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Neural reward response to substance-free activity images in opiate use disorder patients with depressive symptoms

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ABSTRACT

Background: Deficits in the ability to experience reward from natural, substance-free activities and stimuli is a common mechanism contributing to both opiate use disorder and depressive symptoms, and is a target of behavioral-focused treatments for substance use and depression. Although the neural response to monetary, positive affect-eliciting and social images has been investigated, the neural response to images representing substance-free activity engagement remains untested. The current study tested the neural response to anticipation and receipt of substance-free activity engagement images and monetary reward in opiate use disorder patients with elevated depressive symptoms compared to healthy controls.

Methods: Sixteen male opiate use disorder detoxification patients with elevated depressive symptoms (Beck Depression Inventory (BDI-II) ≥ 14) (OUDD M_{age} = 32.19 years, SD = 8.17 years) and seventeen male healthy controls (BDI-II < 14) (HC: M_{age} = 26.82 years, SD = 5.29 years) completed the Monetary Incentive Delay (MID) and newly developed Activity Incentive Delay (AID) tasks. Within- and between-group whole-brain contrasts tested activation during anticipation ([reward]-[non-reward]) and receipt ([win]-[non-win]) of substance-free activity image, monetary, and substance-free activity relative to monetary (AID-MID), reward.

Results: OUDD demonstrated significantly lower activation in reward regions during anticipation and significantly greater activation during receipt of substance-free activity image reward compared to HC. OUDD demonstrated significantly lower activation during anticipation of substance-free activity reward relative to monetary reward, compared to HC.

Conclusions: The observed reduction in frontostriatal response to reward anticipation of substance-free activity engagement images in OUDD, yet increased neural response to reward receipt, supports theory linking reductions in reward processing with deficits in motivation for substance-free activity engagement.

1. Introduction

In 2014, approximately 2.5 million adults in the U.S. met criteria for opiate use disorder (OUD; Substance Abuse and Mental Health Services Administration (SAMHSA, 2015). This number continues to rise, accounting for the dramatic increase in overdose-related deaths (Rudd, 2016) and billions of dollars in economic burden (Kirson et al., 2017; Schuchat et al., 2017). As such, opiate use has been deemed a public health crisis (Kolodny et al., 2015), directing research efforts to identify factors contributing to the maintenance of OUD. One factor linked to poor treatment response, severity of substance use, and increased likelihood of developing a substance use disorder (SUD) is the presence of a co-occurring psychological diagnosis (Conway et al., 2016; Dodge et al., 2005; Hasin et al., 2002; Jane-Llopis and Matytsina, 2009). Depression is among the most common co-occurring mental health conditions for individuals who use substances (Swendsen and Merikangas, 2000), and individuals who use opiates specifically, with 27% of treatment-seeking individuals who use opiates meeting diagnostic criteria for major depressive disorder (MDD) and 57% reporting any depressive symptoms (Goldner et al., 2014). Patients with OUD and co-occurring depressive symptoms report poorer treatment outcomes, including lower rates of treatment completion (Ravndal and Vaglum, 1994), worse post-treatment functioning (e.g., employment, psychological) (Hasin et al., 2002; Rounsaville et al., 1986), a higher likelihood

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of relapse to substance use (Brewer et al., 1998; Tate et al., 2004), and a higher percentage of substance-using days post-treatment (McKay et al., 2002) compared to patients without co-occurring depressive symptoms. As the presence of elevated depressive symptoms is a key risk factor for continued opiate use during and after OUD treatment (Brewer et al., 1998), attention to the mechanisms maintaining these co-occurring conditions and contributing to poor treatment response is warranted.

One potential mechanism common to both OUD and depressive symptoms is altered reward processing (Janiri et al., 2005). Individuals with depression demonstrate decreased pleasure from rewarding stimuli and in turn, reduced engagement in values-congruent activities, the avoidance of which contributes to the maintenance of depressive symptomology (Carvalho and Hopko, 2011; Lewinsohn, 1974; Martell et al., 2001). Similarly, chronic substance use is associated with self-reported and neural evidence of decreased responsivity to natural, substance-free rewards (see Garfield et al., 2014 for review; Huhn et al., 2016) and positive affect-eliciting stimuli (Wang et al., 2010), coupled with increased attention and responsivity to drug-related cues (Zijlstra et al., 2009). Such under-responsivity to natural reward and over-responsivity to drug-related cues are theorized to represent the incentive salience of drugs, and subsequently contribute to the maintenance of SUD (Gradin et al., 2014).

Neural response to reward in SUD and depression has been tested in temporally specific components of the reward system, namely reward anticipation and receipt, which comprise distinct and highly relevant processes related to SUD and depression. Reward anticipation, reflecting motivation for reward and incentive salience of rewarding stimuli, is disrupted in individuals with a SUD and/or elevated depressive symptoms, who evidence decreased motivation for natural, substance-free reward (see Baskin-Sommers and Foti, 2015 for review). Such alterations in reward anticipation are associated with disruptions in frontostriatal neurocircuitry including the ventral striatum, prefrontal cortex, anterior cingulate cortex, and amygdala in both SUD and depression populations (Luijten et al., 2017; Whitton et al., 2015). Receipt of reward, or the hedonic component of a rewarding experience, is also observed in SUD and depression and involves activation of the caudate, medial prefrontal cortex, and insula, in addition to activation in regions implicated in reward anticipation (Luijten et al., 2017; Smoski et al., 2009). Taken together, individuals with a SUD and elevated depressive symptoms tend to evidence reduced recruitment and engagement of such neural regions during reward anticipation and receipt.

To date, the majority of studies reporting the neural response to reward anticipation and receipt in individuals with a SUD or elevated depressive symptoms have utilized monetary reward cues using the Monetary Incentive Delay (MID) task (e.g., Balodis and Potenza, 2015; Jia et al., 2011; Knutson et al., 2000; Knutson and Greer, 2008). Reward cues are an important consideration when attempting to integrate this work with theory-driven perspectives concerning treatment of co-occurring substance use and depression. Reinforcement theories of substance use (McKay, 2017; Vuchinich and Tucker, 1998) and behaviorally-oriented models of depression (Jacobson et al., 1996) point to decreased engagement in positive, substance-free, rewarding activities as a central maintenance factor for these disorders. Such theoretical viewpoints have been empirically supported by research linking engagement in pleasant and rewarding activities to improved treatment outcomes for individuals who use substances and depressed individuals (Daughters et al., 2008, 2018; Jacobson et al., 1996; Zeiss et al., 1979). This work suggests that identifying the neural reward response to natural, substance-free activity engagement may inform reward-related deficits contributing to poor substance use treatment response.

To bridge theoretical orientations and neurobiological perspectives of reward processing in these disorders, we modified the MID by replacing monetary images with images of substance-free activity engagement to examine the neural response to reward in patients with co-occurring opiate use disorder and elevated depressive symptoms (OUDD) relative to a healthy control (HC) sample. The primary aim was to test within- and between-group differences in neural response to anticipation and receipt of substance-free activity engagement images. The secondary aim was to test within- and between-group differences in the neural response to substance-free activity images compared to monetary reward. Given the established deficit in responsivity to natural reward (see Garfield et al., 2014 for review) and positive affect-eliciting stimuli (Wang et al., 2010) in substance users, we hypothesized that compared to HC, the OUDD group would demonstrate a significantly lower frontostriatal response to anticipation and receipt of substance free activity images, monetary reward, and substance-free activity images relative to monetary reward.

2. Material and methods

2.1. Participants

The current study consisted of sixteen participants with DSM-5 opiate use disorder and co-occurring moderate depressive symptoms (OUDD: M_{age} = 32.19 ± 8.17 years) recruited from an inpatient detoxification unit of a UNC-affiliated hospital in Raleigh, NC, and seventeen gender- and education-matched healthy controls (HC: M_{age} = 26.82 ± 5.29 years) recruited from the community using the UNC Biomedical Research and Imaging Center (BRIC) healthy control pool, Craigslist, ResearchMatch, and fliers. Opiate replacement therapy was not routinely prescribed at the detoxification facility. Additional participant characteristics are presented in Table 1. OUDD inclusion criteria were current DSM-5 OUD and self-reported elevated depressive symptoms [Beck Depression Inventory (BDI-II) ≥ 14]. HC exclusion criteria were current or past DSM-V substance use disorder, use of illicit substances in the past 30 days, or elevated depressive symptoms (BDI-II ≥ 14). Exclusion criteria for all participants were < 21 or > 50 years of age, < 5th grade reading level, any current DSM-5 Axis-I disorder (other than OUD and MDD for OUDD participants), or MRI contraindications (e.g., metal devices or fragments, major medical illnesses).

2.2. Procedure

OUDD participants were screened on the detoxification unit, while HC completed an initial phone screen, followed by an additional screen on-campus. All participants provided informed consent approved by the University of North Carolina at Chapel Hill (UNC-CH) Institutional Review Board (IRB). Participants completed self-reported measures, task training, and functional magnetic resonance imaging (fMRI) followed by an image rating task. Participants were compensated at the end of the session with a gift card.

2.3. Reward tasks

Participants completed a structural scan followed by an fMRI scan with two reward tasks presented in counterbalanced order. Both tasks were individually titrated such that participants were successful on 66% of trials, regardless of individual reaction times. Participants completed out-of-scanner task training for each task, during which they were required to achieve ≥66% accuracy to proceed to the scan.

2.3.1. Substance-free activity engagement image reward

2.3.1.1. Image selection. A set of 145 publicly available images of substance-free activity engagement were collected across six life areas from the initial version of the life areas, values, and activities (LAVA) module of the behavioral activation treatment for substance use and depression (Daughters et al., 2018, 2016): physical health, emotional health, relationships, education and work, recreation and hobbies, and spirituality. A separate group of 29 treatment-seeking male substance users (M_{age} = 41.90 ± 11.49 years; 41.40% African American/Black) at the same inpatient detoxification facility provided ratings of these

Table 1
Sample characteristics.

	OUDD (n = 16) **Mean (SD)**	HC (n = 17)	Statistic
Age (years)	32.19 (8.17)	26.82 (5.29)	$t(31) = -2.25$*
Ethnicity/Race (%)			
Caucasian/White	93.33	64.71	($\chi^2(1) = 3.82$
African American/Black	0.00	35.29	($\chi^2(1) = 6.52$*
Native American/American Indian	6.25	11.76	($\chi^2(1) = 2.28$
Hispanic/Latino	13.33	0.00	($\chi^2(1) = 0.30$
Education (years)	12.72 (1.67)	13.68 (1.70)	$t(30) = 1.58$
Marital Status (%)			($\chi^2(5) = 7.62$
Single	66.67	52.94	–
In a Relationship	13.33	23.53	–
Living with Partner	0.00	17.65	–
Married	0.00	5.88	–
Separated	13.33	0.00	–
Divorced	6.67	0.00	–
WRAT Reading	58.25 (5.50)	61.71 (5.54)	$t(31) = 1.80$
Depressive Symptoms (BDI-II)	23.56 (7.13)	3.00 (3.30)	$t(31) = -10.74$**
Minimal (%)	0.00	100.00	–
Mild (%)	31.25	–	–
Moderate (%)	50.00	–	–
Severe (%)	18.75	–	–
Substance Use Characteristics			
# days abstinent before scan	3.38 (1.31)	–	–
# days in detox before scan	2.38 (1.20)	–	–
# days used in last 30 days			
Alcohol	1.44 (3.46)	2.24 (3.35)	$t(31) = 0.67$
Cocaine	1.69 (3.65)	–	–
Marijuana	1.06 (2.41)	0.76 (1.48)	$t(31) = -0.43$
Heroin	19.25 (9.07)	–	–
Painkillers (not prescribed)	1.06 (2.52)	–	–
Amphetamines	0.25 (1.00)	–	–
Benzodiazepines (not prescribed)	1.06 (2.41)		–

Note: *$p < 0.05$, **$p < 0.001$. OUDD = patients with opiate use disorder with elevated depressive symptoms, HC = healthy controls. BDI-II score cut-offs: Minimal (0–13), Mild (14–19), Moderate (20–28), and Severe (29–63).

images using the Self-Assessment Manikin (SAM) scale (Bradley and Lang, 1994) for emotional valence and arousal on a 5-point Likert scale from 1 (more positive/aroused) to 5 (less positive/aroused). Likelihood of completing the depicted activity was rated for each image using a 10-point Likert scale from 1 (not at all likely) to 10 (extremely likely). The 40 images with the lowest composite scores of valence (M = 1.92 ± 0.51) and arousal (M = 3.28 ± 0.99) were used in the substance-free activity engagement reward task. Forty neutral images were selected from the International Affective Pictures System (IAPS) (Lang et al., 1997).

2.3.1.2. Task. The aforementioned substance-free activity and neutral IAPS images were used to create the Activity Incentive Delay (AID) Task (Fig. 1), a modified version of the MID task (Knutson et al., 2000). The trial structure included two randomized, 8-minute runs with 20 reward and 20 non-reward trials each consisting of (1) a 2000 ms cue which indicated whether a correct response could result in a win (reward; gray triangle) or non-win (non-reward; blue circle), (2) a 2000–2500 ms delay with a crosshair, (3) a target bullseye presented up to 500 ms, which participants were instructed to make a button press in response to as quickly as possible, (4) a 3000 ms feedback screen indicating whether the button press resulted in a win, depicted by a substance-free activity engagement image, or non-win, depicted by a neutral IAPS image, and (5) a variable intertrial interval (ITI) so the total trial duration was 12 s.

2.3.2. Monetary reward

The trial structure for the Monetary Incentive Delay (MID) task (Knutson et al., 2000) (Fig. 1) was identical to the AID. Wins consisted of a basket with money and non-wins an empty basket with a red "X". Participants had the potential to win $1 per trial with the running total amount won displayed during the receipt phase of each trial (M = 26.62 ± 1.44 dollars). During the out-of-scanner task training and the task in the scanner, participants were told that they would be able to keep the money they won.

2.4. Assessment Measures

2.4.1. Depressive symptoms

The Beck Depression Inventory-II (BDI-II; Beck et al., 1996) is a 21-item self-report questionnaire administered during screening to assess severity of depressive symptoms. Each item is rated on a 0–3 Likert scale with summary scores ranging from 0-63. Summary score interpretations as reported in the BDI-II manual are minimal = 0–13, mild = 14–19, moderate = 20–28, and severe = 29–63.

2.4.2. DSM-5 axis I disorders

The Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 2014) Version 7.0 for the DSM-5 was used to screen for current post-traumatic stress disorder (PTSD) and/or psychotic disorders, which were exclusion criteria for all participants.

2.4.3. Substance use frequency

The Timeline Followback (TLFB; Sobell et al., 1979) was used to retrospectively determine substance use in the past 30 days using a calendar and other recall-enhancing techniques. The TLFB demonstrates high test-retest reliability, convergent and discriminant validity with other substance use measures (Norberg et al., 2012; Robinson et al., 2014; Roy et al., 2008).

2.4.4. Reading level

The Word Reading subtest of the Wide Range Achievement Test–Revised (WRAT-R; Jastask and Wilkinson, 1984) was administered to screen for individual reading level prior to consenting to determine if an individual could read at a fifth grade level or higher, necessary to comprehend written portions of the procedure.

2.4.5. Image ratings

After the scan, participants completed arousal and valence ratings of 40 substance-free activity images and the likelihood of completing the activities depicted in the images with the same rating scales used in the image selection procedure. Twenty (50%) of the images were substance-free activity images not included in the AID task to reduce the potential impact of familiarity on image ratings.

2.5. Data acquisition and analysis

2.5.1. Acquisition

Whole-brain blood oxygenation level-dependent (BOLD) echo-planar imaging (EPI) data were acquired on a Siemens 7 T Magnetom Trio MR Scanner (Siemens, Erlangen, Germany) equipped with a 32-channel head coil. Seventy slices (1.5 mm) were obtained using whole-brain, single-shot gradient-echo-planar imaging (EPI) sequence in the transverse plane. Imaging parameters were repetition time (TR) = 2000 ms, echo time (TE) = 22 ms, field of view (FOV) = 220 × 220 mm, flip angle (FA) = 80°, and in-plane resolution = 1.5 × 1.5 mm. A whole-brain T1-weighted structural image

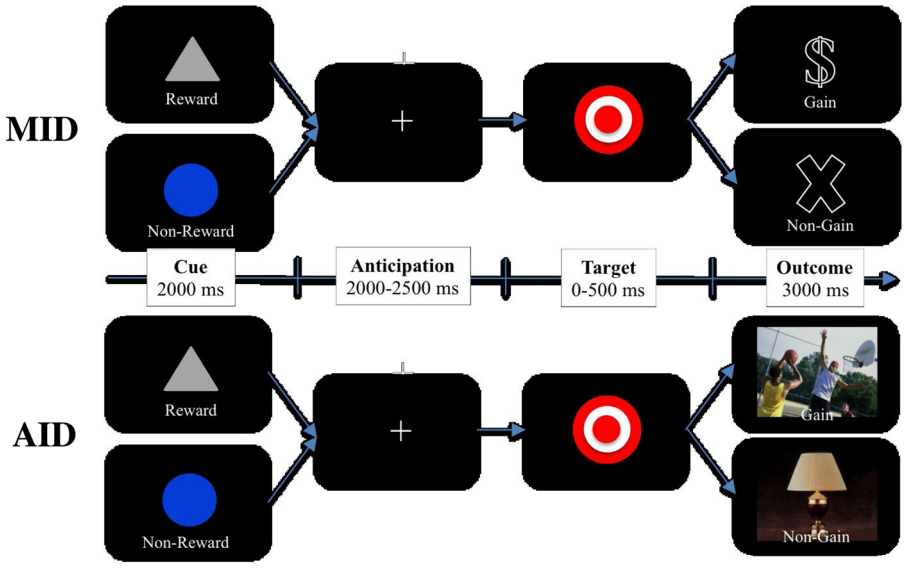

Fig. 1. Trial structure of the Monetary (MID) and Activity (AID) Incentive Delay tasks.
Note: Trial structure figure has been adapted from Smoski et al. (2011).

(MPRAGE) was acquired for each participant (1 mm^3 isotropic voxels, TR = 2200 ms, TE = 2.78 ms, FA = 7°, and FOV = 220 × 220 mm).

2.5.2. Analysis

2.5.2.1. Image ratings and task performance. Two 2 (between-group factor: OUDD, HC) × 2 (within-group factor: reward, non-reward) analyses of variance (ANOVA) were conducted to test group differences in AID and MID task performance, measured by response time. Independent sample t-tests were conducted to examine between-group differences in AID image ratings.

2.5.2.2. Pre-processing. Anatomical and functional data were pre-processed and analyzed using Oxford Centre for Functional Magnetic Resonance Imaging of the Brain's (fMRIB) Software Library (FSL; ww.fMRIb.ox.ac.uk/fsl). Preprocessing (FEAT Version 5.0.1.) included MCFLIRT motion correction (Jenkinson et al., 2002), spatial smoothing with a Gaussian kernel of full-width half-maximum 5 mm, high-pass temporal filtering (Jenkinson et al., 2002), grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, and BET skull stripping of structural images. Registration of functional data to subject-specific T1-weighted anatomical slices and the 1 mm Montreal Neurological Institute (MNI) standard-space template was done with FLIRT utilizing an affine transformation with twelve degrees of freedom. Estimation and correction of voxel-wise temporal autocorrelation used fMRIB's Improved Linear Model (FILM).

2.5.2.3. fMRI. Stimulus timing files were created by extracting event onset times to model whole-brain response for each response type (AID/MID anticipation: reward/non-reward; AID/MID receipt: win/non-win) convolved with a double-γ function to model the hemodynamic response. Functional scans were subjected to censoring (Siegel et al., 2014) based on relative frame displacement values. Individual first-level analyses were conducted for each reward phase (anticipation/receipt) separately, using a whole-brain general linear model (GLM) with the ([reward]-[non-reward]) contrast for anticipation and ([win]-[non-win]) contrast for receipt. Within- and between-group whole-brain activation maps were created with Bayesian estimation-based higher-level analyses, fMRIB's Local Analysis of Mixed Effects (FLAME) stage 1 (Woolrich et al., 2001; Smith et al., 2004) (Aim 1). Two 2 (between-group factor: OUDD vs. HC) x 2 (within-group factor of reward type: AID vs. MID) mixed ANOVAs tested main effects and interactions (Aim 2) separately for reward anticipation and receipt. Z (Gaussianized T/F) statistic images were thresholded at $z > 2.3$ and a corrected cluster significance of $p < 0.05$. Localizations of significant activation clusters were determined using the Harvard-Oxford cortical and subcortical structural atlases, set at 10% and overlaid on the MNI standard-space T1-weighted structural template image. Given group differences in age (p = .03) and ethnicity/race (p = .02), these models were also run with these covariates; however, analyses yielded the same significant clusters of activation. Significant clusters of activation are reported in Tables 3 and 4 and shown in Fig. 2. Additional within-group contrasts for OUDD including BDI-II total score as a covariate were tested to determine the influence of depressive symptoms on task effects.

3. Results

3.1. Image ratings and task performance

Image rating and task performance data are reported in Table 2. Independent sample t-tests did not reveal any significant between-group differences in valence, arousal, or likelihood of engaging in the depicted activities in the substance-free activity reward images.

The 2 (OUDD, HC) x 2 (AID reward, AID non-reward) mixed ANOVA revealed a significant effect of trial type on AID response time, such that participants had significantly faster response times on reward trials compared to non-reward trials, $F(1,31) = 12.64$, $p < 0.01$. The effect of group on AID response time was not significant, $F(1,31) = 2.19$, $p = 0.15$. The 2 (OUDD, HC) x 2 (MID reward, MID non-reward) mixed ANOVA revealed a significant effect of trial type on MID response time such that participants had significantly faster response times on reward trials compared to non-reward trials, $F(1,31) = 26.02$, $p < 0.01$. The effect of group on MID response time was also significant, such that OUDD participants had significantly faster response times than HC, $F(1,31) = 4.65$, $p < 0.05$.

3.2. Neural response to anticipation of substance-free activity reward and monetary reward

Substance-free activity reward. Within-group analyses yielded two significant frontostriatal clusters of activation in HC, including the bilateral superior frontal gyrus, supplementary motor area, and thalamus, and right putamen and caudate during anticipation ([reward]-[non-reward]) of substance-free activity reward. There was no significant

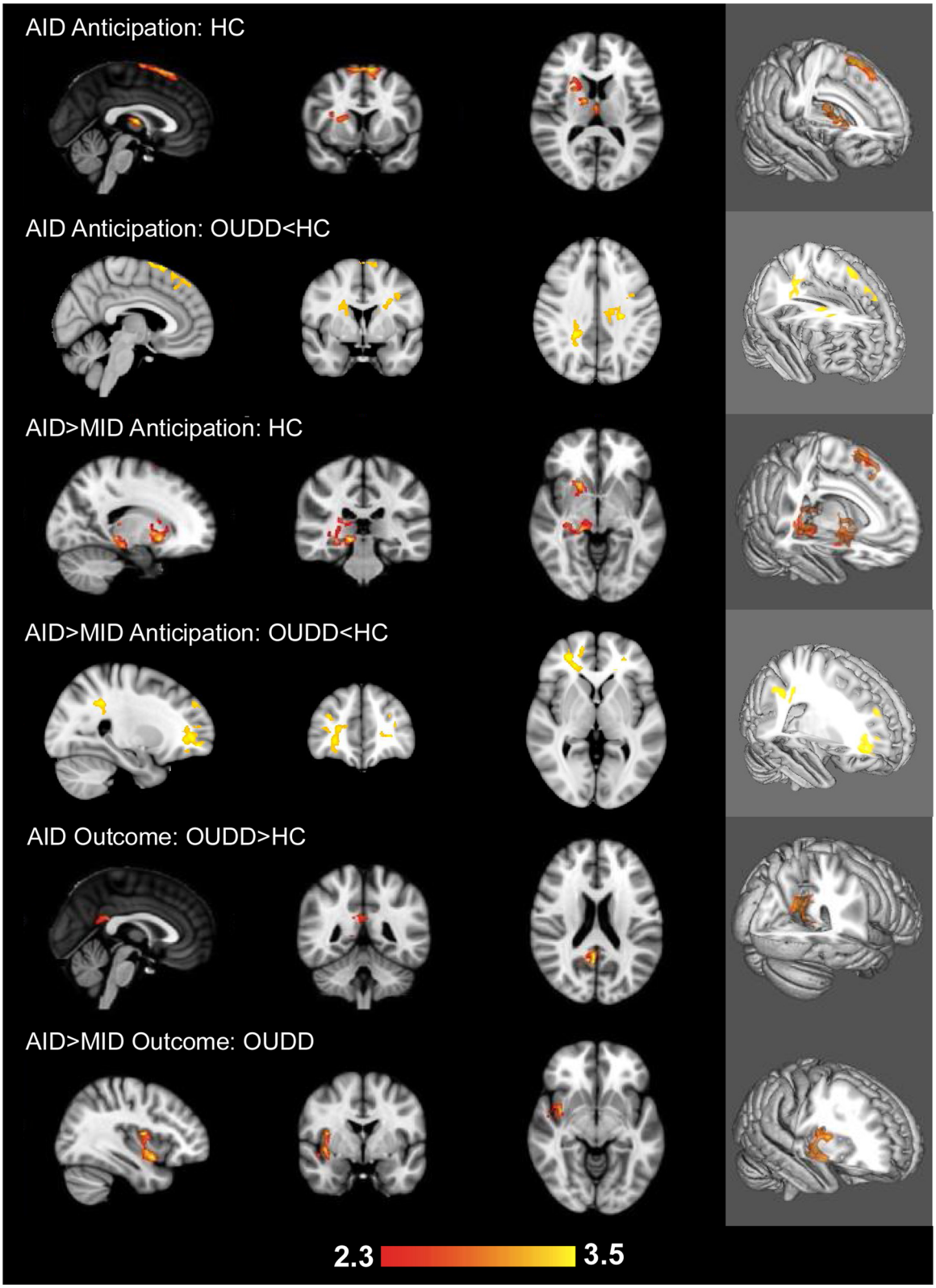

Fig. 2. Significant clusters of functional activation for within and between group whole-brain contrasts of anticipation and receipt of substance-free activity image and monetary reward. Z (Gaussianised T/F) statistic images, thresholded at $z > 2.3$ and a corrected cluster significance threshold of $p = .05$
Note: AID = Activity Incentive Delay Task, MID = Monetary Incentive Delay Task. OUDD = patients with opiate use disorder with moderate depressive symptoms, HC = healthy controls.

effect of anticipation of reward in OUDD participants. Between-group differences in anticipation ([reward]-[non-reward]) yielded four frontostriatal clusters of activation in which OUDD participants demonstrated significantly lower activation than HC including the right superior frontal gyrus, supplementary motor area, paracingulate gyrus, frontal pole, precuneus, caudate, thalamus, posterior cingulate gyrus,

Table 2
Task performance and image ratings.

	Total Sample (n = 33) Mean (SD)	OUDD (n = 16)	HC (n = 17)	Statistic
AID				$F(1,31) = 0.09$, $p = 0.76$[a]
Non-reward RT	213.38 (29.85)	207.29 (31.66)	219.11 (27.76)	–
Reward RT	201.35 (24.13)	194.19 (19.89)	208.09 (26.35)	–
MID				$F(1,31) = 1.61$, $p = 0.21$[a]
Non-reward RT	210.16 (30.47)	199.20 (19.84)	220.48 (35.42)	–
Reward RT	194.39 (20.59)	187.44 (16.45)	200.93 (19.84)	–
Image Ratings				
Valence	1.87 (0.52)	1.87 (0.52)	1.87 (0.54)	$t(31) = -0.03$
Arousal	3.22 (1.01)	3.12 (0.95)	3.31 (1.09)	$t(31) = 0.54$
Engagement	7.43 (1.66)	7.43 (1.76)	7.52 (1.62)	$t(31) = 0.16$

Note: AID = Activity Incentive Delay, MID = Monetary Incentive Delay. OUDD = patients with opiate use disorder and elevated depressive symptoms, HC = healthy controls. RT = response time. Engagement = likelihood of engaging in the activity.
[a] 2 (OUDD, HC) x 2 (reward, non-reward) interaction effect. $^{*}p < 0.05$.

left precentral gyrus, anterior cingulate cortex, middle frontal gyrus, and inferior frontal gyrus.

Monetary reward. Within- and between-group analyses of anticipation ([reward]-[non-reward]) of monetary reward did not yield any significant clusters of activation in either OUDD participants or HC.

3.3. Group comparison of anticipation of substance-free activity and monetary reward

Within-group analyses yielded three significant frontostriatal clusters of activation in HC during anticipation of substance-free activity reward compared to monetary reward (AID-MID), including the bilateral superior frontal gyrus, supplementary motor area, right paracingulate gyrus, putamen, caudate, pallidum, thalamus, posterior cingulate gyrus, hippocampus, lingual gyrus, and posterior parahippocampal gyrus. There was no significant effect of anticipation of reward type in OUDD participants. Group differences in anticipation of reward type (AID-MID) yielded four significant frontostriatal clusters of activation in which OUDD participants demonstrated significantly lower activation than HC including the right frontal pole, paracingulate gyrus, anterior cingulate cortex, frontal orbital cortex, frontal medial cortex, precuneus, pre- and post-central gyrus, supramarginal gyrus, angular gyrus, and superior parietal lobule, left middle frontal gyrus, frontal pole, inferior frontal gyrus, frontal orbital cortex, and caudate. Individual group by condition effects for both tasks are illustrated in Supplementary Fig. S1.

3.4. Neural response to receipt of substance-free activity and monetary reward

3.4.1. Substance-free activity reward

Within-group analyses of receipt ([win]-[non-win]) did not yield any significant clusters of activation in either sample during receipt of substance-free activity reward. Group differences in receipt ([win]-

Table 3
Significant clusters of activation during anticipation and receipt of substance-free activity reward (AID).

Regions	Cluster Size	X	Y	Z	p
Anticipation ([Reward]-[Non-Reward])					
OUDD					
None					
HC					
L. superior frontal gyrus					
R. & L. juxtapositional lobule cortex, R. superior frontal gyrus	3975	−11	7	69	2.34×10^{-4}
R. thalamus					
R. putamen, R. caudate, L. thalamus	2349	2	−10	9	1.11×10^{-2}
OUDD > HC					
None					
OUDD < HC					
R. superior frontal gyrus					
R. juxtapositional lobule cortex, R. paracingulate gyrus, R. frontal pole	3736	3	17	66	8.68×10^{-4}
L. precentral gyrus					
L. anterior cingulate gyrus, L. precentral gyrus, L. middle frontal gyrus, L. inferior frontal gyrus	3174	−25	−21	35	2.85×10^{-3}
R. precuneous cortex					
R. posterior cingulate gyrus	2480	30	−47	10	1.36×10^{-2}
R. caudate					
R. thalamus	2257	24	−3	24	2.32×10^{-2}
Receipt ([Win]-[Non-Win])					
OUDD					
None					
HC					
None					
OUDD > HC					
R. precuneous cortex					
R. & L. posterior cingulate gyrus, R. supracalcarine cortex, R. intracalcarine cortex, R. cuneal cortex, L. precuneous cortex	2083	5	−57	21	3.19×10^{-2}
OUDD < HC					
None					

Table 4
Significant clusters of activation for contrast of anticipation and receipt of substance-free activity image compared to monetary reward (AID > MID).

Regions	Cluster Size	X	Y	Z	*p*
Anticipation ([Reward]-[Non-Reward])					
OUDD					
None					
HC					
R. posterior parahippocampal gyrus					
R. lingual gyrus, R. posterior cingulate gyrus, R. hippocampus, R. thalamus	2534	15	−30	−7	1.05×10^{-2}
L. superior frontal gyrus					
R. & L. juxtapositional lobule, R. superior frontal gyrus, R. paracingulate gyrus	2402	−10	7	68	1.45×10^{-2}
R. putamen					
R. caudate, R. pallidum	2000	19	12	−6	3.98×10^{-2}
OUDD > HC					
None					
OUDD < HC					
R. frontal pole					
R. frontal orbital cortex, R. paracingulate gyrus, R. anterior cingulate gyrus, R. frontal medial cortex	5637	28	46	0	2.38×10^{-5}
L. middle frontal gyrus					
L. frontal pole, L. inferior frontal gyrus, L. frontal orbital cortex, L. caudate	3127	−25	21	23	3.25×10^{-3}
R. supramarginal gyrus					
R. angular gyrus, R. superior parietal lobule, R. postcentral gyrus, R. precentral gyrus, R. precuneous cortex	3115	40	−44	35	3.34×10^{-3}
Receipt ([Win]-[Non-Win])					
OUDD					
R. insular cortex					
R. central opercular cortex, R. precentral gyrus, R. inferior frontal gyrus, R. planum polare	2588	39	4	−11	4.10×10^{-3}
HC					
None					
OUDD > HC					
None					
OUDD < HC					
None					

Note: OUDD = opiate use disorder and moderate depressive symptoms, HC = healthy controls.

[non-win]) yielded one frontostriatal cluster of activation in which OUDD participants demonstrated significantly higher activation than HC including the bilateral precuneus and posterior cingulate gyrus, and right supracalcarine cortex, intracalcarine cortex, and cuneal cortex.

3.4.2. Monetary reward

Within- and between-group analyses of receipt ([win]-[non-win]) of monetary reward did not yield any significant clusters of activation in either sample of OUDD participants or HC.

3.5. Group comparison of receipt of substance-free activity and monetary reward

Within-group analyses yielded one significant frontostriatal cluster of activation in OUDD participants during receipt of substance-free activity reward compared to monetary reward (AID-MID), including the right insula, precentral gyrus, inferior frontal gyrus, central opercular cortex, and planum polare. There was no significant effect of receipt of reward type in HC. Group differences did not yield any significant clusters of activation when comparing receipt of substance-free activity and monetary reward (AID-MID).

3.6. Neural response among individuals with opiate use disorder when controlling for depressive symptoms

Highly similar within-group results for OUDD participants were found in models that included BDI-II total score as a covariate (Supplementary Table S1). Within-group analyses of anticipation ([reward]-[non-reward]) and receipt ([win]-[non-win]) of substance-free activity or monetary reward, as well as anticipation of substance-free activity reward compared to monetary reward (AID-MID), did not yield any significant clusters of activation. Receipt of substance-free activity reward compared to monetary reward (AID-MID) yielded one frontostriatal cluster including the right insula, precentral gyrus, inferior frontal gyrus, central opercular cortex, planum polare, temporal gyrus, and Heschl's gyrus.

4. Discussion

In the current study, we tested the neural response to anticipation and receipt of substance-free activity reward in opiate use disorder patients with elevated depressive symptoms (OUDD) compared to neural response to monetary reward, and relative to healthy controls (HC). OUDD patients demonstrated significantly lower activation in frontostriatal regions during anticipation of substance-free activity reward compared to HC; however, this hypoactivation did not extend to the receipt of substance-free activity reward or the anticipation or receipt of monetary reward. When comparing the response to substance-free activity and monetary reward, OUDD patients demonstrated greater activation in frontostriatal regions relative to HC.

In support of our first hypothesis, OUDD patients demonstrated significantly lower activation in frontostriatal regions during anticipation of substance-free activity reward compared to HC. This finding is in line with previous studies indicating that substance users demonstrate an attenuated response to anticipation of natural, substance-free activity reward, as shown in studies using images of food, positive social interactions, and other positive affect-eliciting stimuli (Garfield et al., 2014; Huhn et al., 2016; Wang et al., 2010). The observed attenuated response in frontostriatal regions, namely the thalamus, caudate, putamen, supplementary motor area, and middle frontal gyrus, correspond to regions implicated in reward cue processing and stimulus representation that inform goal-directed responses. The thalamus is proposed to have a central role linking basic reward signals from stimuli to higher-level processing, including motivational processes informing specific goal-directed actions mediated by the middle frontal gyrus (Galvan et al., 2005; Kirino et al., 2000). This link is engrained through associative learning processes involving the putamen, which receives projections from the supplementary motor area and premotor cortices, while the putamen is involved in the formulation of stimulus-action-reward associations, the caudate encodes predicted and actual

reward (Haruno and Kawato, 2006). Similar patterns of reduced putamen and thalamus responsivity are characteristic of individuals of depression and elevated anhedonia (Keedwell et al., 2005; Pizzagalli et al., 2009) when viewing reward and positive stimuli and are in line with literature delineating the role of fronto-subcortical-thalamic circuitry in emotion regulation of negative and positive stimuli (Drevets, 2000; Epstein et al., 2006; Vataja et al., 2004). Decreased responsivity in these reward regions in OUDD patients during anticipation of substance-free activity reward may reflect challenges in encoding substance-free activities as reward cues, contributing to the reduction of perceived positive emotionality of activity-based stimuli (Disner et al., 2011). These challenges may inform motivational processing of decisions to engage in substance use or substance-free activities and may be a fruitful area for future research.

Contrary to our first hypothesis, OUDD patients demonstrated greater activation during receipt of substance-free activity reward in a frontostriatal cluster, including the bilateral precuneus and posterior cingulate gyrus, relative to HC. These regions are involved in response to reward receipt (Davey et al., 2010), and the precuneus and posterior cingulate gyrus are consistently associated with the processing of self-relevant stimuli (Izuma et al., 2008; Moran et al., 2006; Northoff et al., 2006). Although not initially hypothesized, this finding offers a more nuanced understanding of reward processing in OUDD patients, such that attenuated responsivity to reward may be more related to anticipation, rather than receipt of natural, substance-free activity reward. OUDD patients may not have a generalized reduced response to substance-free activity reward, but rather a greater challenge in learning stimulus-reward associations informing goal-oriented behaviors. This may be further supported by comparably high ratings of positive valence and likelihood of engaging in these activities suggests that both groups found the images pleasant and rewarding. OUDD patients may have demonstrated greater activation during receipt of substance-free activity reward as these images may have been more novel than for HC.

Our second hypothesis comparing monetary and substance-free activity reward processing between OUDD patients and HC was partially supported as OUDD patients demonstrated greater activation in frontostriatal regions during anticipation of monetary reward compared to substance-free activity reward relative to HC. Monetary reward may be more motivationally salient than substance-free activity reward, particularly for OUDD patients given its association with substance-seeking behaviors (e.g., buying substances, related paraphernalia).

The angular gyrus may be particularly relevant in responsivity to stimuli as it is recognized as an “associative cortex” for a variety of semantic, episodic memory, and emotional stimuli (Kohn et al., 2014). Additionally, the middle frontal gyrus is thought to be involved in linking stimulus representations based on reward payoff expectations to goal-directed actions (Bunge et al., 2001; Paulus et al., 2002). For OUDD patients, monetary stimuli may elicit the generation of an internal representation and/or past situations associated with reward, while substance-free activity images may not due to decreased engagement in such activities. Increased activation in the supramarginal gyrus during monetary reward processing compared to substance use-free activity image processing may also reflect this stronger association between money and reward as activation in the supramarginal gyrus has been implicated in preparatory motor attention (Gobel et al., 2001). Our finding was more specific to reward anticipation, as there were no differences between OUDD patients and HC during reward receipt when comparing substance-free activity to monetary reward. As suggested earlier, reduced responsiveness to substance-free activity reward may be more related to anticipation, as opposed to receipt.

4.1. Limitations and future directions

This study had several limitations. Our sample of OUDD patients was comprised of male patients recruited from an inpatient detoxification facility. First, findings may not generalize to other samples of opiate users (e.g., female, non-treatment seeking, non-detoxification). Second, the current analysis did not fully parse apart the distinctive contribution of OUD versus depressive symptoms in our patient sample and results cannot be fully generalized to OUD patients without a co-occurring diagnosis of Major Depressive Disorder. However, this limitation is somewhat tempered given highly similar results yielded from analyses accounting for depressive symptoms. Third, the lack of significant MID activations during this study was unexpected, and in contrast to the findings typically reported in studies utilizing the MID. Although one explanation may be a lack of task engagement, the mean MID response times observed in the current study suggest that both groups responded faster than studies reporting MID results among substance use (Jia et al., 2011; Patel et al., 2013) and depressed samples (Pizzagalli et al., 2009). Nonetheless, MID findings should be interpreted with caution. Finally, given the exploratory nature of the study, a relatively liberal threshold of $z > 2.3$ and a corrected cluster significance threshold $p < 0.05$ was used. Replications and future studies utilizing the AID task would benefit from a larger sample size to allow for stricter thresholds, as well as the use of a white matter mask to facilitate interpretation. Despite these limitations, this study contributes novel findings on distinct components (i.e., anticipation and receipt) of neural response to substance-free activity reward in OUDD patients, which may be more relevant to reductions in reward-related behaviors contributing to treatment outcomes. To our knowledge, this is the first study to examine reward processing in a sample of OUDD patients. Important extensions of these findings include examining the extent to which neural response to substance-free activity reward corresponds to reward-related behaviors and whether treatments specifically targeting engagement in substance-free activities (e.g., behavioral activation [BA]) modulate neural response to anticipation and/or receipt of activity reward.

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Contributors

SDB was responsible for the study concept and design with contributions from JYY, RPB, and GSD and guided all stages of data analysis and manuscript preparation. JYY conducted the statistical analyses, drafted the Methods, Results, and Discussion. RPB and JRS contributed to data acquisition, data analysis, and manuscript preparation. EDR contributed to data acquisition and drafted the Introduction. ADB contributed to data analysis and conducted a literature review for the Discussion. GSD provided critical guidance on data analysis and revision of the manuscript for important intellectual content. All authors critically reviewed content and approved the final version for publication.

Conflict of interest

No conflicts declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.01.047.

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