 2014; Slagter et al., 2015).

Following previous published research (e.g., Chermahini & Hommel, 2010; Colzato et al., 2009; De Jong & Merckelbach, 1990; Ladas, Frantzidis, Bamidis, & Vivas, 2013), I used electrooculogram (EOG) recording to assess spontaneous EBR as an indirect index of available levels of tonic dopamine in the striatum. To record EBR, I followed the procedure described by Fairclough and Venables (2006), in which vertical eyeblink activity was recorded from Ag/AgCl electrodes positioned above and below the left eye, with a ground electrode placed on the center of the forehead. All EOG signals were filtered (at 0.01–10 Hz) and amplified using a Biopac EOG100C differential corneal–retinal potential amplifier.

Eyeblinks were defined as phasic increases in EOG activity of >100 μV and occurring within intervals of 400 ms or less over the recording interval. Eyeblink frequency was quantified using manual count. All recordings were collected during daytime hours of 11 a.m. to 4 p.m. because previous work has shown that diurnal fluctuations in spontaneous EBR can occur in the evening hours (Barbato et al., 2000). A black fixation cross ("X") was displayed on a wall at eye level 1 m from where the participant was seated. Participants were instructed to look in the direction of the fixation cross for the duration of the recording and avoid moving or turning their head. Eyeblinks were recorded for 6 min under this basic resting condition. Each participant's EBR was determined by computing the average number of blinks across the 6-min recording interval.

Reward Wanting. The delay discounting task (Richards, Zhang, Mitchell, & Wit, 1999) was utilized to assess reward-related wanting. Within the Research Domain Criteria (RDoC) framework (Cuthbert & Kozak, 2013), delay discounting is an experimental paradigm that relates to the approach motivation construct under the Positive Valence Systems domain. Previous research indicates that the RDoC approach motivation construct corresponds to physiological reward wanting (Baskin-Sommers & Foti, 2015). In the delay discounting task, participants indicated whether they would prefer a smaller amount of money immediately or a larger amount of money after a time delay (e.g., "Would you prefer $2 now or $10 after 30 days?"). A preference for immediate reward indicated greater disregard for (discounting of) the delayed reward option and, by inference, a higher degree of "wanting" for immediate reward. The dependent measure was the area under the curve; lower values indicate greater discounting of future rewards and thus enhanced reward wanting.

Reward Learning. To examine reward learning, I utilized a complex reinforcement-learning (RL) task, a type of paradigm enumerated under the RDoC reward learning construct. This task involves a choice-history-dependent reward structure and has been used extensively in previous research to investigate learning of immediate and delayed reward outcomes (Cooper et al., 2014; Worthy, Byrne, & Fields, 2014; Worthy, Cooper, Byrne, Gorlick, & Maddox, 2014; Worthy, Gorlick, Pacheco, Schnyer, & Maddox, 2011; Worthy, Otto, & Maddox, 2012). In the task, participants repeatedly chose between two options to learn which option led to the best outcome. One option, the Increasing option, offered fewer points on each trial compared with the second option, but rewards for both options increased over time as it was selected more frequently. The second option, the Decreasing option, offered more points on each trial but as this alternative was chosen more often, rewards for both options decreased in value. Thus, participants needed to choose between both options to learn that the Increasing option was advantageous because it offered more points in the long-run. The dependent measure was the proportion of trials that individuals selection the optimal Increasing option.

2.3 Procedure

Participants began the study by completing demographic questionnaires (age, gender, and the number of hours slept the previous night) and the ESI-BF Disinhibition and Substance Abuse subscales followed by 100 trials of the reward learning task. Participants were given a goal of earning at least 7,200 points on the task, which would require them to select the optimal Increasing option on more than 60% of the trials. After the reward learning task, participants completed the delay discounting task. The session ended with a 6-min assessment of EBR. Then, participants were debriefed about the nature of the study.

2.4 Data Analysis

To evaluate my first hypothesis regarding the association between the EBR index of striatal dopamine and the individual differences and performance measures, bivariate correlations were conducted. I anticipated that negative correlations would be observed between delay discounting reward preference and the EBR index as well as between ESI-BF Disinhibition and the EBR index, whereas a positive relationship between reward learning performance and EBR was expected.

To test my other two hypotheses pertaining to the interaction between the EBR index of striatal dopamine and externalizing tendencies, separate hierarchical regression analyses were conducted for the delay discounting and reward learning tasks. These analyses provided for evaluation of the separate and interactive effects of continuous variations in externalizing tendencies and dopamine levels on decision making. Gender, age, and hours slept were included as covariates in both regression analyses to control for possible effects of these variables. Thus, the predictors for both delay discounting ("reward wanting") and reward learning regressions were identical. Results from the delay discounting preferences reward learning regressions were used to assess for effects of externalizing proneness and its interaction with striatal dopamine on reward wanting and learning, respectively.

2.5 Results and Discussion

Descriptive Statistics. Examination of the spontaneous EBR results revealed that one participant's data was excluded because EBR in this case was more than three standard deviation units above the mean and thus represented an outlier. After this exclusion, individual EBRs ranged from 4.33 to 38.83 blinks/min (M = 17.31, SD = 8.81). Scores on the ESI-BF Disinhibition subscale ranged from 0 to 51 (M = 15.39, SD = 13.60) and the range of

scores on the ESI-BF Substance Abuse subscale ranged from 0 to 34 (M = 13.36, SD = 7.46). No outliers were observed in responses to the ESI-BF subscales.

Correlational Analyses. Bivariate correlations (rs) were computed between each of the measures collected (i.e., EBR index of striatal dopamine and Substance Abuse and Disinhibition scales of the ESI-BF) and performance on the delay discounting task and the reward learning task (Table 1). ESI-BF Disinhibition and Substance Abuse scores were positively correlated as expected with one another (cf. Patrick et al., 2013), r = .46, p < .01. Substance Abuse scores, and to a lesser extent Disinhibition scores, showed negative associations with the EBR index of tonic dopamine level, although these correlations were also nonsignificant.

Regression Analysis for Reward Wanting Task. A three-step hierarchical multiple regression analysis was conducted to examine the effect of disinhibition, substance abuse, and striatal dopamine, as measured by eyeblink rate, on delay discounting performance. In the first step, gender, age, and hours slept were entered as covariates. Omnibus prediction at this step of the model was marginally significant, $F(3, 88) = 2.42$, p = .07. Gender did not emerge as a significant predictor at this step (p=.52), but hours slept showed a significant relationship (β = .23, p = .03), indicating that sleep was associated with less discounting of delayed rewards, and age showed a marginally significant predictive association, β = .17, p =.10. In the second step of the model, disinhibition, substance abuse, and striatal dopamine (as indexed by EBR) were entered to evaluate their independent predictive associations with delay discounting. The model as a whole was not significant at this step (p =.56), and none of the predictors evidenced an independent association with delay discounting preferences, *ps* >.30. In the third step of the model, interaction terms for striatal dopamine by disinhibition

and striatal dopamine by substance abuse were entered as predictors. The addition of these terms accounted for a significant proportion of the variance in delay discounting, $\Delta R^2 = .06$, $F(8, 83) = 3.19$, $p<.05$. At this step of the model, the Striatal Dopamine X Disinhibition interaction ($\beta = .29$, $p = .01$) contributed significantly to prediction of delay discounting choices, whereas striatal dopamine ($p = .91$), disinhibition ($p = .18$), substance abuse ($p = .84$) and the Striatal Dopamine X Substance Abuse interaction ($p = .69$) were not predictive of delay discounting preferences.

Next, simple regression lines for the effect of disinhibition on delay discounting at (a) the mean for striatal dopamine, (b) one standard deviation above the mean for striatal dopamine, and (c) one standard deviation below the mean striatal dopamine were performed. Striatal dopamine, disinhibition, and substance abuse variables were centered prior to creating the centered interaction terms. The simple regression slope coefficients when centered at the mean ($\beta = -.17$, $p = .18$) and one standard deviation above the mean ($\beta = .09$, $p = .54$) were not significant, but the simple regression slope coefficient for one standard deviation below the mean significantly predicted delay discounting, $\beta = -.43$, $p = .02$, such that at low levels of striatal dopamine individuals higher in disinhibition tended to discount future rewards at a greater rate. This result suggests that the impact of increasing disinhibition on delay discounting performance varied as a function of tonic dopamine level as indexed by EBR, such that high-disinhibited individuals with low tonic dopamine showed the most aberrant delay discounting performance, and thus the strongest reward wanting preferences.

Regression Analysis for Reward Learning Task. The same predictors used in the analysis of delay discounting were entered across three steps of a counterpart regression

model for reward learning task performance, operationalized as the average proportion of Increasing optimal option selections on the task. Omnibus prediction at step 1 of the model, at which gender, age, and hours slept were added, was significant, $F(3,64) = 6.05$, $p < .01$, with gender ($\beta = .46$, $p < .01$) but not age ($p = .63$) or hours slept ($p = .30$) emerging as distinctly predictive of reward learning performance. Consistent with previous research (Byrne & Worthy, 2015), males selected the optimal option more frequently than females. The increase in overall prediction was not significant at step 2 of the model ($\Delta R^2 = .01$, $F(6, 61) = 0.16$, $p = .92$), in which disinhibition, substance abuse, and striatal dopamine were included as predictors, but none of these variables accounted uniquely for variance in reward learning performance, all ps >.50. In the last step of the model, interaction terms for striatal dopamine by disinhibition and striatal dopamine by substance abuse were entered. A significant increase in overall prediction was again evident ($\Delta R^2 = .13$, $F(8, 59) = 5.76$, $p < .01$), in this case with the Striatal Dopamine X Substance Abuse interaction effect ($\beta = .41$, $p < .01$) showing unique predictive associations. The effect of striatal dopamine on reward learning performance was marginally significant ($\beta = .23$, $p = .07$), whereas substance abuse ($p = .63$), disinhibition ($p = .23$), and the Striatal Dopamine X Disinhibition interaction ($p = .59$) contributed negligibly. Based on the relationship between EBR and substance abuse, evidence from the regression analysis suggests that heightened striatal dopamine moderates reward learning in high-substance abuse individuals, leading to enhanced performance. Simple regression lines for the association of substance abuse with reward learning performance at (a) the mean for striatal dopamine, (b) one standard deviation above the mean for striatal dopamine, and (c) one standard deviation below the mean for striatal dopamine were also conducted. As with the delay discounting analysis, predictor variables were

centered before the interaction terms were created. The simple regression slope coefficient for the mean (β = .07, p = .63) was not significant, but the slope coefficients for one standard deviation above (β = .54, p = .02) and below (β = -.41, p =.04) the mean significantly predicted reward learning performance.

Discussion. These results provide evidence that baseline tonic dopamine levels moderate the effects of disinhibition and substance abuse on reward processing. Specifically, in the delay discounting task that assessed reward wanting, disinhibitory tendencies were associated with stronger preferences for immediate reward only for individuals with lower tonic dopamine levels. At moderate and high levels of tonic dopamine we observed no relationship between disinhibition and preferences for immediate versus delayed reward. A potential implication of this result is that high-disinhibited individuals with low striatal tonic dopamine may compose a maximum-liability group. There was no effect of substance abuse in this task.

In contrast, for reward learning, a crossover interaction between tonic dopamine and substance abuse was observed. At higher tonic dopamine levels, substance abuse was associated with enhanced reward learning. At lower tonic dopamine levels, an opposing inverse relationship between substance use and reward learning was evident, reflecting comparatively poorer performance for individuals reporting higher levels of substance use. These results suggest that learning of long-term action-reward contingencies depends on tonic dopamine levels in substance abusers. The implication could be that higher levels of tonic dopamine might facilitate improved reward learning in individuals with high levels of substance use. Alternatively, alcohol or drug users with high tonic dopamine levels may be strategically reward-oriented rather than impulsively driven by immediate desires. Thus, a

dissociative effect of disinhibition and substance abuse was found for reward wanting and learning, and these effects depended on striatal tonic dopamine levels.

This study is the first to demonstrate that disinhibition and substance abuse exert different effects on reward processing, depending on variations in striatal tonic dopamine levels. Specifically, these results provide support for the hypothesis that these distinct components of externalizing behavior are differentially related to reward wanting and learning. I conclude that externalizing problems may reflect either an enhanced desire for rewards or augmented associative linking of reward stimuli to their outcomes. Although associative learning regarding reward values and reward predictors may initially be beneficial, it can lead to negative consequences, such as addiction, in certain disposed individuals across time.

Accelerated reinforcement learning of reward options may be beneficial in some situations, such as academics and career goals. However, when the reward is a harmful, like a drug, increased tonic dopamine may still promote learning of action-reward contingencies and lead to difficulty in reward disengagement (Dagher & Robbins, 2009). Therefore, Study 2 was designed to assess the long-term consequences of how baseline dopamine levels interact with substance abuse and disinhibition. To address this issue, Study 2 used a devaluation paradigm to gauge reward disengagement after reward learning has occurred.

3. STUDY 2: HABIT LEARNING AND DEVALUATION

The purpose of Study 2 was to follow up on the reward learning results from Study 1 and determine whether striatal dopamine enhances both reward learning and disengagement, or devaluation, of action-reward contingencies, or if its effects are specific to reward learning in individuals with substance abuse problems. While numerous studies demonstrate that substance abuse is associated with increased perseveration on reversal learning tasks and the Wisconsin Card Sorting task, research on substance abuse and disengagement from previously reinforced behaviors in humans is very limited (Ersche et al., 2008; Fontes et al., 2011; Hoff et al., 1996; Madoz-Gurpide et al., 2011; Woicik et al., 2009). One possible prediction is that similar interactions between striatal dopamine and substance abuse that are expected for reward learning would also be observed for reward disengagement as measured by devaluation sensitivity. Specifically, at high levels of tonic dopamine individuals with substance abuse problems may show better reward learning and disengagement. This outcome would demonstrate that striatal dopamine is a protective factor of addiction—individuals may use substances recreationally without becoming addicted to them because they can easily disengage from those reward associations. Alternatively, once striatal dopamine facilitates the association between an option and its reward, disengaging from those associations may no longer be dopamine-dependent; thus, regardless of dopamine levels, once reward associations are well-learned and become habit-based, individuals with substance abuse problems may struggle to disengage from the learned strategy. Because work on disinhibition and devaluation has not been investigated to my knowledge, analyses for disinhibition were exploratory.

3.1 Participants

Ninety-one undergraduate students (61 females; age range 18 - 22) completed the study for partial course credit in their introduction to psychology course.

3.2 Materials and Design

Externalizing Spectrum Inventory–Brief Form. As with Study 1, the ESI-BF was used to measure disinhibition and substance abuse.

Spontaneous Eyeblink Rate (Tonic Dopamine Index). Spontaneous EBR was used as an index of striatal tonic dopamine. The same procedure that was described in Study 1 was followed for Study 2 to measure EBR.

Two-Stage Reinforcement Learning Devaluation Task. In order to test the effect of substance abuse on both reward learning and disengagement, a two-stage reinforcement learning task in combination with a devaluation procedure (Gillan, Otto, Phelps, & Daw, 2015) was utilized. During the reinforcement learning phase, participants completed two concurrent two-stage reinforcement learning tasks that were structurally equivalent, but had unique stimuli and rewards that were recorded separately. In this task, individuals gain experience with two situations ("states") and reward outcomes in order base future decisions on (Gläscher et al., 2010). These states were indicated by two difference trial types: gold trials and silver trials. On the first stage of each trial, individuals choose between two options, each of which has a distinct probability of transitioning to a unique second state stimulus (a point box; Figure 3). Stimuli in the second state then either provide a reward in the form of points or provide no reward. Each first-stage option has a 70% chance of leading to a "common" second-stage state and a 30% chance of leading to a "rare" second-stage state. The probability that the point boxes in the second stage contained a reward varied

across the task based on independent Gaussian random walks (SD=.025) with a minimum probability of 25% and maximum probability of 75%. Rewards were portrayed in points such the point boxes contained either 0 (unrewarded) or 100 (rewarded) points. After the second stage, the amount of points earned was stored in a gold (gold trial type) or silver (silver trial type) container. The cumulative amount earned was displayed throughout the reinforcement learning phase. For each trial, choosing an option in the first step cost 5 points. Thus, if the point box led to 0 points, then there was a net loss of 5 points for that trial and the 5 points were deducted from the cumulative total. If the point box yielded 100 points, then there was a net gain of 95 points that were added to the cumulative total. The optimal strategy in this phase was to learn which first-stage options yielded common point boxes in the second stage for each trial type and choose those options.

In the devaluation phase, participants were informed that one of their point containers (i.e., gold) was full, and that they would no longer be able to store points in that container. Even if the point box contained 100 points, participants were informed that the points would not be deposited in the container, and they would only be charged the 5 points for that trial. The other point container (i.e., silver) still had room, and they could still keep points for those trial types. Thus, the trial type where the container was full (i.e., gold) became devalued. The optimal strategy was to respond the same way in this phase as the reinforcement learning phase for the valued trial type that still has room (i.e, silver), and choose not to respond for the devalued trial type where the container was full (i.e., gold). The dependent measure as devaluation sensitivity which was computed by subtracting the number of devalued trials that participants responded on from the number of valued trials that participants responded on. A model-based and model-free metric was also computed based

on whether participants stayed or switched following a rewarded or unrewarded trial (model-free) and whether the option on the current trial led to a common or rare box (model-based).

3.3 Procedure

Participants first completed a 6-min assessment of EBR. They then completed demographic questionnaires (age, gender, and the number of hours slept the previous night), the ESI-BF Disinhibition and Substance Abuse subscales. Next, participants completed 200 trials of the reinforcement learning phase of the two-stage reinforcement learning devaluation task followed by 50 trials of the devaluation phase. Following the conclusion of these procedures, participants were debriefed about the study.

3.4 Data Analysis

In order to assess individual differences in model-free and model-based behavior during the reinforcement learning task, model-based and model-free metrics were computed. A mixed-effects logistic regression analysis for Reward (Rewarded vs. Unrewarded) X Transition type (Common vs. Rare) predicting stay probability was performed using the lme4 module of the R statistical package, version 3.0.1. Trial types (silver coded as 0, gold coded as 1) were computed independently in the analysis such that reward and common/rare states pertained to the previous outcomes for that trial type. For instance, for a trial in which participants selected an option on a gold trial type, the reward and common/rare outcome variables were computed based on the trial preceding that trial type. Reward, second state outcome (common or rare), their interaction, and participants were included as random effects. The specific syntax for the mixed-effects logistic regression was: Stay ~ Reward*Transition + (1 + Reward*Transition | Participant). From this analysis, individual beta weights were retrieved. The betas from the Reward variable were used as the model-

free metric, and the betas from the Reward X Transition type interaction were designated as the model-based metric.

To evaluate my first hypothesis regarding the association between the individual differences and performance measures (devaluation sensitivity, model-based index, and model-free index), correlations were computed. I predicted that a negative correlation would be observed between substance abuse and the devaluation sensitivity measure, whereas a positive correlation would be observed between substance abuse and the model-free index. In addition, two other regression analyses were conducted for this measure to test whether striatal dopamine interacts with substance abuse to influence devaluation sensitivity and model-free behavior.

Next, to assess relationships between substance abuse and model-based behavior, I performed regression analyses for this outcome that (1) tested the prediction that substance abuse would negatively predict model-based learning, and (2) explored the possibility that substance abuse interacts with striatal dopamine to influence model-based strategies. These analyses allowed for testing the separate and interactive effects of continuous variations in externalizing tendencies and dopamine levels on devaluation and model-free behavior. Given the lack of a priori predictions for trait disinhibition, I conducted both full and reduced model analyses for each outcome measure. The predictors in the full model included striatal dopamine (as indexed by EBR), substance abuse, disinhibition, the striatal dopamine X substance abuse interaction term, and the striatal dopamine X disinhibition interaction term. The reduced model predictors consisted of striatal dopamine (as indexed by EBR), substance abuse, and their interaction term.

3.5 Results and Discussion

Descriptive Statistics. Individual EBRs ranged from 4.17 to 40.17 blinks/min (M = 15.63, SD = 7.28). Scores on the ESI-BF Disinhibition subscale ranged from 0 to 46 (M = 12.21, SD = 7.71) and the range of scores on the ESI-BF Substance Abuse subscale ranged from 0 to 45 (M = 14.02, SD = 12.27).

Correlational Analyses. Correlations were computed between the independent measures (EBR index of striatal dopamine, ESI-BF Substance Abuse, and ESI-BF Disinhibition) and the outcomes measures (devaluation sensitivity index, model-free index, and the model-based index). Table 2 shows correlations between all variables. ESI-BF Disinhibition and Substance abuse subscales were positively correlated as expected (cf. Patrick et al., 2013), r = .49, p < .01. As predicted, substance abuse was negatively correlated with devaluation sensitivity, r = -.24, p < .05 (Figure 4). Disinhibition was not significantly correlated with any of the outcome measures. However, the EBR index showed a significant negative correlation with devaluation sensitivity (r = -.21, p = .04). None of the demographics variables (gender, age, sleep) were associated with devaluation sensitivity (ps > .40).

Regression Analysis for Devaluation Sensitivity. A hierarchical regression analysis was conducted to examine the effect of Substance Abuse, Disinhibition, and striatal dopamine (as indexed by EBR) on devaluation sensitivity. In the first step, the first-order terms (substance abuse, disinhibition, and striatal dopamine) were entered in the model. Omnibus prediction at this step of the model was significant, R^2 = .11, $F(3, 82)$ = 3.41, p = .02. Substance abuse was a significant predictor of devaluation sensitivity, β = -.31, p = .01. Disinhibition was also significant (β = .26, p = .03), but striatal dopamine was a

nonsignificant predictor at this step, *p*s > .10. In the second step of the model, striatal dopamine X substance abuse and striatal dopamine X disinhibition interaction terms were entered in the model. The omnibus prediction at this step approached significance, $\Delta R^2 = .02$, $F(5,80) = 2.06$, $p = .08$, but none of the individual predictors emerged as significant, $p > .10$.

I also examined results for a reduced model including substance abuse, striatal dopamine, and their interaction term as predictors of devaluation sensitivity.[2] In the first step of the model, substance abuse was a marginally significant predictor, $\beta = -.18$, $p = .09$, while EBR was nonsignificant, $p > .10$. However, the omnibus prediction at the step was nonsignificant, $p = .11$. Similarly, when the interaction term was entered in the second step of the model, the omnibus test and the predictors were nonsignificant, $p > .10$. The reduced model with disinhibition, striatal dopamine, and the substance abuse X striatal dopamine interaction did not reveal any significant effects, *ps* > .15.

Regression Analysis for the Model-Free Index. A parallel set of regression analyses was used to test for effects of the predictor variables on model-free behavior. In the first step of the model, none of the first-order predictors were significantly associated with the model-free index (*ps* > .07), and the omnibus test was nonsignificant, $p = .26$. In the second step of the model when the interaction terms were added to the model, the omnibus test was significant, $\Delta R^2 = .08$, $F(5,79) = 2.33$, $p = .05$. Substance abuse ($\beta = -1.04$, $p < .01$) and the striatal dopamine X substance abuse interaction term ($\beta = 1.08$, $p < .01$) were significant predictors of model-free behavior during the reinforcement learning phase. While

[2] I also conducted logistic regression analyses for the data in Study 2 as the distribution for devaluation sensitivity was relatively bimodal. For the full model, substance abuse was significantly related to devaluation sensitivity in the first step of the model ($\beta = -.26$, $p = .04$), although the omnibus test was nonsignificant, $F(3, 80) = 1.76$, $p = .16$. The interaction terms were not significant in the second step of the full model, *p*s > .20. However, in the reduced model in which substance abuse, striatal dopamine, and their interaction term were included as predictors of devaluation sensitivity (dichotomized), substance abuse ($\beta = -.17$, $p = .12$) did not reach significance.

disinhibition was a marginally significant predictor (β = .55, p = .09), EBR and the striatal dopamine X disinhibition interaction were nonsignificant predictors, p > .30. Thus, as with the devaluation sensitivity regression analysis, a reduced model with substance abuse, striatal dopamine and their interaction terms was also performed.

As in the full model, neither substance abuse nor striatal dopamine predicted significantly in the first step of this reduced model, and the omnibus prediction coefficient was nonsignificant, ps > .20. In the second step of the model, however, substance abuse (β = -.71, p < .05) and the striatal dopamine X substance abuse interaction (β = .82, p < .05) emerged as significant predictors. The omnibus test was nonsignificant, however, ΔR^2 = .06, $F(3,81) = 2.02$, p = .12.

Figure 5 shows simple regression lines for the effect of substance abuse scores on model-free choices at (a) the mean for striatal dopamine, (b) one standard deviation above the mean for striatal dopamine, and (c) one standard deviation below the mean for striatal dopamine. Striatal dopamine and substance abuse variables were centered prior to creating the centered interaction terms. The simple regression slope coefficients when centered at the mean (β = -.09, p = .48) and at one standard deviation below the mean (β = .36, p = .09) were not significant, but the simple regression slope coefficient centered at one standard deviation above the mean significantly predicted model-free behavior, β = -.53, p < .01. At high levels of striatal dopamine, individuals with higher substance abuse tendencies tended to rely less on model-free strategies during the reinforcement learning phase of the task. This result suggests that the effect of increasing levels of substance abuse on model-free strategies varied as a function of tonic dopamine levels such that individuals reporting high levels of

substance abuse with high striatal tonic dopamine showed the least reliance on strategies that depended on recent reward outcomes.

The reduced model with disinhibition, striatal dopamine, and the disinhibition X striatal dopamine interaction revealed no significant main effects, and the interaction was not significant, *p*s > .10.

Regression Analysis for the Model-Based Index. The same full and reduced model analyses were conducted for the model-based index as the devaluation sensitivity and model-free index. All predictors in the first step of the model and the omnibus test were nonsignificant, $p > .10$. Similarly, in the second step of the model, none of the other predictors or the omnibus test were significant, *p*s > .30. Although reduced models were also performed, they did not reveal any significant effects in either the first or second step of the model, *p*s > .30.

Discussion. The results of Study 2 demonstrate that substance abuse, independent of striatal dopamine, is negatively associated with devaluation sensitivity, or reward disengagement. Furthermore, the effect of substance abuse on model-free reinforcement learning depends on striatal tonic dopamine. Specifically, individuals with substance abuse problems and high levels of striatal tonic dopamine were less reliant on model-free strategies. This result is in line with the results of Study 1 that showed that at high levels of striatal dopamine, substance abuse is positively associated with reward learning on a task in which model-free strategies are counterproductive. Thus, the consistency of these findings across different tasks in Study 1 and 2 suggests that high levels of striatal tonic dopamine may be a protective factor against reliance on automatic, reward-driven strategies in individuals with substance use problems.

Striatal dopamine therefore appears to influence reward salience during reinforcement learning in the contexts of extended learning. These data suggest that once reward-outcome associations are well learned, individuals with substance abuse problems—regardless of variation in striatal tonic dopamine levels—have difficulty disengaging from habitual responding. While these results suggest that the effects of striatal tonic dopamine influence reward learning, striatal dopamine does not appear to moderate the effects of substance abuse on devaluation, or reward disengagement.

Moreover, as predicted, trait disinhibition was not associated with reward learning strategies or devaluation sensitivity in either experiment. These findings are in line with the results of Study 1 that showed that substance abuse and disinhibition exert distinct effects on reward processing depending on individual differences in striatal dopamine levels: Substance abuse is more strongly linked with reward learning, whereas disinhibition is associated more with reward wanting.

4. STUDY 3: EFFORT-BASED DECISION-MAKING (EFFORT VALUATION)

Like Study 2, Study 3 was also intended to be a follow-up on the results of Study 1. Because low tonic dopamine levels are predicted to enhance reward wanting in individuals with more disinhibitory tendencies, striatal dopamine may also interact with disinhibition to influence physical and/or cognitive effort-based decision-making. To address this issue, Study 3 examines the interaction between externalizing proneness and striatal dopamine on both physical and cognitive effort expenditure for rewards.

While physical effort expenditure in humans has been widely studied using the Effort Expenditure for Rewards Task (EEfRT), methods for assessing cognitive effort are more nuanced. Current designs to test cognitive effort include choosing different levels of the *N*-back working memory test for easy (i.e., 1-back) versus difficult (i.e., 3-back) selections (Culbreth, Westbrook, & Barch, 2016; Westbrook et al., 2013) and choosing easy versus difficult math problems (Vassena et al., 2014). However, these designs risk confounds with working memory capacity and math ability. The present study was designed to address these confounds in two ways. First, I included a measure of working memory capacity in order to account for individual differences in cognitive resources. Secondly, the task utilized a novel category learning paradigm in which individuals chose to categorize a small number of stimuli (easy task) or a larger number of stimuli (difficult task) on each trial. I hypothesized that good performance in this task would rely less heavily on working memory than current cognitive effort methods. Including both physical and cognitive effort tasks allowed for determining the generalizability of effort effects across domains.

Previous research suggests that reward wanting and willingness to exert effort in order to receive a reward is mediated by dopamine signaling in the ventral striatum (Berridge

& Robinson, 1998; Correa, Carlson, Wisniecki, & Salamone, 2002; Salamone, Correa, Farrar, & Mingote, 2007). Despite reward wanting (reward valuation) and effort-based decision-making (effort valuation) defined as distinct constructs in the RDoC matrix, this finding in the animal literature suggests that effort-based decision-making may be closely related to reward wanting. Animal research suggests that high D_2 receptor signaling (high tonic dopamine) in the ventral striatum enhances willingness to exert effort for larger rewards, while low D_2 receptor signaling (low tonic dopamine) enhances preferences for less effortful, small rewards (Trifilieff et al., 2013; Trifilieff & Martinez, 2014). In humans *d*-amphetamine, which increases both tonic and phasic dopamine (Daberkow et al., 2013), enhances willingness to exert effort for rewards (Wardle et al., 2011). Furthermore, in a recent review, phasic striatal dopamine has been proposed to encode reward prediction errors of task costs and benefits, while tonic dopamine may influence working memory maintenance while engaging in the task (Westbrook & Braver, 2015). However, it is unclear how dopamine interacts with disinhibition and whether phasic or tonic dopamine levels drive willingness to exert effort for rewards in humans. Given these findings, it is possible that individuals with more disinhibitory tendencies and high tonic dopamine levels may exert more effort for larger rewards, while more impulsive individuals with low tonic dopamine may prefer less effortful, smaller rewards. While there has been exceptionally little work aimed at examining the effect of drug use and effort expenditure for rewards (Saunders, Richard, & Janak, 2015), some work suggests that effort-related processes are critical to drug reinforcement (Salamone, Correa, Farrar, & Mingote, 2007). However, given that Study 1 demonstrated that in substance users, low striatal tonic dopamine was associated with increased learning of options that maximized immediate rewards, it is possible that they may

also be more willing to exert effort to attain those immediate rewards. As a result, I predicted that an interaction between substance abuse and striatal dopamine, such that individuals with low tonic dopamine and high substance abuse tendencies would exert more effort to attain rewards.

4.1 Participants

One hundred and thirteen undergraduate participants (77 female, age range 18 – 24) completed the cognitive and physical effort tasks and received partial course credit for their introduction to psychology course. Due to experimenter error, three participants did not complete the physical effort task, two participants did not complete the cognitive effort task, and six participants did not complete the working memory measure (final N = 104).

4.2 Materials and Design

Externalizing Spectrum Inventory–Brief Form. As with Studies 1 and 2, the ESI-BF was used to measure disinhibition and substance abuse.

Spontaneous Eyeblink Rate (Tonic Dopamine Index). Spontaneous EBR was used as an index of striatal tonic dopamine. The same procedure that was described in Study 1 was followed for Study 3 to measure EBR.

Physical Effort Expenditure for Rewards Task. In the physical effort expenditure for rewards task (EEfRT; Treadway et al., 2009), individuals chose between an easy (low effort) or difficult (high effort) task in order to try to receive a reward (Figure 6a). Thus, this task was designed to assess physical effort expenditure. For each trial, participants were presented with the probability that they would receive the reward. Probabilities of reward were either low (12%) medium (50%), or high (88%) on each trial. Then, they chose either the easy or difficult task. The easy task always offered the chance to win $1.00. The

difficult task offered a chance to win a value that varied between $1.25 and $4.25 on each trial. For easy trials, participants needed to press the spacebar 30 times in seven seconds in order to successfully have a chance to win $1.00. For difficult trials, participants needed to press the spacebar 100 times in 21 seconds to have a chance to win the reward offered for that trial. Participants received feedback on whether or not they successfully completed the task, and then received additional feedback about whether they won the amount based on the probability shown at the beginning of the trial. At the end of the task, two of the win trials were randomly selected, and participants received the actual amount they won on those two trials. The dependent measure was the average proportion of difficult selections.

Cognitive Effort Expenditure for Rewards Task. In the cognitive effort task, participants completed a unidimensional rule-based category learning task. Individuals needed to attend to a single stimulus dimension to learn the correct rule and use it to categorize each stimulus into one of two categories. Stimuli were lines that varied in length and orientation. However, only of these dimensions was relevant to classify the stimuli. More specifically, only the length of the lines defined the category rule, so that short lines belonged in category 1 and long lines belonged in category 2. Thus, participants needed to attend to length, but ignore orientation to correctly categorize the stimuli.

Participants first completed a training phase comprised of 50 trials in which they learned the rule that differentiated each category. During the training phase, participants viewed a stimulus, selected either category 1 (i.e., short lines) or 2 (i.e., long lines), and then received feedback on whether their categorization was correct or incorrect. Next, a 50-trial test phase with the cognitive effort component was presented (Figure 6b). The effort portion of the task was designed to closely mirror the physical effort task. To manipulate cognitive

effort, participants were asked to choose between an easy (low effort) or difficult (high effort) task on each trial. Similar to the physical effort task, for each trial participants were presented with the probability that they would receive the reward. Probabilities of reward were either low (12%) medium (50%), or high (88%) on each trial. The easy task always offered the chance to win $1.00. On easy trials, participants were asked to categorize three stimuli in a row correctly within seven seconds in order to have an opportunity to earn the reward. On difficult trials, participants were asked to categorize ten stimuli in a row correctly within 21 seconds in order to have a chance to earn a reward. If individuals chose the easy task and successfully completed it, then they may receive $1, depending on the probability of reward. If they successfully completed the difficult task, then they may receive an amount between $1.25 and $4.25. Incorrect categorizations resulted in $0 earned. As with the physical EEfRT, at the end of the task, two of the win trials were randomly selected, and participants received the actual amount they won on those two trials. The dependent measure was the average proportion of difficult selections.

Working Memory Capacity Assessment. To measure working memory capacity, the operation span (OSPAN) task was employed (Turner & Engle, 1989). Participants viewed a math problem (i.e., (2 * 5) + 4)) for two seconds, and then a new screen with a number (i.e., 15) displayed. Participants needed to respond whether the number on the screen correctly or incorrectly answered the math problem they previously viewed by responding "true" or "false". After making a response, participants received feedback and then a letter appeared. After 3 – 7 math problem and letter trials, participants were asked to recall the letters they viewed in order. Participants were instructed to both maximize accuracy in letter recall performance and maintain a math accuracy score of at least 85%. Thus, participants needed

to both correctly answer the math problems while also maintaining a string of letters in working memory. The OSPAN contained 75 total trials. Working memory capacity was computed as the sum of correctly recalled letter spans.

4.3 Procedure

In this within-subjects design, participants began with a 6-min assessment of EBR. Next, they completed the physical and cognitive effort tasks in a counterbalanced order. The physical effort task entailed 50 effort trials, and the cognitive effort task included 50 training trials and 50 effort trials. Each task was designed to take 15 – 20 minutes so that they were approximately equivalent in terms of fatigue demands. Upon completion of both effort tasks, participants completed the demographics questions, ESI-BF Disinhibition subscale, and Substance Abuse subscale, and then completed the OSPAN working memory assessment. This study was designed to take approximately 90 minutes total. Following completion of the study, participants received their monetary reward from both tasks and then were debriefed about the study.

4.4 Data Analysis

As with Studies 1 and 2, correlations between the independent (EBR, substance abuse, disinhibition), and dependent measures (proportion of difficult selections for each task) were performed. In this study, correlational analyses between the OSPAN working memory scores and the dependent measures were also conducted to determine if working memory should be included as a covariate in further analyses. To test the hypothesis that striatal dopamine will interact with disinhibition to influence effort expenditure for rewards, separate regressions for each dependent measure were conducted with EBR, substance abuse, disinhibition and the EBR X substance abuse and EBR X disinhibition interactions as

predictors. Given the specific predictions for the EBR X disinhibition, a reduced model with just EBR, disinhibition, and EBR X disinhibition was also performed.

4.5 Results and Discussion

Descriptive Statistics. Individual EBRs ranged from 2.17 to 41.20 blinks/min (M = 13.97, SD = 7.26). Scores on the ESI-BF Disinhibition subscale ranged from 0 to 39 (M = 13.97, SD = 7.99) and the range of scores on the ESI-BF Substance Abuse subscale ranged from 0 to 45 (M = 15.95, SD = 12.97). In the physical effort task, average proportions of difficult selections across the task ranged from 0.02 – 1.00 (M = .37, SD = .22). In the cognitive effort task, average proportions of difficult selections ranged from 0.00 – 1.00 (M = .42, SD = .27). Thus, overall rates of difficult selections between the physical and cognitive effort tasks were relatively comparable. Although participants selected difficult task in the cognitive effort task numerically more than they did in the physical effort task, this difference was nonsignificant, $t(107) = 1.63$, $p = .11$.

Order Effects. An independent samples t-test was conducted to determine whether order effects due to counterbalancing influenced physical or cognitive effort expenditure for rewards. The t-test for physical effort showed a marginally significant effect of order. Individuals who completed the physical effort task first (M = .42, SD = .24) selected more difficult selections in the physical effort task than those that completed the cognitive effort task first (M = .33, SD = .42, SD = .20), $t(108) = 2.01$, $p = .047$. In contrast, there was no significant order effects of the cognitive effort task, $t(109) = -1.27$, $p = .21$. Thus, order was included as a covariate in subsequent regression analyses.

Correlational Analyses. Correlations were computed between the independent measures (EBR index of striatal dopamine, ESI-BF Substance Abuse, and ESI-BF

Disinhibition) and the outcomes measures (average difficult selections in the physical and cognitive effort tasks). Correlations between all variables are shown in Table 3. Similar to Studies 1 and 2, ESI-BF Disinhibition and Substance abuse subscales were positively correlated, $r = .36$, $p < .01$. Correlational analyses were also performed to determine whether OSPAN working memory scores should be included as a covariate in subsequent regression analyses. OSPAN scores were positively related to the proportion of difficult selections in the cognitive effort task, $r = .29$, $p < .01$, but were not significantly correlated with difficult selections in the physical effort task, $r = -.05$, $p = .64$. Moreover, the proportion of difficult task selections on the physical and cognitive effort tasks were not significantly correlated, $r = .11$, $p = .26$. This result suggests that physical and cognitive effort expenditure measures are not synonymous, but are instead distinct constructs. No other significant correlations were observed.

Regression Analysis for the Physical Effort Task. A hierarchical regression analysis was conducted to examine the effect of Substance Abuse, Disinhibition, and striatal dopamine (as indexed by EBR) on the average proportion of difficult selections in the physical effort task. In the first step, the OSPAN and Order covariates were entered into the model. The omnibus test was nonsignificant at this step, $R^2 = .04$, $F(2, 101) = 2.04$, $p = .14$, and Order was marginally significantly associated with physical effort expenditure ($\beta = -0.19$, $p = .053$), but the OSPAN working memory measure was a nonsignificant covariate, $p = .63$. In the second step, the first-order terms (substance abuse, disinhibition, and striatal dopamine) were entered in the model. Omnibus prediction at this step of the model was nonsignificant, $\Delta R^2 = .02$, $F(5, 98) = 1.22$, $p = .31$, and none of the first-order predictors were significant, ps > .40. In the third step of the model when the EBR X Substance Abuse

and EBR X Disinhibition interaction terms were added, the omnibus test remained nonsignificant, $\Delta R^2 = .05$, $F(7, 96) = 1.66$, $p = .13$. However, the EBR X Disinhibition interaction was a significant predictor of physical effort expenditure for rewards, $\beta = -0.25$, $p = .03$. None of the predictors were significant, ps > .10.

Given the emerging effects from the EBR X Disinhibition interaction, a reduced model with disinhibition, striatal dopamine, and the disinhibition X striatal dopamine interaction was also conducted. However, the results of this reduced model revealed no significant main effects, and the interaction was not significant, ps > .10.

Figure 7 shows simple regression lines for the effect of disinhibition scores on the proportion of difficult selections in the physical effort task at (a) the mean for striatal dopamine, (b) one standard deviation above the mean for striatal dopamine, and (c) one standard deviation below the mean for striatal dopamine. Striatal dopamine and disinhibition variables were centered prior to creating the centered interaction terms. The simple regression slope coefficients when centered at the mean ($\beta = -.12$, $p = .25$) and at one standard deviation above the mean ($\beta = .16$, $p = .33$) were not significant, but the simple regression slope coefficient centered at one standard deviation below the mean significantly predicted the proportion of difficult task selections during the physical effort task, $\beta = -.45$, $p = .02$. At low levels of striatal dopamine, individuals with more disinhibitory tendencies tended to choose fewer difficult, physically effortful options. This finding indicates that the effect of diminished levels of disinhibition on physical effort expenditure for reward varied as a function of tonic dopamine levels. Specifically, as predicted, individuals reporting high levels of disinhibitory behavior with low striatal tonic dopamine were significantly less willing to exert more physical effort for larger rewards.

Regression Analysis for the Cognitive Effort Task. An additional regression analysis was performed to assess the interaction between externalizing proneness and striatal dopamine on cognitive effort expenditure for rewards. As with the physical effort task regression, in the first step of the model, the Order and OSPAN working memory measure was added as a covariate. Omnibus prediction at this step of the model was significant, R^2 = .09, $F(2, 102) = 5.22$, $p < .01$. OSPAN working memory was a significant predictor of cognitive effort expenditure ($\beta = .29$, $p < .01$), but order effects were not significantly predictive of cognitive effort ($\beta = .09$, $p = .36$). In the second step of the model, the first-order terms (substance abuse, disinhibition, and striatal dopamine) were entered. The omnibus test was marginally significant at this step, $\Delta R^2 = .001$, $F(5, 99) = 2.04$, $p = .08$, but none of the first-order terms were significant predictors, *p*s > .80. In the final step of the model, the EBR X Disinhibition and EBR X Substance Abuse interaction terms were entered into the model. The omnibus prediction was significant at this step of the model, $\Delta R^2 = .045$, $F(7, 97) = 2.12$, $p = .049$. The OSPAN covariate ($\beta = .28$, $p < .01$) and the EBR X Substance Abuse interaction term ($\beta = 0.22$, $p = .046$) emerged as significant predictors of cognitive effort expenditure for rewards.

Figure 8 shows simple regression lines for the effect of substance abuse scores on the proportion of difficult selections in the cognitive effort task at (a) the mean for striatal dopamine, (b) one standard deviation above the mean for striatal dopamine, and (c) one standard deviation below the mean for striatal dopamine. Striatal dopamine and substance abuse variables were centered prior to creating the centered interaction terms. The simple regression slope coefficients when centered at the mean ($\beta = .01$, $p = .93$) and at one standard deviation above the mean ($\beta = -.26$, $p = .10$) were not significant, but the simple regression

slope coefficient centered at one standard deviation below the mean significantly predicted the proportion of difficult task selections during the cognitive effort task, $\beta = .43$, $p = .01$. At low levels of striatal dopamine, individuals with higher substance abuse tendencies tended to choose more difficult, cognitively effortful options. This result suggests that the effect of increasing levels of substance abuse on cognitive effort expenditure for reward varied as a function of tonic dopamine levels. Individuals reporting high levels of substance abuse with low striatal tonic dopamine were willing to exert more cognitive effort in an attempt to attain larger rewards.

Discussion. The results of this study support my hypothesis that striatal dopamine would moderate the effects of trait disinhibition on effort expenditure for rewards. In particular, at low levels of tonic dopamine, individuals with high disinhibitory tendencies were more inclined to choose smaller, less effortful reward options on the physical effort task. This finding is also consistent with the results of Study 1 on reward wanting, as well as other previous research on D_2 receptor availability and effort expenditure (Daberkow et al., 2013; Trifilieff et al., 2013; Trifilieff & Martinez, 2014; Wardle et al., 2011). Contrary to my prediction that more disinhibited individuals with high tonic dopamine levels would have a greater tendency to exert more effort for larger rewards, the simple slopes regression for one standard deviation above the mean of striatal dopamine was nonsignificant. However, the direction of this relationship was positive, suggesting a potential weak relationship between high dopamine levels and high effort expenditure for rewards in individuals with high levels of disinhibitory tendencies. Additionally, in comparison with Studies 1 and 2, disinhibition scores in this study had a smaller range that was more positively skewed. It is therefore

possible that with a broader range of disinhibition scores, this relationship could become significant.

As predicted, a significant interaction between striatal dopamine and substance on cognitive effort expenditure was observed. In particular, at low levels of tonic dopamine, substance abuse was associated with increased cognitive effort expenditure for larger rewards. Moreover, a statistical trend was also observed at high levels of dopamine such that substance abuse was associated with reduced effort expenditure for larger rewards. This result builds on the reward learning findings from Study 1. Collectively, these results indicate that individuals with low tonic dopamine and higher substance abuse tendencies show poor learning of rewards that lead to long-term rewards and are willing to exert more effort for larger immediate rewards. Thus, among individuals with substance abuse problems, low striatal tonic dopamine levels appears to be associated with both enhanced learning of choices that maximize immediate rewards, as opposed to long-term rewards, and increased effort expenditure to attain immediate rewards.

Importantly, the relationship between striatal dopamine and disinhibition on effort expenditure for rewards was specific to physical effort and did not generalize to cognitive effort expenditure. In direct contrast to this relationship, the interaction between striatal dopamine and substance abuse on effort expenditure was specific to the cognitive effort task and did not generalize to the physical effort task. Furthermore, effort expenditure for physical and cognitive effort tasks was not significantly correlated. Together, these results suggest that effort expenditure for rewards appears domain-specific.

Previous neuroimaging work has demonstrated that motivation for large rewards and high effort expenditure on math problems show overlapping activation in the ventral striatum

and anterior cingulate cortex (Vassena et al., 2014). Physical effort expenditure for rewards has been shown to rely on the anterior putamen area of the striatum (Kurniawan et al., 2010). Additionally, theoretical modeling work suggests that while context specific effects may govern willingness to expend effort for rewards, physical effort and cognitive effort entail similar neural circuitry. This model theorizes that deficits in physical and cognitive effort exertion should be correlated (Verguts, Vassena, & Silvetti, 2015). However, the experimental data presented in this study suggest otherwise; specifically, willingness to exert physical effort and cognitive effort are indeed not correlated. Thus, the results of this study challenge existing theoretical work on effort expenditure for rewards and highlight the need to compare the neural and behavioral correlates of each of these types of effort expenditure. For example, one possibility is that physical effort relies more on motor demands, while cognitive effort may instead depend more on cognitive stability, resistance to distraction, and cognitive resources. These factors may be integral to reward motivation and may have different "costs" to some individuals compared to others. Thus, physical and cognitive effort expenditure may be particularly sensitive to individual differences.

5. STUDY 4: COMPETITION BETWEEN INHIBITION AND REWARD

The purpose of Study 4 was to capitalize on the externalizing proneness and reward processing findings in Studies 1 through 3 in order to try to determine how cognitive control is affected by reward motivation in individuals with externalizing tendencies. Broadly, externalizing behaviors are characterized by dysregulation in the cognitive control and positive valence systems RDoC domains. Like reward processing, cognitive control is critically dependent on striatal dopamine, particularly dopamine D2 receptor functioning (Colzato et al., 2010). An abundance of research suggests that individuals with substance abuse problems tend to have deficits in response inhibition, as indicated by slower stop signal reaction times (SSRTs) on the stop signal task (Colzato et al., 2007; Ersche et al., 2011; Goudriaan et al., 2005; Li et al., 2006; Monterosso et al., 2005; Moreno et al., 2012; Rubio et al., 2008; Smith & Mattick, 2013). However, while trait disinhibition and inhibitory motor control may intrinsically seem related, a meta-analysis on the association between trait impulsivity and SSRTs showed only a weak, nonsignificant relationship (Lijffijt, et al., 2004). Other work suggests the possibility that drug users may have had increased trait disinhibition before they start abusing drugs (Van der Plas et al., 2009; Vonmoos et al., 2013). Because impulsivity and substance use are highly correlated, it is possible that impairment in response inhibition is due to a pre-existing liability for impulse-control and substance use problems, rather a consequence of regular drug use.

Given these previous findings on the associations between externalizing proneness and inhibitory control as well as the findings from the present investigation, the task in Study 4 was designed to incorporate a reward motivation component into a classic inhibitory control task: the stop signal task. This paradigm allows for testing individual differences in

the ability to voluntarily inhibit a prepotent or ongoing motor response (Logan & Cowan, 1984). Furthermore, the SSRT measure from this task provides an estimated duration of the time that it takes to inhibit this response, such that longer SSRTs are indicative of poorer inhibitory control.

The findings presented in Studies 1 – 3 of this investigation collectively suggest that trait disinhibition is more strongly associated with reward wanting, while substance abuse is more closely related to reward learning, devaluation, and effort expenditure for rewards. Because both disinhibition and substance abuse are associated with reward motivation, despite different associations with different components of reward processing, it was predicted that:

(1) Disinhibition and substance abuse would be associated with poorer response inhibition, as indicated by slower SSRTs and reduced Stop trial accuracy, in the standard stop signal task.

(2) Individuals with high disinhibition and low tonic dopamine (enhanced reward wanting) would show improved inhibitory control (faster SSRTs and higher accuracy) when there was a reward offered for correct inhibition relative to when there was not a reward offered. This result is expected because increased reward wanting may enhance motivation for immediate rewards, which can only be obtained with accurate inhibitory control on the task in Study 4. Thus, desire for immediate rewards is expected to enhance inhibitory control in this group.

(3) Individuals with high substance abuse and low tonic dopamine (poorer reward learning and increased effort expenditure for rewards) would show poorer inhibitory control (slower SSRTs) when there was a reward offered for correct inhibition

relative to when there was not a reward offered. The results from Studies 1 – 3 suggest that the high substance abuse, low dopamine group shows poorer reward learning and increased effort expenditure for large rewards. These findings suggest that this group is motivated by immediate rewards, even when it leads to a greater effort cost or maladaptive long-term performance. Thus, in an effort to obtain immediate rewards, this group may also be more likely to risk an associated response time "cost," as indicated by slower SSRTs, when rewards are provided for correct inhibition.

5.1 Participants

Ninety-five undergraduate students (62 females; age range 18 - 23) completed the study for partial course credit in their introduction to psychology course.

5.2 Materials and Design

Externalizing Spectrum Inventory–Brief Form. In line with the previous studies in this investigation, the ESI-BF was used to measure trait disinhibition and substance abuse tendencies.

Spontaneous Eyeblink Rate (Tonic Dopamine Index). Spontaneous EBR was used as an index of striatal tonic dopamine. The same procedure that was described in Study 1 was followed for Study 4 to measure EBR.

Stop Signal Reward Task. In the first phase of the task (Figure 9a), participants performed a standard stop signal task in which a green left or right arrow was presented (Logan, Schachar, & Tannock, 1997; Moreno et al., 2012). In line with instructions given in previous research (Congdon et al., 2012), on Go trials, participants were instructed to respond as quickly as possible, while keeping in mind that a red arrow may appear

occasionally, by pressing the left arrow key when the arrow faced leftward and the right key when the arrow faced rightward (see Appendix C for exact instructions). If the arrow turned red after the original arrow was presented, then participants were instructed to inhibit their response on that trial. The red arrow cue was presented at 200ms, 300ms, or 400ms (randomly varied) after the original arrow was presented. Participants had up to 2 seconds to respond on each trial. After they made a response, the arrow would disappear and the screen would be black (for up to 1.9 seconds) until the next trial began. A 1 second delay, indicated by a black screen, was shown before the ITI. The inter-trial interval (ITI) varied between 700ms, 1000ms, or 1300ms (randomly varied) after the end of the previous trial and appeared as a white fixation cross, which was shown for 1 second.

In the second phase of the task (Figure 9b), participants received instructions that they would now have an opportunity to earn a monetary bonus of up to ten dollars based on their performance in the rest of the task. They were told that the bonus was based on both how quickly and accurately they responded on go trials and how accurately they responded on stop trials. Instructions also indicated that if they responded too slowly or made too many mistakes on go trials, then they may not receive a bonus even if they correctly stopped their response on stop trials. In reality, however, half of the Stop trials were accompanied by a reward of $0.50 for correct inhibition. The reward feedback was presented immediately before the ITI screen for 1 second. The probability of each trial being a Go trial was 75%, and the probability of a Stop trial was 25%. For both the standard stop signal and reward phase, the range of Go trials across participants was 141 – 162 trials. Reaction time (RT) and accuracy for Go and Stop trials were measured for each phase separately. Additionally, a

difference measure between unrewarded phase and reward phase stop signal reaction times (SSRTs), Go trial RT, and Stop trial accuracy were computed.

5.3 Procedure

Participants began the session with a 6-min assessment of EBR. Participants then completed demographics questionnaires (gender, age, hours slept), the ESI-BF Disinhibition and Substance Abuse subscales, and then completed 12 (~75% Go trials, ~25% Stop trials) practice trials of the standard stop signal task. Participants completed 200 trials (~75% Go trials and ~25% Stop trials) of the standard stop signal phase, and 200 trials of reward phase of the task (~75% Go trials and ~25% Stop trials). Upon completion of the study, participants received their monetary bonus and were debriefed about the nature of the study.

5.4 Data Analysis

Correlations between independent variables (EBR, substance abuse, and disinhibition) and dependent measures (SSRT, Go trial RT, Stop trial accuracy, rewarded – unrewarded SSRT, rewarded – unrewarded Go trial RT, rewarded – unrewarded Stop trial accuracy) were performed. To compute SSRT, the integration approach was employed (Verbruggen & Logan, 2009). In this approach, the Go trial reaction times are rank ordered. Then, the average unsuccessful stop trials, or errors, are multiplied by the number of Go trials. The rank ordered Go trial RT that corresponds to that value is the RT value. For example, if a participant was unsuccessful on 36% of stop trials and completed 150 trials, the RT value would correspond to the RT for the 54^{th} percentile. The average stop signal delay (.27s - .34s) is then subtracted from the RT value. Additionally, regression analyses with EBR, substance abuse, disinhibition, and their interaction terms will be performed separately for each of the dependent measures. A reduced model with EBR, disinhibition, and EBR X

disinhibition and a model with EBR, substance abuse, and EBR X substance abuse was also performed when one of interaction terms was significant or trended towards significance.

5.5 Results and Discussion

Descriptive Statistics. Individual EBRs ranged from 2.50 to 40.80 blinks/min (M = 14.82, SD = 8.55). Scores on the ESI-BF Disinhibition subscale ranged from 0 to 33 (M = 11.61, SD = 6.37) and the range of scores on the ESI-BF Substance Abuse subscale ranged from 0 to 51 (M = 15.71, SD = 13.31).

In the standard stop signal phase of the task, Go trial accuracy rates ranged from .96 – 1.0 (M = .99, SD = .01), and Stop trial accuracy rates ranged from 0.0 – 1.0 (M = .52, SD = .28). Average Go RT ranged from 0.34s – 0.88s (M = .55, SD = .12), and average SSRT ranged from 0.6s - .53s (M = .21, SD = .07). In the rewarded phase of the stop signal task, Go trial accuracy rates ranged from .81 = 1.0 (M = .99, SD = .02), and Stop trial accuracy ranged from 0 – 1 (M = .64, SD = .27). Average Go RT in the reward phase ranged from .35s - .95s (M = .58, SD = .12), and average SSRT ranged from .12s - .49s (M = .20, SD = .06). Paired samples t-tests between these dependent measures in the standard stop signal and reward phase were also computed. No significant differences in Go trial accuracy (p = .40) or SSRT (p = .15) between tasks were observed. However, participants were significantly more accurate in inhibiting their response on Stop trials in the reward phase than in the standard phase, $t(94) = -6.10$, $p < .001$. Participants were also significantly slower in their Go trial response times in the reward phase and in the standard phase, $t(94) = -2.78$, $p < .01$. One possible implication of these results is that providing a reward for correct inhibition successfully improved inhibitory control across all participants, but this came at a cost of approximately a 250ms delay in response for Go trials in the reward phase. However, it is

important to note that the reward phase was performed after the standard phase, and thus this difference could also be due to an effect of practice, rather than an effect of providing a reward.

Correlational Analyses. Correlations were computed between the independent measures (EBR index of striatal dopamine, ESI-BF Substance Abuse, and ESI-BF Disinhibition) and the outcomes measures (Standard stop signal task Stop trial accuracy, Go trial RT, SSRT, and rewarded – unrewarded Stop trial accuracy, Go trial RT, and SSRT). Correlations between all variables are presented in Table 4. ESI-BF Disinhibition and Substance abuse subscales were positively correlated, $r = .37$, $p < .01$. Of the demographics variables, age was significantly correlated with SSRT ($r = .26$, $p = .01$), rewarded – unrewarded phase SSRT ($r = .24$, $p = .04$), and rewarded – unrewarded phase Stop trial accuracy ($r = .27$, $p < .01$). However, no other factors showed significant correlations, ps > .10.

Regression Analysis for Stop Accuracy in the Standard Stop Signal Phase. A hierarchical regression analysis was performed to test the effect of Substance Abuse, Disinhibition, and striatal dopamine (as indexed by EBR) on Stop trial accuracy in the standard stop signal phase of the task. In the first step, age was entered into the model as a covariate. However, the omnibus prediction at this step was nonsignificant, $R^2 = .01$, $F(1, 93) = 0.56$, $p = .46$. In the second step of the model, the first-order terms (substance abuse, disinhibition, and striatal dopamine) were added. Omnibus prediction at this step remained nonsignificant, $\Delta R^2 = .04$, $F(4, 90) = 1.20$, $p = .32$. Disinhibition was a marginally significant predictor ($\beta = -0.20$, $p = .07$), but none of the other factors significantly predicted Stop trial accuracy, ps > .30. In the last step, the EBR X Substance Abuse and EBR X

Disinhibition interaction terms were entered into the model. The omnibus test was nonsignificant $\Delta R^2 = .003$, $F(6, 88) = 0.83$, $p = .55$, and the none of the predictors were significantly associated with Stop trial accuracy, ps > .30.

Regression Analysis for Go Trial Reaction Time in the Standard Stop Signal Phase. The same hierarchical regression analysis was conducted for Go trial RT as for Stop trial accuracy. The omnibus test for the age covariate in the first step was nonsignificant, $p = .88$. In the second step of the model, all predictors and the omnibus test were nonsignificant, ps > .10. Similarly, in the third step of the model, none of the interaction terms, first-order predictors, or the omnibus test was significant, ps > .20.

Regression Analysis for SSRT in the Standard Stop Signal Phase. A parallel regression analysis was performed for SSRT in the standard stop signal portion of the task. Age was entered as a covariate in the first step of the model, and the omnibus test was significant, $R^2 = .07$, $F(1, 93) = 6.69$, $p = .01$. In the second step of the model, the first-order factors were entered. None of the predictors nor the omnibus test was significant at this step, ps > .09. Similar, when the interaction terms were added in the last step of the model, none of the predictors, interaction terms, or omnibus test was significant, ps > .20.

Regression Analysis for the Stop Accuracy Difference Measure. A hierarchical regression analysis was conducted for the difference in Stop trial accuracy between the rewarded and unrewarded task (rewarded Stop trial accuracy – unrewarded Stop trial accuracy). Age was entered into the model in the first step as a covariate, and the omnibus test was significant, $R^2 = .07$, $F(1, 93) = 7.36$, $p < .01$. In the second step, the EBR proxy measure of striatal dopamine, Substance Abuse, and Disinhibition were added to the model. Omnibus prediction was marginally significant at this step, $\Delta R^2 = .014$, $F(4, 90) = 2.14$, $p =$

.08, but none of the first-order predictors were significant, *p*s > .20. In the final step of the model, the interaction terms were entered into the model. However, the interaction terms, first-order predictors, and omnibus prediction were nonsignificant, *p*s > .10.

Regression Analysis for Go Trial Reaction Time Difference Measure. The same hierarchical regression analysis was conducted for the Go trial RT difference measure (rewarded Go trial RT – unrewarded Go trial RT) as for Stop trial difference measure. The omnibus test for the age covariate in the first step was nonsignificant, $p = .11$. In the second step of the model, all predictors and the omnibus test were nonsignificant, *p*s > .10. Similarly, in the third step of the model, none of the interaction terms, first-order predictors, or the omnibus test was significant, *p*s > .10.

Regression Analysis for SSRT Difference Measure. A final hierarchical regression was performed for the SSRT difference measure (rewarded SSRT – unrewarded SSRT). In the first step of the model, Age was added as a covariate. The omnibus test was significant at this step, $R^2 = .04$, $F(1, 93) = 4.15$, $p = .045$. In the second step, the first-order terms were entered (EBR, Substance Abuse, Disinhibition). However, neither the first-order predictors (*p*s > .60) nor the omnibus prediction was significant, $\Delta R^2 = .01$, $F(4, 90) = 1.13$, $p = .35$. Age remained a significant predictor ($\beta = -.21$, $p = .048$). In the last step of the model, the EBR X Substance Abuse and EBR X Disinhibition interactions were added, $\Delta R^2 = .05$, $F(6, 88) = 1.51$, $p = .19$. At this step, the EBR X Substance Abuse interaction term ($\beta = .48$, $p = .08$) was a marginally significant predictor in the difference in SSRT from the standard stop signal task to the rewarded task. None of other predictors were significant in this step, *p*s > .10.

Given the statistical trend for the EBR X Substance Abuse interaction, a reduced model with Age, EBR, Substance Abuse, and the EBR X Substance Abuse interaction term was conducted. As with the full model, Age was entered as a covariate in the first step of the model, and the omnibus prediction was significant, $R^2 = .04$, $F(1, 93) = 4.15$, $p = .045$. In the second step of the model, EBR and Substance Abuse were entered. At this step, the omnibus test was nonsignificant, $\Delta R^2 = .003$, $F(3, 91) = 1.46$, $p = .23$, and neither predictor was significant, ps > 50. The Age covariate was significant at this step, $\beta = -.22$, $p = .04$. In the final step, the EBR X Substance Abuse interaction term was entered. Omnibus prediction was marginally significant, $\Delta R^2 = .04$, $F(4, 90) = 2.22$, $p = .07$. However, the EBR X Substance Abuse interaction emerged as a significant predictor of SSRT at this step, $\beta = .52$, $p = .04$.

Figure 10 shows simple regression lines for the effect of substance abuse scores on the SSRT difference measure at (a) the mean for striatal dopamine, (b) one standard deviation above the mean for striatal dopamine, and (c) one standard deviation below the mean for striatal dopamine. Striatal dopamine and substance abuse variables were centered prior to creating the centered interaction terms. The simple regression slope coefficients when centered at the mean ($\beta = .06$, $p = .54$) and at one standard deviation above the mean ($\beta = -.17$, $p = .27$) were not significant, but the simple regression slope coefficient centered at one standard deviation below the mean significantly predicted the difference in SSRT from the unrewarded to rewarded part of the stop signal task, $\beta = .30$, $p = .058$. At low levels of striatal dopamine, individuals with higher substance abuse tendencies had slower SSRTs on the rewarded part of the task relative to the unrewarded phase. This result suggests that striatal tonic dopamine moderates the effect of substance abuse on incentivized inhibitory

control. Specifically, individuals reporting high levels of substance abuse with low striatal tonic dopamine were slower, indicative of poorer cognitive control, in inhibiting their responses on Stop trials in the rewarded phase of the task.

Discussion. The results of Study 4 support the hypothesis that dopamine would moderate the effect of substance abuse on inhibitory control. In particular, individuals with high substance abuse and low striatal tonic dopamine showed deficits in inhibitory control in the rewarded phase of the task. Despite the decrements in inhibitory reaction time, no performance deficits in stop signal accuracy were observed, suggesting that individuals with substance abuse problems and low tonic dopamine are still able to inhibit their responses, but that reward motivation significantly slows this ability. Consequently, rather than reward improving cognitive control, motivation for immediate rewards slowed performance in this group, resulting in slower response inhibition. Thus, reward motivation seems to essentially "backfire" in this group: when there is a competition between reward and inhibitory control, dopamine involved in reward processing overrides inhibitory control mechanisms. As a result, individuals with substance abuse problems and low tonic dopamine may be less successful in attaining the rewards that motivate them and have greater difficulty in inhibiting their responses. One potential mechanism for this result is that at low tonic dopamine levels, phasic bursts release more striatal dopamine than individuals with high tonic dopamine (Grace, 1995; 2000). Thus, in this low tonic dopamine group, phasic bursts may release an excess of dopamine that impairs inhibitory control mechanisms, but heightens motivation for immediate rewards. Future work is needed to test this possibility conclusively, however.

In contrast to the hypothesis that externalizing proneness would be associated with poorer SSRTs and accuracy in the standard stop signal phase of the task, no significant correlations or main effects of substance abuse or disinhibition on these factors was observed. This result, though unexpected, may indicate that heavier or longer duration of drug use may drive previously observed deficits in inhibitory control. Additionally, the hypothesis that striatal dopamine and disinhibition would interact to improve response inhibition was not observed in this study. An important consideration in this sample, however, is that disinhibition scores represented a smaller range and lower mean that those reported in Studies 1 – 3. Consequently, the high disinhibition group in this sample may be more similar to the moderate or average disinhibition group in the studies reported previously. A restriction of range for disinhibition therefore tempers the conclusions that can be drawn from this study about disinhibition and the competition between reward and inhibitory control processes, and future work is needed to determine how higher levels of disinhibition influence the interaction between these cognitive processes.

6. SUMMARY AND CONCLUSIONS

The goal of the present investigation was to characterize the effects of externalizing proneness on distinct aspects of reward processing and determine the role of striatal dopamine in moderating these relationships. Previous work broadly suggests that externalizing behavior may be associated with dysregulation in reward sensitivity and inhibitory control (e.g., Bechara & Damasio, 2002; Krueger et al., 2007; Patrick et al., 2013). However, the RDoC matrix portrays a complex picture of the distinct behavioral and neural correlates that underlie different aspects of reward processing. Despite the moderate prevalence of externalizing behaviors, prior to this investigation, there had not been any studies that systematically examined which aspects of reward processing were altered in individuals with externalizing tendencies. The findings of this investigation demonstrate that phenotypically unique manifestations of externalizing behaviors, namely disinhibition and substance abuse, exert differential effects on reward processing. In particular, disinhibition was associated with reward wanting and physical effort expenditure for rewards. In contrast, substance abuse was more strongly linked to reward learning, reward devaluation sensitivity, cognitive effort expenditure for rewards, and reward-incentivized inhibitory control. Although previous research has shown that a common heritable vulnerability, including variation in striatal dopaminergic genes, contributes to externalizing behaviors (Krueger, 1999; Krueger & Markon, 2006; Krueger, McGue, Iacono, 2001; Krueger et al., 2002), results from the current study demonstrate that the specific manifestation of the behavior can differentially impact unique behavioral aspects of reward processing.

In addition to examining specific behavioral correlates of reward processing, this investigation also incorporated a measure of striatal tonic dopamine. This assessment was

included to assess how differences in individuals' underlying neurobiology influence the relationship between externalizing behaviors and reward processing. The results demonstrate that the effects of externalizing proneness on reward processing are critically dependent on striatal dopamine. Specifically, the effect of disinhibition on reward wanting and physical effort expenditure for rewards were exclusive to individuals with low striatal tonic dopamine levels. Additionally, the effects of substance abuse on reward learning, cognitive effort expenditure for rewards, and reward-incentivized cognitive control vary depending on individual differences in tonic dopamine levels. Thus, these results uniquely demonstrate that substance abuse and disinhibition not only affect distinct reward processes, but that these effects depend on variation in striatal dopamine levels.

In line with my predictions, among individuals with high disinhibitory tendencies, only those with low tonic dopamine showed increased reward wanting and chose smaller, less physically effortful reward options. This finding suggests that phasic dopamine (*low* tonic dopamine) increases immediate desire for rewards, or wanting, and enhances preferences for less effortful, small rewards in individuals with higher disinhibitory traits. This result is also consistent with previous research showing that disinhibition is associated with increased preference for immediate rewards (de Wit et al., 2007) as well as work on dopamine and effort expenditure for rewards (Trifilieff et al., 2013; Trifilieff & Martinez, 2014). A potential implication of this result is that high-disinhibited individuals with low striatal tonic dopamine may comprise a maximum-liability group. Specifically, it appears that in high-disinhibited individuals, low tonic dopamine increases preference for immediate, less effortful rewards at the expense of more effortful, goal-directed options that could

increase long-term rewards. This group therefore seems to be driven by easy, immediately rewarding choices without considering or seeking options that offer larger long-term benefits.

The effects of substance abuse on reward processing were also dependent on individual variation in striatal tonic dopamine levels. Individuals with more substance abuse problems and high tonic dopamine showed enhanced long-term reward learning. As such, these findings also support previous work showing that substance abuse is associated with enhanced associative learning of rewards (Hogarth et al., 2013). The implication of this result could be that higher levels of tonic dopamine might facilitate improved reward learning in individuals with high levels of substance use. Alternatively, alcohol or drug users with high tonic dopamine levels may be strategically reward-oriented rather than impulsively driven by immediate desires.

In contrast, individuals with more substance abuse problems and low tonic dopamine showed comparatively poorer long-term reward learning, indicating that this group tended to learn action-reward contingencies that maximized immediate reward as opposed to long-term rewards. These results suggest that learning of long-term action-reward contingencies depends on tonic dopamine levels in individuals with substance abuse problems. Furthermore, individuals with substance abuse problems and low tonic dopamine were willing to exert more cognitive effort in an attempt to attain larger immediate rewards. They also showed inhibitory control deficits on the reward incentivized portion of the stop signal task relative to the unrewarded phase. Thus, individuals with high substance abuse problems and low tonic dopamine show better learning reward-action contingencies that maximize immediate reward, as opposed to long-term rewards, and are willing to exert greater cognitive effort to attain such rewards. In a drug context, one possible extension of these

findings is that these individuals may be more willing to exert greater effort to obtain and use drugs to attain the immediately rewarding feeling that drugs elicit. Furthermore, in contexts when there is a competition between reward motivation, such as the positive feelings drug use elicit, and inhibitory control, such as trying not to use drugs, these individuals may have greater difficulty in inhibiting the urge or desire to use. Outside of reward contexts, substance users may not show substantial deficits in inhibitory control. However, in contexts where rewards (like drugs) are at stake, individuals with low tonic dopamine may be more motivated to attain the reward at the expense of inhibitory control processes. Collectively, these findings suggest that substance users with low tonic dopamine may be at higher risk for transitioning from recreational substance use to addiction, while high striatal tonic dopamine may be a protective factor in risk for addiction and maladaptive reward processing.

However, Study 2 demonstrated that substance abuse, independent of striatal dopamine, was associated with reduced reward devaluation sensitivity. Once reward-outcome associations are well learned, individuals with substance abuse problems—regardless of variation in striatal tonic dopamine levels—have difficulty disengaging from habitual responding. Thus, while striatal dopamine influences reward learning, habit formation, effort expenditure, and inhibitory control, it does not appear to moderate the effects of substance abuse on reward disengagement, or "habit breaking," in individuals with substance abuse problems. Striatal dopamine therefore appears to influence reward salience during contexts of extended learning, but not disengagement from those reward-outcome associations.

Limitations. One limitation to these tasks is that they are designed to assess learning from rewards only. In particular, elevated tonic dopamine levels have been shown to support

reward learning, whereas diminished tonic dopamine levels reinforce avoidance, or punishment, learning (Frank, Seeberger, & O'Reilly, 2004). The distinction between reward and punishment learning is important for understanding the mechanistic effect of tonic dopamine on disinhibition and substance abuse. However, the question of how disinhibition and substance abuse relate to punishment learning, such as learning from monetary losses, lies outside the scope of this investigation. In addition, further work is needed to determine whether the effect of tonic dopamine on reward wanting and learning extends to contexts involving both gains and losses.

In considering the generalizability of the current results, it should be noted that the goal of this study was primarily to examine individual differences in externalizing tendencies in the general population, and not to characterize individuals with severe clinical-level impulse control or substance use disorders. It is certainly conceivable that severe problems of these types may be associated with different reward processing patterns than those observed in our college student sample. Furthermore, spontaneous eyeblink rate is an indirect marker of striatal tonic dopamine levels and thus inferences should be made with caution. Additional techniques, such as PET imaging, are needed to directly establish relationships between externalizing problems and altered striatal dopamine activity in reward processing contexts. Finally, while current results provide evidence for associations between externalizing problems and aberrant reward processing, I do not purport that striatal tonic dopamine levels causally affect reward processing.

Conclusions. This investigation is the first to demonstrate that disinhibition and substance abuse exert different effects on reward processing, depending on variations in striatal tonic dopamine levels. Externalizing problems may reflect either an enhanced desire

for rewards, or augmented associative linking of reward stimuli to their outcomes and willingness to exert cognitive effort to attain them. Moreover, problems with substance abuse extend beyond reward learning, effort expenditure, and habit formation. Substance abuse, independent of dopaminergic variation, is also associated with increased difficulty in disengaging from, or "breaking," learned habits. The results of these studies not only reveal the exact nature of the dissociable role of trait disinhibition and substance abuse on specific aspects of reward processing, but also provide a neural mechanism to account for these relationships. Moreover, these results demonstrate that low striatal tonic dopamine in individuals with externalizing proneness may represent a risk factor for addiction or additional externalizing problems. These findings underscore the importance of considering individual differences in dopaminergic functioning to determine cognitive correlates of externalizing proneness and risk for addiction.

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APPENDIX A

FIGURES

Figure 1. Reward structure (left) and sample screen shot (right) of the reward learning task in Study 1.

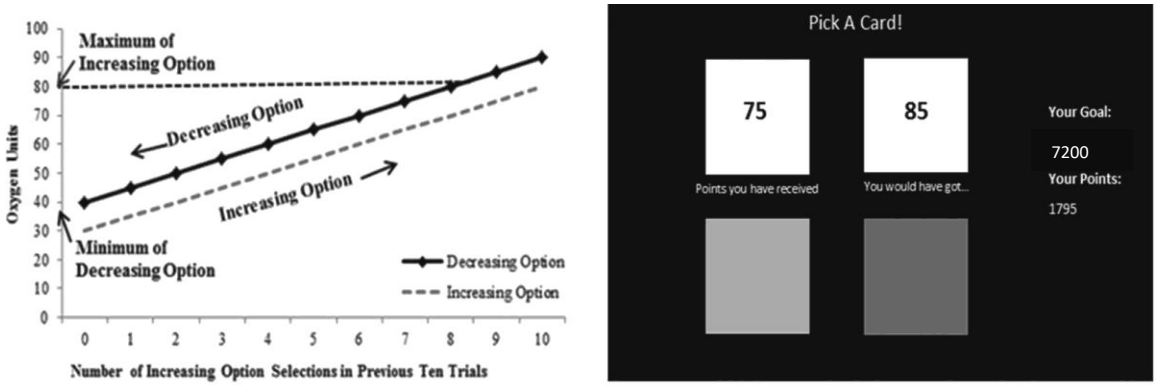
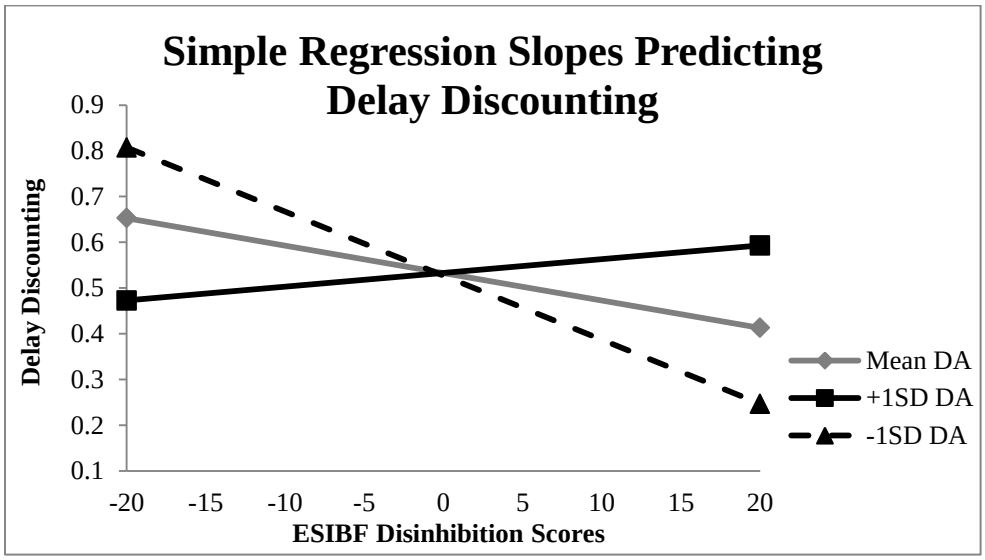


Figure 2. Simple regression slopes for the effect of disinhibition on reward wanting and substance abuse on reward learning in Study 1.



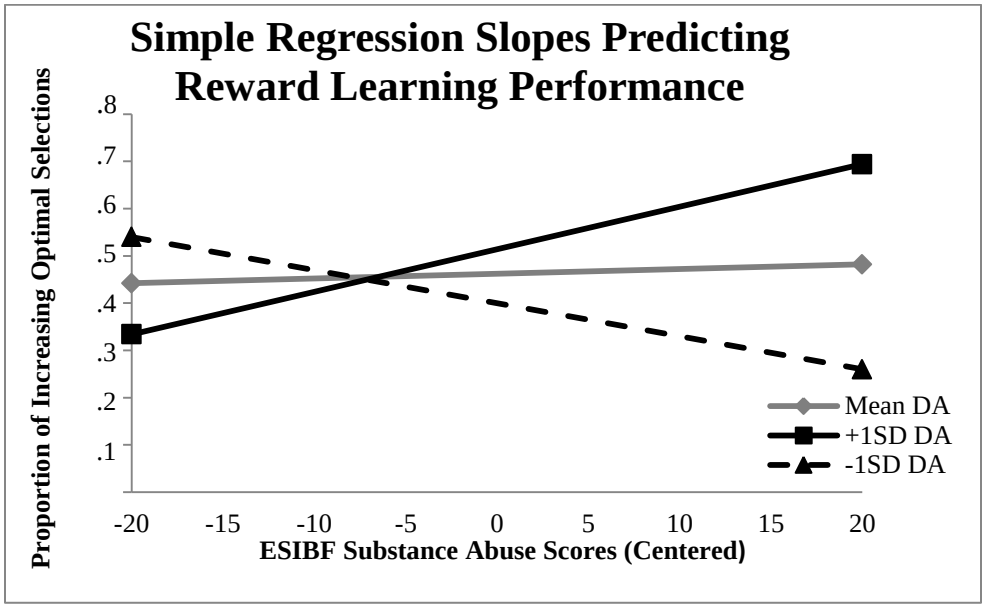


Figure 3. Overview of the two-stage reinforcement learning task in Study 2.

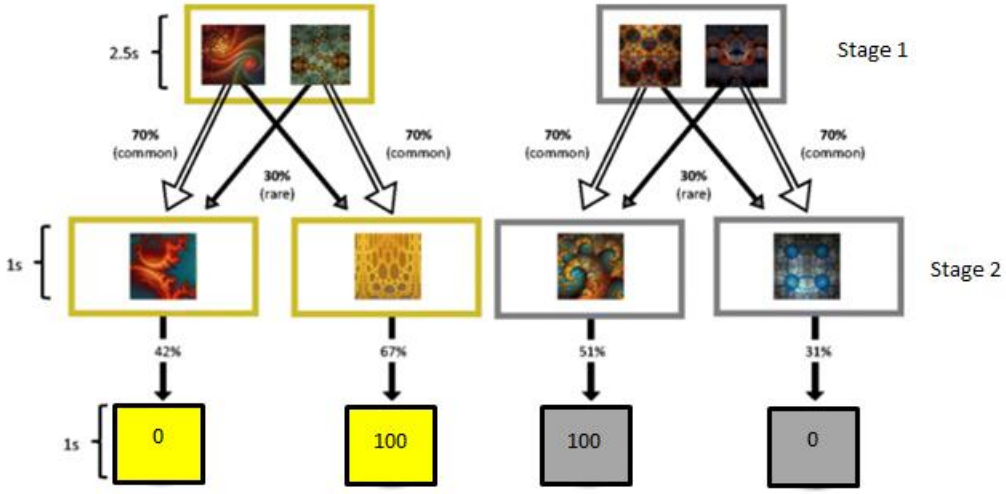


Figure 4. Scatterplot of the relationship between substance abuse and devaluation sensitivity (valued – devalued trials) in Study 2.

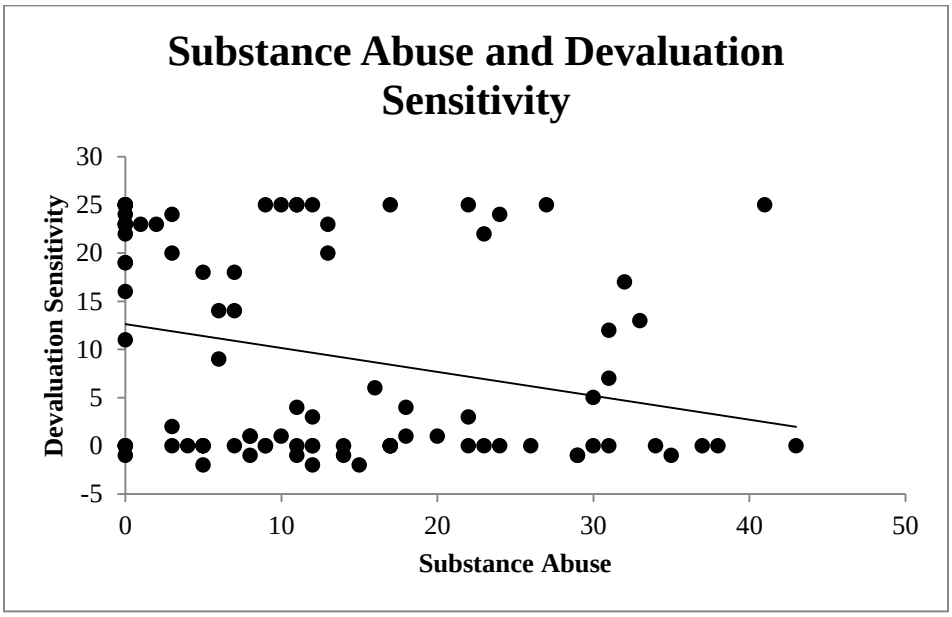


Figure 5. Simple regression slopes for the effect of substance abuse on the model-free index in Study 2.

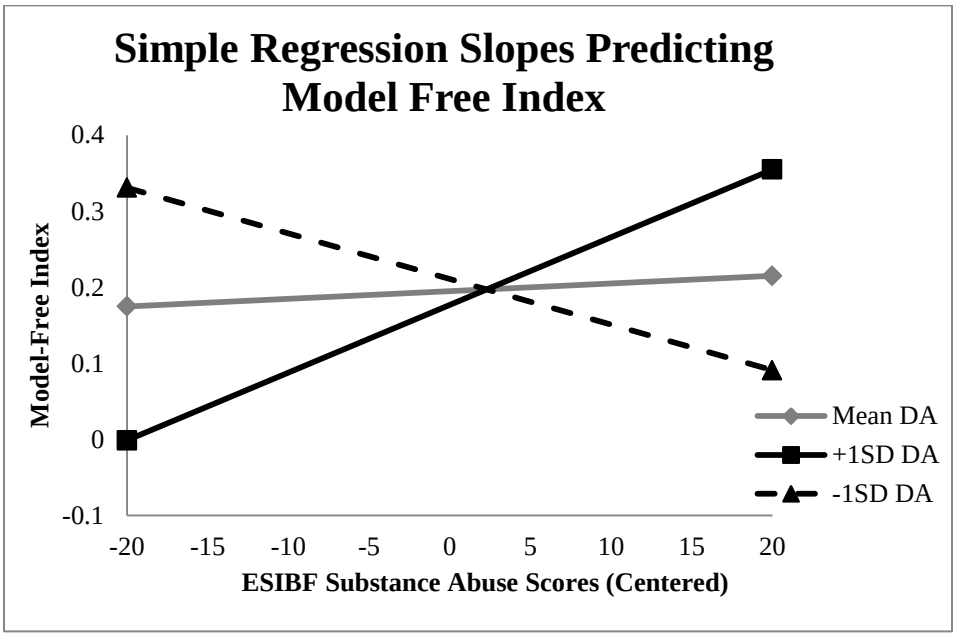


Figure 6. Sample trial of the physical effort task (top) and cognitive effort task (bottom) in Study 3.

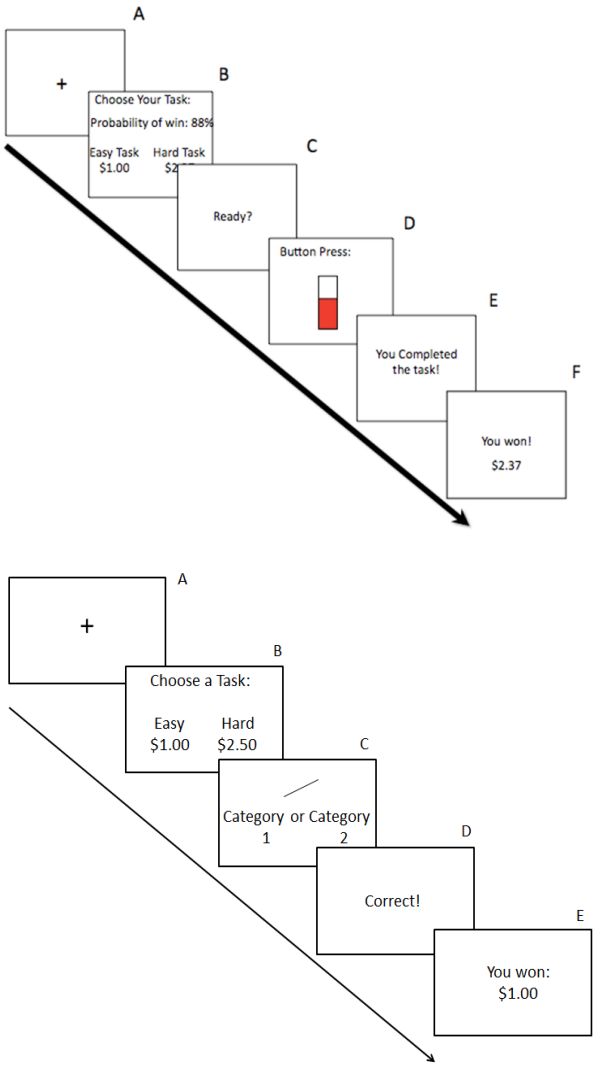


Figure 7. Simple regression slopes for the effect of disinhibition on physical effort expenditure for rewards in Study 3.

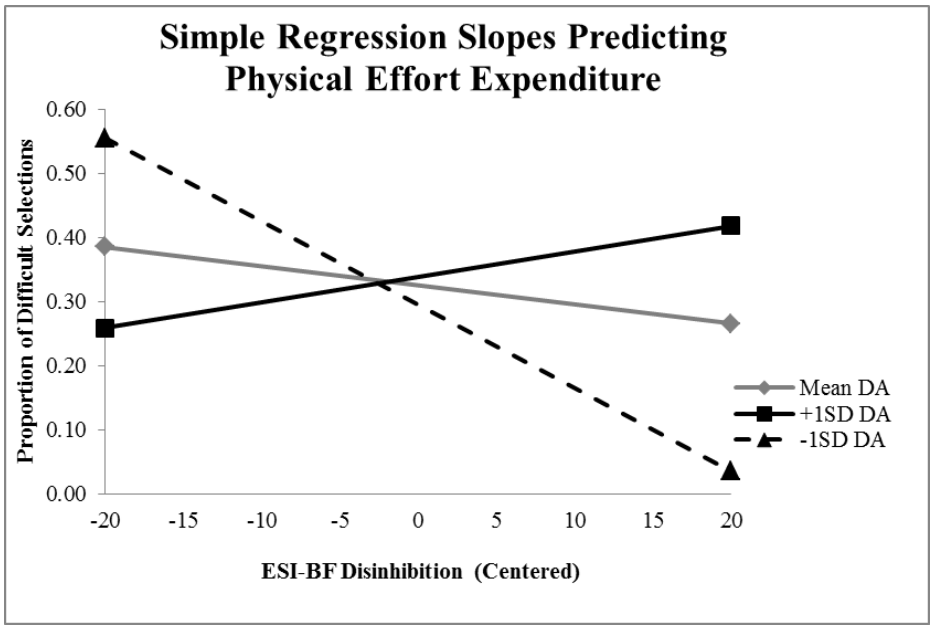


Figure 8. Simple regression slopes for the effect of substance abuse on cognitive effort expenditure for rewards in Study 3.

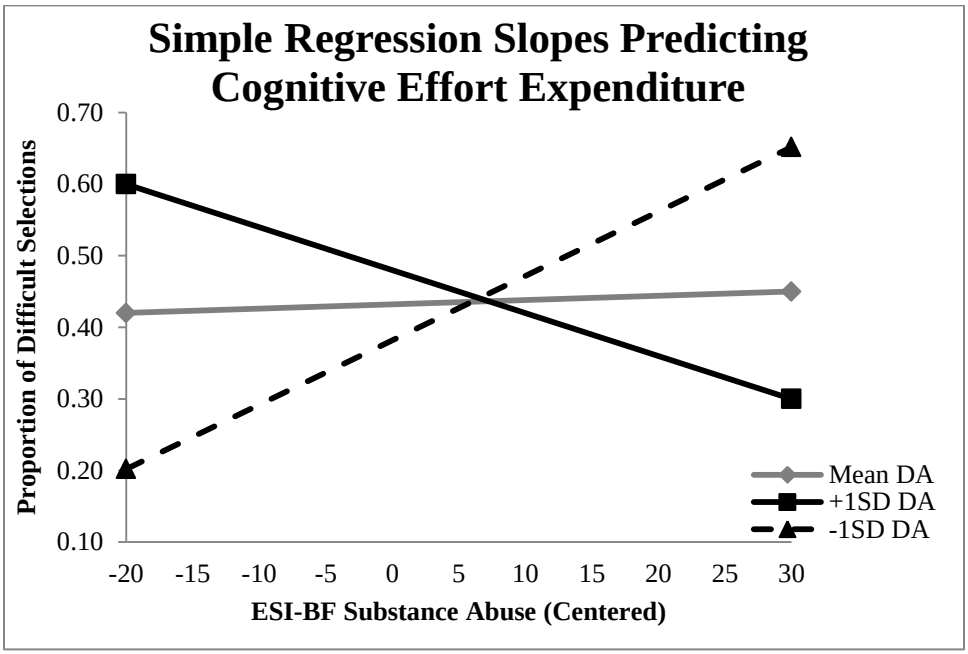


Figure 9. Sample of a stop trial in the standard stop signal phase of the task and a stop trial of the stop signal reward phase of the task in Study 4.

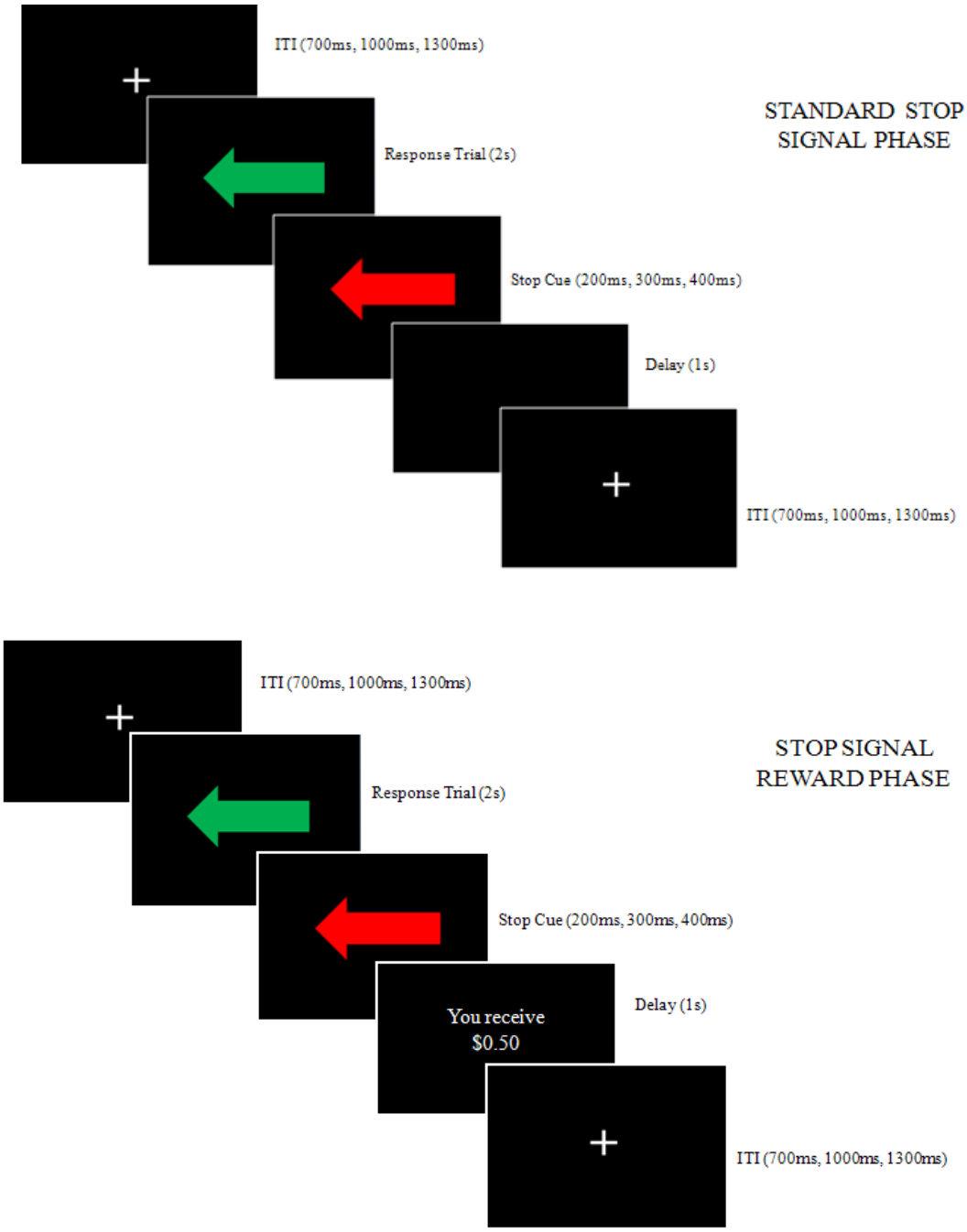
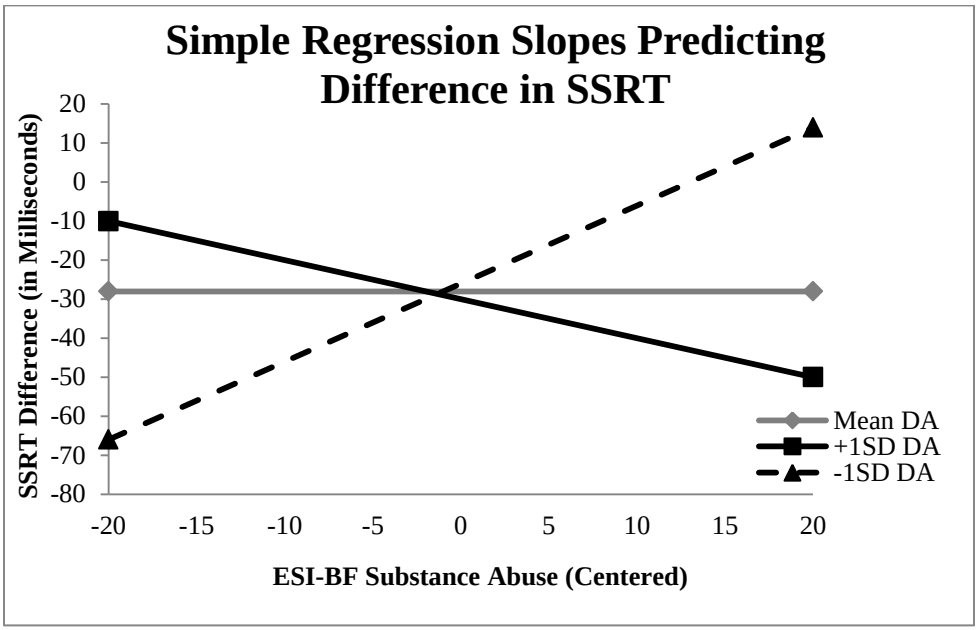


Figure 10. Simple regression slopes for the effect of substance abuse on the difference in SSRT (rewarded phase SSRT – unrewarded phase SSRT) in Study 4.



APPENDIX B

TABLES

Table 1

Correlational Analyses for Study 1

	Substance Abuse	Disinhibition	EBR	Delay Discounting
Substance Abuse				
Disinhibition	0.46**			
EBR	-0.16	-0.05		
Delay Discounting	-0.10	-0.11	0.05	
Reward Learning Task	0.11	0.18	-0.02	-0.18

Note. Lower delay discounting scores indicate more discounting.
**indicates significance at the $p<.01$ level.

Table 2

Correlational Analyses for Study 2

	Substance Abuse	Disinhibition	EBR	Devaluation	MF Index
Disinhibition	0.49**				
EBR	0.11	0.03			
Devaluation	-0.24*	0.04	-0.21*		
MF Index	-0.03	0.15	0.01	0.02	
MB Index	-0.10	0.07	-0.03	0.07	0.11

**indicates significance at the $p < .01$ level.
*indicates significance at the $p < .05$ level.

Table 3

Correlational Analyses for Study 3

	Substance Abuse	Disinhibition	EBR	Physical Effort	Cognitive Effort
Substance Abuse					
Disinhibition	.36**				
EBR	0.08	0.01			
Physical Effort	-0.12	-0.11	-0.06		
Cognitive Effort	0.02	0.01	-0.05	0.11	
OSPAN	0.18	0.08	-0.18	-0.05	.29**

Note. Physical effort indicates the average proportion of difficult selections in the physical task. Cognitive effort reflects the average proportion of difficult selections in the cognitive task. OSPAN indicates the OSPAN working memory assessment measure.
**indicates significance at the $p < .01$ level.

Table 4

Correlational Analyses for Study 4

	Substance Abuse	Disinhibition	EBR
Substance Abuse			
Disinhibition	.37**		
EBR	0.05	0.03	
SST Stop Accuracy	-0.01	-0.17	-0.11
SST Go RT	-0.02	-0.17	-0.13
SST SSRT	0.04	-0.13	-0.03
Stop Accuracy Diff.	0.03	-0.12	0.04
Go RT Diff.	-0.05	-0.07	0.06
SSRT Diff.	0.02	0.07	-0.01

Note. Rewarded – unrewarded dependent measures are indicated by "Diff."
SST refers to the standard stop signal task phase.
**indicates significance at the $p < .01$ level.

APPENDIX C

In this task, you will see green arrows that point either left or right. As soon as you see the arrow, you should respond as QUICKLY AND ACCURATELY as possible by pressing the LEFT arrow key if the arrow points LEFT or the RIGHT arrow key if the arrow points RIGHT. On some trials, the green arrows may turn red. If the arrow turns RED, you should STOP your response immediately and NOT RESPOND to that particular arrow. Still respond to the other green arrows after it, unless the arrow turns red. Both going and stopping are equally important. Your performance on this task will be measured equally by both how fast and accurately you respond.

This task is designed to be difficult and for people to make mistakes because we are interested in looking at those mistakes. So, don't get frustrated if it's difficult. Just make sure not to slow down your responses to wait for the red arrow so that you are no longer going when you are supposed to, because then you are no longer doing the task.

You won't always be able to stop when you see a red arrow, so just try your best. As long as you respond quickly all of the time without pushing the wrong button for arrow direction and can stop some of the time, you're doing the task correctly.

It's also important to concentrate while you're doing the task.

If you have any questions, please ask the experimenter now.