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History of withdrawal modulates drug- and food-cue reactivity in cocaine dependent participants

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ABSTRACT

While the centrality of withdrawal in the diagnosis of addiction has been decreasing with each successive edition of the *Diagnostic and Statistical Manual of Mental Disorders,* psychometric and neurobiological evidence provides withdrawal a central role in the development and maintenance of addiction. The current study offers insight into these conflicting positions by using secondary analyses to assess how a history of DSM-assessed withdrawal influences the magnitude of bias in neural reactivity to drug- and/or food-related reward cues. To this end, we separated an existing sample of cocaine-dependent participants (Denomme et al., 2018) into those with (WD) and without (N-WD) a history of withdrawal, and compared food- and drug-cue reactivity between these groups, and to a non-dependent control group (ND). Analyses indicated that biases in neural reactivity towards drug- versus food-related cues only occurred among the WD participants (within: left dorsomedial prefrontal cortex, left anterior cingulate cortex, left orbitofrontal cortex, left caudate nucleus, and right ventrolateral prefrontal cortex). Thus, withdrawal status may be an important factor to consider when interpreting dependence-related biases in neural reactivity following reward-related cues. Interestingly, while N-WD participants did not show these broad biases in neural reactivity, the magnitude of their bias correlated positively with years of lifetime substance use history, particularly when psychopathic traits were low. It may be that for individuals who's addiction has not yet reached a compulsive state (see Wise and Koob, 2014), the magnitude of their drug > food bias could serve as a valuable biomarker of addiction severity.

1. Introduction

The role of withdrawal in the diagnosis of substance use disorders (SUD) has been diminishing with progressive versions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). According to the DSM-III (American Psychiatric Association [APA], 1980), withdrawal was one of two necessary symptoms to meet threshold for a substance dependence disorder. Within the DSM-IV/DSM-IV-TR (APA, 2000) this role was reduced, with withdrawal being removed as a necessary symptom, and included only as one of two specifiers of physiological dependence (thus, individuals could meet for substance dependence with or without manifestation of withdrawal symptoms). The most recent edition, DSM-5 (APA, 2013), has reversed course again, reinstating withdrawal as a core symptom and removing any specifiers for physiological dependence; however, in contrast to DSM-III, withdrawal is only included as one (non-essential) symptom (out of 11) that can contribute toward a diagnosis of SUD. Thus, individuals can meet DSM-5 criteria for SUD with or without meeting criteria for withdrawal.

In contrast, prominent neurobiological models of addiction posit withdrawal as central to the development and maintenance of SUDs. For instance, both the reward-deficit/stress-surfeit model (rd/ss; Koob and Le Moal, 1997, 2008; Koob and Volkow, 2010, 2016; Uhl et al., 2018) and the Impaired Response-Inhibition and Salience-Attribution model (i-RISA; Goldstein and Volkow, 2002, 2011) view withdrawal as playing a key role in the addiction cycle: both view it as following intoxication and bingeing, and as serving as a necessary precursor for an increase in preoccupation/craving. According to the rd/ss model, withdrawal propagates neuroplastic changes (including neurochemical changes at the level of corticotropin-releasing factor transmission and δ-Fos intracellular activation (see Koob et al., 2013, Uhl et al., 2018, and Koob and Volkow, 2010 for comprehensive reviews on the neurochemical basis for addiction)) that promote a progression from voluntary substance use (for reward) to compulsive dependence (for alleviation of negative affect; Koob and Le Moal, 2008; Koob and Volkow,

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2010). According to i-RISA, dysfunctions within prefrontal systems, coupled with alterations within the mesocorticolimbic dopaminergic system, lead to the attachment of greater incentive salience to drug-relative to non-drug-rewards (i.e., food, sex, money; Goldstein and Volkow, 2002, 2011; Volkow and Morales, 2015; Volkow et al., 2016). While the purported underlying mechanisms differ somewhat, both models converge in hypothesizing a critical role for withdrawal in the development/maintenance of SUDs.

Consistent with these theoretical models, the empirical literature has demonstrated an important role for withdrawal in the development of addiction. First, animal work has consistently shown that withdrawal facilitates the development of compulsive, operationalized responding for drug rewards (as demonstrated through increased available-drug intake (Ahmed et al., 2002), locomotor sensitization for cocaine-rewards (Valdez et al., 2002), conditioned place-preference (Dreumont and Cunningham, 2013), and lever presses/self-administration (Grimm et al., 2001)). In addition, neurochemical studies have demonstrated that withdrawal mediates neuroplastic changes underlying the incubation of cue-induced craving sensations in animals, such as through calcium-permeable-AMPA receptor-mediated long-term potentiation in the mesocorticolimbic reward pathway (Lee et al., 2013; Ma et al., 2014), and through Fos expression and glutamatergic projection in an insula–central nucleus of the amygdala pathway (Venniro et al., 2017). In humans, the existence and severity of withdrawal symptoms have consistently been shown to predict both past and future substance use patterns (Allen et al., 2008), substance-use-related biopsychosocial problems (Schuckit et al., 2003), and odds of relapse (Allen et al., 2008). Moreover, the existence/severity of withdrawal symptoms have been related to the development of a wide variety of neurocognitive dysfunctions within the domains of attention, working memory, response inhibition, reward-processing and visuospatial processing (Ashare et al., 2014; McClernon et al., 2015).

One particularly reliable neurocognitive characteristic of individuals with diagnosed SUDs is a biased allocation of neural resources toward drug-related stimuli (Garavan et al., 2000; Goldstein and Volkow, 2011; Hester et al., 2006; Kober et al., 2016; Mogg et al., 2003; Denomme et al., 2018). Proposed to stem from an addiction-specific imbalance in the attribution of incentive salience to drug- versus non-drug-rewards (Goldstein and Volkow, 2002, 2011; Volkow and Morales, 2015; Volkow et al., 2016), this bias has been demonstrated both behaviorally (e.g., via faster reaction times: Hester et al., 2006, and longer eye-gaze: Mogg et al., 2003) and neurally (via increased neural response following drug-related reward, relative to sex-related (Garavan et al., 2000), monetary (Goldstein and Volkow, 2011), or gambling-based (Kober et al., 2016) rewards)). These changes in drug-cue reactivity have been found to persist months into abstinence and to predict future drug use (Witteman et al., 2015), suggesting that it may present as a quite pervasive neurocognitive feature of addiction. In a recent study from our lab (Denomme et al., 2018), 47 cocaine-dependent and 58 non-dependent offenders received functional magnetic resonance imaging (fMRI) while viewing video clips related to the creation/administration of either drugs or food (i.e., preparing or using cocaine through various means [snorting, injecting]; preparing or eating various foods [hamburger, sandwich]). Consistent with a handful of previous studies in this area, and with i-RISA (Goldstein and Volkow, 2011), dependent participants showed a pronounced drug > food bias in neural response, while non-dependent participants showed an opposite food > drug reactivity pattern.

However, the extent to which withdrawal status influences the nature of these reward-related processing biases remains unknown. Indeed, we are unaware of any work that has yet investigated the effect of withdrawal on reactivity to drug/non-drug cues (though a small amount of work has identified specific influences of withdrawal on resting-state functional connectivity (see Faulkner et al., 2018 & Fedota et al., 2016)). The closest work to date has come from investigations on the effect of abstinence. To this end, a recent review of nicotine/alcohol abstinence has reported that acute abstinence (12 − 14 hours post cessation) related to increased neural response to drug-relevant cues within several corticolimbic regions, including the striatum, ACC, and dorsomedial prefrontal cortex (DMPFC; Jasinska et al., 2014); and similar results have been reported in heroin users (Li et al., 2016; Lou et al., 2012). However, because acute (or even prolonged) abstinence may not coincide with the manifestation of withdrawal (see Schuckit et al., 1999), conclusions regarding the effect of withdrawal remain difficult to discern.

With this in mind, the present study involved a reassessment of the Denomme et al. (2018) results, to carefully evaluate the influence of withdrawal status on the magnitude of biases in neural reactivity to drug-related and food-related stimuli. Based on evidence supporting the centrality of withdrawal to the addiction process, we hypothesized that cocaine-dependent participants who experienced withdrawal (WD) would exhibit a significantly greater bias in neural response to drug-related relative to food-related videos than two groups of control participants: dependent participants who did not experience withdrawal (N-WD), and participants who did not meet DSM-IV-TR criteria for dependence (ND). Additionally, as the results from Denomme et al. (2018) indicated that participants' drug-use history and level of psychopathy influenced the magnitude of their drug > food biases, we once again evaluated the role of these important variables in participants with/without DSM-IV-TR-assessed withdrawal symptoms.

2. Methods

2.1. Participants

All data comes from a sample of 101 adult probation/parolees (66 male; 62.3 %), residing in the greater Albuquerque area, who either did (n = 44) or did not (n = 57) meet DSM-IV criteria for cocaine dependence. Four participants from our previous dataset (N = 105) were excluded from the current study due to insufficient data for categorization iwithdrawal status . As reported in Denomme et al. (2018), the sample had a mean age of 35.49 (SD = 9.92, range = 21–59) and a mean IQ score of 105.71 (SD = 12.14, range = 77–140). Here, we further separated the dependent participants into those who did (WD; n = 20) and did not (N-WD; n = 24) show DSM-IV-derived evidence of lifetime withdrawal (see below for assessment details) to carefully evaluate the influence of withdrawal status on the magnitude of biases in neural reactivity towards drug and non-drug reward cues. Proportions of WD and N-WD participants are comparable to previous studies that have used DSM-IV criteria (e.g. Schuckit et al., 1999).

2.2. Clinical/Forensic measures

2.2.1. Psychiatric assessment

The Structured Clinical Interview for DSM Disorders (SCID-IV; First et al., 2002) was administered by trained MA-level research staff (trained by RC – see acknowledgements) to assess all psychiatric disorders, including the presence of lifetime cocaine dependence disorder. Evidence of lifetime psychotic disorder, major depressive disorder in the last 6 months, or current use of antipsychotic medication, were grounds for exclusion. All other psychiatric disorders, including comorbid SUDs, were assessed and noted, but were not grounds for exclusion.

2.2.2. Withdrawal status

For the present study, participants meeting diagnosis for cocaine dependence disorder were separated further into WD and N-WD subgroups based on whether they met DSM-IV-TR criteria for cocaine withdrawal. Specifically, participants were asked the following two questions: “Did you have/have you ever had withdrawal symptoms, that is, felt sick when you cut down or stopped using cocaine?” and “After not using cocaine for a few hours or more, did you/have you

often used cocaine [or another drug] to keep yourself from getting sick with withdrawal symptoms?" (First et al., 2002, Alt-E. 14, E88, [square brackets added]; APA, 2000). Participants who answered 'yes' to either of these questions were then asked to confirm the presence of dysphoric mood, and at least two of the following symptoms, within a few hours to several days following cessation of cocaine use: fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation (First et al., 2002; APA, 2000). Participants who confirmed these criterion were classified as WD, participants who did not confirm these criterion, or who responded 'no' to both of the parent questions, were classified as N-WD.

2.2.3. Drug-use history

Drug use history was evaluated via a modified version of the Addiction Severity Index-Expanded (McLellan et al., 1992). To calculate a Major Drug Use (MDU) composite score for each participant, we summated the number of years of regularuse of cocaine, heroin, methamphetamine, and other amphetamine/opiates (see Denomme et al., 2018; Claus and Shane, 2018). More detailed information regarding participants' use of cocaine over the 90 days prior to the scanning session was also collected using a Timeline Follow-Back (Sobell and Sobell, 1992).

2.2.4. Psychopathy

Psychopathic traits were assessed by trained research staff (trained by MS) using the Psychopathy Checklist-Revised (PCL-R; Hare, 2003), a semi-structured clinical assessment consisting of 20 items, each rated 0–2, with total scores ranging from 0 (low psychopathy) to 40 (high psychopathy). As participants official criminal files were not available, PCL-R scores were assessed from the interview only. All interviews were videotaped; 20 % of all lab videos have been double-rated by a second trained research staff member, achieving inter-rater reliability of ICC_1 = .952.

2.2.5. Weschler abbreviated scale of intelligence (WASI)

Full-scale IQ estimates were obtained via the two-subset WASI (Wechsler, 1999). All participants scored > 70 full-scale IQ.

2.3. Cue-elicited craving task

Participants performed cue-reactivity paradigm within a 3T Siemens TrioTim MRI scanner. Participants were presented with two identical runs during which they viewed 29 videos (duration: ~10,000–14,000 ms): 15 videos depicted individuals preparing or using cocaine, and 14 videos depicted individuals preparing or eating food. Videos were separated by an inter-trial jitter of either 2000, 3500, or 5000 ms to aid deconvolution from the standard hemodynamic response function.

2.4. Data analytic strategy

fMRI data were previously preprocessed (realigned, normalized, smoothed) for Denomme et al. (2018). First-level analyses evaluated and compared the hemodynamic response during presentation of FOOD and DRUG videos . Six movement parameters (x,y,z, pitch, yaw, roll) were also included in the first-level design matrix.

Second-level analyses were undertaken in Statistical Parametric Mapping 12 (SPM12; Friston et al., 1995; Penny et al., 2007). A mixed-model flexible-factorial analysis included Group (WD, N-WD, ND), VideoType (DRUG, FOOD) and the Group*VideoType interaction in the model. In addition, exploratory analyses to assess the influence of MDU and PCL-R scores on the magnitude of observed biases in neural reactivity were also undertaken. To this end, a hierarchical multiple regression analysis was conducted among dependent participants, with Group (WD or N-WD), PCL-R scores and MDU scores entered as separate first-level regressors, two-way interaction terms (i.e., Group * PCL-R, Group * MDU, PCL-R * MDU) entered as second-level regressors, and the three-way interaction term entered as a third-level regressor. Models were run both with and without age included in the model to ensure observed results were not confounded by participant age. All reported results are those that did not include age as a covariate, as inclusion in relevant models led to no demonstrable change in reported effects.

Whole-brain results were threshold at 0.001 uncorrected, and an extended cluster threshold of 102 voxels (equivalent to $p < .05$ FWE), based on a series of Monte-Carlo simulations run through the Alpha Simulator (REST toolbox; Song et al., 2011). While some work has demonstrated an increased risk of false positives when applying extended cluster thresholds in this way (Eklund et al., 2016), more recent work on fMRI clustering suggests that elevation of false-positive rates may be moderate (Cox et al., 2017).

In addition, small-volume corrected search spheres (10 mm for cortical regions; 6 mm for subcortical regions) were created within six regions of interest (ROIs) that distinguished biases in food/drug reactivity between dependent and non-dependent participants in Denomme et al. (2018): left ACC (x, y, z = -6, 18, 21), left amygdala (x, y, z = -39, 0, -21), left DMPFC (x, y, z = -3, 45, 24), left orbitofrontal cortex (OFC; x, y, z = -42, 24, -6), right insula (x, y, z = 36, 0, -21), and right ventral striatum (x, y, z = 6, 12, -6). The possibility that activity within these regions also varies according to withdrawal status is entirely independent of our original analyses, and thus meets appropriate criteria for formation of ROIs (Kriegeskorte et al., 2009).

3. Results

3.1. Demographic/forensic measures and group differences

Mean PCL-R score across the whole sample was 18.48 (SD = 7.14, range = 4–34); mean MDU score was 7.13 years (SD = 7.97, range = 0–33). Cocaine-dependent participants showed significantly higher PCL-R and MDU scores than ND participants (Denomme et al., 2018). To identify differences between WD, N-WD and ND participants, separate one-way ANOVA models identified group differences, PCL-R scores, MDU scores, IQ and age. Subsequent t-tests indicated that the WD and N-WD groups showed both higher MDU scores, and higher PCL-R scores, than the ND group. Neither Age nor IQ differed between groups. Mean scores and groupwise analyses on all demographic/forensic measures are presented in Table 1.

A series of chi-square analyses identified no group differences in

Table 1
Descriptive statistics and group-level differences in clinical/forensic variables.

Variable	ND (n = 57)	N-WD (n = 24)	WD (n = 20)	t (N-WD > ND)	t (WD > ND)	t (WD > N-WD)
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
MDU	2.79 (4.14)	11.33 (8.66)	14.45 (7.61)	5.66*	7.20*	1.66
PCL-R	16.12 (6.66)	21.56 (7.43)	21.54 (5.68)	3.35*	3.13*	.009

Note. t-values represent test statistic of difference between N-WD, WD and ND participants. Unbracketed values represent means, bracketed values represent standard deviations.

* p (FWE) < .05.

Table 2
Frequency of comorbid disorder diagnoses per group.

Disorder	ND	N-WD	WD	χ^2
Major depressive disorder	5 (8.8 %)	6 (25 %)	3 (15 %)	3.75
Panic disorder	3 (5.3 %)	6 (25 %)	1 (5 %)	8.05*
Social phobia	0 (0 %)	2 (8.3 %)	2 (10 %)	5.76†
Phobia	1 (1.8 %)	1 (4.2 %)	2 (10 %)	2.65
OCD	1 (1.8 %)	1 (4.2 %)	0 (0 %)	1.01
PTSD	4 (7 %)	4 (16.7 %)	6 (30 %)	6.76*
GAD	3 (5.3 %)	4 (16.7 %)	0 (0 %)	5.26†
Anxiety due to Medical Condition	0 (0 %)	0 (0 %)	0 (0 %)	–
Anxiety due to substance use	0 (0 %)	0 (0 %)	0 (0 %)	–
Anxiety disorder not otherwise specified	0 (0 %)	0 (0 %)	0 (0 %)	–
Alcohol dependence	21 (36.8 %)	17 (70.8 %)	12 (60 %)	8.91*
SDA dependence	1 (1.8 %)	0 (0 %)	1 (5 %)	1.44
Cannabis dependence	16 (28.1 %)	13 (54.2 %)	10 (50 %)	6.22*
Stimulant dependence	11 (19.3 %)	13 (54.2 %)	7 (35 %)	9.98**
Opioid dependence	12 (21.1 %)	9 (37.5 %)	8 (40 %)	3.78
Hallucinogen dependence	1 (1.8 %)	2 (8.3 %)	2 (10 %)	2.91

OCD = Obsessive compulsive disorder; PTSD = Post-traumatic stress disorder; GAD = Generalized anxiety disorder; SDA = Sedative-hypnotic dependence. †p (FWE) < .10, * p(FWE) < .05, ** p(FWE) < .01.

rate of comorbid SUD diagnoses between N-WD and WD participants, however PTSD was more prevalent among WD participants, and panic disorder was more prevalent among N-WD participants. Conditional distributions and significance tests are presented in Table 2.

3.2. Neural reactivity to DRUG and FOOD videos

The 3 (Group) x 2 (VideoType) flexible-factorial model revealed main effects of Group and VideoType (see supplementary materials, and Denomme et al., 2018). In addition, a significant Group * VideoType interaction was identified within left caudate and right VLPFC, and within left ACC, left DMPFC, and left OFC ROIs. Of particular interest for the present report was the extent to which withdrawal status would influence the nature of these interaction effects. To this end, parameter estimates from the DRUG and FOOD conditions were extracted from peak voxels within each of the five clusters where a significant Group x VideoType interaction was found, and DRUG > FOOD bias scores were calculated for WD, N-WD and ND groups by subtracting FOOD-related parameter estimates from DRUG-related parameter estimates. A series of Bonferroni-corrected between-subject t-tests confirmed that the WD group exhibited significantly greater DRUG > FOOD reactivity within all five clusters (left caudate, right VLPFC, left ACC, left DMPFC, and left OFC) compared to both the N-WD and ND groups (see Fig. 1). In the left caudate and left ACC, the WD group's increased bias appeared to be driven by both enhanced reactivity to the DRUG stimuli and reduced reactivity to the FOOD stimuli, compared to the N-WD and ND groups. In the right VLPFC, left DMPFC, and left OFC, the WD group only showed reduced reactivity to FOOD videos (see Table 3).

3.3. Moderating role of drug use history and psychopathic traits

In Denomme et al. (2018) we reported differential moderating effects of drug use history and psychopathic traits on the magnitude of dependent participants' biases in neural reactivity. As such, as a final step, we repeated the hierarchical regression analysis from Denomme et al. (2018), but added Group (N-WD vs WD) as an additional predictor of DRUG > FOOD bias scores. Results are presented in Table 4. Consistent with the notion of differential effects in WD and N-WD groups, this analysis revealed significant 2-way Group x MDU interactions within left ACC, left PFC, right ventral striatum and left hippocampus, and significant 3-way Group x MDU x PCL-R interactions within right DMPFC and right insula. The 2-way interactions appeared due to a positive relationship between MDU and DRUG > FOOD reactivity in the N-WD group, but not the WD group (in fact, the WD group showed a negative relationship within the left ACC). Thus, length of drug use history served as an important predictor of biases in neural reactivity only in participants who had not experienced withdrawal symptoms. Interpretation of the 3-way interaction was similar, if slightly more complicated: the 3-way interactions were also due to a positive relationship between MDU and DRUG > FOOD reactivity in the N-WD group, however, PCL-R scores also influenced this relationship, such that only N-WD participants with low PCL-R scores showed this positive relationship (see Fig. 2).

4. Discussion

The present study sought to undertake secondary analyses on an existing sample of cocaine dependent and non-dependent individuals, to examine the extent to which a history of withdrawal, as evaluated via the DSM-IV-TR criteria (APA, 2000), would influence neural reactivity following presentation of drug- relative to non-drug reward cues. To this end, results indicated that the drug > food processing bias identified in our previous work (Denomme et al., 2018) was only characteristic of those dependent participants who reported a history of withdrawal. These biases were identified within several corticolimbic regions, including left caudate nucleus, right VLPFC, left ACC, OFC, and DMPFC, which have each previously been shown to underlie processing biases towards drug-related rewards in individuals with a substance dependence disorder (Kühn and Gallinat, 2011). Thus, dependent participants meeting withdrawal criteria appear to be a subgroup of SUD individuals with more severe neurocognitive processing biases. Consistent with this notion, biases of this nature have previously been posited as potential biomarkers of addiction severity, and found to predict future drug use and relapse (Witteman et al., 2015).

While somewhat counter to the decreased emphasis placed on withdrawal in DSM-5, these findings contribute to the sparse, but growing empirical work demonstrating an important role for withdrawal in the development/maintenance of neurocognitive biases in addiction. For instance, abstinence (from nicotine, alcohol or heroin (while not synonymous with withdrawal) has been associated with a sensitized neural response to drug-related stimuli in several recent studies (Jasinska et al., 2014; Li et al., 2016). Similarly, in animal work,

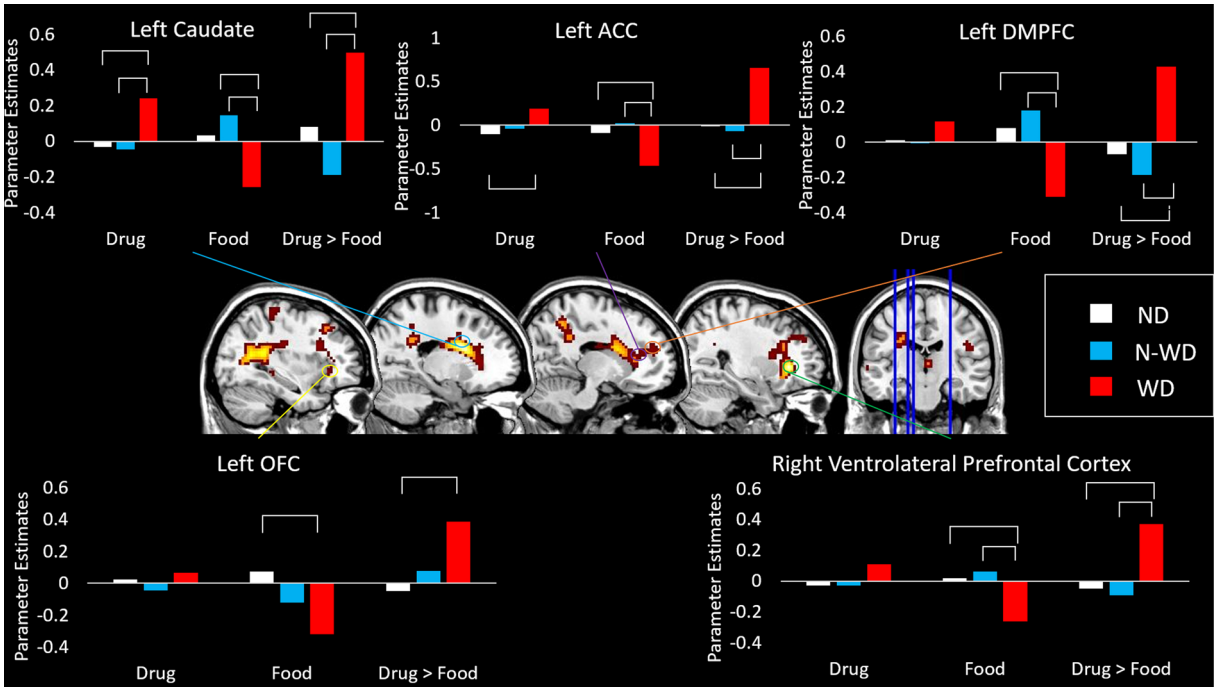

Fig. 1. Group differences in DRUG, FOOD, and DRUG > FOOD reactivity.
Neural images depict spatial maps of DRUG > FOOD reactivity. Voxels highlighted in orange to yellow hues are displayed at p (uncorr.) < 0.001; voxels highlighted red are displayed at p (*uncorr.*) < .005, to display both whole-brain [p(uncorr.) < .001] and ROI [p (svc-FWE) < 0.05] results, respectively. Bar graphs display parameter estimates of neural response to DRUG > Baseline, FOOD > Baseline, and DRUG > FOOD in ND, N-WD and WD participants. Horizontal brackets denote significant group differences from independent-samples t-tests, at p(FWE) < .05 (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

withdrawal has been associated with a sensitized cue-induced operant response in rats (Dreumont and Cunningham, 2013; Grimm et al., 2001). This operant response has been associated with synaptic activation between the amygdala/prefrontal cortex and ventral striatum following withdrawal (through an upregulation of cell-surface GluA2-lacking calcium-permeable α-amino-3-hydroxy-5-methyl-4-isozazolepropionic (AMPA) receptors on ventral striatal post-synaptic medium spiny neurons (Lee et al., 2013; Ma et al., 2014), and with increased insular/amygdalar glutamatergic activity in response to drug-related cues (Venniro et al., 2017). Consistent with these findings, we have demonstrated that neurocognitive biases in cue-reactivity may only be experienced in dependent individuals who exhibit withdrawal symptoms. In further delineating the heterogeneous nature of cocaine use disorders, these findings further highlight the importance of withdrawal in the nature of addictive disorders.

Our results also reconcile well with prominent models of addiction (e.g. rd/ss, Koob, 2017; Koob and Le Moal, 1997, 2008, Koob and Volkow, 2010; i-RISA, Goldstein and Volkow, 2002, 2011, Volkow and Morales, 2015; Volkow et al., 2016), which ascribe a central role for withdrawal in the development of SUDs. For instance, the stress-surfeit

Table 3
Between-group differences in DRUG and FOOD reactivity.

Region	t (N-WD > ND)	t (WD > N-WD)	t (WD > ND)
	DRUG > FOOD		
Left caudate	−1.10	4.93***	4.71***
Right VLPFC	−.540	4.34***	4.54***
Left ACC	−.220	3.92***	4.36***
Left OFC	−.955	2.39†	3.69**
Left DMPFC	−.808	3.34**	3.14**
	DRUG > Baseline		
Left caudate	−.153	2.69*	3.00*
Right VLPFC	−.034	1.90	2.22†
Left ACC	−.592	1.90	2.77*
Left OFC	−.588	.758	.328
Left DMPFC	−.183	.953	.946
	FOOD > Baseline		
Left caudate	.991	−2.86*	−2.42†
Right VLPFC	−.536	−3.09**	−3.11**
Left ACC	−.629	−2.69*	−2.54*
Left OFC	−1.35	−1.77	3.32**
Left DMPFC	−.771	2.99*	2.79*

Post-hoc FWE-corrected between-sample t-tests of DRUG > FOOD, DRUG > Baseline and FOOD > Baseline peak-voxel parameter estimates. VLPFC = Ventrolateral prefrontal cortex; ACC = Anterior cingulate cortex; OFC = Orbitofrontal cortex; DMPFC = Dorsomedial prefrontal cortex. †p(FWE) < 0.10, * p(FWE) < 0.05, ** p(FWE) < 0.01, *** p(FWE) < 0.001.

Table 4
Interaction effects between Total PCL-R scores, Major Drug Use, and Group (WD and N-WD).

Region	Hemi.	MNI (x, y, z)	*t*	Cluster size
		All dependent participants (WD and N-WD)		
*PCL-R * Group*				
		No significant results		
*MDU * Group*				
Cerebellum	R	24, -57, -27	5.11*	240
	R	39, -48, -36	4.22	
	R	27, -36, -36	4.15	
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
Ventral striatum	R	6, 6, -6	2.30†	
ACC	L	−3, 12, 24	4.58†	
OFC	L	−42, 15, -3	2.96†	
	L	−45, 18, 0	2.90†	
	L	−33, 27, -3	2.83†	
*PCL-R * MDU*				
Cerebellum	R	30, -57, -33	4.82	127
ACC	L	−3, 12, 15	2.80†	
OFC	L	−45, 21, 3	3.02†	
	L	−42, 15, -3	2.95†	
*PCL-R * MDU * Group*				
Insula	R	33, -3, -30	2.81†	
DMPFC	R	3, 51, 24	2.79†	
		WD results (within group)		
PCL-R				
		No significant results		
MDU–Positive				
		No significant results		
MDU–Negative				
ACC	L	−3, 9, 24	3.55†	
*MDU*PCL-R*				
		No significant results		
		N-WD results (within group)		
PCL-R—Positive				
DMPFC	L	−9, 48, 30	3.10†	
PCL-R—Negative				
		No significant results		
MDU—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	R	3, 15, 24	4.08†	
	L	−3, 12, 27	3.77†	
Ventral striatum	R	6, 9, -3	3.14†	
MDU—Negative				
		No significant results		
*MDU*PCL-R*				
Cerebellum	R	27, -57, -36	5.21	111
	R	36, -69, -42	4.22	
OFC	L	−45, 21, 3	4.05†	
Insula	R	39, -9, -21	2.91†	
DMPFC	R	6, 48, 21	2.96†	

Regions where activity correlated significantly with MDU and/or PCL-R scores. *p(FWE) < .05; †p(svc-FWE) < .05; all other regions p(uncorr) < .001. ACC = Anterior cingulate cortex; DMPFC = Dorsomedial prefrontal cortex. Hemi = Cerebral Hemisphere; MNI = x, y, z coordinates according to Montreal Neurological Institute template.

theory of addiction (Koob, 2017; Koob and Le Moal, 1997) holds that withdrawal underlies the development of compulsive drug use, and increases the propensity for drug-seeking behavior. Similarly, i-RISA (Goldstein and Volkow, 2002, 2011) posits each of bingeing, withdrawal and craving as comprising critical stages within the cycle of addiction. Consistent with these models, our findings highlight the importance of considering DSM-IV-TR diagnosed withdrawal when considering the development of neurocognitive biases toward drug- and food-related cues. One possibility is that the existence of lifetime withdrawal symptomology serves as an indication of increasingly severe addiction, characterized by larger-magnitude neurocognitive processing biases (see Wise and Koob, 2014). The development of these neurocognitive biases may impose further disadvantage to these dependent individuals, by biasing salience and motivational systems towards future indication of drug-relevant stimuli.

Of note, in some regions (left caudate and left ACC) observed biases were due to differences in neural response to both drug and food cues; in other regions (right VLPFC, left DMPFC, and left OFC) these biases were due solely to decreased neural response to food cues. Broadly consistent with hypotheses, and existing theory (e.g. Goldstein and

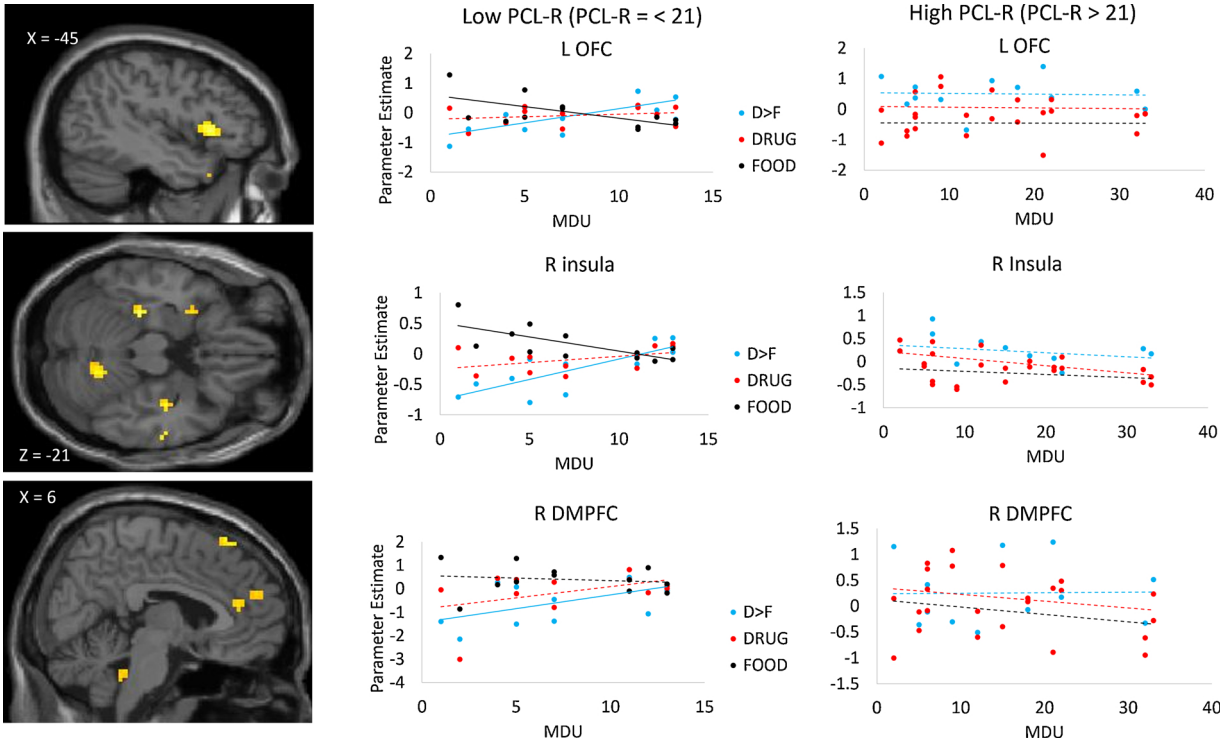

Fig. 2. Correlations between MDU scores and neural reactivity among high and low PCL-R N-WD participants.
Neural images depict PCL-R*MDU interaction effects on DRUG > FOOD neural reactivity within N-WD participants. Images are thresholded at *p*(*uncorr*) < .005 to demonstrate *svc-FWE* < 0.05 level results in ROI regions. Scatterplots depict correlations between MDU scores and neural reactivity to DRUG > FOOD (D > F; blue), DRUG > Baseline (DRUG; red) and FOOD > Baseline (FOOD; black) among high and low PCL-R scorers, based on a median split (median = 21). Positive correlations between MDU scores and DRUG > FOOD reactivity were observed within the low PCL-R group. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

Volkow, 2011), this suggests that the state of withdrawal may be characterized as much by a decreased incentive salience for non-drug rewards as by an increased incentive salience for drug rewards. Moreover, it further highlights the importance of considering the *balance* between drug/non-drug responsivity, rather than the absolute level of responsivity to either drug or food stimuli.

In contrast, the role of withdrawal in the official DSM-based diagnosis of SUDs has been diminishing with progressive versions of the DSM. For instance, the most recent edition of the DSM (DSM-5; APA, 2013) has included withdrawal as only one (non-essential) symptom (out of 11) towards diagnosis of a SUD. This reduced emphasis on withdrawal appears to be in the service of increasing the consistency and reliability of clinical assessments; however, it also appears to represent a substantive disconnect from the empirical literature, and from developing models of addiction, which consistently emphasize the central role of withdrawal in the development and maintenance of the addiction cycle (Koob and Le Moal, 1997; Goldstein and Volkow, 2002). Our results further highlight this growing disconnect and suggest that a reconsideration of the role of withdrawal in the diagnosis of SUDs may be in order. Ignoring these underlying neurocognitive distinctions may limit both empirical and clinical appreciation for the heterogeneity of substance dependent populations.

More exploratory analyses indicated that N-WD participants' biases were modulated by both substance use history and level of psychopathy. In particular, substance use history correlated positively with drug > food reactivity in a number of regions, including regions involved in allocating salience-attribution (i.e., ACC; Goldstein and Volkow, 2011; Goldstein et al., 2007), contextual memory (i.e., hippocampus; Weiss, 2005) and motivation (i.e., ventral striatum; Weiss, 2005), and (in N-WD participants with lower levels of psychopathic traits), within regions involved in stimulus-response learning and goal-directedness (i.e., OFC and DMPFC; Weiss, 2005; Jasinska et al., 2015) and interoceptive reward processing (i.e., insula; Naqvi and Bechara, 2010). It may be that for individuals where addiction has not yet reached a compulsive state (see Wise and Koob, 2014), the strength of one's drug > food bias may serve as a valuable biomarker of behavioral risk factors for addiction severity.

Interestingly, the ACC was the only region in which we observed a negative correlation in WD participants. Recent studies have suggested that deactivation of the ACC may underlie self-control deficits, leading to a disinhibited craving response to drug-related stimuli (Kober et al., 2010; Tang et al., 2015). For instance, Kober et al. (2010) demonstrated that decreased prefrontal control over ventral striatum reward-related activity was associated with increases in craving responses to drug-related rewards. Moreover, a mindfulness-based self-control training program resulted in increased resting-state ACC activity, as well as a reduction in drug use (Tang et al., 2013). One possibility is that the negative correlation we observed between substance use history and ACC activity is due to decreased ACC-mediated self-control capabilities, which may further disinhibit drug-reward processing and drug-seeking behavior in WD participants.

4.1. Limitations

The present study helps advance knowledge regarding the role of withdrawal in influencing the magnitude of reward-related processing biases in addiction; however, it is not without its limitations. For one, WD and N-WD groups were approximately half the size of the non-dependent group, which may have affected the statistical power of the study or precluded the ability to observe smaller effect sizes. Second, as this study was conducted within an offender sample, who are known to have higher estimates of substance use severity and psychopathic traits (Hare, 2003; Canadian Centre on Substance Abuse, 2004), it is possible that the distribution of psychopathic traits and substance use patterns

does not reflect what would be observed in the general population. Future studies should thus investigate these phenomena within a non-offender sample with more moderate MDU/PCL-R characteristics. Third, as this study measured withdrawal symptomology categorically, rather than continuously, it is unable to evaluate the extent to which the severity of withdrawal symptomstrack with the magnitude of drug- versus non-drug processing biases.

Author contributions

WJD contributed to hypothesis generation regarding the involvement of withdrawal, to data analysis, to interpretation of study data, and to primary writing and preparation of the manuscript. MSS contributed to the design, collection and management of the study data, to regulatory oversight and project management, to interpretation of the study data, and to preparation of the manuscript.

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Declaration of Competing Interest

The authors report no conflict of interests.

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Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.107815.

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