Neuroimaging metrics of drug- and food-cue reactivity as a function of psychopathic traits, substance use, and substance dependence

by

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Abstract

We conducted two fMRI studies assessing the relationship between psychopathy and drug- and food-related neural reactivity. In the first study, we assessed the relationship between psychopathic traits and neural reactivity among 47 cocaine-dependent and 58 non-dependent participants. The cocaine-dependent group exhibited a neural processing bias towards drug-related stimuli within a corticolimbic circuit involved in decision-making, salience attribution, and motivation. Psychopathic traits both sensitized this neural processing bias and modulated the effect of substance use severity. In the second study, we separated dependent participants into psychologically- (n =25) or physiologically-dependent (n = 20) participants and observed a neural processing bias towards drug-related stimuli among physiologically-dependent participants alone. Interestingly, both psychopathic traits and substance use severity exhibited positive correlations to drug > food reactivity within psychologically-dependent participants. These results further our understanding of the comorbidity between psychopathy and addiction and help conceptualize a new comprehensive model for the development of addiction.

Keywords: Addiction, psychopathy, fMRI, neural processing, corticolimbic, substance use disorders, substance dependence, substance use.

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Table of contents

List of tables

List of figures

CHAPTER 1

INTRODUCTION

According to the 2016 World Drug Report from the United Nations Office on Drugs and Crime (UNODC), 5.2% of the world's population used illicit substances in 2014, with 0.6% demonstrating drug use problems (UNODC, 2016). Moreover, the most-recent statistics on a current global opioid-use epidemic reported a 900% increase in the number of individuals with an opioid addiction seeking treatment, and a 171% increase in the number of heroin-related overdoses and deaths in the preceding 15 years (Kolodny et al., 2015). The problem was equally concerning in Canada according to the 2012 Canadian Community Health Survey (Statistics Canada, 2012), where lifetime diagnoses of substance use disorders (SUDs) were prevalent at 21.6%, and 4.4% when assessing diagnostic criteria in the preceding 12 months.

These prevalence rates increased in Canadian antisocial populations, with 70% of offenders reporting substance use and abuse during the year prior to their incarceration (Canadian Centre on Substance Abuse [CCSA], 2004). Moreover, 50 – 90% of offenders had a SUD, with 51% of offenders exhibiting alcohol use disorders and 48% exhibiting SUDs other than alcohol (CCSA, 2004), and 4.3% of reported offences were drug related offences in 2012 (Public Safety Canada, 2013). Furthermore, substance use was considered one of the Central Eight Risk Factors for criminal behaviour according to Andrews and Bonta (2006) and was an item on widely used risk assessment instruments for violence and recidivism, such as the Historical-Clinical-Risk Management scale (HCR-20; Webster, Douglas, E1aves, & Hart, 1997) and the Violence Risk Appraisal Guide (VRAG; Quinsey, Harris, Rice, & Cormier, 1998).

The economic impact of these substance abuse problems is staggering. In 2002, substance use problems had a cost the Canadian economy $39.8 billion, with substance-use-related law enforcement costs accounting for $3.33 billion dollars; substance-use-related court costs accounting for $843 million dollars; and substance-use-related correctional costs accounting for $1.23 billion dollars (CCSA, 2006).

Another disorder that exhibited a greater prevalence among antisocial populations is psychopathic personality disorder, with a prevalence of roughly 12%-21% of the prison population (Hare, 2003; Hart & Hare, 1989), a higher percentage when compared to the community population's prevalence of roughly 1% (Coid, Yang, Ullrich, Roberts & Hare, 2009; Neumann & Hare, 2008). Psychopathic traits were also considered predisposition for violent criminal behaviour on the VRAG (Quinsey et al., 1998) and are also positively correlated with scores on the HCR-20 (Neves et al., 2011).

These disorders have been found to share several common risk factors. For instance, psychopaths have been reported as impulsive (Andershed, Kerr, Statin, & Levander, 2002; Dean et al., 2013; Hare, 2003; Levenson, Kent, & Fitzpatrick, 1995; Lilienfeld & Fowler, 2006; Morgan, Gray, & Snowden, 2011), irresponsible (Hare, 2003; Andershed et al., 2002), and have demonstrated a strong inclination towards making risky decisions, (Mitchell, Colledge, Leonard, & Blair, 2002; Vassileva et al., 2007; Beszterczey, Nestor, Shirai, & Harding, 2013; Hosker-Field, Molnar, & Book, 2016; Swogger, Walsh, Lejuez, & Kosson, 2010). Psychopathic individuals have also been commonly considered sensation seekers with a high sensitivity for rewarding stimuli (Haapasalo, 1990; Hare, 2003; Hopley & Brunelle, 2012). These characteristics have also been noted as predictors of SUDs (Koob & Volkow, 2010; Woicik, Stewart, Pihl, & Conrod, 2009), with impulsivity (Bernstein et al., 2015; Coskunpinar & Cyders,

2013; Leeman, Hoff, Krishnan-Sarin, Patock-Peckham, & Potenza, 2014; Leung et al., 2017; Rodríguez-Cintas et al., 2016; Shin, Chung & Jeon, 2013), sensation seeking (Horvath, Milich, Lynam, Leukefeld, & Clayton, 2004; Leeman et al., 2014; Shin et al., 2013; Stautz & Cooper, 2013), reward sensitivity (Dissabandara et al., 2014; Franken, Muris, & Georgieva, 2006; Murphy, Murphy, & Garavan, 2014), and risky-decision-making (Ekhtiari, Victor, & Paulus, 2017; Kim-Spoon et al., 2016) being associated with substance use frequency and the incidence of substance dependence.

However, the comorbidity between these two disorders remains rather controversial, particularly due to a disconnect between psychometric/behavioral empirical studies and neuroimaging studies. To reconcile these two camps of research, I have conducted two studies that further investigated the relationship between psychopathic traits and neurocognitive abnormalities apparent in addiction (i.e. neural processing of drug-related stimuli). Before presenting this research, a thorough background review will be provided. This review will be organized in the following way: first, I will be presenting definitions of addiction and psychopathic personality disorder, with a primary emphasis on theoretical models of these disorders that this research will be specifically testing. Next, I will review studies on the comorbidity between addiction and psychopathy, followed by an overview of the relationship between psychopathy and the neural processing of drug-related stimuli, which will include a discussion on the implication of such a relationship, as well as limitations of this field of research. Finally, I will outline how this thesis attempts to reconcile these limitations and further our understanding of addiction, and the psychopathy-addiction comorbidity.

Defining addiction

According to the fifth and most recent edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association [APA], 2013), SUDs consist of the continued use of a substance despite negative consequences on one's biopsychosocial health. This can include disruptions of one's social, recreational and occupational responsibilities; be associated with problems and dysfunctions in one's personal life and interpersonal relationships; and may or may not be associated with physiological reactions to drug use, including tolerance to the drug's effects and withdrawal symptoms following cessation of use.

One must have met the threshold for two of the 11 DSM criteria for SUDs to be diagnosed with a SUD. These criteria consist of a combination of criteria used to characterize two subcategories of SUDs that were diagnosed as separate disorders in the revised fourth edition of the DSM *(DSM-IV-TR*; APA, 2000). One of these categories, assumed to be the more severe SUD, is substance dependence, characterized by a continuous maladaptive pattern of substance use that persists despite aversive consequences on one's biopsychosocial health and a growing inability to cease use and resort to other sources of reward to satiate one's hedonic needs. It is diagnosed according to seven of the 11 criteria of SUDs, and this diagnostic scheme also contains two specifiers, tolerance and withdrawal, which specify whether the participant meets the threshold for substance dependence with a physiological (i.e. meets threshold for tolerance and withdrawal) or psychological dependence (i.e. important obligations are disrupted, and use is persistent, however there are no physiological signs of dependence). If the patient did not meet threshold for substance dependence, the interviewer must then proceed to examine the other subcategory of SUD: substance abuse, characterized by the continued use of a substance accompanied by legal problems and disruptions of social and occupational obligations.

Table 1

DSM criteria for substance use disorders, substance abuse and substance dependence disorders

Symptom	SUD (DSM-5)	SA (DSM-IV-TR)	SD (DSM-IV-TR
1. The substance is often taken in larger amounts over a longer period than intended	X		X
2. There is a persistent desire or unsuccessful efforts to cut down or control substance use	X		X
3. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects	X		X
4. Craving, or a strong desire or urge to use alcohol	X		
5. Continued use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the drug.	X		
6. Important social, occupational, or recreational activities are given up or reduced because of substance use.	X	X	X
7. Recurrent use in situations in which it is physically hazardous	X	X	
8. The substance use is continued despite knowledge of having a persistent physical or psychological problem that is likely to have been caused or exacerbated by the substance	X		X
9. Tolerance defined by either of the following: a) A need for markedly increased amounts of the substance to achieve intoxication or the desired effect b) Markedly diminished effect with continued use of the same amount of the substance	X		X
10. Withdrawal manifested by either of the following: a) The characteristic withdrawal syndrome for the substance b) The same substance is taken to relieve or avoid withdrawal symptoms	X		X
11. Recurrent drug-related legal problems		X	

Note. SUD = Substance use disorder (according to DSM-5[APA, 2013] criteria); SA = Substance abuse disorder (according to DSM-IV-TR [APA, 2000] criteria); SD = Substance dependence (according to DSM-IV-TR [APA, 2000] criteria).

The decision to combine abuse and dependence into a single category for the DSM-5 stems from item-response theory analyses (i.e. confirmatory principal component analyses) that demonstrated a single latent construct of all DSM abuse/dependence items (Saha et al., 2012). In addition, the separation of substance abuse and dependence was criticized for having similarities in severity and real-world impact (Schuckit & Smith, 2001; Schuckit, Smith, & Landi, 2000). However, DSM-5 SUD-assessments have been associated with inflated diagnostic rates of SUDs and false positives (Goldstein et al., 2015; Peer et al., 2013). These inflated diagnostic rates may have been due to the combination of abuse and dependence and a lower threshold to attain a diagnosis (2/11 criteria to meet threshold for a SUD compared to three of the seven criteria for meet threshold for substance dependence; APA, 2000, 2013). In addition, DSM-5 SUD diagnosis added a new symptom that was not included into the diagnosis of neither substance dependence nor substance abuse: craving (APA, 2013), whom Agrawal, Heath, and Lynskey (2011) demonstrated that many interviewees endorsed this craving symptom, which may explain the inflated SUD diagnostic rates. This is not to say that the DSM-IV-TR criteria did not have criticisms beyond the distinction of substance dependence and substance abuse, as the criteria for substance dependence has been criticized for redundancy, excessive focus on use in inappropriate situations and contexts, high false positive rates, and poor to modest construct and predictive validity (DiFranza et al., 2010; Hasin et al., 2003; Hendricks, Prochaska, Humfleet, & Hall, 2008; Widiger & Smith, 1994).

However, the distinction between physiological and psychological substance dependence may hold incremental value. While the DSM-5 no longer utilizes this specifier, many have called for the importance in separating DSM-5 SUD diagnoses from physiological substance dependence (Blanco, Wall, Okuda, Wang, Iza, & Olfson, 2017). Such a position was related to

the fact that there is unanimous consensus that physiologically-dependent individuals exhibited more addiction-related behavioral patterns relative to psychologically-dependent individuals, including more severe drug use patterns, higher relapse rates, and a greater number of psychiatric, psychosocial and health-related problems (Lejoyeux, Claudon, McLoughlin, & Adès, 2001; Schuckit et al., 1998, 1999, 2003). In addition, diagnostic models that placed a greater emphasis on physiological reactions to drug use have exhibited greater reliability and validity compared to DSM diagnostic models. Such an example is the Withdrawal-Gate Model (Langenbucher et al., 2000), which held that drug withdrawal is a gate criterion – a criteria necessary to meet o be categorized as dependence. This model has demonstrated significantly greater reliability, concurrent, and predictive validity when separating participants as either having a substance dependence or substance abuse disorder compared to the DSM-IV (Langenbucher et al., 2000). Finally, the physiological/-psychological dependence distinction may have incremental value to testing a theoretical model explaining the development and maintenance of addiction from a neurocognitive perspective: The Impaired-Response Inhibition and Salience Attribution model of addiction (i-RISA; Goldstein & Volkow, 2002, 2011).

The i-RISA model was constructed on the theory that an individual's substance use can be conceptualized as a continuum of severity, with impulsive-voluntary drug use at the beginning and compulsive-habitual/uncontrollable drug use at the end (Everitt & Robbins, 2005, 2016). In addition, it incorporated another theory that chronic drug use dissociates "liking" from "wanting" the drug, in which case the reward-stimulating effects of the drugs decrease with repeated use while the incentive salience of the drug and drug-associated stimuli will increase (Berridge & Robinson, 2016; Lambert, McLeod, & Schenk, 2006; Robinson & Berridge, 1993, 2000). This incentive salience is the motivational value of drug-related reward, and its ability to exhibit a

rewarding response in an organism. This is a theoretical explanation for continued substance use despite increasing tolerance (Calipari, Ferris, & Jones, 2014; Gardner, 2011; Kawa, Bentzley, & Robinson, 2016; Koob & Volkow, 2010, 2016; Siciliano, Fordahl, & Jones, 2016).

The primary hypothesis of the i-RISA model (Goldstein & Volkow, 2002, 2011) is that individual with an addiction escalated from impulsive to compulsive drug use due neurological dysfunctions that underlie a salience misattribution, rendering drug-related stimuli to be more salient than non-drug stimuli. The authors theorized that the incentive sensitization of drug-related stimuli is concomitant with an incentive desensitization of non-drug related rewards (i.e. food, sex and money), concomitant with growing response-inhibition impairments, leading to a growing inability to inhibit drug-seeking behavior in response to cues and cue-induced craving (Goldstein & Volkow, 2002; Koob & Volkow, 2010).

This salience misattribution and response-inhibition dysfunction are thought to be due to neurological dysfunctions within the prefrontal cortex (PFC) and the anterior cingulate cortex (ACC) (Goldstein & Volkow, 2002, 2011; Koob & Volkow, 2010). Interestingly, the i-RISA model holds that this dysfunction was due to chronic substance use and factors related to physiological dependence, particularly drug withdrawal. The authors hypothesized that neuroplastic changes following these opposing hedonic mechanisms (drug reward vs drug withdrawal) lead to the manifestation of saliency and stimulus processing biases towards drugs relative to non-drug rewards and response-inhibition dysfunctions by altering the functionality of these cortical systems. This was an extension of an older model holding that addiction manifests by repeatedly cycling through three stages: binge/intoxication, withdrawal/negative affect, and craving/preoccupation (Koob & LeMoal, 1997, 2005, 2008a, 2008b).

According to this three-stage model of addiction, neuroplastic changes occurred by cycling through these three stages repeatedly, which would have sensitized the incentive salience of drug-related stimuli. These changes are thought to be due to activity within the reward-system (i.e. ventral striatum, ventral tegmental area) in response to drug administration, and antireward-system activity during drug-withdrawal (Koob, 2017; Koob & Le Moal, 2005; Koob & Volkow, 2010, 2016). This antireward-system, consisting primarily of anxiety and stress related regions (i.e. amygdala, bed nucleus of the stria terminalis), would have acted as an allostatic mechanism to return the brain to a hedonic and physiological baseline (Gardner, 2011; Koob, 2009, 2010, 2013, 2017; Koob & Le Moal, 2008a, 2008b). The i-RISA model holds that the neuroplastic changes leading to drug-reward incentive sensitization would be concomitant with non-drug-reward incentive desensitization.

While untested, one might suspect that individuals with a physiological dependence to a substance, characterized by drug-related behavioral dysfunctions, chronic substance use, tolerance and periods of withdrawal following use-cessation, would exhibit the most severe i-RISA deficits, consistent with the three-stage model of addiction and the i-RISA model itself. The current thesis will test this hypothesis as a means of empirically testing the accuracy of this widely accepted model of addiction, as well as the implication of physiological and psychological dependence dichotomization on understanding and assessing addiction.

Defining psychopathy

Psychopathic personality disorder, more commonly referred to as psychopathy, is a personality disorder characterized by interpersonal, affective, lifestyle and antisocial features (Hare, 2003). Psychopathic individuals are characterized by callous-unemotional traits, such as manipulativeness, lack of remorse and empathy, a shallow range of emotions, a self-destructive

lifestyle, impulsivity, irresponsibility, resistance to stress, a superficial charm and narcissistic view of himself and a strong inclination to commit antisocial behaviour (Hare, 2003; Cleckley, 1955).

While there has been some disagreement with regard to the specific diagnostic criteria for the disorder, particularly in terms of whether psychopathy is characterized as a combination of two factors (Hare, 2003), three factors (Cooke & Michie, 2001), or four factors (Hare, 2003), the "gold-standard instrument" used to diagnose psychopathy is the *Hare Psychopathy Checklist-Revised* (PCL-R; Hare, 2003; Lynam & Gudonis, 2005). The PCL-R conforms to a two factor model, which separates psychopathy into a) interpersonal and affective traits (which attempts to characterize a "selfish, callous and remorseless use of others" [Hare, 2003, p.79]); and b) lifestyle and antisocial traits (which attempts to characterized a "chronically unstable, antisocial and socially deviant lifestyle" [Hare, 2003, p.79]). A summary of this model, and the breakdown of each factor, can be found in Table 2. It should be noted that factor analyses have yielded two items, "promiscuous sexual behaviour" and "many short-term marital relationships" that do not adhere to a particular factor.

Results on the comorbidity between psychopathy and addiction

Many studies have noted a comorbidity between SUDs and psychopathic traits (see Table 3 for a list of research studies which have focused on the psychopathy-SUD comorbidity). For instance, Stålenheim and von Knorring (1996) demonstrated that roughly 93% of participants with psychopathy had a substance use disorder. Moreover, participants noted as psychopaths were more likely to engage in polysubstance use, and have a diagnosis of alcohol, amphetamine, barbiturate, and opioid use disorder (Smith & Newman, 1990), and psychopathic traits exhibited positive correlations with symptoms of alcohol, cannabis, opioid, and cocaine use disorders

(Walsh, Allen, & Kosson, 2007). Finally, a meta-analysis demonstrated positive correlations between psychopathic traits and non-alcohol SUDs, however no significant correlation was observed between psychopathic traits and alcohol use disorder (Hemphil, Hart, & Hare, 1994).

Table 2
Factor structure of the Hare Psychopathy Checklist-Revised

Trait	Factor 1	Factor 2	Other
1. Glibness/superficial charm	X		
2. Grandiose sense of self-worth	X		
3. Pathological Lying	X		
4. Conning/manipulativeness	X		
5. Lack of remorse/guilt	X		
6. Shallow affect	X		
7. Callousness/Lack of empathy	X		
8. Failure to accept responsibility for own actions	X		
9. Need for stimulation/proneness to boredom		X	
10. Parasitic lifestyle		X	
11. Early behavioral problems		X	
12. Poor behavioral problems		X	
13. Lack of realistic, long-term goals		X	
14. Impulsivity		X	
15. Irresponsibility		X	
16. Juvenile delinquency		X	
17. Revocation of conditional release		X	
18. Criminal versatility		X	
19. Promiscuous sexual behavior			X
20. Many short-term marital relationships			X

Note. Adapted from Hare (2003).

While this body of research generalized SUDs as a category of psychopathologies that includes substance use, abuse, and dependence disorders, studies have assessed specific relationships between psychopathic traits and substance use severity, substance abuse, and substance dependence. Coid, Yang, Ullrich, Roberts, and Hare (2009) demonstrated that participants who had used cannabis within the last year and had ever used heroin, cocaine, and/or amphetamines, and were diagnosed with a substance dependence disorder, had a greater number of psychopathic traits. Psychopathic traits also correlated with the number of years regularly using addictive substances among adult participants (excluding alcohol; Cope et al., 2012,

2014a) and youth subjects (Hillege, Das, de Ruiter, 2010). Individuals with a high level of psychopathic traits are also more likely to receive a diagnosis of substance abuse or substance dependence (Cauffman, Kimonis, Dmitrieva, & Monahan, 2009; Jones & Miller, 2012). Finally, the severity of dependence on opioids, hallucinogens, and stimulants positively correlated with psychopathic traits (Hopley & Brunelle, 2012).

More recently, neuroimaging work has aimed to better understand the underlying nature of the relationship between psychopathic traits and SUDs. While the early evidence remains nascent, and has elicited somewhat inconsistent findings, several patterns begin to emerge. While certain neuroimaging studies coincide with empirical studies of the comorbidity between psychopathy and SUDs (i.e. Buckholtz et al., 2010), others (i.e. Cope et al., 2014a) coincide more with clinical case reports suggesting a disconnection, and moreover, a resilience in psychopathic individuals to substance dependence (Cleckley, 1941). Such inconsistencies between neuroscience and psychometric research on the comorbidity between psychopathy and SUDs raise question about the implication of psychopathy on the development of neurocognitive abnormalities promoting addiction; in particular: neural processing of drug- and non-drug-rewards. I present a body of research assessing the relationship between psychopathic traits and neural processing of drug and non-drug rewards within participants with varying levels of substance dependence, as a means to reconcile the psychopathy-addiction inconsistency and further our understanding of the development of substance dependence and the implication of psychopathy on this process.

Table 3
Summary table of the comorbidity between psychopathy and SUDs

	Psychopathy is associated with…			
Study	SUDs	Substance use	Substance abuse	Substance dependence
Blackburn & Coid, 1998	X			
Cauffman et al., 2009			X	X
Coid et al., 2009		X		
Colins, Andershed, & Pardini, 2015		X		
Cope et al., 2012		X		
Cope et al., 2014a		X		
Hart, Forth, & Hare, 1991				X
Hawes et al., 2015*	X	X		
Hemphil et al., 1994*	X			
Hillege et al., 2010		X		
Hopley & Brunelle, 2012				X
Jones & Miller, 2012			X	
Kennealy et al., 2007	X	X		
Mailloux, Forth, & Kroner, 1997			X	
Reardon, Lang, & Patrick, 2002	X			
Stålenheim & von Knorring, 1996	X			
Smith & Newman, 1990	X			
Sylvers, Landfield, & Lilienfeld, 2011			X	
Walsh et al., 2007	X			X

* Meta-analysis.

Drug-cue neural activity in addiction: Relationship to psychopathy

One neurocognitive feature of addiction that may yield important implications for understanding the comorbidity between psychopathy and addiction is drug-cue reactivity. Individuals with SUDs exhibit greater physiological, cognitive, and behavioral reactivity (Carter & Tiffany, 1999; Cooney et al., 1997; Drobes, 2002), as well as an increased craving for the drug in response to these cues (Kuhn & Galinat, 2011; Koob & Volkow, 2010). Drug-cue reactivity has also been assessed using neuroimaging methods, including functional magnetic resonance imaging (fMRI) and positron-emission tomography (PET). Meta-analyses of the neural response

to drug-cues have demonstrated that individuals with SUDs exhibit significantly greater drug-cue reactivity within the ventral striatum, amygdala, orbitofrontal cortex (OFC), posterior cingulate cortex, ACC, putamen, caudate, insula, dorsolateral and dorsomedial prefrontal cortex (DMPFC), and cuneus/precuneus (Chase, Eickoff, Laird, & Hogarth, 2011; Engelmann et al., 2012; Schacht, Anton, & Myrick, 2013; Yalachkov, Kaiser, & Naumer, 2012). Studies have assessed cue-reactivity within individuals with alcohol, nicotine, and cocaine use disorders. Recently, Kuhn & Gallinat (2011) conducted a meta-analysis of common drug-related neural activation patterns between nicotine, alcohol, and cocaine-cue reactivity, and demonstrated that only the ventral striatum exhibited significant concurrence of activation to cocaine-, alcohol-, and nicotine-cues.

This increased neural reactivity towards drug-related rewards may have come at the expense of non-drug rewards. For example, Garavan et al. (2000) demonstrated that cocaine users exhibited significantly greater reactivity within the PFC and ACC in response to cocaine-related stimuli relative to sex-related stimuli. Goldstein et al. (2009) demonstrated greater reactivity among individuals with a cocaine use disorder within the ACC in response to cocaine-related stimuli relative to monetary rewards. Finally, George et al. (2001) demonstrated greater neural reactivity within the PFC among individuals with an alcohol use disorder in response to alcohol-related pictures relative to pictures of non-alcohol beverages. This drug-cue reactivity may have implications in determining one's prognosis of this disorder, as drug-cue reactivity being associated with an increased propensity to relapse once abstinent, and shorter abstinence periods (Claus & Shane, 2018; Courtney, Schacht, Hutchison, Roche, & Ray, 2016; Janes et al., 2010).

Surprisingly, the relationship between psychopathic traits and drug-related stimulus-processing contrasted psychopathy-comorbidity research. Cope et al. (2014) assessed the relationship between psychopathic traits (measured with the PCL-R) and drug-cue reactivity among offenders with a substance dependence disorder. The authors demonstrated a negative correlation between psychopathic traits and neural reactivity to drug-related stimuli within several regions noted to have an increased sensitivity to drug-related stimuli in individuals with SUDs, including the DMPFC, precuneus, ACC, ventral striatum, caudate, and putamen (Cope et al., 2014). Another study among young offenders also demonstrated a negative correlation between psychopathic traits and drug-cue reactivity within the ACC, ventral striatum, caudate, putamen, amygdala, hippocampus, and insula (Vincent et al., 2017). This countered what we would have expected considering studies have demonstrated that psychopathic traits exhibited positive correlations to substance use (i.e. Coid et al., 2009) and antisocial and lifestyle psychopathic traits were positively associated with ventral striatal dopaminergic response to drug-related stimuli (Buckholtz et al., 2010), a theoretically central component to neural reactivity increases to drug-related stimuli and neural processing biases to drug-related rewards in addiction (Goldstein & Volkow, 2002; Koob & Le Moal, 1997; Koob & Volkow, 2010; Robinson & Berridge, 1993, 2000). Therefore, this raises questions about the nature of the comorbidity between psychopathic traits and SUDs.

However, there are limitations of both Cope et al. (2014) and Vincent et al. (2017) that must be addressed prior to making conclusions on the relationship between psychopathic traits and drug-stimulus processing. The first is the use of neutral stimuli as a control condition. Such a control condition may not have served as a control condition capable of arousing the brain's reward-processing and motivational neural systems in drug-independent individuals as drug-

related stimuli arouses such systems in individuals with SUDs (Versace et al., 2017). Non-drug rewards, such as food, may serve as a more appropriate control condition, as they would allow to assess the extent to which drug-related rewards are held to a higher accord than non-drug reward in addiction. In non-dependent healthy individuals, food has been found to activate reward-processing neural regions that overlap with regions exhibited drug-related reactivity substance-dependent individuals (Noori et al., 2016; Tang et al., 2012; Tomasi et al., 2011). Therefore, we know that individuals without a substantial history of substance use exhibited increased neural reactivity in response to food rewards that is similar to the neural response to drug-related stimuli in individuals with SUDs. This approach is also more in line with the i-RISA model (Goldstein & Volkow, 2002), which holds that the incentive sensitization of drug-related stimuli comes at the expense of the incentive salience of other non-drug rewards, and that this may lead to a neural processing bias in reward- and motivational regions towards drug-related stimuli compared to biologically-necessary rewards (i.e. food).

By examining the relationship between psychopathic traits and drug-related neural processing relative to a non-drug reward, we could determine whether the decreased neural reactivity in highly psychopathic individuals was specific to drug-related rewards or would generalize to all reward. In the studies presented in this thesis, we assessed the relationship between psychopathic traits and drug- and food-related neural processing, testing two possibilities. The first possibility was that while drug-related neural reactivity was decreased in highly psychopathic individuals, non-drug reward neural reactivity would be further decreased to compensate for this abnormality, rendering these individuals more likely to use the substance, and explaining the comorbidity between psychopathic personality disorder. Structural abnormalities related to psychopathy within several corticolimbic regions, including the

DMPFC, OFC, ACC, insula, striatum, and the amygdala (Boccardi et al., Cope et al., 2014b; de Oliveria-Souza et al., 2010; Ermer et al., 2012, 2013; Glenn et al., 2010; Hyde et al., 2014; Pardini et al., 2014; Yang et al., 2009, 2010), may have caused a different decalibration of this corticolimbic network with chronic substance use that rendered non-drug reward further decreased in value compared to drug-related rewards, which were devalued themselves.

This first possibility was assessed by examining the individual and shared effect of psychopathic traits and substance use severity on drug- and food-stimulus processing in the brain. This would have demonstrated not only how substance use severity and psychopathic individual affect drug- and food-stimulus processing, but also whether and how psychopathic traits modulate the effect of substance-use severity on the magnitude of the difference in neural reactivity between drug-related neural reactivity and food-related neural reactivity. If the first possibility is correct, psychopathic traits should increase a drug > food neural processing bias and modulate the effect of substance use severity in which high levels of psychopathic traits would increase drug > food processing in participants with low and high levels of substance use.

However, the second possibility was that psychopathic traits would fail to show this neural processing bias towards drug-related rewards rather than non-drug rewards. As psychopathic traits positively correlated with substance use (i.e. Coid et al., 2009) and were associated with sensitized dopaminergic response to substances (Buckholtz et al., 2010), it is possible that psychopaths did experience the strong positive reinforcement properties of drug use. However, psychopathic traits may have also facilitated a resilience to the development of these neural processing biases, possibly due to abnormalities in the experience of physiological factors that promotes the development of this bias. The i-RISA model holds that the experience of physiological factors of dependence, such as withdrawal and tolerance, would facilitate the

development of such biases towards drug-related rewards (Goldstein & Volkow, 2002, 2011). Consistent with this theory, neuroimaging studies have demonstrated that withdrawal sensitizes drug-cue reactivity in individuals with SUDs within the striatum, ACC, DMPFC, hippocampus, and posterior cingulate cortex (Jasinska, Stein, Kaiser, Naumer, & Yalachkov, 2014; Lou, Wang, Shen, & Wang, 2012; McClernon, Hiott, Huettel, & Rose, 2005; McClernon, Kozink, Lutz, & Rose, 2009). While no study has assessed the specific relationship between psychopathy and either psychological/-physiological dependence, nor between psychopathic traits and specific SUD symptomology, clinical case examinations offer evidence that psychopathic individuals may be resilient to withdrawal (Cleckley, 1955), and therefore, potential neural changes. This may have rendered highly psychopathic individuals unable develop this incentive sensitization of drug-related rewards and incentive desensitization of non-drug rewards, leading to the results from Cope et al. (2014) and Vincent et al. (2017). As a result, highly psychopathic individuals may be at risk for high rates of substance use and may in fact develop a psychological dependence to the drug of choice, however they may be resilient to the development of a physiological dependence and associated neurocognitive dysfunctions. This second possibility was assessed by examining the relationship between psychopathic traits and the two forms of dependence (psychological/- physiological dependence), followed by an examination of how the relationship between psychopathic traits and drug- and food-stimuli neural processing changed based on the variant of dependence.

The current thesis: Overview of studies

This body of work looked to further our understanding the nature of the comorbidity between psychopathic traits and addiction by assessing the relationship between psychopathic traits and neural reactivity to drug- and food-related stimuli, and whether psychopathic traits

modulates the effect of substance use severity on this neural reactivity. This relationship was first assessed in cocaine-dependent and cocaine-independent individuals and was followed by subsequent analyses that separated cocaine dependence into two variants: psychological and physiological dependence. The following gives a brief overview of each study and the attempt made to understand the psychopathy-addiction comorbidity using a sample of probation/parolees from the Albuquerque, New Mexico area.

Study 1

First, we assessed the relationship between psychopathy and substance dependence, as well as the relationship between psychopathic traits and drug- compared to food-stimulus processing in the brain using an fMRI cue-reactivity task. We additionally assessed how psychopathic traits interacted with substance use severity to affect any neural processing abnormalities seen in dependent individuals. This study will assess whether psychopathic traits plays a role in components of the i-RISA model, in particular the neural-processing bias for drug-related rewards relative to non-drug rewards. The results of this study have already been submitted for publication into the academic journal *Frontiers in Human Neurosciences.*

Study 2

We then assessed how this neural reactivity to drug- and food-related neural reactivity is modulated by whether the participant had a physiological or psychological dependence. This analysis would determine whether theories on physiological dependence being a more severe form of an addictive disorder could be true based on the magnitude of the neural reactivity bias hypothesized by the i-RISA model. We then assessed the relationship between substance use and psychopathic traits with the variant of dependence and assessed how the variant of dependence

modulated the effect of psychopathic traits, substance use severity, and their interaction on this drug > food neural reactivity.

In particular, I was interested in evaluating the four following questions: 1) whether the hypothesized processing bias outlined in contemporary theories of addiction could be observed in human subjects with a SUDs in an fMRI study; 2) whether physiological SUD patterns (i.e. withdrawal and tolerance) have a significant effect on neural processing biases; 3) whether psychopathic traits are truly associated with a desensitized neural response to drug-cues, or exhibit a similar or even sensitized processing bias observed in substance-dependent individuals; 4) whether psychopathic traits interact with the effects of substance use, tolerance and withdrawal on drug- and food-stimulus neural processing.

CHAPTER 2

THE STUDIES

Study 1[1]

Psychopathic individuals have frequently been characterized as impulsive and irresponsible risk takers, with an altered sensitivity to reward and reward-related stimuli (Beszterczey et al., 2013; Cleckley, 1955; Dean et al., 2013; Hare, 2003; Hopley & Brunelle, 2012; Mitchell et al., 2002; Morgan et al., 2011; Ross et al., 2007; Salim, van der Veen, van Dongen, Franken, 2015; Wallace, Malterer, & Newman, 2009). Given that these are also characteristics that predict initial and prolonged drug use (Koob & Volkow, 2010; Leeman et al., 2014; Woicik et al., 2009), it may come as no surprise that psychopathy has been associated with heightened levels of substance use (Coid et al., 2009; Cope et al., 2012, 2014; Hawes et al., 2015; Hillege et al., 2010; Kennealy et al., 2007), as well as increased diagnosis of both substance abuse (Cauffman et al., 2009; Colins et al., 2015; Jones & Miller, 2012; Mailloux et al., 1997; Sylvers et al., 2011) and substance dependence (Hart et al., 1991; Hopley & Brunelle, 2012; Walsh, et al. 2007).

Beyond this behavioral and diagnostic overlap are additional commonalities. For instance, both disorders appear characterized by dysfunction within common corticolimbic regions underlying reward-related processing (psychopathy: Blair, 2015; substance use disorders: Koob & Le Moal, 2001). Within adults with psychopathic traits, this dysfunction appears to manifest as consistently heightened sensitivity to a wide variety of rewarding stimuli within the ventral striatum, including monetary (Bjork et al., 2012; Buckholtz et al., 2010; Carré et al.,

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2013; Pujara et al., 2013) and drug-related (Buckholtz et al., 2010) rewards (though we note that children/adolescent with heightened callous-unemotional traits often show a normal [Byrd et al., 2018; Murray et al., 2017] or hyposensitive [Veroude et al., 2016] ventral striatal response to reward). Psychopathic traits have also been associated with increased functional connectivity between the ventral striatum and the dorsomedial prefrontal cortex (DMPFC) in response to monetary rewards (Geurts et al., 2016).

A considerably larger body of work indicates that individuals with substance use disorders also exhibit a heightened reward sensitivity throughout the corticolimbic system (Stewart et al., 2013). However, whereas psychopathic traits appear predictive of broadly increased sensitivity that spans multiple reward categories, individuals with prolonged drug use histories show a sensitivity-profile wherein reward-sensitivity shifts in favor of the individuals' drug of abuse, particularly within the DMPFC, ACC, striatum, amygdala, and insula (Chase et al., 2011; Engelmann et al., 2012; Garavan et al., 2000; Kilts et al., 2001; Kühn & Gallinat, 2011; Ray et al., 2015; Tomasi et al., 2016), at the expense of non-drug rewards (e.g., sex-related [Garavan et al., 2000], monetary [Goldstein et al., 2009]). This substance-induced decalibration of the reward system has been theorized as central to the development and maintenance of craving, drug-seeking, and compulsive drug use, wherein the individual is motivated to seek out the strong reward properties of the drug, and has difficulty obtaining that level of reward through non-drug rewards (Goldstein & Volkow, 2002, 2011; see also Koob & Le Moal, 1997, 2008a; Koob & Volkow, 2010).

How these reward-dysfunctions are related and whether they explain the comorbidity between the two disorders remains poorly understood. It is possible that heightened psychopathic traits predisposes to a sensitized reward-response to drugs, which would be related to a reward-

processing bias towards drug-related rewards compared to non-drug rewards. While little work has yet been directed towards such issues, one recent study provides preliminary support. In this study, drug-naïve individuals had their neural reactivity evaluated during a controlled amphetamine administration (Buckholtz et al., 2010). Results indicated that impulsive/antisocial psychopathic traits were associated with an increasingly sensitized ventral striatal dopaminergic response to the amphetamine administration. Such a heightened corticolimbic dopamine response to drugs is believed to serve as a catalyst for the development of longer-term neuroplastic changes to drug-related incentive salience, and a resultant processing bias for drug- compared to non-drug-rewards (Goldstein & Volkow, 2002; Koob & Le Moal, 1997; Koob & Volkow, 2010; Robinson & Berridge, 1993, 2000). Thus, the inclination for individuals with heightened psychopathic traits to select highly risky rewards (Mitchell et al., 2002), combined with their initially-heightened reward sensitivity (e.g., Bjork et al., 2012), may increase the likelihood of corticolimbic sensitization to drug-related rewards (followed by a substance induced desensitization to non-drug rewards). As a result, they would continue to abuse these drugs and may be more likely to develop substance dependence disorders.

Recently, a small amount of work has begun to investigate this hypothesis by assessing drug-stimulus processing in substance users with varying levels of psychopathy. Cope et al. (2014) assessed the relationship between psychopathy and the neural response to drug-related and neutral stimuli among 137 male offenders meeting the *DSM-IV-TR* (American Psychiatric Association, 2000) criteria for lifetime dependence to heroin, cocaine or methamphetamines. Results identified a negative correlation between psychopathic traits and neural response to drug versus neutral images in the ACC, putamen, caudate, amygdala, and ventral striatum. Vincent et al. (2017) largely replicated these results utilizing the same stimulus-presentation task in 54 male

adolescent offenders (44 of which had a stimulant use disorder) who manifested a negative correlation between psychopathic traits and neural response to drug versus neutral images in the ACC, amygdala, caudate, hippocampus, insula, and striatum.

While these results seemingly counter our hypothesis, several features of Cope et al. (2014) and Vincent et al. (2017) suggest that additional investigation may be in order. First, both studies used on a non-reward control condition. While this provides a true non-reward baseline, it precludes the ability to determine whether the psychopathy-related reduction in cue-elicited reactivity was specific to drug-related stimuli or could instead be due to a more general reduction in reactivity to all reward-related stimuli (see Versace et al., 2017 for commentary on the pitfalls of neutral conditions). This distinction may be particularly important given that substance use disorders are known to preferentially bias neural systems towards drug-related stimuli and away from other categories of non-drug rewards (i.e. food; Baler & Volkow, 2006; Rubinstein et al., 2011; Schwienteck & Banks, 2015; Schwienteck et al., 2015; Versace et al., 2017; Volkow et al., 2016; Volkow et al., 2010). To this end, the present study made use of a carefully matched non-drug reward (i.e., food) condition as our control condition. By including a food-reward condition, the paradigm afforded careful isolation of drug reward-related neural activity from natural reward-related activity. Thus, we could assess whether psychopathic traits are related to an abnormal neural sensitivity to all types of reward, or whether this abnormality is specific to drug-related rewards.

A second potential limitation of Cope et al. (2014) and Vincent et al. (2017) is that they did not include a non-dependent control condition. While we would not necessarily expect psychopathy to mediate neural responses to drug cues in a non-dependent group, the inclusion of this group can confirm the specificity of any mediated response in individuals with a previous

drug-use history. Such specificity may provide additional clues towards the etiological basis of any observed psychopathy-related influences. To this end, we recruited both dependent and non-dependent subjects into the present study.

We hypothesized drug- and food-related hemodynamic signal-change differences in the insula, DMPFC, ACC, amygdala, and the striatum between dependent and non-dependent groups. We additionally hypothesized that psychopathic traits would mediate neural reactivity to drug versus food stimuli in the dependent group. Finally, we predicted that psychopathic traits would interact with substance use, such that the influence of psychopathic traits on drug and food processing would be modulated by the level of substance use.

Methods

Participants

Our sample consisted of 105 adult probation/parolees (70 males) residing in the great Albuquerque, New Mexico area. Participants were recruited through probation/parole offices, halfway houses, and drug treatment centers, as well as through targeted advertisements in local print and online classifieds. Classified ads specifically targeted probation/parolees who did and did not meet *DSM-IV-TR* diagnostic criteria for lifetime cocaine dependence. Exclusion criteria included loss of consciousness for longer than 30 minutes, lifetime history of psychotic disorder, diagnosis of major depressive disorder within last 6 months, and standard MR-related exclusion criteria including metallic implants, permanent retainer or braces, irremovable piercings, other metal irremovable metallic objects, and pregnancy. Diagnosis of anxiety disorders, including obsessive-compulsive disorder, were documented but not used as exclusion criterion. This study was approved by the Institutional Review Board of the University of New Mexico and the Research Ethics Board of the University of Ontario Institute of Technology and carried out in

accordance with their recommendations. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Clinical/forensic measures

Cocaine dependence. Lifetime history of cocaine dependence was diagnosed via the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders (SCID-I/P; First et al., 2002). Psychiatric symptoms of all disorders are coded 1 to 3, representing absent (1), subthreshold (2), or threshold/present (3). As per SCID I/P procedures, a diagnosis of cocaine dependence required that the participants score '3' on at least three of seven diagnostic criteria. Highly trained graduate research personnel conducted each interview, under the guidance of a senior SCID trainer (R.C.; see acknowledgements).

Psychopathic traits. The Psychopathy Checklist-Revised (PCL-R; Hare, 2003) was utilized to measure psychopathic traits. The PCL-R is widely considered the gold-standard instrument to diagnose psychopathy (Lynam & Gudonis, 2005), and has demonstrated good reliability and construct validity in substance abuse patients (Alterman et al., 1993; Rutherford, et al., 1996; Rutherford et al., 1997) and offenders (Cooke & Michie, 1997; Neves et al., 2011; Poythress et al., 2010; Shine & Hobson, 1997; Sullivan et al., 2006). For the present study, PCL-R scores were calculated based on an in-depth interview administered by highly-trained research personnel (trained by Dr. Shane); no subsequent file review was undertaken. It consisted of 20 items scored 0-2, with scores ranging from 0 to 40. Both Total and Factor scores were calculated and evaluated with regard to primary variables of interest. Factor 1 contained eight items assessing interpersonal and affective deficits; Factor 2 contained 10 items assessing lifestyle and antisocial deficits.

Drug use. In addition to SCID-I/P diagnoses substance dependence disorders, a trained examiner also administered a modified version of the Addiction Severity Index-Expanded (ASI-X; McLellan et al., 1992) to assess the frequency and duration of participants' regular substance use history. Following data collection, three composite drug use scores were calculated by summing the total number of years of use of drugs that fell into one of three categories: Major Drugs (e.g., Cocaine, heroin, methamphetamines), Minor Drugs (e.g., Cannabis, nicotine, hallucinogens), and Alcohol (see Claus & Shane, 2018). For example, if a participant used cocaine for five years, methamphetamines for five years, and heroin for three years, the effective rate of Major Drug use was calculated as 13 years.

Cue-elicited craving task

Participants performed two identical runs of a cue-elicited block-design craving task randomly sequenced and presented via E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA). Within each run, participants were presented with 14 videos ranging from ~10,000-14,000ms in duration. Videos were organized into two categories: video depicting people preparing or using cocaine/crack (DRUG); or videos depicting people preparing/eating various foods (FOOD). The distinction between use and preparation of drugs and food was made for purposes outside the scope of this study — thus they were collapsed for all analyses within the current study. Participants were simply asked to watch the videos and were not required to make any formal assessments during video playback. However, following each video, participants were prompted to rate their level of craving on a scale from 1 (lowest) to 4 (highest) on a four-button keypad. Following a jittered inter-trial interval (2500ms, 3500ms, 5000ms) to aid deconvolution from the standard hemodynamic response function (HRF), the next video was presented.

Image acquisition parameters and preprocessing

Participants were scanned using a Siemens 3T TrioTim MRI scanner with advanced SQ gradients (max slew rate 200 T/m/s) at the Mind Research Network imaging center. Whole-brain T2*-weighted images were acquired from a 16-element phased-array head coil and an iPAT echo-planar imaging (EPI) gradient-echo pulse sequence (TR=2000ms; TE=29ms). Image acquisition utilized a 75º flip angle and created a 24 x 24 cm FOV on a 64 x 64 matrix, generating 33 slices of 3.5mm covering the entire brain (roughly 150mm) and creating a 3.4 x 3.4 mm in-plane resolution. Head motion was limited using padding and restraints.

Brain images were preprocessed using a custom pipeline with Statistical Parametric Mapping 5 (SPM5; http://www.fil.ion.ucl.ac.uk/spm). Motion parameters were collected along six dimensions (x, y, z; pitch, yaw, roll) and corrected using INRIAlign (Freire & Mangin, 2001), which applies an algorithm with a non-quadratic function, unbiased by local signal changes, that reduces the influence of intensity differences between slice images. No participants demonstrated head movement exceeding 5mm. Images were then normalized according to the standard single-subject MNI template and smoothed with a 10mm Full Width Half-Maximum (FWHM) Gaussian smoothing kernel.

Data analytic strategies

Psychometric data and correlations with psychometric data were analyzed within the Statistical Package for the Social Sciences 24 (SPSS 24; Industrial Business Machines [IBM], 2016).

First-level neuroimaging analyses were performed using a custom SPM5 analysis script to extract blood-oxygen-level-dependent (BOLD) signals throughout the task. The first-level design matrix included video presentation as one event separated into four conditions (depicting

drug preparation, drug use, food preparation, and food use). Mean functional images of blood oxygen-level-dependent signals throughout the whole brain were extracted from each of the four conditions. This model also included six movement parameters (x, y, z, yaw, pitch, roll) that were covaried out of the model as variables of no interest. T-contrasts were then computed at the first level to assess changes in hemodynamic response during the duration of the DRUG and FOOD videos relative to baseline and to each other.

Second-level neuroimaging analyses were conducted using a mixed-model flexible-factorial ANOVA in SPM12. Subject and Video Type (DRUG, FOOD) were included as within-group factors, and Group (Dependent, Non-Dependent) was included as a between-group factor. Higher-order main effects of VideoType and Group, the Group*VideoType interaction, and targeted T-contrasts to evaluate between- and within-group differences in neural responses to DRUG > FOOD were interrogated within the flex-factorial model. All second level analyses were conducted with and without age as a null covariate; results reported below were modelled without age.

Of particular interest was the extent to which PCL-R scores and/or substance use severity would predict the magnitude of any DRUG > FOOD processing bias identified within the Dependent group. To investigate this, multiple linear regression models were undertaken, with PCL-R Total Scores, Major Drug Use, and the PCL-R*Major Drug Use interaction term, included as regressors to predict BOLD response in the DRUG > FOOD contrast. These regressions were run separately among Dependent and Non-dependent groups, however results focus on the Dependent results, as these were of primary theoretical importance. Similar regression models were also conducted with Factor 1 and Factor 2 scores as regressors to evaluate the unique influence of interpersonal/affective and lifestyle/antisocial traits.

Whole-brain results were interpreted using an uncorrected threshold of .001, combined with an extended cluster threshold of 132 voxels (equivalent to a $p < .05$ [FWE] threshold) based on a series of Monte-Carlo simulations run through the Alpha Simulator (AlphaSim) in the Resting-State fMRI Data Analysis Toolkit (REST; Song et al., 2011).

ROI analysis

In addition to whole-brain analyses, small-volume correction ($p < .05$ FWE-svc) was used to assess activity within six regions of interest (ROIs) : right insula (x = 40, y = -8, z = -18), left ACC (-6, 4, 44), left DMPFC (-5, 46, 34), right ventral striatum (11, 13, -7), left amygdala (-32, 0, -27), and left caudate nucleus (-9, -4, 12). All central coordinates were obtained from a recent meta-analysis, which identified these regions within individuals with cocaine use disorders show specifically reactivity following presentation of cocaine-related cues (Kühn & Gallinat, 2011). A 6mm spherical search space was used for subcortical ROIs (i.e., ventral striatum, amygdala and caudate) while a 10mm sphere was used for cortical ROIs (i.e., insula, ACC, DMPFC).

Parameter estimates of signal change to DRUG and FOOD videos were extracted from each ROI were evaluated via ANOVA and correlational models in SPSS. Both parameter estimates from peak-voxel coordinates and average parameter estimates from all coordinates within the ROI were evaluated, exhibiting identical results. Within the current study, we report peak-voxel coordinate analyses and results.

Results

Descriptive statistics and correlations between variables of interest

Descriptive statistics of all clinical/forensic variables are displayed in Table 4; correlations between these variables are displayed Table 5. The mean sample age was 35.86 (SD

= 9.04; range = 21-59), and the mean IQ was 105.47 (SD = 12.13; range = 77-140). As may be expected, Dependent participants reported greater lifetime drug use than Non-dependent participants, t=6.70, p<.001 particularly with regard to major, t=8.08, p<.001, but not minor, t=.224, p=.82, drug use. Moreover, Dependent participants had higher PCL-R Total, t=4.57, p<.001, and Factor (Factor 1, t=3.42, p=.001; Factor 2, t=4.14, p<.001) scores than Non-dependent participants. Finally, Dependent participants also had a higher mean age, t=2.53, p=.013.

Baseline sensitivity to DRUG and FOOD stimuli

Neural responses to DRUG and FOOD stimuli were first evaluated using a 2 (VideoType) x 2 (Group) flexible-factorial ANOVA. This analysis revealed significant main effects of both Group and VideoType that spanned across frontal, temporal, parietal, occipital and limbic cortices (see Table 6). These main effects were influenced by a significant Group x VideoType effect, which presented within several clusters that encompassed the left ACC, right insula, right ventral striatum, left amygdala, and right hippocampus.

To evaluate the nature of this interaction effect, parameter estimates from these four ROIs were extracted from DRUG and FOOD trials and entered into mixed-factor ANOVA models in SPSS. As seen in Figure 1, Bonferroni-controlled t-tests indicated that the Dependent group exhibited greater DRUG-related activity within the right ventral striatum ROI, t = 2.48, p(FWE) =.015; and reduced FOOD-related activity within the left ACC, t = 2.31, p(FWE) =.023, left amygdala, t = 2.13, p(FWE) =.036, and right insula, *marginal* t = 1.94, p(FWE) =.055.

Table 4

Descriptive statistics and group-level differences in clinical/forensic variables

Variable	Whole sample	Dependent group	Non-dependent group	*t*
Age	35.86 (9.04)	38.28 (8.56)	33.90 (9.02)	2.53*
IQ	105.47 (12.13)	105.47 (12.13)	105.91 (11.69)	.418
Major drug use	7.44 (8.26)	13.36 (8.40)	2.64 (3.87)	8.08***
Minor drug use	21.67 (16.26)	22.06 (16.38)	21.35 (16.29)	.224
Alcohol use	8.32 (9.86)	11.51 (10.50)	5.74 (8.57)	3.10**
PCL-R Total	18.78 (7.33)	22.11 (6.83)	16.08 (6.62)	4.57***
Factor 1	6.40 (3.39)	7.60 (3.20)	5.43 (3.26)	3.42**
Factor 2	11.08 (4.20)	12.83 (3.91)	9.66 (3.91)	4.14***

Note. t values represent test statistic of difference between Dependent and Non-dependent participants. Unbracketed values represent means, while bracketed values represent standard deviations. Factor 1 and Factor 2 scores represent scores on interpersonal/affective (Factor 1) and antisocial/lifestyle (Factor 2) psychopathic trait assessment on the PCL-R.

* p <.05, ** p<.01, *** p<.001

Table 5

Correlations between clinical/forensic variables among Dependent and Non-dependent participants

	1	2	3	4	5	6	7	8
Dependent group								
1. Age	--	-.31*	.41**	.-.27	.16	.18	.24	.13
2. IQ		--	-.17	.09	-.12	-.10	.02	-.21
3. Major drug use			--	-.10	.12	.33*	.17	.46**
4. Minor drug use				--	-.06	.04	.13	.02
5. Alcohol use					--	.10	.06	.12
6. PCL-R Total						--	.88***	.89***
7. Factor 1							--	.62***
8. Factor 2								--
Non-dependent group								
1. Age	--	-.10	.13	-.07	.38**	-.15	-.06	-.15
2. IQ		--	-.14	.04	-.30*	-.10	.05	-.20
3. Major drug use			--	-.11	-.16	.11	-.02	.16
4. Minor drug use				--	-.09	-.09	-.04	-.13
5. Alcohol use					--	.21	.22	.12
6. PCL-R total						--	.85***	.87***
7. Factor 1							--	.53***
8. Factor 2								--

*p <.05, ** p<.01, *** p<.001

Relative sensitivity to DRUG versus FOOD stimuli. To assess participants' *relative* responses to DRUG versus FOOD stimuli, we conducted separate within-sample *t*-tests on the DRUG > FOOD contrast in each of the Dependent and Non-dependent groups (see Table 7). As hypothesized, Dependent participants exhibited significantly greater DRUG than FOOD reactivity within the right insula, left ACC, right ventral striatum, and left amygdala ROIs, as well as the left DMPFC. Greater FOOD > DRUG reactivity was only observed within the bilateral occipital cortex. In contrast, Non-dependent participants did not exhibit any regions with greater DRUG than FOOD reactivity yet demonstrated greater reactivity to FOOD than DRUG stimuli within the right insula, right ventral striatum, and left caudate nucleus. Between-group differences were evaluated via a between-group *t*-test, which confirmed that the Dependent group exhibited significantly greater DRUG > FOOD activation bias than the Non-dependent group within the right insula, left DMPFC, right ventral striatum, left amygdala, and left DMPFC.

Table 6
Higher-order ANOVA results

Region	Hemi.	MNI (x, y, z)	F	Cluster size
Main effect of Group				
Angular gyrus	R	60, -54, 12	29.12*	140
	R	57, -60, 18	20.81*	
Middle temporal cortex	R	45, -42, -6	16.32	
Middle occipital cortex	R	48, -72, 27	23.23*	192
	R	45, -78, 18	22.52*	
Calcarine cortex	R	6, -69, 12	22.71*	
Ventral striatum	R	12, 12, 0	6.89†	27
Amygdala	L	-9, -6, 12	7.14†	22
Main effect of Condition				
Middle occipital cortex	L	-18, -99, 3	58.24*	193
Fusiform gyrus	L	-30, -78, -18	33.95*	
Middle occipital cortex	R	12, -99, 9	56.18*	268
Fusiform gyrus	R	30, -81, -15	17.57	
Superior occipital cortex	L	-24, -78, 30	39.36*	244
Superior parietal cortex	R	24, -54, 60	38.22*	218
Middle frontal cortex	R	45, 18, 3	28.37*	768
Inferior temporal cortex	L	-45, -45, -9	19.07	180
ACC	L	-9, 6, 54	15.91†	70
DMPFC	L	-3, 36, 36	9.50†	35
Ventral striatum	R	18, 12, -6	6.94†	1
Interaction effect				
Orbitofrontal cortex	R	42, 36, -3	21.75*	342
Insula	R	48, 15, -12	15.12	
	R	33, 21, -12	14.01	
Middle frontal cortex	R	51, 15, 18	20.11*	230
Superior frontal cortex	R	36, 15, 36	15.10	
DMPFC	R	51, 33, 18	14.71	
ACC	L	-6, 18, 21	19.47*	349
	L	-6, 27, 6	18.61	
Middle temporal cortex	L	-63, -24, -12	19.27*	159
	L	-57, -6, -6	17.83	
Superior temporal cortex	L	-48, 12, -18	12.21	
Insula	R	36, 0, -21	9.48†	73
Ventral striatum	R	6, 12, -6	8.48†	15
	R	12, 18, -6	6.90†	
Amygdala	L	-36, 0, -24	7.87†	27

Table represent significant activity within a mixed factors (Group * VideoType) flexible factorial ANOVA model. All regions show significant activity at p(uncorr) < .001; * p(FWE) < .05; † p(svc-FWE) <.05; ACC = Anterior cingulate cortex; DMPFC = Dorsomedial prefrontal cortex; Hemi = Cerebral Hemisphere; MNI = X, Y, Z coordinates on a Montreal Neurological Institute template.

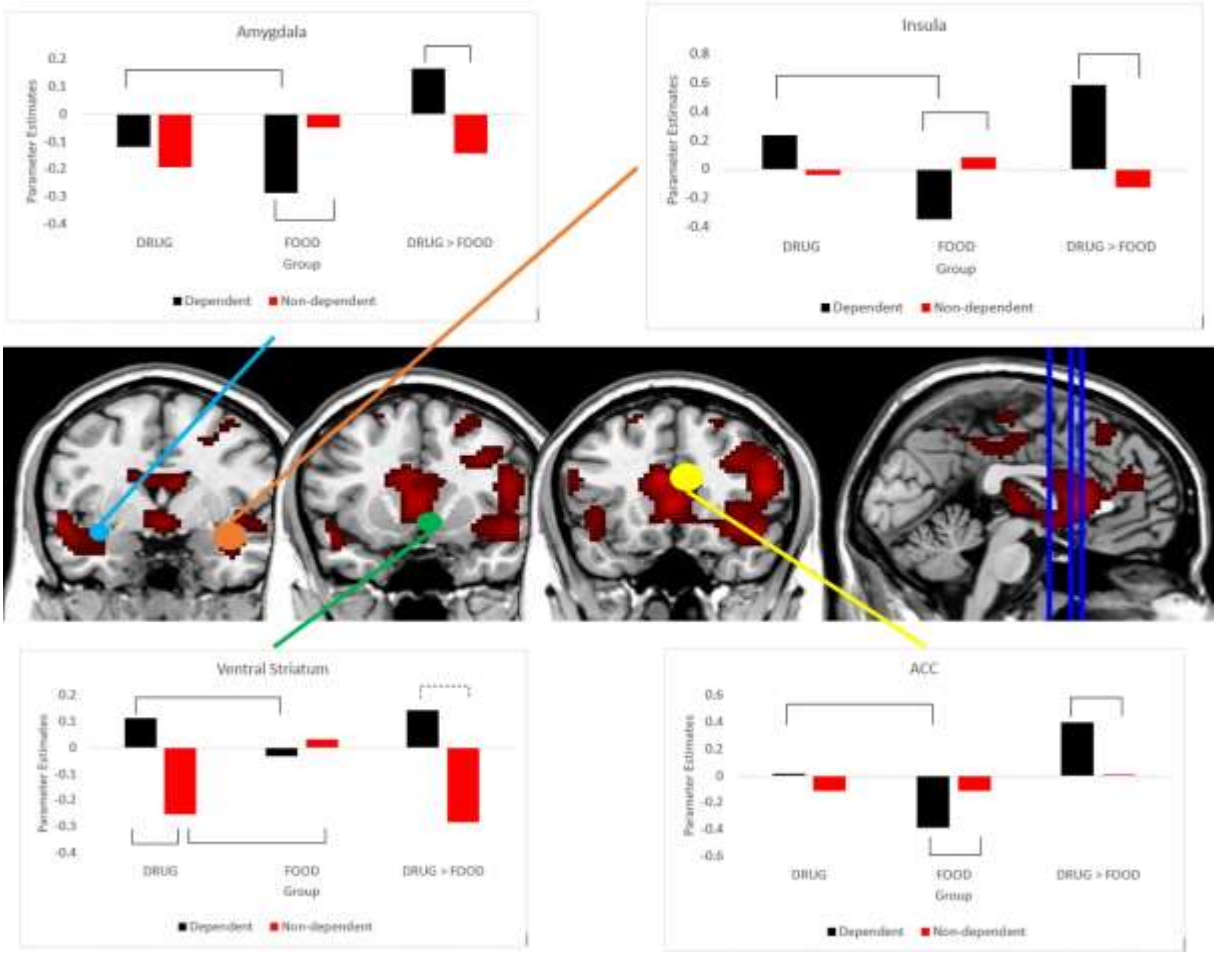
Table 7
Within- and between-group drug and food neural activity

Region	Hemi.	MNI (x, y, z)	*t*	Cluster size
Drug > Food – Dependent Group				
ACC	L	-9, 21, 18	6.07*	2980
Lateral prefrontal cortex	R	45, 21, 3	5.74*	
Lateral prefrontal cortex	L	-42, 21, -3	5.07*	615
Dorsolateral prefrontal cortex	L	-45, 39, 15	4.95*	
Middle frontal cortex	L	-57, 21, 15	4.73*	
Middle occipital cortex	R	9, -99, 12	5.05*	226
Fusiform gyrus	R	30, -81, -15	4.08	
Angular gyrus	R	48, -48, 42	4.84*	150
Postcentral gyrus	L	-12, -21, 57	4.27*	147
Precentral gyrus	L	-6, -9, 54	3.61	
Insula	R	30, -6, -15	2.82†	44
	R	36, 0, -15	2.69†	
ACC	L	-9, 9, 51	4.00†	117
	L	-9, -6, 48	2.86†	
DMPFC	L	0, 39, 33	3.46†	96
	L	-3, 36, 36	3.44†	
Ventral striatum	R	18, 12, -6	2.87†	14
Amygdala	L	-33, -3, -24	2.35†	23
Drug > Food – Non-dependent Group				
No significant results				
Drug > FOOD – Dependent > Non-dependent				
Ventrolateral prefrontal cortex	R	42, 36, -3	4.66*	1455
Middle frontal cortex	R	51, 15, 18	4.48*	
ACC	L	-6, 18, 21	4.41*	
Middle temporal cortex	L	-63, -24, -12	4.39*	249
	L	-57, -6, -6	4.22*	
Superior temporal cortex	L	-48, 12, -18	3.49	
Orbitofrontal cortex	L	-42, 24, -6	3.87	177
Lateral prefrontal cortex	L	-42, 36, 12	3.86	
Ventrolateral prefrontal cortex	L	-36, 39, 0	3.32	
Insula	R	36, 0, -21	3.08†	117
DMPFC	L	-3, 45, 24	2.71†	89
Ventral striatum	R	6, 12, -6	2.91†	22
	R	12, 18, -6	2.63†	
Amygdala	L	-39, 0, -21	2.81†	32

All regions show significant activity at p(uncorr) < .001; * p(FWE) < .05; † p(svc-FWE) <.05; DMPFC = Dorsomedial prefrontal cortex; ACC = Anterior cingulate cortex. Hemi = Cerebral Hemisphere; MNI = X, Y, Z coordinates on a Montreal Neurological Institute template.

Figure 1

Differential sensitivity to DRUG and FOOD videos between groups



Bar-charts demonstrate differences in DRUG and FOOD reactivity between the Dependent and Non-dependent groups. Brackets indicate significant differences at $p < .05$. MRIcron images display intensity thresholds ranging from T = 6.17 – 22.56. Coronal slices register to MNI coordinate y = 0, y = 12, and y = 18, respectively.

Influence of PCL-R Scores and drug use severity among the Dependent group

Given that between-group analyses confirmed that cocaine-dependent individuals were characterized by a DRUG > FOOD processing bias compared to non-dependent participants, we next, evaluated the extent to which psychopathic traits and substance use history would relate to this processing bias. To this end, we undertook a series of regression models in SPM12, entering PCL-R Total scores, years of major drug use, and the PCL-R x Major Drug Use interaction term, as regressors predicting DRUG > FOOD reactivity. We ran models within both Dependent and Non-dependent groups but focused primarily on the Dependent group given the unknown response to drug cues within the Non-dependent group. Dependent group results are presented in Table 8, and non-dependent group results are presented in Table 9.

Results indicated that PCL-R scores, but not major drug use, were positively correlated with activity within several regions, including right insula and left amygdala ROIs. We followed up these regressions by correlating parameter estimates from these ROIs with PCL-R scores and observed positive correlations between PCL-R scores and DRUG-related activity in the right insula, $r = .30$ $p = .043$, and negatively correlated with FOOD-related activity in the right insula, $r = -.35$ $p = .018$, and left amygdala, $r = -.33$ $p = .025$.

In addition, we observed a significant PCL-R x Major Drug Use interaction within the left DMPFC, bilateral insula, and left caudate nucleus. To decipher these interaction effects, we separated our Dependent group into high and low PCL-R groups (via median split; median PCL-R = 22). The high PCL-R group exhibited greater DRUG > FOOD activity within left DMPFC, $t = 2.62$, $p = .012$, and right insula, $t = 3.23$, $p = .002$. We then correlated Major Drug Use composite scores to parameter estimates within each group separately. Parameter estimates from FOOD trials were subtracted from DRUG trials to obtained DRUG > FOOD reactivity estimates.

Within the low PCL-R group, Major Drug Use correlated positively with DRUG > FOOD reactivity within the left DMPFC, $r = .59$ $p = .003$, right insula, $r = .56$ $p = .005$, and left caudate, $r = .65$ $p = .001$. In contrast, the high PCL-R group exhibited a marginally significant negative correlation between Major Drug Use and DRUG > FOOD within the right insula $r = -.38$ $p = .071$. These correlations were followed by correlations between Major Drug Use and parameter estimates extracted from FOOD and DRUG trials relative to baseline. Among the low PCL-R group, Major Drug Use correlated positively with DRUG-related left DMPFC, $r = .53$ $p = .009$, and left caudate, $r = .48$ $p = .021$, activity and correlated negatively with FOOD-related right insula, $r = -.46$ $p = .028$, and left caudate. $r = -.45$ $p = .032$, activity. The high PCL-R group did not exhibit any significant correlations.

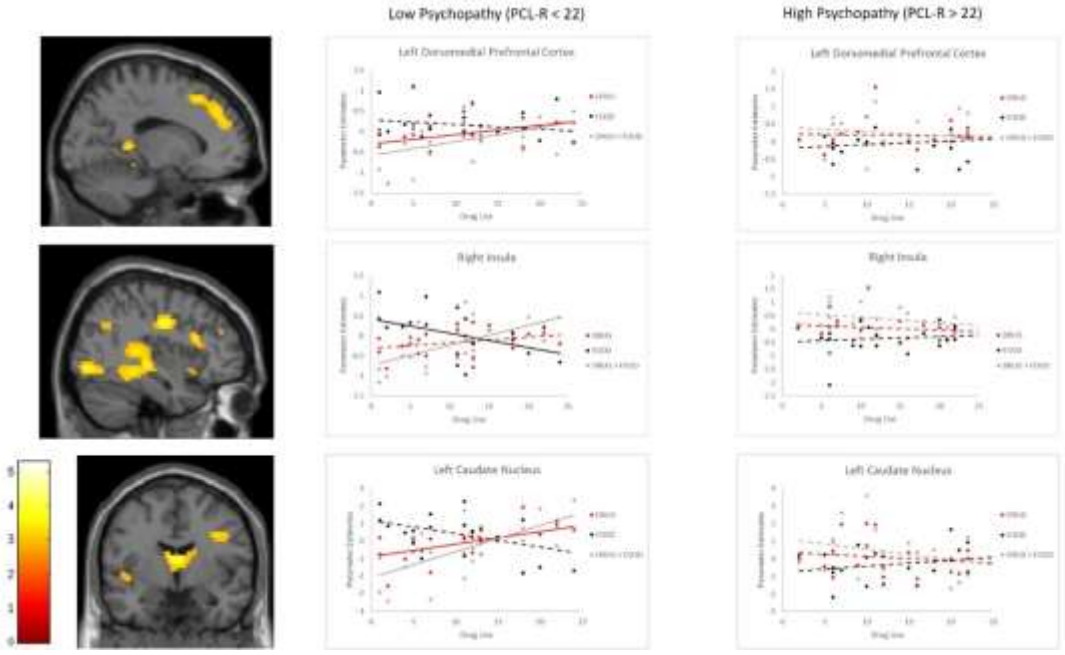
Table 8
Multiple regression results: Total PCL-R scores, Major Drug Use, and DRUG > FOOD-related hemodynamic activity among the Dependent group

Region	Hemi.	MNI (x, y, z)	*t*	Cluster size
PCL-R				
Positive				
Insula	R	36, -15, -15	3.46†	151
	R	36, -12, -21	3.34†	
Amygdala	L	-30, -3, -24	2.95†	23
Negative				
No significant results				
Major Drug Use				
No significant results				
PCL-R * Major Drug use				
DMPFC	R	24, 30, 33	5.28*	150
Superior frontal cortex	R	15, 27, 48	3.61	
Insula	R	39, -9, -9	2.78†	63
DMPFC	L	-15, 42, 36	3.40†	168
	L	3, 48, 30	2.72†	
Caudate	L	-3, -3, 12	3.72†	33
	L	-6, 0, 15	3.63†	

All regions show significant activity at p(uncorr) < .001; * p(FWE) < .05; † p(svc-FWE) <.05; DMPFC = Dorsomedial prefrontal cortex. Hemi = Cerebral Hemisphere; MNI = X, Y, Z coordinates on a Montreal Neurological Institute template.

Figure 2

Correlations between parameter estimates and Major Drug Use among Dependent participants with high and low PCL-R scores



Scatterplots demonstrate correlations between Major Drug Use and parameter estimates of neural activity in response to DRUG and FOOD videos, as well as their calculated difference in activity (DRUG > FOOD). Solid lines indicate significant correlations at $p < .05$. Brain images are at a significance threshold of p(uncorr) < .005, with an extended cluster threshold of k =73.

Table 9
Multiple regression results: Total PCL-R scores, Factor scores, Major Drug Use, and DRUG > FOOD-related hemodynamic activity among the Non-dependent group

Region	Hemi.	MNI (x, y, z)	*t*	Cluster size
Positive – PCL-R * Major drug use				
Caudate	L	-6, 0, 6	3.94	406
Precentral gyrus	L	-15, -3, 69	4.84	559
	L	-42, 0, 57	4.02	
DMPFC	L	-15, 39, 45	4.61	
DMPFC	R	15, 51, 21	4.81	1159
Insula	R	42, -15, -15	3.18†	132
	R	42, 0, -21	2.99†	
DMPFC	L	-9, 45, 42	3.99†	171
	L	-12, 51, 30	3.86†	
	R	3, 48, 36	3.04†	
Ventral striatum	R	6, 12, -6	3.44†	26
	R	9, 9, -3	3.43†	
Positive – Factor 1*Major drug use				
DMPFC	L	-9, 42, 42	2.90†	132
	L	-12, 48, 33	2.71†	
Positive – Factor 2*Major drug use				
Caudate nucleus	L	-9, -3, 6	2.98†	33
	L	-6, -6, 9	2.88†	
	L	-6, 0, 9	2.90†	

All regions show significant activity at *p*(uncorr) < .001; * *p*(FWE) < .05; † *p*(svc-FWE) <.05; DMPFC = Dorsomedial prefrontal cortex. Hemi = Cerebral Hemisphere; MNI = X, Y, Z coordinates on a Montreal Neurological Institute template.

Influence of PCL-R scores and drug use severity among the Non-dependent group

The Non-dependent group, on the other hand, demonstrated no significant relationships between PCL-R scores, major drug use, and DRUG > FOOD reactivity. However, we noted significant PCL-R * Major Drug Use interaction effects in the bilateral DMPFC, right ventral striatum, and the left caudate (see Table S2). Analysis of parameter estimates demonstrated that among the High PCL-R group (PCL-R > 15), Major Drug Use positively correlated with DRUG > FOOD activity within the left DMPFC, r =.44, p = .012, right insula, r =.49, p = .005, and left caudate, r =.34, p = .058. Among the Low PCL-R group, Major Drug Use negatively correlated with DRUG > FOOD activity within the left DMPFC, r = -.59, p = .001, left ACC, r =-.67 p <.001, right ventral striatum, r =-.47, p = .014, right insula, r =-.34, p = .080, and left caudate, r =-.47, p = .014.

When correlating Major Drug Use to DRUG- and FOOD-related activity relative to baseline, the high PCL-R group demonstrated positive correlations between Major Drug Use and activity to DRUG videos within the right insula, r =.30, p = .098, and negative correlations with activity to FOOD videos within the left DMPFC, r =-.33, p = .071, and left caudate, r = -.43, p = .016. The low PCL-R group exhibited negative correlations to DRUG videos within the right insula, r =-.42, p = .029, left DMPFC, r =-.53, p = .005, right ventral striatum, r =-.50, p = .008, and left caudate, r =-.48, p = .011. In addition, they exhibit positive correlations to FOOD videos within the left DMPFC, r =.40, p = .037.

Influence of psychopathy factors and drug use severity

Finally, to better understand how PCL-R factors differentially influenced neural reactivity, we undertook additional regression models with PCL-R Factor scores (and Major Drug Use) entered as separate regressors to predict activity in the DRUG > FOOD contrast.

Within the Dependent group, these analyses indicated that Factor 1 was associated with activity in several regions, including the right insula, right ventral striatum, and left amygdala (Table 6; see Table S2 for results in the Non-dependent group). Analysis of parameter estimates from each of the FOOD and DRUG contrasts confirmed that Factor 1 scores were positively correlated with DRUG-related activity within right insula, $r = .39$ $p = .006$, and left amygdala, $r = .30$ $p = .042$, and negatively correlated with FOOD-related activity within ventral striatum, $r = -.31$ $p = .034$, and left amygdala, *marginal* $r = -.26$ $p = .084$. Factor 2 showed no associated with DRUG > FOOD reactivity, and no interaction effects between Major Drug Use and Factor scores were identified.

The Non-dependent group demonstrated no significant relationship between Factor 1 nor Factor 2 scores and DRUG > FOOD reactivity, however they did exhibit a significant Factor * Major Drug Use and Factor 2 * Major Drug Use interaction effects in the left DMPFC and left caudate, respectively. Among participants high in Factor 1 (Factor 1 > 5), Major Drug Use predicted an increased DRUG > FOOD reactivity within the left DMPFC, $r = .46$, $p = .009$, due to a positive correlation between Major Drug Use and DRUG-related activity relative to baseline, $r = .40$, $p = .027$. No significant correlations were observed in participants low in Factor 1 scores (Factor 1 < 5). Participants high in Factor 2 (Factor 2 > 10) exhibited a positive correlation between Major Drug Use and DRUG > FOOD reactivity within the left caudate, $r = .51$, $p = .004$, due to a negative correlation between Major Drug Use and FOOD reactivity, $r = -.42$, $p = .022$. Among participants low in Factor 2, in contrast, Major Drug Use was negatively correlated with DRUG > FOOD reactivity within the left caudate, $r = -.51$, $p = .006$, due to negative correlations to DRUG-related activity, $r = -.54$, $p = .003$.

Table 10
Multiple regression results: PCL-R Factor scores, Major Drug Use, and DRUG > FOOD-related hemodynamic activity among the Dependent group

Region	Hemi.	MNI (x, y, z)	*t*	Cluster size
Factor 1				
Positive				
Cerebellum	R	39, -63, -48	4.71	116
	R	21, -78, -42	3.93	
Parahippocampal gyrus	L	-24, -21, -27	4.71	285
Fusiform gyrus	L	-27, -36, -21	4.69	
	L	-39, -60, -12	3.57	
Fusiform gyrus	R	27, -39, -18	4.46	200
	R	36, -33, -18	4.18	
Lingual gyrus	R	33, -51, -3	3.52	
Insula	R	39, -12, -24	4.06†	164
Ventral striatum	R	9, 9, -9	3.12†	32
	R	9, 15, -6	3.10†	
Amygdala	L	-30, -3, -24	2.89†	26
Negative				
No significant results				
Factor 2				
No significant results				
Use				
No significant results				
Factor 1*Major Drug Use				
No significant results				
Factor 2*Major Drug Use				
No significant results				

All regions show significant activity at *p*(uncorr) < .001; * *p*(FWE) < .05; † *p*(svc-FWE) <.05; Hemi = Cerebral Hemisphere; MNI = X, Y, Z coordinates on a Montreal Neurological Institute template.

Discussion

We used an fMRI cue-elicited craving task to assess neural reactivity to drug-related and food-related stimuli within individuals with and without a cocaine dependence disorder. We first noted a neural processing bias for drug-related relative to food-related stimuli among cocaine-dependent participants relative to non-dependent participants, within a variety of regions including the ACC, DMPFC, amygdala, ventral striatum, and insula. These results are consistent with a large body of neuroimaging work which has demonstrated increased corticolimbic responsivity to drug-related rewards compared to either neutral (Bonson et al., 2002; Chase et al., 2011; David et al., 2005; Engelmann et al., 2012; Garavan et al., 2000; Kühn & Gallinat, 2011; Kilts et al., 2001; Ray et al., 2015), or non-drug rewards (Garavan et al., 2000; Goldstein et al., 2009; George et al., 2001). Specifically, analysis of parameter estimates indicated that certain corticolimbic regions (i.e., right ventral striatum) exhibited increase neural sensitivity to cocaine-related stimuli, and other corticolimbic regions (i.e., left ACC and left amygdala) exhibited decreased sensitivity to food-related stimuli. Together, these findings offer further support for the notion that individuals with substance dependence disorders exhibit a specifically heightened reward response for drug-related rewards, and a concomitant decrease in reactivity to non-drug rewards (see Goldstein & Volkow, 2002, 2011). Contemporary models of addiction (i.e., I-RISA: Goldstein & Volkow, 2002; antireward-theory: Koob & Le Moal, 1997; Blum et al., 2000; Franken, 2003) argue that destabilization of this neural sensitivity may contribute to substance-dependent individuals' engagement in habitual, uncontrollable drug-seeking behavior.

Of particular interest was the extent to which either psychopathic traits or duration of substance use history would influence the magnitude of this neural processing bias. No main effect of substance use history was identified, suggesting that the addiction-related processing

bias for drug-related stimuli may develop early in the addiction cycle (see Koob & Le Moal, 1997), and remain stable with prolonged use. In contrast, a main effect of psychopathic traits was identified within the right insula and left amygdala, such that an increase in psychopathic traits was associated with a more severe bias Drug > Food reactivity within these regions. Analysis of parameter estimates indicated that the right insula, psychopathic traits were associated with increase in drug-related responsivity and decrease in food-related responsivity; in the left amygdala, decrease in food-related responsivity were found. These findings support the hypothesis that psychopathic traits would moderate the magnitude of drug-related reward sensitivity in substance abusing individuals. Considering that the insula has been noted to be involved in the interoceptive reward-processing of drug use (Koob & Volkow, 2016; Naqvi & Bechara, 2009, 2010), and the amygdala is involved in salience attribution to rewarding stimuli (Ding et al., 2013; Lee et al., 2013; Murray et al., 2015), psychopathic traits may impart an enhanced incentive sensitization to drugs and drug-related interoceptive reward, as well as an enhanced incentive desensitization to food-related reward.

These results run somewhat counter to the results of Cope et al. (2014) and Vincent et al. (2017), which reported decreased drug-related reactivity with increasing levels of psychopathy. One difference worth noting is that our study focused only on cocaine dependence and utilized a cocaine-cue craving task, whereas Cope et al. (2014) utilized methamphetamine, heroin, and cocaine users, and Vincent et al. (2017) focused on stimulant users. However, we believe that a more important distinction between our study and these prior reports is that our study made use of a non-drug reward (food) control condition (rather than a neutral control condition). By using such a non-drug reward control condition, the present study was able to interrogate the extent to which psychopathy-induced variation in neural reactivity to drug-related stimuli was due to

consistent changes in reactivity to all forms of rewarding stimuli or was instead specific to the processing of drug-related stimuli (see Versace et al., 2017 for discussion of problems with neutral control conditions). The present results appear to support the latter hypothesis: individuals with heightened psychopathic traits showed greater Drug > Food processing biases, suggestive of particularly strong desensitization of non-drug rewards. It is likely that the use of a neutral control condition in previous studies would have had difficulty identifying this distinction, and that a negative Drug > Neutral bias may preclude a positive Drug > NonDrug bias. For instance, psychopathic traits could associate with a decrease in drug-related reward-processing, while also associating with a greater decrease in non-drug reward-sensitivity. Future research should evaluate whether the present findings, and those of Cope et al. (2014) and Vincent et al. (2017) can be reconciled along such lines.

Interestingly, we also observed an interaction between psychopathic traits and substance use history, such that the positive correlations between substance use history and Drug > Food processing occurred only within participants with a low level of psychopathic traits. In contrast, we observed a marginally significant negative correlation within participants with a high level of psychopathic traits. These results suggest that the development of a specific affinity towards drug-related rewards in substance users may only be apparent when in combination with a low level of psychopathic traits. In highly psychopathic individuals, on the other hand, we observed a decreased sensitivity to drug-related rewards. While highly psychopathic individuals, characterized by a high sensitivity to rewarding stimuli (Bjork et al., 2012), initially exhibit this drug-specific reward sensitivity, they may begin to exhibit a premature desensitization of this reward-processing bias with increasing substance use. This raises further question about the implication of psychopathic traits on the development, maintenance of substance use disorders.

Further study should be allocated towards the nature of the comorbidity between psychopathy and addiction. The fact that in the current study, and in the previous literature (Cope et al., 2014), we observe decreases in reward-related reactivity rather than increases, raises question about how reward dysfunction in psychopathic individuals moderates the development and maintenance of substance dependence. However, two possibilities may explain how psychopathic traits may be associated with decreases in drug-cue reactivity and increases in substance use disorders. One is that with increasing substance use, highly psychopathic individuals begin to lose interest in the drug, possibly due to a decrease in the novelty and stimulatory effect of the drug. As psychopathic individuals are characterized as novelty and sensation seekers (Cleckley, 1941; Haapasalo, 1990; Hare, 2003, the decrease in the novelty and stimulatory effect of the drug may render psychopathic individuals disinterested in the drug with an increasingly severe substance use history. The other explanation is a deficit in cue-processing within the psychopath. Psychopathic individuals have commonly been noted to exhibit deficits in external stimulus and cue processing, such as through gambling tasks (Mitchell et al., 2002) or through choice-paradigms, in which case the psychopath must decide in response to cues of both reward and punishment (Blair et al., 2006). As a result, presenting drug- and non-drug rewarding-cues in an fMRI paradigm may lack the necessary saliency for the psychopath to elicit strong neural activity that we hypothesize would be an explanatory factor for their high substance use disorder prevalence.

Implications for treatment

Non-invasive neurostimulation techniques have been associated with moderate success in reducing drug craving sensations. Most work to date has targeted the dorsolateral PFC in particular (Hayashi et al., 2013; Jansen et al., 2013; Shahbabaie et al., 2014), to try to increase

inhibitory processing. Less work has to date targeted subcortical structures directly associated with reward processing. It may be that the regions identified as exhibiting abnormalities within our study could serve as useful targets as a means of treatment in neurostimulation protocols in individuals with substance use disorders. Considering our results, it is possible that such treatment may be successful in individuals with substance use disorders, potentially both psychopathic and nonpsychopathic. This corticolimbic circuit should be investigated in terms of its implications in treatment amenability utilizing a variety of treatment strategies.

In addition, this study suggests that an externalizing behavior often associated with psychopathy could be due to neural processing biases. While it strays somewhat beyond our current data, it would also be interesting to consider whether neurostimulation protocols targeting similar regions could also benefit individuals with high levels of psychopathic traits.

Limitations

One limitation with the current study is that we were unable to correlate psychometric craving responses with psychopathic traits or neural reactivity to food and drug stimuli due to lack of variance in craving responses. As a result, the relationship between psychopathic traits and cue-induced craving, as well as the neural underpinnings of craving, remain difficult to discern. In addition, as is common in forensic and addiction research, our study was only able to recruit a moderate sample size. Power to detect relevant effects may be particularly reduced for analyses that required separating our participants into those with high and low psychopathic traits. The modest statistical power may preclude the ability to identify smaller effect sizes. In addition, very few of our participants would be diagnosed officially as psychopathic, as it is typically required to achieve a PCL-R score of 30 to be considered psychopathic (Hare, 2003), and the highest PCL-R score within our sample was 34. However, there is a large body of

research demonstrating that psychopathy is a dimensional disorder that can be conceptualized as a spectrum rather than through a categorical and dichotomized personality disorder (Neumann & Hare, 2008).

Study 2

In the first study, we demonstrated a neural processing bias towards cocaine-related stimuli relative to food stimuli in cocaine dependent participants within in several regions, including the DMPFC, ACC, ventral striatum, insula, and amygdala. We then demonstrated that psychopathic traits modulated this neural processing bias, sensitizing drug > food reactivity in cocaine-dependent individuals within the insula and the amygdala. Finally, while substance use did not have a main effect on drug > food reactivity, there was a significant interaction effect between psychopathic traits and substance use severity, in which case substance use increased this neural processing bias among participants with a low number of psychopathic traits, while slightly decreasing this neural processing bias among highly psychopathic individuals.

Study 1 was the first attempt at answering whether psychopathic traits were a predisposition or a resilience factor against neural processing biases towards drug-related rewards compared to non-drug rewards. From these results, we inferred that psychopathic traits may be a predisposition towards a neural processing bias, which might explain why psychopathic traits are commonly reported to be comorbid with SUDs (i.e. Coid et al., 2009; Hemphil et al., 1994; Walsh et al., 2007). Essentially, psychopathic traits may have predisposed substance users to developing neurocognitive abnormalities noted to be characteristic of an addictive disorder according to the i-RISA model (Goldstein & Volkow, 2002). According to this theoretical model of addiction, chronic substance users exhibit an incentive salience misattribution, in which case a greater amount of salience to attributed towards drug-related rewards relative to non-drug rewards and facilitates further drug use and development of a dependence on this substance. It appears that psychopathic traits sensitized this salience misattribution, which would facilitate a neural processing bias we observed towards drug-related stimuli relative to food stimuli.

In contrast, highly psychopathic individuals began to show a desensitization of this neural processing bias with increasing levels of substance use. This was consistent with other studies on the relationship between psychopathic traits and drug-stimulus processing relative to a neutral control condition, in which case a negative correlation was observed between psychopathic traits and the neural reactivity to drug-related stimuli relative to neutral stimuli (Cope et al., 2014; Vincent et al., 2017). This raised the likelihood of an opposing possibility that psychopathic traits are a resilience factor against this drug-related neural processing bias despite high levels of substance use.

In summary, psychopathy was associated with either increases or decreases in this neural processing bias in substance dependent participants depending on the level of substance use severity, and therefore we are still unsure of the nature of the relationship between psychopathic traits and drug-reward and non-drug reward neural processing. However, substance dependence, according to DSM-IV-TR guidelines (APA, 2000), was typically sub-diagnosed into either psychological or physiological dependence. The primary distinction between these two forms of dependence is that psychological dependence consists the behavioral dysfunctions revolving substance use and disregard for one's psychosocial and occupational responsibilities, and physiological dependence consisting of behavioral dysfunctions accompanied by symptoms of tolerance and withdrawal. In study 1, we grouped psychologically- and physiologically-dependent participants into one dependent category, therefore any differences between these groups could not be evaluated, nor their interactions with psychopathic traits and substance use severity in terms of drug-stimulus processing modulation. To address this, we assessed drug- and food-stimulus processing using the same cue-reactivity task as Study 1 in participants

categorized as either psychologically-dependent (Psyc-D), physiologically-dependent (Phys-D), or non-dependent (ND).

While no study has compared of Phys-D and Psyc-D participants in terms of neural processing of drug-related stimuli, several studies have already demonstrated behavioural differences between these two variants of substance dependence. Subjects categorized as Phys-D exhibited more severe drug use patterns, endorse a larger number of health problems, were more likely to relapse in abstinence, and experienced a greater number of psychiatric, psychosocial and health-related problems in their daily lives (Lejoyeux, Claudon, McLoughlin, & Adès, 2001; Schuckit et al., 1998, 1999, 2003). In addition, empirical studies assessing neural reactivity to drug-cues have demonstrated that drug withdrawal may potentiate drug-cue neural reactivity in substance-dependent individuals (Jasinska et al., 2014). Such effects have been observed in heroin dependent (Lou et al., 2012) and nicotine-dependent participants (McClernon et al., 2005; McClernon et al., 2009) in several regions, including the striatum, ACC, DMPFC, hippocampus and posterior cingulate cortex. Finally, the i-RISA model (Goldstein & Volkow, 2002; Goldstein et al., 2011; Koob & Volkow, 2010), hypothesized that withdrawal played a pivotal role in the development of incentive salience biases towards drug-related rewards relative to non-drug rewards. Therefore, it is possible that physiological dependence, compared to psychological dependence, would be associated with a more severe neural processing bias and i-RISA dysfunctions.

The role of psychopathic traits in this dichotomization of substance dependence was also uninvestigated, as was the moderation effect of psychopathic traits on neural processing differences between Phys-D and Psyc-D participants. While no study has determined the relationship between psychopathy and psychological/-physiological substance dependence,

clinical case studies have suggested that these psychopathic individuals may be resilient to symptoms of withdrawal (Cleckley, 1941) while no conclusion could be made about psychopathy and drug tolerance. Therefore, psychopathic individuals may exhibit a resilience to the development of a physiological dependence to a substance, particularly due to abnormalities in their drug use patterns and a weakened withdrawal response. This may be consistent with structural neuroimaging research that has demonstrated that psychopathic traits are negatively correlated with grey matter volume within the amygdala, particularly within the basolateral and central nuclei of the amygdala (Hyde et al., 2014; Yang et al., 2009, 2010). The amygdala is commonly reported to play a substantial role in withdrawal symptomology (Koob, 2009, 2013, 2017; Koob & Volkow, 2010; Lee, Coehlo, McGregor, Waltermire, & Szumlinski, 2015), and the succeeding neuroplastic changes that render drug-related incentive salience to be increasingly sensitized (Koob & Volkow, 2010; Lee et al., 2013). Such structural abnormalities could render these individuals resilient to withdrawal, and potentially unable to exhibit a physiological dependence to a substance. As withdrawal is considered to play a substantial role in the development of deficits noted in the i-RISA model (Goldstein & Volkow, 2002, 2011), this raises questions about not only whether psychopathic individuals could be found physiologically-dependent to a substance, but also whether psychopathic traits could act in a compensatory manner to sensitize neural processing biases in individuals with a decreased likelihood of being physiologically-dependent. Essentially, the i-RISA model would need to consider the fact that certain individual differences, such as psychopathic traits, may compensate for abnormalities in the three-stage addiction cycle (Koob & Le Moal, 1997), and render the neural processing bias towards drug-related rewards heightened despite a lack of physiological dependence.

However, psychopathic traits were associated with decreases in drug-related neural reactivity (relative to a neutral control [Cope et al., 2014; Vincent et al., 2017]), and highly psychopathic individuals exhibited a decrease in drug-stimulus processing with increasing levels of use (Study 1), it is possible that psychopathic traits may be associated with decreases in drug-stimulus processing among Phys-D participants. Such participants would have exhibited greater levels of substance use, as well as symptoms of withdrawal and tolerance. Based on Study 1, and since psychopathic traits are hypothesized to make one resilient to physiological dependence, we might expect that psychopathic traits would decrease this drug-related neural reactivity among Phys-D individuals.

As a means of further understanding the relationship between psychopathic traits and neural processing biases towards drug-related stimuli, we assessed how psychopathic traits were related to drug- and food-stimulus processing in the brain, primarily within the DMPFC, insula, ACC, caudate, ventral striatum, and amygdala within Psyc-D and Phys-D participants. Dependent participants were separated into their rightful categories based on their responses to questions relating to two criteria in the assessment of substance dependence disorder: tolerance and withdrawal. In addition, we assessed the influence of substance use severity on this neural processing bias and assessed the interaction between psychopathic traits and substance use severity on neural processing within each group. This essentially tests whether there is a three-way interaction between the level of dependence, psychopathic traits, and substance use severity on the magnitude of this stimulus-processing bias.

We first hypothesized that Phys-D participants would exhibit a greater neural processing bias towards drug-related stimuli when compared to Psyc-D and ND participants, followed by Psyc-D participants exhibiting a greater neural processing bias when compared to ND

participants. In addition, we hypothesized that psychopathic traits would be associated with a sensitized neural processing bias towards drug-related stimuli within Psyc-D participants. In Phys-D participants, on the other hand, we hypothesized that psychopathic traits would be associated with a decreased drug-related reactivity relative to food-related reactivity. Finally, we expected that psychopathic traits would modulate the effect of substance use in both groups, however in opposite manners. We expected that our original interaction effect from Study 1 would be observed in the Phys-D group, while the psychopathic traits would increase drug > food reactivity among Psyc-D participants with increasing levels of substance use. Essentially, Psyc-D participants would exhibit the highest levels of this neural processing bias towards drug-related rewards relative to non-drug rewards among individuals with the highest levels of psychopathy and substance use severity within this group. However, with the highest levels of use across the sample being among Phys-D participants, psychopathic traits would decrease drug > food reactivity with increasing levels of use among Phys-D participants.

Method

Participants

We analyzed 101 adult probation/parolees residing in the great Albuquerque, New Mexico area from our previously used dataset of 105 participants in Study 1. Four participants were excluded from the analyses due to insufficient data from the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders (SCID-I/P; First et al., 2002), particularly in terms of the participant's cocaine-dependence symptomology and whether we were able to determine non-dependence, psychological, and physiological cocaine dependence. All inclusion and exclusion criteria from Study 1 applied to the current study, with the addition that participants must have sufficient information within their documented files to determine cocaine dependence diagnoses,

categorization into non-dependent, psychologically-dependent, or physiologically-dependent groups.

Assessment and categorization of psychological and physiological cocaine dependence

Lifetime history of physiological and psychological cocaine dependence was diagnosed based on an item-level analysis of participants' SCID-I/P (First et al., 2002). To meet the diagnostic criteria for physiological cocaine dependence, participants had to meet threshold (scored 3) for two specifiers: tolerance and withdrawal. Participants met the threshold for tolerance if they reported "a need for markedly increased amounts of substance to achieve intoxication or desired effect" or "markedly diminished effect with continued use of the same amount of substance" (exact wording on the SCID [Alt-E. 13, E80], refer to APA [2000], p.192). Withdrawal was rated based on whether the participant experienced "the characteristic withdrawal syndrome for the substance [i.e. fatigue, irritability, nausea]" or "the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms" (Alt-E. 14, E88, [square brackets added], refer to APA (2000), p. 193). As per DSM-guidelines, participants meeting threshold for either tolerance or withdrawal, but not both, were categorized as Psyc-D. To be diagnosed with psychological dependence, participants had to meet the diagnostic threshold for cocaine dependence, have experienced at least one of the criteria outside of the specifiers for physiological dependence, and not meet threshold for both criteria for physiological dependence. Due to the fact that there were only 9 participants who did not meet threshold for cocaine dependence, but did meet threshold for cocaine abuse, they were included into the ND group for all analyses.

Data analytic strategies

Image acquisition, preprocessing, and first-level neuroimaging analyses can be found in Study 1. Descriptive statistics, comparative and correlational analyses of psychometric behavioral results were also conducted utilizing the SPSS 24 (IBM, 2016). Second-level neuroimaging analyses were conducted using SPM12. We first conducted a mixed-model flexible-factorial analysis of variance to assess effects of Video Type (DRUG and FOOD) and Group (Phys-D, Psyc-D, and ND), as well as the Group*VideoType interaction, on hemodynamic activity while participants watched the videos. This analysis was followed by post-hoc within-group and between-group comparisons of hemodynamic reactivity to DRUG and FOOD videos.

To assess differences between Psyc-D and Phys-D participants in terms of the effects of psychopathic traits and Major Drug Use on activity in the DRUG > FOOD contrast, we ran a multiple regression model among all dependent participants including total PCL-R scores, Major Drug Use, and a dummy-coded Group (Phys-D [1] and Psyc-D [0]) variable as predictors within the model. This model also interaction terms between the three predictors (Group*Total PCL-R, Group*Major Drug Use, and Total PCL-R*Major Drug Use), as well as a three-way Group*Total PCL-R*Major Drug Use interaction term.

Whole-brain results were interpreted using an uncorrected threshold of .001 and a cluster threshold of 34 voxels (equates to a $p < .05$, FWE) based on a series of Monte-Carlo simulations run through an Alpha Simulator (AlphaSim) on the Resting-State fMRI Data Analysis Toolkit (REST; Song et al., 2011).

ROI analysis

As we predicted group-level activity differences within the same constellation of regions assessed in Study 1, we assessed activity within the same ROI coordinates as Study 1 in our Flexible-Factorial ANOVA model. Activity within the right insula (x = 40, y = -8, z = -18), left ACC (-6, 4, 44), left DMPFC (-5, 46, 34), right ventral striatum (11, 13, -7), left amygdala (-32, 0, -27), and left caudate nucleus (-9, -4, 12) was assessed through small-volume corrected spherical search spaces. A 6mm spherical search space was used for subcortical ROIs (ventral striatum, amygdala and caudate) while a 10mm sphere was used for cortical ROIs (insula, ACC, DMPFC).

For ROIs that demonstrated significant effects in relevant SPM models, we extracted parameter estimates from SPM of signal changes in response to DRUG and FOOD videos, relative to baseline. These parameter estimates were evaluated using multivariate analysis of variance (MANOVA) models and correlational models in SPSS.

Results

Demographics and group differences

Twenty participants (19.8%) met the diagnostic criteria for Phys-D, while 24 (23.8%) were categorized as Psyc-D, and 57 (56.4%) as ND. Interestingly, while participants were significantly more likely to meet the diagnostic criteria for cocaine dependence if they met the threshold for tolerance (n = 39, 88.6%, $\chi^2(1)=64.36$ with Yate's continuity correction, $p<.001$), participants were also more likely to be diagnosed with a cocaine dependence disorder (regardless of whether they were psychologically-dependent or physiologically-dependent) if they did not meet the diagnostic criteria for withdrawal (n = 24, 54.5%, $\chi^2(1)=29.51$ with Yate's continuity correction, $p<.001$). Moreover, while 100% of participants meeting the diagnostic

criteria for withdrawal were categorized as Phys-D, $\chi^2(1)=40.06$ with Yate's continuity correction, $p<.001$, 48.7% of participants meeting the threshold for tolerance were categorized as Psyc-D, whereas the other 51.3% were categorized as Phys-D, $\chi^2(1)=2.86$, $p=.091$. Therefore, the primary distinction between both groups appears to be the experience of withdrawal.

The sample was composed of 66 (62.3%) males, with a mean age of 35.49 (*9.92*); mean IQ of 105.71 (*12.14*); regularly used major drugs for 7.13 (*7.97*); and had a mean total PCL-R score of 18.48 (*7.14*). The sample also had a mean Factor 1 score of 6.29 (*3.32*) and mean Factor 2 score of 10.93 (*4.14*). Group-based demographics can be found in Table 1. A multivariate analysis of variance was conducted to assess differences in demographics and our clinical/forensic variables of interest between Psyc-D, Phys-D, and ND participants. We observed a significant univariate effect of Group on total PCL-R scores, $F(2, 98)=8.23$, $p<.001$, and major drug use, $F(2, 98)=33.28$, $p<.001$, but not Age, $F(2, 98)=2.18$, $p=.119$, nor IQ, $F(2, 98)=.060$, $p=.942$. A separate model with only Factor scores included as dependent variables demonstrated that another significant Group effect on both Factor 1, $F(2, 98)=5.02$, $p=.008$, and Factor 2 scores, $F(2, 98)=6.83$, $p=.002$. Post-hoc Bonferroni corrected *t*-tests demonstrated that both the Phys-D and Psyc-D groups had significantly higher Total PCL-R, Factor 2, and Major Drug Use scores than the ND group (see Table 11). In addition, the Psyc-D group had significantly higher Factor 1 scores relative to the ND group. There were no significant differences between two dependent groups on any demographic or clinical/forensic variables.

While no significant correlations were observed, the Phys-D group exhibited a marginally significant correlation between Major Drug Use and age, $r = .42$, $p = .065$, while the Psyc-D group exhibited marginally significant correlations between PCL-R and Major Drug Use, $r = .38$, $p = .064$, and between Factor 2 and Major Drug Use, $r = .39$, $p = .061$ (see Table 12).

Table 11
Descriptive statistics and group-level differences in clinical/forensic variables

Variable	ND	Psyc-D	Phys-D	*t* (Psyc-D > ND)	*t* (Phys-D > ND)	*t* (Phys-D > Psyc-D
Age	33.88 (8.90)	37.62 (8.51)	37.50 (8.92)	1.75	1.58	-.049
IQ	105.82 (11.77)	105.79 (13.35)	105.30 (12.33)	-.010	-.163	-.132
Major Drug	2.79 (4.14)	11.33 (8.66)	14.45 (7.61)	5.66*	7.20*	1.66
PCL-R Total	16.12 (6.66)	21.56 (7.43)	21.54 (5.68)	3.35*	3.13*	.009
Factor 1	5.46 (3.26)	7.83 (3.14)	6.80 (3.04)	2.38*	1.34	-1.03
Factor 2	9.70 (3.94)	12.04 (4.32)	13.10 (3.29)	2.34*	3.40*	1.06

Note. t values represent test statistic of difference between Dependent and Non-dependent participants. Unbracketed values represent means, while bracketed values represent standard deviations.
* *p* (FWE)<.05

Table 12
Correlations among clinical/forensic variables within each dependence group

	1	2	3	4	5	6
Psychologically-dependent						
1. Age	--	-.19	.42†	.07	.13	.09
2. IQ		--	-.15	.07	.08	-.04
3. Major drug use			--	.38†	.33	.39†
4. PCL-R total				--	.91***	.91***
5. Factor 1					.71***	--
6. Factor 2						--
Physiologically-dependent						
1. Age	--	-.39†	.42†	.17	.23	-.013
2. IQ		--	-.21	-.19	.11	-.33
3. Major Drug Use			--	.23	.13	.28
4. PCL-R Total				--	.86***	.86***
5. Factor 1					--	.54*
6. Factor 2						--

†*p*<.10, **p* <.05, ****p* < .001

Sensitivity to DRUG and FOOD videos

We first evaluated neural reactivity to DRUG and FOOD stimuli within the three groups with a 3 (Group) x 2 (VideoType) mixed-factors flexible factorial ANOVA. Results are presented in Table 13. We observed a significant main effect of Group on activity within several clusters, including the right insula, left ACC, left amygdala, left dorsomedial, right medial and right ventromedial PFC. We also observed significant main effects of VideoType within the left ACC and right insula, as well as the left caudate nucleus. These main effects were influenced by a Group*VideoType interaction effect within the left caudate, right ventrolateral, left dorsolateral, and left dorsomedial PFC, and left ACC.

In order to decipher this interaction effect, parameter estimates of regions identified to have a significant Group*VideoType interaction effect were entered as the dependent variable in a 3(Group) x 2(VideoType) MANOVA model. This analysis allowed us to assess differences in DRUG and FOOD reactivity relative to baseline between our three groups. While neither Group, $F(6, 192)=.684$, $p = .661$, nor VideoType, $F(3, 96)=.957$, $p = .417$, had significant multivariate main effects, there was a significant multivariate interaction effect, $F(6, 192)=5.20$, $p <.001$. Univariate interaction effects were observed within the left caudate, $F(2, 98)=14.24$, $p <.001$, left DMPFC, $F(2, 98)=6.71$, $p =.002$, and left ACC, $F(2, 98)=5.99$, $p =.004$. According to post-hoc Bonferroni corrected pairwise comparisons, Phys-D participants had significant greater DRUG-related caudate activity when compared to ND, $t=3.00$, $p = .010$, and Psyc-D, $t=2.69$, $p = .025$, and greater FOOD-related left caudate, $t=2.41$, $p = .053$; $t=2.86$, $p = .015$, and DMPFC deactivation, $t=2.93$, $p =.013$; $t=3.05$, $p = .009$ when compared to the ND and Psyc-D groups, respectively. In addition, Phys-D participants had greater left ACC FOOD-related deactivation when compared to the Psyc-D group, $t=2.36$, $p = .059$, but not when compared to the ND group,

t=1.93, *p* = .182. There were no significant differences between the three groups in terms of DRUG-related left ACC reactivity, however the Phys-D group exhibited a marginally significant greater deactivation of the left ACC in response to FOOD-related videos when compared to Psyc-D participants, *t*=2.37, *p* = .059. There were no significant differences between the Psyc-D and ND groups in terms of DRUG-related and FOOD-related activity. Results are visually depicted in Figure 3.

Such effects were further investigated by comparing DRUG and FOOD reactivity within each group separately, followed by a between-group comparison of VideoType effects. Results are presented in Table 14.

Within-group effects. Surprisingly, the Psyc-D group exhibited greater FOOD > DRUG reactivity in several clusters throughout the posterior and dorsal regions of the brain (i.e., occipital and parietal cortices), as well as the left caudate nucleus. The Phys-D group, in contrast, exhibited significantly greater DRUG > FOOD activity within the left ACC, left DMPFC, and right insula, while exhibiting no significant FOOD > DRUG activity throughout the brain.

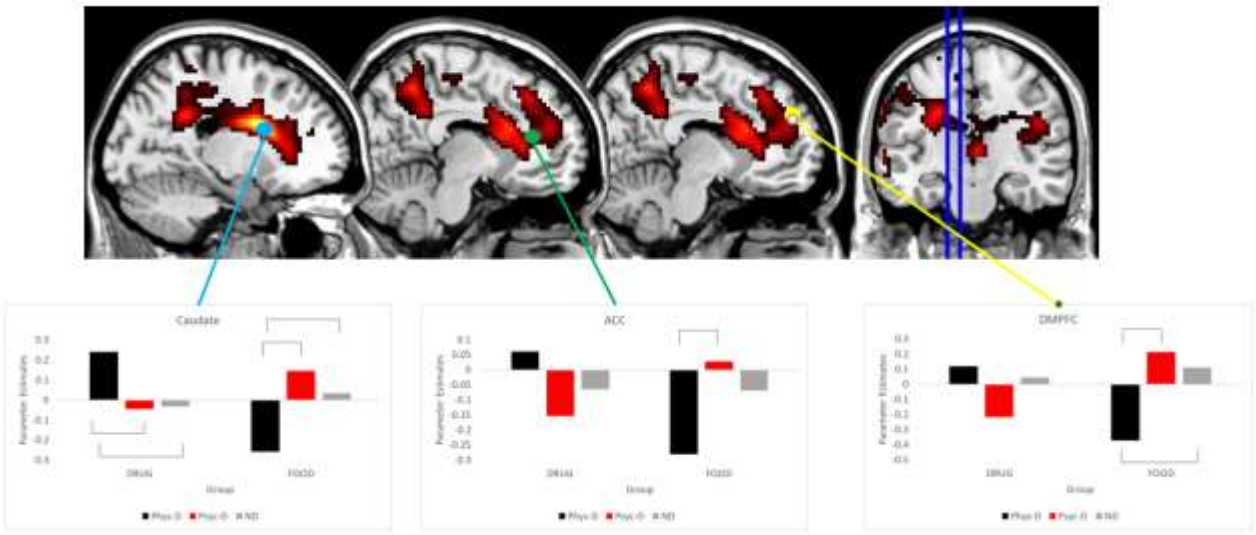
Between-group effects. Finally, we compared DRUG > FOOD reactivity between groups. Phys-D participants exhibited several clusters of greater DRUG > FOOD reactivity, relative to the Non-dependent group. Such effects were observed within the left caudate nucleus, left DMPFC, and right insula. In addition, Phys-D participants also exhibited greater DRUG > FOOD reactivity within the left ACC, left DMPFC, and left caudate nucleus when compared to Psyc-D participants. Results are visually depicted in Figure 4. Another interesting observation was there were no significant differences between Psyc-D participants and Non-dependent participants in terms of DRUG > FOOD reactivity.

Table 13
Higher-order ANOVA results

Region	Hemi.	MNI (x, y, z)	F	Cluster size
Main effect of Group				
Inferior frontal cortex	L	-42, 24, 0	15.51*	522
	L	-51, 12, -9	14.21*	
Precentral gyrus	L	-60, 15, 21	15.37*	
Medial prefrontal cortex	N/A	0, 48, 3	10.69	108
	R	12, 51, 6	10.55	
Ventromedial prefrontal cortex	R	15, 51, -3	10.31	
Supplementary motor area	L	-6, -15, 63	10.46	170
	N/A	0, -9, 57	9.78	
Postcentral gyrus	R	3, -33, 63	8.68	
Insula	R	39, 18, -15	10.80†	92
	R	39, 3, -12	8.17†	
ACC	L	-3, -3, 51	7.24†	57
DMPFC	L	-9, 42, 24	6.39†	71
Amygdala	L	-33, 0, -27	4.57†	15
Main effect of Condition				
Superior occipital cortex	R	12, -99, 12	24.60*	109
Middle occipital cortex	R	24, -93, 0	17.49	
Caudate nucleus	L	-9, 18, 18	19.76*	124
Inferior frontal cortex	R	45, 21, 3	17.13	112
Middle occipital cortex	R	33, 30, 9	12.75	
Insula	R	36, 12, -9	8.59†	23
ACC	L	-9, 6, 54	8.55†	28
Interaction effect				
Caudate nucleus	L	-18, 9, 24	12.78*	394
Ventrolateral prefrontal cortex	R	27, 30, 3	12.52*	
ACC	L	-9, 3, 36	5.50†	35
DMPFC	L	-9, 45, 24	6.44†	157
	L	-9, 36, 36	6.01†	

All regions show significant activity at p(uncorr) < .001; * p(FWE) < .05; † p(svc-FWE) <.05; ACC = Anterior cingulate cortex; DMPFC = Dorsomedial prefrontal cortex; Hemi = Cerebral Hemisphere; MNI = X, Y, Z coordinates on a Montreal Neurological Institute template.

Figure 3
Differential sensitivity to DRUG and FOOD videos between groups



Note. Bar-charts demonstrate differences in DRUG and FOOD reactivity between the Physiologically-dependent (Phys-D), Psychologically-dependent (Psyc-D), and Non-dependent (ND) groups. Brackets indicate significant differences at *p*(FWE)< .10. MRIcron images display intensity thresholds ranging from F = 4 – 13. Sagittal slices register to MNI coordinate x = -18 and x = -9, respectively.

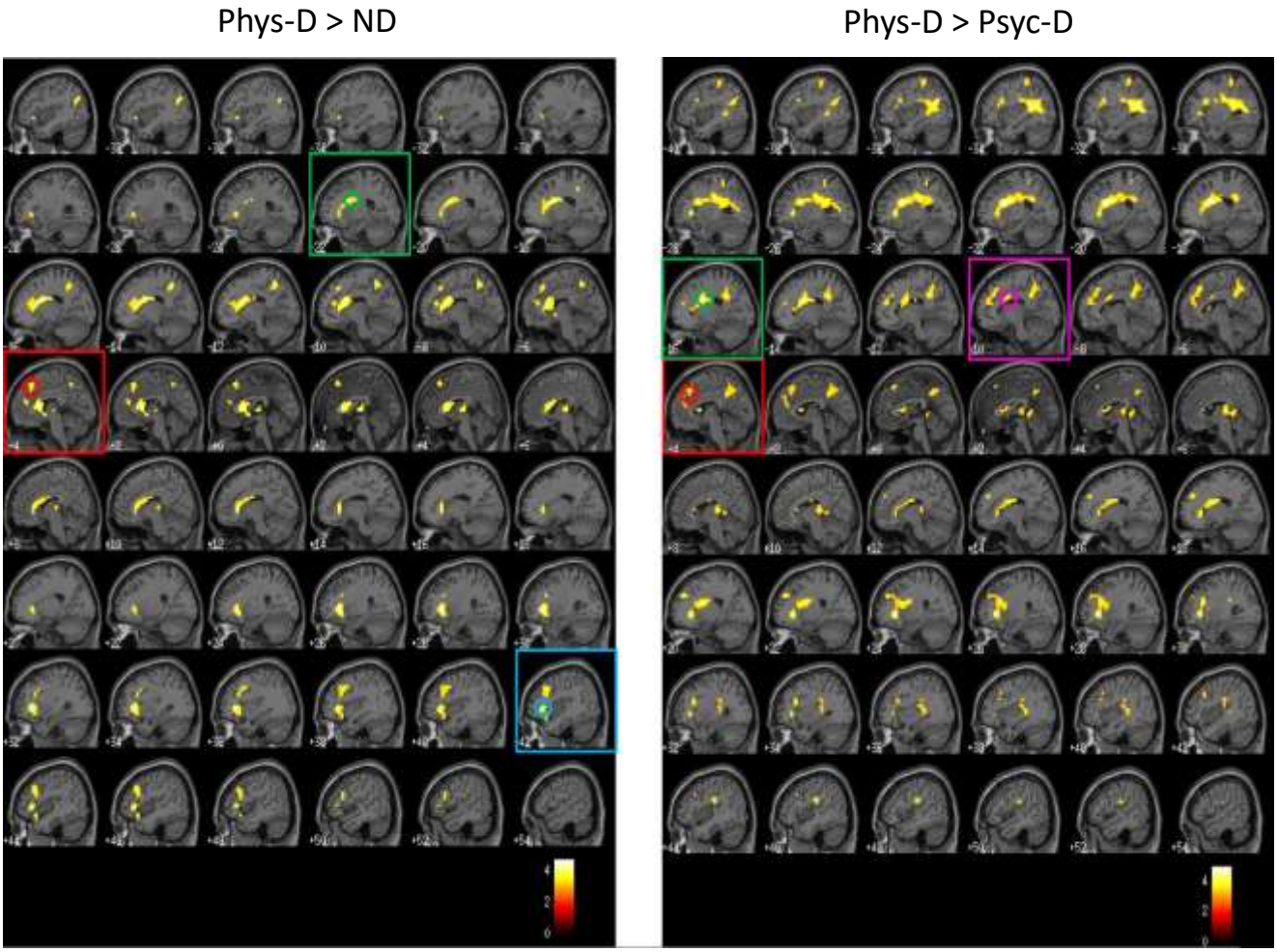
Table 14
Within-group DRUG and DRUG neural activity

Region	Hemi.	MNI (x, y, z)	*t*	Cluster size
Psychologically-Dependent Group				
DRUG > FOOD				
No significant results				
FOOD > DRUG				
Middle occipital cortex	L	-36, -69, 6	4.05	120
Caudate nucleus	L	-3, -3, 12	2.43†	13
Physiologically-Dependent Group				
DRUG > FOOD				
Middle frontal cortex	R	30, 30, 3	4.85*	1546
Middle frontal cortex	L	-57, 18, 21	4.46*	151
Dorsolateral prefrontal cortex	L	-48, 42, 12	3.96	
Postcentral gyrus	L	-63, -6, 30	3.67	
DMPFC	N/A	0, 30, 51	3.85	165
	L	-6, 30, 42	3.82	
Superior frontal cortex	L	-9, 12, 54	3.32	
Insula	R	42, 18, -15	2.99†	43
	R	39, 12, -9	2.88†	
ACC	L	-9, 9, 51	3.02†	161
	L	-9, 6, 36	2.71†	
	L	-3, -3, 51	2.54†	
DMPFC	L	-3, 36, 36	3.50†	170
	L	-3, 42, 24	3.19†	
FOOD > DRUG				
No significant effects				
Group Differences in DRUG > FOOD				
Psychologically Dependent > Non-Dependent				
No significant effects.				
Physiologically Dependent > Non-Dependent				
Inferior prefrontal cortex	R	30, 30, 0	4.66*	1050
Caudate	L	-15, 6, 24	4.40*	
Middle frontal cortex	L	-57, 21, 21	4.14	122
Postcentral gyrus	L	-63, -9, 27	3.93	
Precentral gyrus	L	-57, 3, 33	3.48	
Middle frontal cortex	R	45, 21, 27	3.54	171
	R	33, 24, 24	3.47	
Superior frontal cortex	R	42, 24, 36	3.51	
Insula	R	42, 18, -15	3.28†	58
DMPFC	L	-3, 42, 24	3.14†	171
	L	-6, 36, 36	2.92†	

Physiologically Dependent > Psychologically Dependent				
Caudate nucleus	L	-21, 12, 21	4.93*	1982
Middle frontal cortex	R	27, 30, 3	4.69*	
Middle frontal cortex	L	-60, 15, 24	4.08	117
Precentral gyrus	L	-60, 0, 30	3.94	
Postcentral gyrus	R	48, -18, 24	3.68	132
DMPFC	L	-6, 33, 45	3.62	183
	L	-21, 48, 21	3.57	
ACC	L	-9, 3, 36	3.32†	162
	L	-15, 6, 42	3.16†	
DMPFC	L	-9, 45, 24	3.54†	171
	L	-9, 36, 36	3.44†	
Non-dependent > Psychologically Dependent				
No significant results				
Non-dependent > Physiologically Dependent				
No significant results				
Psychologically Dependent > Physiologically Dependent				
No significant results				

All regions show significant activity at p(uncorr) < .001; * p(FWE) < .05; † p(svc-FWE) <.05; DMPFC = Dorsomedial prefrontal cortex; ACC = Anterior cingulate cortex; Hemi = Cerebral Hemisphere; MNI = X, Y, Z coordinates on a Montreal Neurological Institute template.

Figure 4
Group differences in DRUG > FOOD reactivity



Note. Brain images are at a significance threshold of *p*(uncorr) < .001, with an extended cluster threshold of k =34. Slices displayed range from X=-40 to X=+50, with a X = 2mm interval between each slice image. Green markings identify caudate activity; red marking identify DMPFC activity; blue marking indicate insula activity; and pink marking indicates ACC activity.

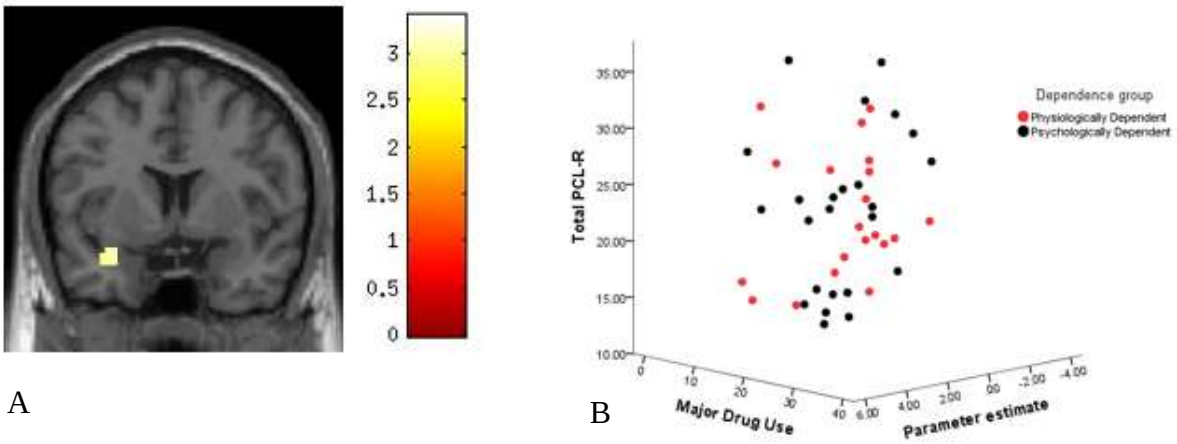
Psychopathy, drug use, and DRUG > FOOD reactivity

According to our between-groups analyses, it appears that the neural processing bias towards drug- compared to food-related stimuli in substance-dependent participants is particularly found in physiologically-dependent participants. In fact, individuals meeting the criteria for psychological cocaine dependence exhibited a similar pattern of neural reactivity to non-dependent participants, in which case food continues to yield a greater neural response than drugs. We next assessed whether Major Drug Use and psychopathic traits would modulate these group levels differences.

Consistent with our previous analyses, our multiple regression analysis (see Table 14) demonstrated that Group had a significant main effect on DRUG > FOOD reactivity, with the Phys-D group exhibiting significantly greater activity within several regions, including the bilateral caudate nucleus, ACC, and DMPFC, as well as the right insula. While total PCL-R scores had no significant main effect on DRUG > FOOD reactivity throughout the brain, Major drug use was associated with increases in left cerebellar and left caudate nucleus activity. Group and Major Drug Use main effects were significantly modulated by a Major Drug Use * Group interaction effect within several clusters overlapping with the left ventral striatum, ACC, as well as the hippocampus. In addition, there were significant PCL-R*Use interaction effects within the cerebellum and inferior occipital cortex, however none of these effects were observed within our ROIs. Finally, there was a significant three-way interaction effect (PCL-R*Use*Group) on DRUG > FOOD reactivity within the left amygdala. By visually assessing a three-dimensional scatterplot (Figure 5), it appears total PCL-R scores are associated with greater DRUG > FOOD amygdala activity when there is also a low amount of Major Drug Use. Moreover, participants with higher levels of Major Drug Use exhibited a slight negative correlation between total PCL-

R scores and DRUG > FOOD reactivity within the amygdala. While this was observed in both groups, it appears that correlations from PCL-R scores and Major Drug Use to amygdala activity were more pronounced in the Psyc-D group. We conducted subsequent analyses to further mathematically decipher this interaction effect.

Figure 5
Three-way interaction between total PCL-R scores, Major Drug Use, and Group on amygdala reactivity to DRUG > FOOD videos



A B

Note. (A) Bain image is from a three-way interaction term (PCL-R*Group*Major Drug Use) from our multiple regression analysis, with total PCL-R scores, Group, and Major Drug Use entered as interacting predictors and DRUG > FOOD reactivity as the dependent variable. Brain image is set at a significance threshold of p(uncorr) < .005, with an extended cluster threshold of k =73. Brain image coordinate is y = 6. (B) Three-dimensional scatterplot demonstrates the relationship between total PCL-R scores, Major Drug Use and parameter estimates and left amygdala DRUG > FOOD reactivity among Phys-D and Psyc-D participants.

To understand the nature of these interaction effects, we ran multiple regression models within the Phys-D and Psyc-D group independently as a means of comparing the effect of total PCL-R scores, Major Drug Use, and a PCL-R*Major Drug Use interaction term using the DRUG > FOOD contrast. Interestingly, correlations were only observed within the Psyc-D group (see Table 15). Total PCL-R scores were associated with increases in DRUG > FOOD reactivity within the left DMPFC. Analysis of parameter estimates extracted from this DMPFC coordinate demonstrated that Total PCL-R scores were negatively correlated with FOOD-related activity, *r*

= -.66, $p < .001$, while also positively correlated with DRUG-related activity, $r = .35$, $p = .095$, with marginal significance. Major drug use, on the other hand, predicted increased DRUG > FOOD reactivity within the bilateral ACC, right ventral striatum and left amygdala. Analysis of parameter estimates demonstrated that Major Drug Use negatively correlated with FOOD-related activity within the right ventral striatum, $r = -.66$, $p < .001$, left amygdala, $r = -.48$, $p = .017$, and left ACC, $r = -.43$, $p = .037$; and positively correlated with DRUG-related activity within the ACC, $r = .49$, $p = .015$.

Finally, there was a significant PCL-R*major drug use interaction effect on right insula DRUG > FOOD reactivity among the Psyc-D group. To understand the nature of this interaction effect, Psyc-D participants were separated into two sets of dichotomous groups based on median splits of Total PCL-R scores and Major Drug use. We correlated parameter estimates of DRUG- and FOOD-related signal changes relative to baseline to Total PCL-R scores among Psyc-D participants with high and low Major Drug Use scores (median = 10), as well as Major Drug Use among Psyc-D participants with high and low PCL-R scores (median = 21.53). Independent-samples *t*-tests demonstrated that there were no significant differences between high and low Major Drug Use participants in Total PCL-R scores, $t=.557$, $p = .584$, and right insula DRUG > FOOD reactivity, $t=1.82$, $p = .088$. However, the high PCL-R group has significantly higher Major Drug Use scores, $t=2.32$, $p = .036$; greater DRUG > FOOD reactivity within the right insula, $t=3.45$, $p = .002$; and greater FOOD-related right insula deactivation, $t=3.32$, $p = .003$.

Correlational analyses demonstrated that among the low PCL-R group, Major Drug Use positively correlated with DRUG > FOOD right insula activity, $r = .83$, $p = .001$. This correlation is due to a negative correlation between Major Drug Use and right insula activity, $r = -.74$, $p = .006$, to FOOD videos. Total PCL-R scores among the low Major Drug Use group were also

positively correlated with right insular DRUG > FOOD reactivity, $r = .64$, $p = .024$, however there were no significant correlations between PCL-R scores and insula activity to DRUG, $r = .50$, $p = .099$, nor FOOD videos, $r = -.49$, $p = .106$. Results are visually depicted in Figure 5.

Factors, drug use, and DRUG > FOOD reactivity

We then assessed which constellation of psychopathic traits, interpersonal/affective or lifestyle/antisocial, was primarily responsible for total PCL-R's main effect and interaction effect with Major Drug Use (see Table 17). Interestingly and in contrast to regression models with Total PCL-R scores as a predictor, Factor score regression models only demonstrated significant Factor effects within the Phys-D group, and not the Psyc-D group. While no ROIs exhibited significant DRUG > FOOD reactivity correlating with Factor 1 or Factor 2 traits, Factor 1 traits did predict increased DRUG > FOOD reactivity within several clusters throughout the brain in Phys-D participants, including the dorsolateral PFC. Among the Psyc-D group, Major Drug Use predicted increase DRUG > FOOD reactivity within the bilateral ACC, ventral striatum, amygdala. As peak-voxel coordinates within our ROIs overlapped with our previous analyses, we assumed that this relationship was due to increase in DRUG-related activity within the left ACC and decreases in FOOD-related activity in the ventral striatum and amygdala compared to baseline. There were no significant interaction effects between either Factors and Major Drug Use on DRUG > FOOD reactivity.

Table 15
Multiple regression results: Total PCL-R scores, Major Drug Use, Group effects on DRUG > FOOD reactivity

Region	Hemi.	MNI (x, y, z)	*t*	Cluster size
Group				
Positive				
Angular gyrus	L	-33, -57, 15	5.12*	1060
Caudate nucleus	L	-18, 3, 27	5.06*	
Precuneus	R	3, -66, 39	4.14	252
	R	21, -54, 30	3.98	
Inferior parietal cortex	R	45, -21, 27	3.95	
Middle frontal cortex	R	30, 24, 24	3.88	104
Caudate nucleus	R	18, 0, 27	3.77	
Putamen	R	27, 12, 12	3.56	
ACC	L	-9, 3, 36	3.19†	138
	L	-15, 6, 42	3.13†	
DMPFC	L	-9, 48, 24	3.51†	171
	L	-6, 54, 33	3.39†	
	L	-9, 36, 33	3.14†	
	L	-3, 45, 42	3.02†	
Negative				
No significant results				
PCL-R				
No significant results				
Major Drug Use				
Positive				
Caudate nucleus	L	-6, 0, 9	2.55†	16
Negative				
No significant results				
Interaction effects				
*PCL-R * Group*				
No significant results				
*Major Drug Use * Group*				
Cerebellum	R	24, -57, -27	5.11*	240
	R	39, -48, -36	4.22	
	R	27, -36, -36	4.15	
Amygdala/parahippocampal gyrus	L	-21, -9, -9	4.88	152
Hippocampus	L	-33, -24, -9	4.38	
	L	-27, -21, -24	3.47	
Middle cingulate cortex	L	-3, -6, 24	4.77	199
ACC	L	-3, 12, 24	4.59	
Parahippocampal gyrus	R	18, -27, -15	4.12	110

Inferior occipital cortex	R	33, -78, -6	4.31	105
*PCL-R * Use*				
Cerebellum	R	30, -57, -33	4.82	127
*PCL-R * Use * Group*				
Amygdala	L	-33, 6, -27	2.63†	31
	L	-30, -3, -30-33	2.43†	

All regions show significant activity at *p*(uncorr) < .001; * *p*(FWE) < .05; † *p*(svc-FWE) <.05; ACC = Anterior cingulate cortex; DMPFC = Dorsomedial prefrontal cortex. Hemi = Cerebral Hemisphere; MNI = X, Y, Z coordinates on a Montreal Neurological Institute template.

Table 16

Multiple regression results: Total PCL-R scores, Major Drug Use, and DRUG > FOOD-related hemodynamic activity among the Psyc-D group

Region	Hemi.	MNI (x, y, z)	*t*	Cluster size
PCL-R				
Positive				
DMPFC	L	-9, 51, 39	4.01†	126
Negative				
No significant results				
Major Drug Use				
Positive				
Parahippocampal gyrus	R	24, -30, -21	5.97*	129
Hippocampus	L	-33, -27, -6	4.89	188
Fusiform gyrus	L	-18, -45, -21	4.31	
Parahippocampal gyrus	L	-27, -27, -24	4.10	
ACC	L	-3, 0, 36	2.81†	70
Ventral striatum	R	9, 9, -3	2.81†	28
Amygdala	L	-36, 3, -30	2.38†	7
Negative				
No significant results				
PCL-R * Major Drug use				
Cerebellum	R	27, -57, -36	5.21	111
	R	36, -69, -42	4.22	
Insula	R	39, -12, -21	3.66†	108

All regions show significant activity at *p*(uncorr) < .001; * *p*(FWE) < .05; † *p*(svc-FWE) <.05; ACC = Anterior cingulate cortex; DMPFC = Dorsomedial prefrontal cortex. Hemi = Cerebral Hemisphere; MNI = X, Y, Z coordinates on a Montreal Neurological Institute template.

Table 17
Multiple regression results: Factor scores, Major Drug Use, and DRUG > FOOD-related hemodynamic activity among the Psyc-D group

Region	Hemi.	MNI (x, y, z)	*t*	Cluster size
Physiologically Dependent				
No significant results				
Psychologically Dependent				
PCL-R Factors				
No significant results				
Major Drug Use				
Positive				
Parahippocampal gyrus	R	24, -30, -21	5.95*	147
	R	15, -27, -12	3.86	
ACC	R	9, 15, 27	5.39	106
	R	3, 6, 30	4.94	
	R	15, 3, 33	4.48	
Hippocampus	L	-33, -27, -6	4.92	203
Cerebellum	L	-21, -48, -21	4.54	
Parahippocampal gyrus	L	-27, -30, -21	4.26	
ACC	L	-3, 0, 36	2.95†	95
Ventral striatum	R	9, 9, -3	2.93†	31
	R	6, 12, -6	2.85†	
	R	15, 15, -9	2.34†	
Amygdala	L	-36, 3, -30	2.47†	8
	L	-33, 0, -33	2.46†	
Negative				
No significant results				

All regions show significant activity at p(uncorr) < .001; * p(FWE) < .05; † p(svc-FWE) <.05; ACC = Anterior cingulate cortex; DMPFC = Dorsomedial prefrontal cortex; Hemi = Cerebral Hemisphere; MNI = X, Y, Z coordinates on a Montreal Neurological Institute template.

Discussion

We looked to further understand the neural processing bias towards drug-related rewards relative to non-drug rewards by assessing differences in this neural processing bias between participants who were physiologically-dependent and psychologically-dependent to cocaine. We demonstrated that this neural processing bias varies as a function of the type of substance dependence. In this case, participants with a physiological cocaine dependence, characterized by use-promoting behavioural dysfunctions and symptoms of tolerance and withdrawal, exhibited a significantly greater neural processing bias towards drug-related videos relative to food videos compared to both psychologically-dependent, characterized by use-promoting behavioural dysfunctions alone, and non-dependent participants. In fact, psychologically-dependent participants exhibited no significant difference in drug-related neural reactivity relative to non-dependent participants and exhibited the same pattern of activation in response to food-related content as non-dependent participants.

Specifically, physiologically-dependent participants exhibited greater reactivity to drug-related stimuli within the ACC, ventral striatum, amygdala, DMPFC, and caudate nucleus when compared to non-dependent participants. The ACC has been found to underlie attentional biases towards drug-related stimuli (Goldstein et al., 2007; Luijten et al., 2011), which has been found to predict relapse into substance use (Marhe, Luijten, van de Wetering, Smits, & Franken, 2013). The ventral striatum has been thought of as a corticolimbic interface underlying motivational salience of drug-related stimuli, integrating visuospatial and incentive salience of drug-related stimuli and, and promoting drug-seeking behavior (Floresco, 2015; Ikemoto & Panksepp, 1999; McFarland, Lapish, & Kalivas, 2003; Salamone, Correa, Mingote, & Weber, 2005; Weiss, 2005). The caudate has been found to underlie stimulus-reinforcement learning and the

development of habitual drug-seeking behaviour (Ito, Dalley, Robbins, & Everitt, 2002; Koob & Volkow, 2010; Murray et al., 2014, 2015; Vollstädt-Klein et al., 2010; Weiss, 2005; Yin, Ostlund, Knowlton, & Balleine, 2005). The amygdala plays a pivotal role in salience attribution and salience sensitization of drug-related stimuli, particularly following withdrawal (Ding et al., 2013; Lee et al., 2013; Murray et al., 2015). Finally, the DMPFC has been found to underlie drug-seeking behavior by guiding decision-making in a biased manner, leading to goal-directed behavior to be the sum of drug-related sensori-information integration and focused only on obtaining a drug-reinforcer (Jasinska, Chen, Bonci, & Stein, 2015). Therefore, physiologically-dependent participants may exhibit greater drug-related dysfunction within these areas, leading to a greater attentional, saliency, and motivational bias towards drug-related stimuli. This could then translate to a higher drug-related neural processing bias in physiologically-dependent participants relative to non-dependent and psychologically-dependent participants, substantiating our results.

Importantly, these results also indicate that the distinction between psychological and physiological dependence should no longer be ignored. For instance, our findings of greater neural dysfunction within physiologically-dependent participants is consistent with psychometric studies demonstrating a greater number of health-related and psychosocial problems in the daily lives of individuals with a physiological dependence to a substance (Lejoyeux et al., 2001; Schuckit et al., 1998, 1999, 2003). Combining psychological and physiological dependence into a single substance dependence category may reduce the validity of the assessment in diagnostics and research by ignoring the moderating effect of dependence-category, and therefore ignoring the behavioral and neural differences that significantly distinguish these categories. Indeed, while DSM-IV-TR nosology is no longer commonly used, experts diagnosing SUDs using the

DSM-5 have called for an investigation of further differences of physiologically-dependent individuals relative to other substance user groups (Blanco et al., 2017). This study demonstrated that physiologically-dependent individuals can be separated from other substance-user groups, including but perhaps not limited to psychologically-dependent individuals, based on functional neural features that raise the possibility of further drug use. Future studies in addiction should consider separating their substance-dependent/substance user groups into physiologically-dependent and either psychologically-dependent or another term that distinguishes between participants with a substance use disorder characterized by behavioral and physiological symptoms and participants with only dysfunctional behavioral symptomology. This could increase the external validity of their results to generalize to real-world scenarios and populations.

This is the first study to investigate abnormalities in the neural processing of drug- and non-drug reward in physiologically- and psychologically-dependent participants separately, rather than combining both in a single dependent category. Moreover, this is the first study to demonstrate that only physiologically-dependent individuals exhibit the neural processing abnormalities noted as distinctive factors of drug addiction within the i-RISA model (Goldstein & Volkow, 2002, 2011). The i-RISA model hypothesizes that individuals with an addictive disorder fail to inhibit further hazardous substance use due to a saliency bias towards drug-related rewards relative to non-drug rewards, particularly due to a combination of severe drug use and periods of drug withdrawal. Studies have previously demonstrated a preference for drug-related relative to non-drug rewards (Study 1; Garavan et al., 2000; Goldstein et al., 2009; George et al., 2001), and demonstrated increased drug-related reactivity (relative to a neutral control condition) following/during drug withdrawal in overlapping neural regions (Jasinska et

al., 2014; Lou et al., 2012; McClernon et al., 2005, 2009). However, no study has assessed the distinction between physiologically-dependent and psychologically-dependent participants in terms of the neural processing of drug- and non-drug rewards, and therefore, we further support the i-RISA model by demonstrating that this processing bias towards drug-related rewards is only found among participants that experienced symptoms of tolerance and withdrawal.

Importantly, the above effect occurred despite there being no significant difference in the level of substance use between participants who were physiologically and psychologically dependent to cocaine. Moreover, as the only significant difference between participants with either form of dependence whether they had experienced withdrawal symptoms following use-cessation, we can carefully speculate that the neural processing bias in substance-dependent individuals may be primarily due to withdrawal. This is consistent with theoretical models of addiction that hold that withdrawal has a pivotal role in the incentive sensitization process of drug-related stimuli and facilitation of compulsive drug use (Koob, 2010, 2017; Koob & Le Moal, 1997; Koob & Volkow, 2010; Wise & Koob, 2014). In addition, while also being closely consistent with other empirical studies demonstrating increased drug-related reactivity following/during drug withdrawal in overlapping neural regions (Jasinska et al., 2014; Lou et al., 2012; McClernon et al., 2005, 2009), this study may also provide the first empirical evidence that withdrawal plays a strong faciliatory role in the development of a bias towards drug-related rewards, as hypothesized by the i-RISA model (Goldstein & Volkow, 2002, 2009). Therefore, withdrawal may play a faciliatory role in creating this neural processing bias towards drug-related rewards and an inability to resort to other forms of reward to satiate hedonic needs.

Interestingly, substance use only had an effect among psychologically-dependent participants, such that increases in the number of years regularly using major drugs increased the

magnitude of the drug > food bias, while no effect was observed among the physiologically dependent group. This is interesting considering psychologically-dependent participants normally exhibit a similar activation pattern to food-related relative to drug-related stimuli as non-dependent participants. However, it appears that with increasing levels of regular drug use, psychologically-dependent participants may begin to exhibit the dysfunctional neural processing bias as physiologically-dependent participants. It is possible that with increasing drug use, psychologically-dependent participants will begin to show a neural-reactivity preference for drug-related rewards relative to non-drug rewards, which reaches its greatest and most devastating magnitude once they experience both tolerance and withdrawal, and therefore, qualify as physiologically-dependent.

The effect of substance use was observed through an increase in ACC drug-related reactivity and decrease in food-related reactivity within the ventral striatum, amygdala, and ACC. Considering the ACC has been commonly reported to underlie attentional biases towards drug-related stimuli (Goldstein et al., 2007; Luijten et al., 2011), it appears that increases in substance use may facilitate the development attentional biases to drug-related stimuli among psychologically-dependent participants. Moreover, the effects on the ventral striatum, which has been noted to promote drug-seeking behavior with increasing substance use (Floresco, 2015; Weiss, 2005), suggests that increasing substance use may further bias the ventral striatum into promoting drug-seeking behavior in response to drug-related cues. Finally, the effects on the amygdala, which has been noted to play a role in salience misattribution (Ding et al., 2013; Lee et al., 2013; Murray et al., 2015), suggests that increasing substance use may lead to this amygdalar dysfunction that results in a greater amount of incentive salience being attributed to drug-related stimuli relative to non-drug rewards. By affecting these drug-related neurocognitive

factors, continued regular substance use may promote an inability to resort to non-drug related rewards to satiate hedonic needs by increasing the neural processing bias to drug- compared to non-drug rewards in psychologically-dependent participants, which may promote further drug use, and make cessation of use all the more onerous by eventually leading to physiological dependence (i.e. withdrawal symptomology). As a result, these psychologically-dependent participants would eventually develop the most extreme magnitude of this neural processing bias as they become physiologically-dependent to the substance. Future research should investigate whether the transition from psychological- to physiological-dependence is as linear as stated above, or whether these categories may not be placed on a linear continuum.

Finally, psychopathic traits were also found to modulate the drug > food processing bias. Psychopathic traits were associated with an increased neural processing bias to drug relative to food stimuli in the DMPFC in psychologically dependent participants, and similarly to substance use severity, no effect was observed among physiologically-dependent participants. This suggests that psychopathic traits may have a similar effect as substance use, in which case they may be associated with a potentially accelerated development of a neural processing bias towards drug-related stimuli among psychologically-dependent participants that could render drug-use increasingly difficult to abstain, and potentially, facilitating the development of a physiological substance dependence. With psychopathy being associated with reduced gray matter volume within the DMPFC (Cope et al., 2012), it is possible that pre-existing psychopathy-related neural abnormalities predispose individuals to a sensitized drug-related goal-directness in their decision-making, the neurocognitive factor that to be supported by the DMPFC (Jasinska et al., 2015). This may predispose such individuals to further complications with substance abuse, leading them into the vicious cycle of addiction similar to how increased

substance use severity may increase the odds of psychologically dependent individuals developing a physiological dependence through neural processing changes. This may therefore be an explanation for how psychopathic traits are comorbid with SUDs, as they are more prevalent among psychological and physiological dependent participants and could potentially increase neural processing abnormalities in psychologically dependent individuals to levels similar to physiologically dependent individuals.

Psychopathic traits also exhibited an interaction effect with substance use severity within the insula, a region known to be associated with interoceptive reward-processing in addiction (Koob & Volkow, 2016; Naqvi & Bechara, 2009, 2010). Interesting, this was a similar pattern as noted in Study 1. Among individuals with a low level of psychopathic traits, major drug use positively correlated with increased drug > food reactivity, whereas there was a non-significant relationship between major drug use and drug > food reactivity in high psychopathy psychologically dependent participants. In fact, there was a slight downwards trend in the high psychopathy group, with an extensive major drug use history being associated with a reduced neural processing bias to drug- relative to non-drug rewards. This raises further question about the effect of psychopathy in this psychologically dependent group. While certain regions and certain processes are sensitized by psychopathic traits (i.e. DMPFC-related processes), which may translate to a sensitized neural processing bias, other processes may become desensitized with increasing drug use and psychopathic traits. It appears that insula drug > food reactivity, possibly due to changes in interoceptive reward-processing, undergoes a desensitization in highly psychopathic individuals as their substance use severity increases. This may further our understanding of previous reports on the relationship between psychopathy and drug-stimulus processing (i.e. Cope et al., 2014; Vincent et al., 2017), by demonstrating that decreases in neural

reactivity to drug-stimuli in highly psychopathic individuals may be the result of an interaction between psychological substance dependence accompanied by a high level of substance use and a high level of psychopathic traits with no indication of physiological dependence.

The fact that only effects of substance use and psychopathic traits, and an interaction effect, were observed within psychologically-dependent participants, while there were no differences in psychopathic traits and substance use severity between groups, suggests that other factors may be promoting this neural processing bias. It is possible that psychopathic traits and substance use severity exhibit a ceiling effect within this subgroup of substance dependent individuals, and that other factors may be playing a greater role in this neural processing abnormality. Considering withdrawal-experience was the only variable that differed between these two groups, one could speculate that withdrawal may play a substantial role in the neural processing bias severity, and future studies should investigate, using neuroimaging methods, whether this hypothesis is correct.

Finally, we did observe effects within the physiologically dependent group of interpersonal/affective psychopathic traits on this drug-related neural processing bias, notably in the dorsolateral prefrontal cortex. The dorsolateral prefrontal cortex, although not an ROI, has been found to be involved in drug-related neural reactivity relative to a non-drug reward control condition (George et al., 2001). Interestingly, the dorsolateral prefrontal cortex has also been found to be a reliable target of neurostimulation to reduce cue-induced craving sensations in addiction (Conti & Nakamura-Palacios, 2014; Li et al., 2013). This structure, with its numerous inputs to the limbic regions including the ventral striatum, is thought to select contextual information appropriate to the individual's goals and may further potentiate the biased-goal directness of other regions (i.e. DMPFC) in individuals with a SUD and regulate inhibitory

control in response to cues (Feil et al., 2010). Interpersonal/affective psychopathic traits may be associated with the more biased selection of drug-related contextual information to motivate one's goal-directed behaviour in concordance with abnormalities in the ACC, DMPFC, and limbic regions.

These results may have a practical implication for the diagnosis of SUDs and the definition of addiction. Analyses support the idea of a spectrum of addiction, in which case a neural processing bias towards drug-related stimuli compared to non-drug rewards may be found in the most severe forms of addiction accompanied by physiological factors of dependence. Moreover, these severity levels could also be separated by the contribution of individual differences, such as psychopathic personality traits, and patterns of major substance use. Future studies should assess what other factors, be them behavioral, cognitive, personality-related, social or biological, further separates these levels of addiction, and whether a substantial distinction between these two forms of dependence have value despite their no-longer inclusion in the DSM. In addition, these results raise question about the role of psychopathic traits in the severity-levels of other externalizing behaviors and comorbid mental disorders. In addition, while psychopathic traits were at similar levels between psychologically dependent and physiologically dependent participants, studies should assess whether psychopathic traits could be a contributing factor to understanding other mental disorders and developing more accurate diagnostic measures utilizing psychopathic traits.

Limitations

One obvious limitation with our study is the size of the psychologically- and physiologically-dependent participants, which were less than half the size of the non-dependent group. This may have affected the statistical power of the study, which may have precluded the

ability to observe smaller effect sizes at a significant threshold. In addition, this study was conducted only among an offender sample, who are known to have higher estimates of substance use severity and psychopathic traits (CCSA, 2004; Hare, 2003). Therefore, it is possible that the distribution of psychopathic traits and substance use patterns does not reflect what we would observe in the general population, limiting the external validity of our neuroimaging results to healthy non-offending individuals. Future studies should investigate this phenomenon among the general population, assessing the influence of substance use severity and psychopathic traits on neural reactivity to drug- and non-drug rewards in psychologically- and physiologically-dependent participants. Finally, very few of our participants would be diagnosed officially as psychopathic, as it is typically required to achieve a PCL-R score of 30 to be considered psychopathic (Hare, 2003), and the highest PCL-R score within our sample was 34. However, there is a large body of research demonstrating that psychopathy is a dimensional disorder that can be conceptualized as a spectrum rather than through a categorical and dichotomized personality disorder (Neumann & Hare, 2008).

CHAPTER 3

GENERAL DISCUSSION

The first goal of this thesis was to investigate abnormalities in drug- and food-related stimulus processing in the brain of individuals with a substance dependence disorder. We demonstrated a neural processing bias towards drug-related stimuli compared to food-related stimuli within a corticolimbic circuit consisting of reward-processing, salience attribution and decision-making regions, including the insula, DMFC, amygdala, ventral striatum, and ACC. Next, we compared this neural processing bias between two variants of substance dependence: physiological and psychological dependence and demonstrated that this neural processing bias is found only in physiologically dependent participants. This was the first time that neural processing of drug-related stimuli was assessed in subcategories of substance dependent individuals, and therefore the first body of work demonstrating differences between physiologically- and psychologically-dependent individuals in functional neurological factors.

The second goal of this thesis was to further understand the comorbidity between psychopathic traits and addiction by investigating the relationship between psychopathic traits and drug- and food-stimulus processing, and how this interacted with the severity of one's substance use. We demonstrated a significant role of psychopathic traits on this neural processing bias towards drug-related stimuli, such that psychopathic traits sensitized the neural processing bias to drug-related rewards in substance dependent individuals. Interestingly, psychopathic traits were also found to modulate the effect of substance use on this bias, with individuals with the highest level of psychopathic traits exhibiting a decrease neural processing bias as substance use severity increased. What is interesting is that the effect of psychopathic traits was modulated by whether the individual was psychologically- or physiologically-

dependent to the substance, such that psychopathic traits were only found to have a main effect and an interaction effect with substance use among psychologically-dependent participants. While studies have previously assessed the relationship between psychopathic traits and drug-stimulus processing in the brain relative to a neutral control (Cope et al., 2014; Vincent et al., 2017), this was the first body of work investigating the relationship between psychopathic traits and the neural processing of drug-related rewards compared to non-drug rewards; the modulating effect of psychopathic traits on substance use-mediated neural processing abnormalities; the effect of psychopathic traits and neural reactivity in both dependent and non-dependent participants; and the effect of psychopathy in psychologically- and physiologically-dependent participants as individual and separate categories of substance dependence.

The results of this thesis have several implications for our understanding of addiction, including contributions to contemporary models of addiction, and how psychopathic traits affect the development and maintenance of addiction. These implications will be explored individually throughout these remaining subsections.

Evidence for the i-RISA and three-stage models of addiction

The results of this thesis have fundamental implications for our understanding of addiction, as they provide support for the contemporary Impaired Response-Inhibition and Salience Attribution model of addiction (i-RISA; Goldstein & Volkow, 2002). The i-RISA model holds that drug-related stimuli will be more salient and stimulating than non-drug-related stimuli, which would make drug-use increasingly difficult to abstain. This thesis, in addition to other studies demonstrating a drug-reward relative to non-drug reward processing bias (Garavan et al., 2000; George et al., 2001; Goldstein et al., 2009), substantiated this model by demonstrating that individuals with a substance dependence disorder exhibit a neural processing

bias towards drug-related stimuli relative to non-drug rewards. In addition, as we observed a neural processing bias within cortical regions (i.e. anterior cingulate cortex, dorsomedial prefrontal cortex), this further supports the localized hypotheses of the i-RISA model that dysfunction within the prefrontal and anterior cingulate cortices underlie this neural processing bias in individuals with an addiction (Goldstein & Volkow, 2002; Goldstein et al., 2011).

The results of this thesis offer support for the three-stage model of addiction. This theory holds that individuals develop a compulsive and uncontrollable need to use a substance by cycling through three-stages: binge/intoxication, withdrawal/negative affect, and craving/preoccupation (Koob & Le Moal, 1997, 2005, 2008a, 2008b). Moreover, this model suggests that neuroplastic changes occurring throughout this cycle makes drug-related stimuli increasingly salient and addiction increasingly severe. In addition to demonstrating that physiologically-dependent participants were the only ones to exhibit this neural processing bias, physiologically-dependent participants were the only one's to report experiencing withdrawal, while tolerance (the other physiological dependence specifier) was equally reported by both physiologically- and psychologically-dependent participants. Therefore, we can speculate that withdrawal may have sensitized this neural processing bias towards drug-related rewards relative to non-drug rewards. Not only is this hypothesis consistent with the three-stage model of addiction, but it is also consistent with another tenet of the i-RISA model, which holds that drug-related stimuli gains greater salience than non-drug rewards by cycling through these three stages of addiction (Goldstein & Volkow, 2002, 2011). Individuals with a physiological dependence may be distinct from psychologically-dependent individuals due to their experience of drug-withdrawal following use cessation, in addition to heavy drug use, which may lead to

neuroplastic changes that facilitates the most severe magnitude of this neural processing bias, and potentially, the greatest difficulty in abstaining from further drug use.

Evidence for an addiction-severity model

These results have implications for further understanding addiction, and the development of a more comprehensive and complete model of addiction that reconciliates 1) the DSM and other contemporary models of addiction, and 2) opposing camps within the field of addiction research. The three-stage model of addiction has been criticized for placing such a large emphasis on the role of withdrawal in addiction, with such critics holding that addiction develops sooner and independently of withdrawal (Wise & Koob, 2014). On this premise, Roy Wise (Wise & Koob, 2014) criticized those using physiological dependence as synonymous to addiction. This camp of addiction research hold addiction is due to the strong positive reinforcement properties of drug-reward, and that dopamine reactivity to drug-related stimuli will lead to compulsive drug use and addiction (Wise, 1988; Wise & Koob, 2014).

However, George Koob argued that he, himself as the author of the three-stage model of addiction, was not disregarding the role of positive reinforcement in addiction and held that positive reinforcement was the initial catalyst of the development of addiction (Wise & Koob, 2014). The role of withdrawal, according to this contrasting camp of addiction research, is that is may lead to addiction becoming more severe, more difficult to extinguish, and predict increasingly worse prognoses (Wise & Koob, 2014). Essentially, early neurobiological changes in the brain as a result of drug use, including changes in dopamine receptor availability in the mesocorticolimbic reward pathway, will catalyze the development of addiction, while changes as a result of the allostatic antireward system activation will lead to more profound neurocognitive dysfunctions, drug-seeking behavior and more profound inability to cease use (Di Chiara, 1998;

Koob & Le Moal, 2005, 2008a, 2008b; Koob & Volkow, 2010; Robinson & Berridge, 1993, 2000; Wise & Koob, 2014).

Withdrawal is hypothesized to lead to neuroplastic changes, particularly within the amygdala, ventral striatum, and cortical regions, that underlie profound drug-related incentive sensitization, and would ultimately lead to the deficits not only found within the current thesis but noted as central within the i-RISA model (Goldstein & Volkow, 2002, 2011; Koob & Volkow, 2010). An empirical example of such a phenomenon is an animal-based study by Lee et al. (2011). Rats were repeatedly administered cocaine, which was associated with synaptogenesis between amygdala and ventral striatum neurons, however these synapses were considered "silent-synapses" due to their inactivity. After no longer having access to cocaine, the rats underwent a withdrawal syndrome. Following withdrawal, these silent-synapses became active, and were associated with increased drug-seeking behavior in response to a cocaine-related cue and cocaine craving within the rats. When blocking withdrawal, these silent-synapses failed to activate, and changes in cocaine-related incentive salience were blocked. While this was an isolated study with a singular focus on connections between amygdalar and ventral striatal neurons, it is theorized that neuroplastic changes extend to cortical regions as well following periods of heavy drug use and drug withdrawal, which underlies i-RISA related dysfunctions.

Koob (2009, 2013, 2017; Koob & Le Moal, 1997, 2005, 2008a; Koob & Volkow, 2010) holds that withdrawal will lead to more severe forms of addiction as he claims that antireward systems (amygdala and bed nucleus of the stria terminalis) become increasingly sensitized to denote an increasingly severe withdrawal syndrome, which will then promote further drug use and a more severe addiction. Based on the opponent process model (Solomon & Corbitz, 1974, 1980), Koob theorizes that reward, known as process A, will raise the mind's hedonic arousal to

a peak, and process B, known as withdrawal, will be a neurological mechanism that will return the brain to a hedonic baseline (Koob, 2017; Koob & Le Moal, 1997). He posits that the A process will become increasingly lower in peak levels, which denotes a growing tolerance to the effects of the drug. The B process, on the other hand, will become increasingly stronger and more severe, essentially denoting that withdrawal is becoming increasingly severe. Hence, withdrawal becomes increasingly more severe, the motivation to use a drug extends beyond simply wanting reward but also a growing desire to end the negative affect accompanying drug-abstinence. As a result, drug use becomes ever more compulsive, difficult to cease, and addiction is at its most severe form.

While the results of this thesis do not specifically support the latter camp of addiction research in terms of the pivotal role of withdrawal, one can suggest of how DSM substance dependence subcategories may relate and perhaps reconcile this debate within the field based on the observations within this thesis. It is possible that physiological dependence may not be interchangeable with the term ‘addiction’, but may denote a more severe form of addiction, similar to Koob’s position on the role of withdrawal and negative reinforcement in addiction (Wise & Koob, 2014). Essentially, the DSM distinction between psychological and physiological dependence may help distinguish various severity levels of addiction from mild to severe. Psychological dependence may be an earlier and milder form of addiction, in which case there is an incentive sensitization of drug-related stimuli, and a decrease in the reward-response from the drug. Physiological dependence represents a severe form of addiction, characterized by drug-related incentive sensitization, non-drug related incentive desensitization, increased negative affect and withdrawal in abstinence periods, heightened craving, and an increasing tolerance to the drug’s rewarding effects.

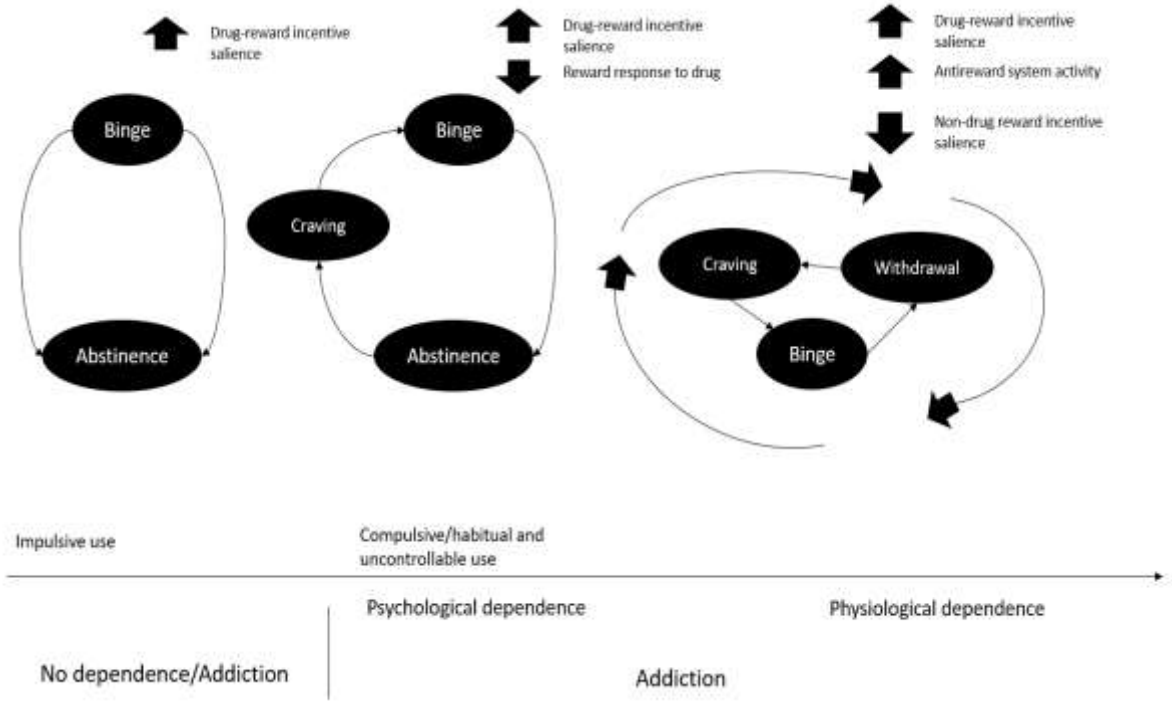
When considering the results of the current thesis, psychological dependent subjects exhibited a more severe drug-use pattern and behavioral dysfunctions relative to non-dependent subjects. Therefore, we can suggest that psychological-dependence is an early and milder form of addiction based on these results. Moreover, as they used more and more substances at a regular rate, they began to exhibit a preference in neural systems for drug-related rewards compared to non-drug rewards. Physiologically-dependent participants demonstrated a similar substance use pattern as psychologically-dependent participants that was more severe than non-dependent subjects. What distinguished physiologically-dependent participants was the neural processing bias towards drug-related stimuli relative to non-drug stimuli. Therefore, it could be suggested that physiological dependence is a more severe form of addiction than psychological dependence, characterized by behavioral dysfunctions with the neural processing bias that may facilitate a more severe and compulsive addictive substance use pattern and increasingly worse prognoses for the individual. As psychologically-dependent participants use more and more substances, they would start to exhibit physiological-dependence symptoms, concomitant with increasing neurocognitive dysfunctions that underlying the distinction of psychological and physiological substance dependence. There addiction would thus be at its most severe form, and prognoses would become ever-more negative.

Combining DSM-categorizations with other contemporary models of addiction, I propose the following comprehensive model of addiction. In accordance with the continuum theory by Everitt and Robbins (2016), individuals transition from an impulsive to a compulsive pattern of drug use that is increasingly uncontrollable. They transition through this continuum is initialized by the positive reinforcement of drug use, consistent with dopamine-based theories of addiction (Di Chiara, 1998; Wise, 1988), which will facilitate the development of a psychological

dependence to the drug. Concomitantly, there will be a sensitization the incentive salience of drug-related cues, consistent with the incentive sensitization hypothesis (Robinson & Berridge, 1993), as well as a growing tolerance to the neurochemical effect of the drugs that lead to reward. The individual will then transition from psychological to physiological dependence by cycling through three-stages: binge/intoxication, abstinence, and craving, taken directly from the three-stage model of addiction (Koob & Le Moal, 1997). As the individual cycles through these stages, the stages will begin to change, and the individual will begin to experience withdrawal following cessation of drug use rather than simply abstinence (Koob & Le Moal, 1997, 2005, 2008a; Koob & Volkow, 2010). The individual will then become physiologically-dependent to the substance, repeatedly cycling through the binge/intoxication stage, withdrawal/negative affective stage, and craving/preoccupation stage. These stages will become increasingly severe with repeated cycles of these addiction stages, leading to a sensitized antireward system and withdrawal syndrome (Koob, 2017; Koob & Le Moal, 2008a; Koob & Volkow, 2010). The individual will begin to develop neurocognitive abnormalities supporting further drug use, including further drug-related incentive sensitization, non-drug-reward incentive desensitization, and a neural processing bias towards drug-related relative to non-drug rewards, consistent with the i-RISA model (Goldstein & Volkow, 2002, 2011). Drug use will become increasingly difficult to resist, rendering individuals in the physiological dependence stage of the addiction spectrum to exhibit the most compulsive form of drug use, and therefore, the most severe form of addiction. A visual presentation of this model of addiction is presented in Figure 6.

Figure 6

Contemporary model of addiction: Transition from impulsive to compulsive use.



Note. Adapted from to contemporary addiction models and associated figures in Koob & Le Moal (1997), Robinson & Berridge (1993), Everitt and Robbins (2005), and Goldstein & Volkow (2002), with an added distinction in the role of physiological and psychological dependence. Individuals transition from impulsive use to compulsive use by repeatedly using the drug, and the positive reinforcing effects sensitize the incentive salience of the drug-reward, while also creating a tolerance due to allostatic mechanisms. As the individual continues to use the drug, abstinence becomes associated with withdrawal which intensifies with repeated cycles of the addiction. This leads to a continuous sensitization of the antireward system and desensitization of the reward systems. In addition, the incentive salience of non-drug rewards decreases, which creates a reward and motivational bias towards drug- compared to non-drug rewards and predisposes individuals to greater cue-induced cravings and compulsive drug use.

The contemporary and integrative model proposed above uses categories defined by the American Psychiatric Association (APA, 2000) in the fourth edition of the DSM. Such a model could thus be communicated and advocated to clinicians to consider when they made their assessment of substance users, in order to develop a treatment program tailored towards the severity of their addiction disorder. Separating the addiction spectrum according to DSM categories may help clinicians be able to distinguish levels of addiction severity, which may have practical implications on treatment efficacy. However, while these DSM categories served our purposes for the current thesis, and participants were previously assessed using the DSM-IV-TR (DSM edition corresponding to the SCID-I/P; First et al., 2002), the current version of the DSM (DSM-5) no longer separates participants based on dependent or non-dependent, nor are substance users separated based on physiological or psychological dependence (APA, 2013). Rather, the DSM-5 combined diagnoses of substance abuse and substance dependence disorders into one broad category: substance use disorder. The fact that we demonstrated differences between physiologically- and psychologically-dependent participants raises question about the DSM-5 diagnostic criteria, the accuracy of such diagnoses, and whether specifying SUD diagnoses according similar to the DSM-IV-TR could yield greater prognostic validity. While distinguishing between abuse and dependence may lack incremental value, a different categorization may yield more positive outcomes, one that does not ignore the behavioral and neurological differences between psychologically-dependent and physiologically-dependent individuals. One solution is to return to the separation of psychological and physiological dependence, however other options have been suggested prior to the release of the DSM-V, such as the the Withdrawal-Gate Model (Langenbucher et al., 2000) and the separation of physiological substance dependence from a new terminology of psychological dependence:

substance dyscontrol disorder (Widiger & Smith, 1994). Regardless, there should be investigation as to whether separating dependence disorders may be a more clinically appropriate solution compared to DSM-5 SUD diagnoses.

Psychopathic traits and individual differences in predisposition for addiction

The second aim of this thesis, in which case we targeted the effect of psychopathic traits on this drug-stimulus processing bias, was primarily to reconciliate psychometric research on the relationship between psychopathic and SUDs and functional neuroimaging research on psychopathic traits and drug-stimulus processing. While our results further explain the comorbidity between psychopathic traits and substance dependence, they did somewhat counter studies by Cope et al. (2014) and Vincent et al. (2017), who both found that psychopathic traits were associated with decreases in drug-cue reactivity within corticolimbic regions when compared to a neutral cue. We found that the nature of the relationship between psychopathic traits and drug > food processing was due to a negative correlation between psychopathic traits and neural reactivity to food stimuli. Therefore, it is possible that, in accordance with Cope and Vincent's reports, that psychopathic traits may predispose individuals to addiction by a compensatory decrease in non-drug reward-reactivity that is more severe than the abnormal drug-cue reactivity in psychopaths.

However, the interaction we observed demonstrated that as highly psychopathic individuals continue to use an addictive substance, they may start to exhibit the abnormal drug-stimulus response identified by Cope et al (2014) and Vincent et al (2017). Therefore, highly psychopathic individuals may exhibit a decreased response to drug-related stimuli, regardless of the control condition utilized with increasing levels of substance use.

What is interesting is that we observed another interaction effect, occurring between psychopathic traits, substance use severity, and variant of substance dependence: psychological vs physiological dependence. Essentially, the psychopathy main effect and psychopathy*use interaction effects on drug > food processing within corticolimbic regions were only observed within psychologically-dependent participants, while no significant contribution of psychopathic traits was observed among physiologically-dependent participants. The sum of this research has implications for our understanding of the effect of psychopathic traits on drug-stimulus processing in the brain, as well as the comorbidity between psychopathy and drug addiction.

As psychopathic traits were associated with a sensitized neural processing bias towards drug-related stimuli, particularly in psychologically-dependent participants, it is possible that psychopathic traits may potentially accelerate the one's transition through the addiction severity spectrum, essentially accelerating one's transition from impulsive and substance-independent substance use to an addiction. This could explain why psychopathic traits are more abundant in individuals with a substance dependent disorder. However, psychopathic traits were indifferent in number between psychologically- and physiologically-dependent participants. Moreover, if psychopathic traits only sensitized the neural processing bias towards drug-related stimuli, one might expect that increasingly psychopathic individuals would be more likely to be physiologically-dependent to a substance, and that psychopathic traits would have been greater among physiologically- compared to psychologically-dependent participants. This was not the case, and the interaction between psychopathic traits and substance use severity in psychologically-dependent participants may be the key in understanding this phenomenon. It is possible that psychopathic traits may sensitize the neural processing bias, which may lead to a psychological dependence to the substance at an accelerated and more aggressive rate. With an

ever-increasing usage pattern, highly psychopathic individuals may show a premature desensitization of drug-related incentive salience leading to a dampening of the neural processing bias in highly psychopathic psychologically-dependent individuals. Therefore, psychopathic individuals may be psychologically-dependent to a substance for a longer period before eventually ceasing use and experiencing physiological-dependence symptoms, such as withdrawal. Subsequently, physiologically-dependent participants, regardless of high or low level of psychopathy or history of substance use, would be all similar in terms of neural processing bias towards drug-related reward, and potentially all similar in terms of addiction-severity in this stage of the addiction spectrum.

These results also have implications for understanding individual differences in predisposition to develop an addiction. Obviously, these results warrant further investigation in how traits characterizing psychopathy, such as impulsivity, reward sensitivity, abnormal empathy and callousness, affect neural processing abnormalities and transitions through addiction in non-offender and non-psychopathic populations. Moreover, these results may also warrant investigation into the extent that such traits, and their underlying neurological abnormalities, predict one's transition from voluntary to compulsive drug use, and the experience of the three-stages of addiction, development of neural processing biases, and prognoses in terms of treatment. To elaborate, psychopathic individuals exhibit not only a behavioral sensitivity to rewarding stimuli, but also an enhanced dopaminergic reward response within the mesolimbic dopaminergic tract in response to rewarding cues (Bjork et al., 2012). In addition, psychopathic traits have been associated with a sensitized reward-response to amphetamine (Buckholtz et al., 2010). However, our analyses demonstrated Factor 1 traits were the more influential constellation of psychopathic traits in drug > food processing, and Buckholtz et al. (2010)

demonstrated that Factor 2 traits were the most influential in this abnormal dopamine response, demonstrating contrasting phenomena. However, one must question the effect of such a sensitized dopaminergic response to rewards, drug rewards in particular, on the development of neural processing abnormalities, and what effect this would have on one's transition from non-dependence to dependence to a substance, and furthermore, the escalation from psychological to physiological dependence. It is possible that this sensitized dopaminergic response may be a strong underlying factor that may sensitized neural processing biases in psychologically-dependent subjects, which may exacerbate the severity of their addictive disorder by potentially accelerating the transition from psychological to physiological dependence. Therefore, individuals with this heightened dopamine responsivity may be at an increased risk, regardless of the level of psychopathy, to develop an addiction.

Towards a new diagnostic method and categories

Finally, this body of research, including prior studies on the comorbidity between psychopathy and addiction, the relationship between psychopathic traits and neural processing abnormalities, and the relationship between psychopathic traits and dopaminergic reward to drugs of abuse, warrant the investigation into whether these are two distinct disorder that should have their own categories (as is currently the case), or whether a new diagnostic method should consider these a combined and special category in and of itself. Using this addiction-related neurocognitive abnormality that is, itself, affected by psychopathic traits, we may be able to characterize new and more accurate forms of addiction that may yield more effective in treatment and prevention of these disorder.

There has been a recent call for new manners through which to characterize and diagnose mental disorders, including SUDs, based on observable behavioral and neurobiological features.

Such an example is the National Institute of Health's (NIH) Research Domain Criteria (RDoC) project, which is part of the NIH's Strategic Plan for Research (NIH, 2015). The RDoC project identifies complex behaviors and their underlying molecular, cellular, and neural underpinnings in order to create new flexible and increasingly accurate diagnostic categories that can yield more effective treatment and preventative methods.

Using an RDoC approach, we may be able to categorize individuals based on a broader range of dysfunctions that encompass both behavioral and neurological. This could render diagnostic categories more specific, accurate and effective in identification and treatment of addictive disorders, as well as associated externalizing disorder like psychopathy. Considering psychopathic traits are highly abundant in populations with SUDs, and psychopathic traits play a significant role in addiction-related dysfunctions, targeting these dysfunctions in diagnostics may help identify the psychopathy-addiction category that would be separate from less-psychopathic-addiction groups and non-addicted psychopathic groups. Neural processing of drug- and non-drug rewards may be used as a marker for the severity of one's addiction, and following a separation of the groups based on this neural processing bias, groups could be further subdivided based on the level of psychopathy and substance use; the influence of these factors on this bias; and differences in a variety of other factors that could have incremental value to the categorization.

Subjects within these novel categories would then be recommended for treatments that were tailored to target the specific dysfunctions characterizing the group that have previously been rendering treatment protocols limited in their effectiveness. For instance, proportions of the SUD population with a high level of psychopathic traits may have been treatment resistant due to confounding factors that are not addressed in substance abuse treatment. For instance,

psychopathic traits have been considered highly treatment resistant, and the implication of that clinically-relevant limitation on the treatment of other concomitant dysfunctions remains unknown. Creating new, and more representative categories, based on both neurological dysfunctions and behavioural abnormalities, would help create highly tailored treatment methods, which may be able to effectively reduce substance misuse, psychopathic tendencies, and the psychosocial impact of these factors.

However, an important issue must also be addressed when attempting to create this novel diagnostic model. In the current thesis, and studies alike, standard parametric data analyses may solve for high effect sizes that are statistically insignificant, particularly among small samples sizes. As a result, research-based diagnostic models may overlook important neural features that may help distinguish between psychopathological categories by ignoring statistically insignificant, yet clinically significant, underlying neural features, and committing a Type II error. When considering the data for the current thesis, limitations in terms of sample and group sizes may have precluded the ability to achieve significant effects, yet effect sizes (including Pearson *r* correlations, variance explained, and *t* values) would still be large according to the literature (Cohen, 1988, 1992). The current thesis compensated for this fact by interpreting results nearly reaching or marginally significant, with consideration of the risk of Type I errors. Similarly, studies with similar sample sizes that present large effect sizes with a lack of statistical significance should include emphases on the clinical significance of the results to the understanding of psychopathology. However, researchers must also be careful not to over-interpret null effects, and risk making Type I errors for future research to build upon. Therefore, one must consider the importance of clinical versus statistical significance, and experts should

work to establish standards that both reduce the risk of Type I False Positive errors, but also emphasize the importance of clinical yet statistically insignificant findings.

Future studies

There are several frontiers for future studies to investigate based on the presented body of research. While psychopathic traits and substance use severity were certainly influential, there could be several other variables that could be influential as well, including gender, ethnicity, as well as the severity of physiological and psychological dependence. Future studies should investigate the impact of these factors, as well as the impact of the severity of withdrawal, substance-use-related behavioral dysfunctions, and the severity of tolerance on this neural processing bias, and how these factors interact with psychopathic traits and substance use severity.

In addition, research should focus on understanding what structural and functional neural mechanisms underlie not only this neural processing bias, but also differences between psychologically- and physiologically-dependent participants, and what structural correlates to psychopathic traits may be an explanatory factor for psychopathy's role in neural processing abnormalities in addiction. Psychopathic traits are associated with a number of structural abnormalities, including grey matter alterations to corticolimbic regions (Boccardi et al., 2013; Cope et al., 2012, 2014b; de Oliveira-Souza et al., 2008; Ermer et al., 2012; Hyde et al., 2014; Yang et al., 2009, 2010); white matter alterations within the uncinate fasciculus, a white matter tract connecting fronto-cortical within mesolimbic regions (Sobhani, Baker, Martin, Tuvblad, & Aziz-Zadeh, 2015; Wolf et al., 2015); and with altered resting-state network connectivity (Philippi et al., 2015). These could all be underlying explanatory factors for the effect of

psychopathic traits on drug-stimulus processing and should be carefully examined as means of further understanding the comorbidity between psychopathy and addiction.

Moreover, understanding the structural and functional neural underpinnings for various levels of addiction, and how individual differences (i.e., psychopathic traits, impulsivity, substance use history) moderate these neural underpinnings, could help create a multi-modal statistical model to use as a research-driven (e.g., RDoC) diagnostic tool. Neuroimaging research has become increasingly aware of the limitations of individual neuroimaging metrics (i.e., BOLD-signal based analyses, Positron-Emission Tomography, Electroencephalogram; Coltheart, 2006; Stufflebeam & Rosen, 2007). For instance, BOLD-signal neuroimaging contrasts (used in the current study) have the limitation of being is highly sensitive to signal loss at orbitofrontal and temporal regions near the skull, as well as limitations in temporal resolution (Detre & Wang, 2002). However, experts have noted that multi-modal approaches may exploit differences obtained from various neuroimaging strategies and offer a more convergent and complete model to use in diagnostic and research-based contexts (Gouws, Woods, Millman, Morland, & Green, 2009; Stufflebeam & Rosen, 2007). Future studies should assess the multi-modal statistical models that best represent various levels of addiction, that best separates various levels of addiction, and best implicates individual differences and non-neuroimaging-related factors into the model.

Furthermore, another future direction could be utilized as a possible means of finding clinically-significant neural features that may appear insignificant according to theory-based data analysis strategies. Researchers should assess neurocognitive abnormalities in addiction using big-data data-driven computational approaches, which would have the benefit of identifying patterns in a complete post-hoc and unbiased manner from typical theory-driven analytical

techniques (Mazzochi, 2015). Typical-theory driven approaches, such as General-Linear Model analyses, compare the data to what would be expected from the Gaussian normal distribution, and are based on preconceived hypotheses on the results of the analyses (Kim, 2008; Mazzochi, 2015). Other approaches, such as Independent-Component Analysis (McKeown et al., 1998) and Principal Component Analysis (Friston, 1994), have the added benefit to typical data analysis techniques of identifying interesting, and more importantly, clinically-significant findings that could be used in these research-driven diagnostic model-developments (Kim, 2008). Conducting these data-driven analyses on exceptionally large datasets that abate the need for a Gaussian distribution-comparison would be useful for the development of new thresholds that could be used for future theory-driven research that will ensure the publication of both statistically sound and clinically-significant results, while also reducing the risk of Type I and Type II errors. These data-driven, and reconceptualized theory-driven, study protocols could be targeted towards neurocognitive abnormalities in addiction and help create new research-driven diagnostic categories while also considering the role of individual differences, such as psychopathic traits and drug use history.

Finally, an important distinction between the DSM-IV-TR substance dependence diagnostic criteria, and criteria for DSM-5 SUD, is the implication of craving. Craving is considered one of the three-stages of the addiction cycle that is considered to increase with increasing levels and history of substance use and periods of withdrawal (Koob & Le Moal, 1997, 2005, 2008a, 2008b; Koob & Volkow, 2010; Robinson & Berridge, 1993, 2000). While our separation of psychological and physiological dependence was appropriate for DSM-IV-TR operationalizations of SUDs, studies looking to separate levels of addiction should also investigate whether craving fits into either physiological or psychological substance dependence,

or perhaps both. Furthermore, studies should assess whether the inclusion of craving has an interaction with both psychopathic traits and substance use severity, and whether it could further separate physiological and psychological dependence based on this neural processing bias. This initiative would be another attempt to empirically demonstrate, in human subjects, whether the i-RISA model and the three-stage model of addiction are, in fact, as accurate or provide incremental validity to DSM operationalizations of SUDs and could further improve novel categorizations of these psychopathological disorders for ameliorated clinical applications.

Conclusion

We successfully furthered our understanding of not only neural dysfunctions in substance dependence, but also how psychopathic traits modulate these neural dysfunctions as a means of facilitating a SUD. By sensitizing neural processing biases towards drug-related stimuli, psychopathic traits may be a predisposing to the development of a psychological substance dependence disorder characterized by a neural preference towards drug-related rewards compared to non-drug rewards. This effect may lead to such individuals eventually developing a physiological substance dependence disorder, which would be characterized by severe behavioral dysfunctions and the highest magnitude of this neural processing bias towards drug-related rewards.

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