ATTENUATION OF NEURAL RESPONSE DURING SUBSTANCE-FREE ACTIVITY AND MONETARY REWARD PROCESSING IN INDIVIDUALS WITH OPIATE USE DISORDER AND MODERATE DEPRESSIVE SYMPTOMS

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ABSTRACT

Jennifer Youngshin Yi: Attenuation of Neural Response during Substance-Free Activity and Monetary Reward Processing in Individuals with Opiate Use Disorder and Moderate Depressive Symptoms
(Under the direction of Stacey B. Daughters)

Co-occurring opiate use disorder and depressive symptoms is prevalent and especially concerning given its association with more severe substance use characteristics and poorer outcomes compared to opiate use disorder in the absence of depressive symptoms. Theories and findings propose dysfunctional reward processing, namely reduced reward responsivity in populations with individuals with substance use disorder and depression; however, inconsistencies across studies prompt the consideration of alternative conceptualizations of reward dysregulation, such as attenuation of reward responsivity across time. Thus, the current study tested attenuation of neural response in *a priori* regions-of-interest and task-based functional connectivity between reward-related and prefrontal cortical regions during anticipation and receipt of both substance-free and monetary reward among individuals with opiate use disorder and co-occurring depressive symptoms (OUDD) relative to healthy controls (HC). Sixteen OUDD participants from an inpatient detoxification facility and seventeen HC from the community underwent functional magnetic resonance imaging (fMRI) and completed two reward tasks, the Activity Incentive Delay (AID) and Monetary Incentive Delay (MID) tasks. Results indicate attenuation of activation in the right anterior cingulate cortex (ACC) across both OUDD and HC groups. Group differences in global connectivity and connectivity

attenuation between reward-related and prefrontal cortical regions were observed. Specifically, greater attenuation of connectivity between the right ACC and left middle frontal gyrus (MFG) predicted more frequent substance use at a one-month follow-up. Findings support attenuation of connectivity during reward processing as a potential biomarker for opiate use disorder and co-occurring depressive symptoms.

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LIST OF ABBREVIATIONS

AID	Activity Incentive Delay
BADS	Behavioral Activation for Depression Scale
BDI	Beck Depression Inventory-II
Cau	Caudate
CI	Confidence interval
HC	Healthy controls
Ins	Insular cortex
lACC	Left anterior cingulate cortex
lMFG	Left middle frontal gyrus
MID	Monetary Incentive Delay
NAcc	Nucleus accumbens
OFC	Orbitofrontal cortex
OUDD	Opiate use disorder with moderate depressive symptoms
PPI	Psychophysiological interaction
Put	Putamen
rACC	Right anterior cingulate cortex
RPI	Reward Probability Index
SD	Standard deviation
TLFB	Timeline Followback

INTRODUCTION

Opioid Use Disorder and Co-Occurring Depressive Symptoms

The co-occurrence of substance use disorders and depression has been well established as studies estimate the prevalence of this co-occurrence to range from 8.5% to 21.4% and the lifetime prevalence of this co-occurrence to range from 27% to 40% in the general population (see Davis et al., 2008 for review). In the midst of the ongoing opioid epidemic (Skolnick, 2018), it is especially important to examine this co-occurrence within the context of opiate use disorder. Unsurprisingly, the prevalence of depression among individuals who use opioids is concerning with one study estimating 27% of individuals who use non-medical prescription opioids to have a diagnosis of depression and 57% of these individuals endorsing depressive symptoms (Goldner, Lusted, Roerecke, Rehm, & Fischer, 2014). Furthermore, patients with opioid use disorder and co-occurring depressive symptoms evidence more severe substance use characteristics and poorer outcomes including earlier age of onset of illicit opioid use, greater number of lifetime substance use diagnoses, greater risk for relapse, continued use during and after substance use treatment, poorer psychosocial adjustment, and poorer current functioning (i.e., employment, family, and psychological problems) compared to patients without co-occurring depressive symptoms (Brewer, Catalan, Haggerty, Gainey, & Fleming, 1998; Hasin et al., 2002; Rounsaville, Kosten, Weissman, & Kleber, 1986). Furthermore, in a sample of treatment-seeking substance users, depressive symptoms significantly predicted post-treatment substance use frequency only among individuals with opioid dependence compared to dependence on other substances (Anand, Paquette, Bartuska, & Daughters, 2019). Given the high

prevalence and considerable impact of co-occurring opiate use disorder and depressive symptoms on clinical severity, efforts to investigate the contributing mechanisms are warranted to better understand the etiology and maintenance of this co-occurrence and ideally inform the targets for intervention.

Reward Processing as a Shared Mechanism Contributing to Substance Use Disorders and Depressive Symptoms

One of the most prominent explanations emerging from clinical and epidemiologic research for the co-occurrence of substance use disorders and depressive symptoms is the shared etiologic factor of neurobiological alterations in reward processing and related marked dysfunction in reward-seeking behaviors (Brady & Sinha, 2005; Rao, 2006). Drawing upon the principle of operant conditioning, reward processing serves the vital function of enabling individuals to make predictions about future events and adapt their behaviors accordingly to maximize reward and minimize punishment (Balodis & Potenza, 2015; Lutz & Widmer, 2014). In other words, rewards serve as positively reinforcing stimuli that have the potential to increase the probability of a specific behavior. Rewards can be dichotomously categorized as either primary or secondary. Primary rewards (e.g., food, sex, water) reinforce behavior without having to be learned, while secondary rewards (e.g., money) reinforce behavior after an association is learned between engaging in the behavior of interest and the increased likelihood of receiving or experiencing reward (McClure, York, & Montague, 2004). Although such learned associations allow for adaptive goal-oriented behaviors and efficient allocation of cognitive resources, habitual responding can become maladaptive and overly rigid when associated behaviors are no longer desirable (McKim, Bauer, & Boettiger, 2016).

Indeed, such a maladaptive shift away from initially rewarding experiences due to disruptions in reward-based learning is understood as an established principle of substance use

disorders (Baler & Volkow, 2006). The development and maintenance of substance use disorders can be conceptualized as a series of transitions from voluntary and casual drug-seeking and –taking behaviors to compulsive drug use (Everitt & Robbins, 2005). This transition involves neurobiological alterations in reward circuitry, contributing to overlearned reward-seeking behaviors towards drugs. More specifically, initial substance use is described as largely voluntary and goal-oriented, motivated by the hedonic and reinforcing effects of drugs. However, repeated substance use results in habit-based learning processes during which internal and external stimuli become more strongly associated with drug-seeking and –taking behaviors at the expense of other behaviors related to previously rewarding and positive-affect eliciting substance-free activities. Through this process, attribution of primary motivational salience shifts to drug-related stimuli and these drug-related behavioral patterns are integrated through associative memory consolidation particularly of self-administration of substances (Goldstein & Volkow, 2002; Hyman, Malenka, & Nestler, 2006; Wise & Koob, 2014). These associations and behavioral patterns become what have been described as overlearned and automatic in the presence of learned cues (Hyman, 2005), procuring continued substance use, even in the face of a myriad of negative consequences (e.g., financial, social, legal; Volkow & Li, 2004). Accordingly, individuals who engage in chronic substance use demonstrate decreased motivation for previously rewarding and natural, substance-free behaviors, as evidenced by decreased responsivity and impaired capacity to experience pleasure (i.e., anhedonia) to natural, substance-free, and positive affect-eliciting stimuli (for a review, see Garfield, Lubman, & Yucel, 2004).

Prominent theories and empirical findings on the development and maintenance of depression also highlight the central role of dysregulated reward processing (Forbes, 2009; Forbes & Dahl, 2005). Early etiological models of depression implicate the role of avoidant

behaviors and cognitions, which are thought to predispose individuals to depression (Ferster, 1973; Lewinsohn, 1974). Later behavioral models of depression have expanded on this conceptualization by more comprehensively describing avoidant behaviors as reducing contact with subjectively aversive or minimally rewarding internal or external stimuli in the form of thoughts, behaviors, emotions, social interactions, or memories (Hayes, Wilson, Gifford, Follette, & Strosahl, 1996; Ottenbreit & Dobson, 2004). Depressed affect is then generated or sustained through the reduction of positively reinforced behaviors by continued engagement in avoidant behaviors (Manos, Kanter, & Busch, 2010; Martell, Addis, & Jacobson, 2001). In support of these behavioral models of depression, depressed individuals and individuals at risk for developing depressive symptoms demonstrate maladaptive responses to negative feedback, which manifest as increased sensitivity to punishment or blunted responsivity to positive reinforcement (Eshel & Roiser, 2010). The central role of dysregulated reward processing in depression and the chronicity of these maladaptive responses is perhaps most illuminated by substantial evidence suggesting that depression is associated with anhedonia, or the reduced capacity to experience pleasure or interest (Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008). In line with this conceptualization, depressed individuals report reduced emotional responsivity and demonstrate reduced psychophysiological responses to rewarding and positive affect-eliciting stimuli (for reviews, see Bylsma, Morris, & Rottenberg, 2007 and Dunn, 2012). Taken together, theoretical and empirical evidence describe the shared etiologic factor of blunted responsivity to natural and positive affect-eliciting reward between substance use disorders and depression. Further support for this shared etiologic factor can be drawn from examinations of the neural mechanisms contributing to reward processing among individuals with substance use disorders and depression.

Neural Mechanisms of Reward Processing in Substance Use Disorders and Depressive Symptoms

Studies utilizing functional neuroimaging provide additional empirical evidence for the shared etiologic factor of disrupted reward processing between substance use disorder and depression. Functional neuroimaging allows for the examination of distinct components of maladaptive behavioral processes, as well as its interaction with psychological conditions of interest (Disner, Beevers, Haigh, & Beck, 2011; Sanislow, Pine, Quinn, Kozak, & Garvey, 2010). Of particular importance, reward-based functional neuroimaging tasks, such as the commonly utilized Monetary Incentive Delay (MID) task, allow for the critical decomposition of the neural response during related, yet temporally distinct phases of reward processing, namely, reward anticipation and receipt.

Reward anticipation. Motivational theories of behavior posit that individuals may differentially recruit and engage neural regions in response to reward and non-reward cues (Grusser et al., 2004; Sinha & Li, 2007). Reward anticipation, the component of reward processing traditionally known as the appetitive phase (Craig, 1918; Sherrington, 1907), reflects the temporal phase during which individuals are processing the incentive salience of a presented reward or non-reward cue and simultaneously preparing to engage in a behavior (e.g., speeded button press) to obtain a potential reward. Typically, reward anticipation activates the ventral striatum (VS), anterior insula, anterior cingulate cortex (ACC)/supplementary motor area (SMA), inferior parietal lobule (IPL), and brain stem, suggesting ongoing processing of reward valuation, risk and loss monitoring, comparison of numerical information, and information integration when a reward or non-reward cue is presented (Liu, Hairston, Schrier, & Fan 2011; Lutz & Widmer, 2014).

In line with self-reported reductions in reward responsivity, individuals with substance use disorders and/or depression demonstrate differential patterns of neural response relative to healthy controls during reward anticipation. In a review of studies examining neural response during monetary reward anticipation among substance use populations, studies reporedt reduced activation in reward regions including the left VS, ACC, caudate, putamen, and right superior frontal gyrus (SFG) among substance use populations relative to healthy controls (for a review, see Balodis & Potenza, 2015). Moreover, activation in these reward-related regions during monetary reward anticipation was positively associated with various substance use disorder characteristics, including impulsivity and craving (Beck et al., 2009; Wrase et al., 2007).

Similarly, depressed individuals also demonstrate differential patterns of neural response relative to healthy controls during monetary reward anticipation. Results from an activation likelihood estimation (ALE) meta-analysis of reward processing among depressed individuals reported reduced activation in the caudate and increased activation in the middle frontal gyrus (MFG) and dorsal ACC, while a different review highlights reduced activation in the nucleus accumbens (NAcc) among depressed individuals relative to healthy controls (Whitton, Treadway, & Pizzagalli, 2015; Zhang, Chang, Guo, Zhang, & Wang, 2013). Furthermore, reduced activation in these reward-related regions during reward anticipation predicted depression characteristics, including a greater number of lifetime depressive episodes among depressed individuals (Dichter, Kozink, McClernon, & Smoski, 2012). Importantly, some studies have examined reward processing with non-monetary stimuli, such as positive stimuli (e.g., pleasant images). One such study revealed decreased activation in reward-related regions, such as the ACC, paracingulate gyrus, right MFG, and precuneus among depressed individuals relative to healthy controls (Smoski, Rittenberg, & Dichter., 2011).

Although there is some consistency across these studies in patterns of neural responsivity during reward anticipation, not all studies report differences in neural responsitivity between individuals who use substances and healthy controls in reward-related regions. For instance, studies comparing differences among alcohol detoxification patients and patients with substance dependence with healthy controls did not demonstrate activation differences in the VS during monetary reward anticipation (Bjork, Smith, Chen, & Hommer, 2012; Bjork, Smith, & Hommer, 2008). Additionally, two studies did not report any significant differences in activation of reward-related regions-of-interest between treatment-seeking individuals with cocaine dependence and healthy controls and among individuals who currently used cocaine, individuals who formerly used cocaine, and healthy controls, respectively, during monetary reward anticipation (Jia et al., 2011; Patel et al., 2013). Additionally, a recent study did not report any significant differences in neural activation between opiate use disorder patients in detoxification and healthy controls during monetary reward anticipation (Yi et al., 2019)

Reward receipt. Reward receipt is a distinct phase of reward processing traditionally known as the consummatory phase (Craig, 1918; Sherrington, 1907). During this phase, individuals are presented with reward or non-reward feedback, allowing for the examination of recruitment and engagement of neural regions as a function of the motivational salience of the outcome (Knutson, Fong, Bennett, Adams, & Hommer, 2003). Reward receipt consistently activates the VS, ventromedial prefrontal cortex (vmPFC), medial orbital frontal cortex (OFC), and amygdala, suggesting engagement in processes involved in emotional arousal and introspection when reward feedback is provided (Knutson et al., 2003).

Although group differences between clinical samples and healthy controls have been found more consistently during reward anticipation as opposed to reward receipt (Balodis &

Potenza, 2015), a number of studies report differential patterns of neural response during reward receipt among individuals with substance use disorders and/or depression relative to healthy controls. Patients with a substance dependence diagnosis demonstrated increased activation in the right NAcc, left anterior insula, and the mesofrontal cortex relative to healthy controls during reward receipt (Bjork, Smith, & Hommer, 2008). Individuals with cocaine dependence also demonstrated greater activation in the bilateral VS and right insula relative to healthy controls (Jia et al., 2011). Furthermore, among individuals with cocaine dependence, lower activation in the VS and culmen during reward receipt was associated with a longer length of cocaine abstinence and a higher percentage of cocaine-negative urine toxicology results during the course of substance use treatment. Additionally, individuals who use cannabis regularly demonstrated reduced activation in the bilateral NAcc and bilateral caudate and increased activation in regions including the bilateral precuneus, bilateral putamen, and right caudate relative to healthy controls (Van Hell et al., 2010). A recent study also reports increased activation of the precuneus during reward receipt among individuals with opiate use disorder and co-occurring elevated depressive symptoms relative to healthy controls (Yi et al., 2019). Zhang and colleagues' (2013) meta-analysis reported reduced activation in the caudate during reward receipt in depressed individuals relative to healthy controls. As with reward anticipation, it is also important to consider the nature of reward processing with non-monetary stimuli during reward receipt. In one study using pleasant images, depressed individuals demonstrated reduced activation in reward-related regions including the ACC, right caudate and putamen, and bilateral precuneus, relative to healthy controls during reward receipt (Smoski et al., 2011). Furthermore, depressed individuals demonstrate reduced activation in the right precentral gyrus and insula when comparing

responsivity to monetary stimuli to pleasant images during reward receipt relative to healthy controls.

Similar to studies that examined neural response to reward anticipation, not all studies that examined reward receipt reported differences between individuals who use substances and healthy controls. Abstinent males with cocaine dependence and healthy controls did not demonstrate any significant activation differences in reward regions-of-interest (Bustamente et al., 2013). Similarly, Patel and colleagues (2013) did not report any significant activation differences in reward regions-of-interest among individuals who currently used cocaine, individuals who formerly used cocaine, and healthy controls.

Taken together, the majority of studies examining neural response during reward activation and receipt among individuals with substance use disorders and/or depression draw attention towards reduced recruitment and engagement of reward-related regions during reward anticipation relative to healthy controls. However, substantial challenges of interpretation arise from the inconsistencies across findings. When studies have reported group differences in activation of individuals with substance use disorders and depressed individuals relative to healthy controls, the yielded clusters have predominantly been found in reward-related regions, such as the NAcc, caudate, putamen, precuneus, and insula. Some of the inconsistencies in patterns of neural response during reward anticipation and receipt in the aforementioned studies among individuals with substance use disorders and depressed individuals may result from heterogeneity in sample characteristics including the presence of comorbidities, medications, remission status, treatment-seeking status, duration of depressive episode(s) among depressed individuals, and length of abstinence, smoking status, and withdrawal status among individuals with substance use disorders (Balodis & Potenza, 2015). In addition to acknowledging the

heterogeneity in sample characteristics across studies, inconsistent findings prompt the consideration of other conceptualizations and measurement approaches surrounding the nature of reward processing among individuals with substance use disorders and/or depression.

Sustained Neural Response during Reward Processing

A different, yet arguably more nuanced conceptualization of disrupted reward processing in individuals with substance use disorders and/or depressed individuals draws from theories of anhedonia, the loss of interest or responsivity to rewarding or pleasurable stimuli (American Psychiatric Association, 2013). More specifically, it has been suggested that anhedonia may reflect responsivity to reward over time or reduced capacity to sustain positive affect rather than a more simple tonic reduction in the propensity to respond to positive affect and reward-related cues (Myerson, 1922). Expanding upon this conceptualization, Tomarkenand and Keener (1998) propose that reduced capacity to sustain positive affect and responsivity to reward over time may result from dysregulation of positive emotion. Supporting evidence can be drawn from studies with rodents and healthy controls that implicate critical signaling from the prefrontal cortex to the nucleus accumbens, during the regulation of positive affect (Kim & Hamann, 2007; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008).

Accordingly, neurobiological theories of depression propose dysfunction in circuitry between the prefrontal cortex and reward-related regions (Nestler, Barrot, DiLeone, Eisch, Gold, & Monteggia, 2002; Nestler & Carlezon, 2006), leading to difficulties engaging in and maintaining goal-directed behavior such as the regulation of positive affect in response to reward. Experimentally, this conceptualization has been tested by measuring capacity to sustain response to reward or attenuation of response over time among depressed individuals (Pizzagalli et al., 2008). In line with these theories, depressed individuals demonstrated impaired ability to

modulate behavior as a function of reinforcement provided in previous trials of the probabilistic monetary task. Specifically, depressed individuals evidenced a lower rate of correct identification of cues associated with maximal reward relative to healthy controls. Moreover, higher rates of incorrect identifications were associated with the presence of anhedonic symptoms. Liu and colleagues (2011) reported similar findings as depressed individuals demonstrated difficulty sustaining behavior to maximize reward under both non-stress and stress conditions, which was in turn was associated with lower levels of self-reported pleasure during a probabilistic reward task. In comparison, healthy controls only demonstrate a trend towards a decreased response bias to stimuli signaling maximal reward under the stress condition.

Heller and colleagues (2009) extend these behavioral findings by examining alterations in neural activation that may contribute to attenuation of neural response to reward. Depressed individuals demonstrated reduced activation in the NAcc over the course of an emotion regulation task when asked to attend to their emotional response and when instructed to up-regulate positive emotion while viewing positive images. Furthermore, greater reduction in NAcc activation predicted greater reductions in self-reported positive affect among depressed individuals. In comparison, healthy controls did not demonstrate attenuated activation in the NAcc, suggesting a specific difficulty among depressed individuals in sustaining neural response to reward. Further, Heller and colleagues (2009) also examined functional connectivity between prefrontal and reward-related regions during the emotion regulation task and reported that depressed individuals demonstrated reduced connectivity between the left nucleus accumbens and the left MFG relative to healthy controls, supporting the hypothesized role of circuitry between the prefrontal cortex and reward-related regions in the capacity to sustain positive affect and responsivity to reward. Heller and colleagues (2009) argued that these results are likely not

due to differences in task engagement as depressed individuals and healthy controls did not demonstrate differences in attention or motivation throughout the emotion regulation task. Two more recent studies linked these characterizations of anhedonia and deficits in sustained reward response among depressed individuals by testing their ability to predict treatment responsivity. In one study, greater sustained activation in ACC during reward receipt predicted greater reductions in depressive symptoms following behavioral activation (BA) therapy for depression (Carl et al., 2016). In another study, depressed individuals demonstrated attenuated functional connectivity between a left caudate seed and clusters in the ACC and paracingulate gyrus, as well as attenuated connectivity between orbitofrontal seeds and clusters in the left and right caudate and left putamen during reward anticipation. Furthermore, greater connectivity between the left putamen and paracingulate gyrus during reward anticipation predicted greater reductions in depressive symptoms following BA therapy for depression among depressed individuals (Walsh et al., 2017).

Although preliminary support for reduced capacity to sustain reward responsivity and positive affect and its relation to clinical characteristics drawn from depressed individuals is promising, this proposed deficit has not yet been examined in individuals with substance use disorders. Additionally, the vast majority of studies testing neural response and circuitry involved in reward anticipation and receipt have utilized monetary reward cues, such as with the Monetary Incentive Delay (MID) task (e.g., for a review, see Balodis & Potenza, 2015). Reinforcement theories of substance use (e.g., McKay, 2017) and behavioral models of depression (e.g., Jacobsen et al., 1996) highlight the central role of reduced engagement in substance-free activities at the expense of drug-seeking and –taking behaviors for individuals with substance use disorders and continued avoidant behaviors among depressed individuals. In

support, studies have demonstrated the association between engagement in rewarding substance-free activities and improved rates of post-treatment abstinence for individuals with substance use disorders (Daughters et al., 2008; Daughters, Magidson, Anand, Seitz-Brown, Chen, & Baker, 2018; Jacobson et al., 1996). Thus, testing reward responsivity to natural, substance-free activity engagement may be more relevant than existing approaches using monetary reward cues in understanding reward-related deficits contributing to the etiology and maintenance of substance use disorders.

In order to begin to address this limitation, a recent study utilizes a modified version of the MID with substance-free activity engagement images in the place of monetary stimuli among opiate use disorder patients with moderate depressive symptoms (Yi et al., 2019). During reward anticipation, opiate use disorder patients with mild depressive symptoms demonstrated reduced activation in reward-related regions including the precuneus, caudate, thalamus, ACC, inferior frontal gyrus (IFG), and MFG relative to healthy controls. Meanwhile, during reward receipt, patients demonstrated increased activation in reward-related regions including the precuneus and posterior cingulate gyrus (PCG) relative to healthy controls. In line with reinforcement models of substance use disorders and depression, these results suggest that opiate use disorder patients may demonstrate challenges during reward anticipation in encoding substance-free activity images as reward cues. Additionally, greater novelty of substance-free activity images may, in turn, inform decisions to engage in substance-seeking or –taking behaviors. Unexpectedly, opiate use disorder patients and healthy controls do not demonstrate significant neural response during the anticipation or the receipt of monetary reward. However, it is premature to conclude that opiate use disorder patients and healthy controls do not engage in monetary reward processing or that there is a lack of group differences. Rather, this study does not consider alternative

possibilities, such as attenuation of neural response to substance-free activity images over time and potential differences in the capacity to sustain reward response and positive affect between opiate use disorder patients with depressive symptoms and healthy controls. Thus, examining the capacity to sustain neural response to substance-free reward cues, as well as monetary reward cues, presents a logical next step to further elucidate the nature of dysfunctional reward processing in individuals with opiate use disorder and co-occurring moderate depressive symptoms.

Current Study

The current study proposes to test attenuation of neural response during reward anticipation and receipt of (1) substance-free activity images using the AID task and (2) monetary images using the MID task among individuals with opiate use disorder and co-occurring moderate depressive symptoms (OUDD) relative to gender- and education-matched healthy controls (HC) through three aims.

Aim 1. To test attenuation of neural response in reward-related regions. The OUDD group was hypothesized to demonstrate greater attenuation of neural response in reward-related regions relative to HC during the AID and MID tasks.

Aim 2. To test functional connectivity and attenuation of functional connectivity between reward-related and prefrontal cortical regions. The OUDD group was hypothesized to demonstrate reduced functional connectivity and greater attenuation of functional connectivity between reward-related and prefrontal cortical regions relative to HC during the AID and MID tasks.

Aim 3. To test if attenuation of neural response, as defined in Aims 1 and 2, predicts reward-related clinical correlates (i.e., anhedonia, substance use) and mechanisms (i.e.,

behavioral activation, environmental reward) at one- and three-month follow-ups in the OUDD group. It was hypothesized that greater attenuation of neural response at baseline, as defined in Aims 1 and 2, will be associated with greater severity of anhedonia, lower levels of behavioral activation, decreased availability of environmental reward, and greater frequency of substance use at 1- and 3-month follow-ups.

METHODS

Participants

Participants were 16 individuals with opiate use disorder and co-occurring moderate depressive symptoms (OUDD; M_{age}=32.19±8.17 years) recruited from an inpatient detoxification unit in Raleigh, NC and 17 gender- and education-matched healthy controls (HC; M_{age}=26.82±5.29 years) recruited from the community via the Internet (i.e., Craigslist, ResearchMatch, Join the Conquest), fliers, and UNC's Biomedical Research Imaging Center's (BRIC) healthy control pool. Inclusion criteria for all participants were 21 to 50 years of age. Inclusion criteria for OUDD participants were current opiate use disorder (OUD), according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5; American Psychiatric Association, 2013) and endorsement of elevated depressive symptoms, as measured by a total score of 14 or greater on the Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996) and a specific exclusion criterion was current DSM-5 Axis I disorder other than OUD and major depressive disorder (MDD). Exclusion criteria for all participants were less than a fifth grade reading level, as measured by a score of 40 or less on the Word Reading Subtest of the Wide Range Achievement Test – Revised (WRAT-R; Jastak & Wilkinson, 1984), current posttraumatic stress disorder or psychotic disorder, as assessed by the Mini International Neuropsychiatric Interview (MINI) 7.0 for the DSM-5 (Sheehan, 2014), or magnetic resonance imaging (MRI) contraindications (e.g., pacemaker, defibrillator, aneurysm clip, cochlear implant, metallic foreign body). Participant characteristics are presented in **Table 1**.

Procedure

OUDD participants were screened on the inpatient detoxification unit, while HC engaged in an initial phone screen, followed by an onsite screen at UNC. At the baseline assessment, participants provided written informed consent approved by the UNC Institutional Review Board (IRB). Participants completed a scan assessment at the BRIC, which involved self-report measures, out-of-scanner task trainings, MRI safety screening, and functional magnetic resonance imaging (fMRI) with task stimuli displayed with E-Prime 2.0 (Psychology Software Tools, Incorporated, Pittsburgh, PA), followed by an image rating task. At the one- and three-month follow-up assessments, participants completed self-report measures. At the end of each assessment, participants were compensated with a gift card.

Reward Tasks

At the baseline assessment, participants completed a structural scan, followed by a functional scan with two reward tasks presented in counterbalanced order. Both reward tasks were individually titrated such that participants were successful on approximately 66% of trials, regardless of individual response times. Before the scan, participants completed out-of-scanner task trainings during which they were required to achieve greater than or equal to 66% accuracy in order to proceed to the scan portion of the assessment. Response time to the target bullseye on reward and non-reward trials will be measured for each reward task.

Monetary Incentive Delay (MID) Task. The Monetary Incentive Delay (MID; Knutson et al., 2000) consists of two randomized, 8-minute runs, each with 20 reward and 20 non-reward trials. Each trial has the following structure: (1) a 2000 ms cue indicating whether a fast enough response to a forthcoming bullseye could result in a reward (gray triangle) or non-reward (blue circle), (2) a 2000-2500 ms delay with a crosshair, (3) a target bullseye presented up to 500 ms,

(4) a 3000 ms feedback screen indicating whether the response resulted in a win, depicted by an image of a basket with money (win) or a red "X" (non-win), and (5) a variable intertrial interval (ITI) so the total trial duration is 12 seconds **(Figure 1**). Participants had the potential to win $1 per trial and the running total amount won was displayed during the receipt phase of each trial (*M*=26.62±1.44 dollars).

Activity Incentive Delay (AID) Task. The Activity Incentive Delay (AID; Yi et al., 2019) task is a modified version of the Monetary Incentive Delay (MID) task (Knutson et al., 2000) with identical trial structure **(Figure 1**). However, on the 3000 ms feedback screen, participants were presented with either a substance-free activity image (win) or a neutral image (non-win). Details of the development of this modified task are described elsewhere (Yi et al., 2019).

Assessment of task performance. Task performance for the MID and AID tasks was measured with response time to the target bullseye to reflect task engagement and motivation (Balodis & Potenza, 2015).

Measures

Screening measures.

Demographics. At the baseline assessment, participants completed the self-report Demographics Form, which included questions about basic demographic information such as age, ethnicity/race, and years of education.

Reading level. Participants were administered the Word Reading subtest of the Wide Range Achievement Test – Revised (WRAT-R; Jastak & Wilkinson, 1984) during the screening procedure to assess individual reading level. All participants were required to demonstrate a

reading level of fifth grade or higher (score>40) in order to read and comprehend written portions of the study.

***DSM-IV Axis I disorders*.** The Mini International Neuropsychiatric Interview (MINI) 7.0 for the DSM-5 (Sheehan, 2014) is a structured interview administered during the screening procedure to assess for the presence of current posttraumatic stress disorder (PTSD; Module J) and/or psychotic disorders (Module K), which were exclusion criteria for all participants.

***Magnetic resonance imaging (MRI) safety*.** BRIC's MRI screening form includes questions about MRI contraindications (e.g., pacemaker, cochlear implants, pregnancy, claustrophobia). It was administered during the screening procedure and again with a MRI technician before the participant entered the scanner to determine eligibility and ensure that all participants would be able to safely undergo the scan.

***Depressive symptoms*.** The Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) is a 21-item self-report questionnaire administered during the screening procedure to assess depressive symptoms. Each item is rated on a 0-to-3 Likert scale. Depressive symptoms were measured by total scores ranging from 0 to 63, with greater scores indicating greater severity of depressive symptoms. The BDI-II for the total sample in the current study demonstrated high internal consistency at the baseline assessment (α=0.95).

Outcome measures.

Behavioral activation. The Behavioral Activation for Depression Scale (BADS; Kanter et al., 2007) is a 25-item self-report questionnaire administered to all participants at the baseline, one-month, and three-month follow-ups to assess level of behavioral activation over the past week on a 7-point Likert scale ranging from 0 (not at all) to 6 (completely). The BADS is composed of four subscales: Avoidance/Rumination, eight items assessing avoidance of negative

aversive states and rumination, Social Impairment, five items assessing social consequences of inactivity, passivity, and isolation, School/Work Impairment, five items assessing school- and work-related consequences of inactivity and passivity, and Activation, seven items assessing focused, goal-directed activation and completion of scheduled activities; however, the total score was used in the current study with higher scores reflecting greater levels of behavioral activation. The BADS for the total sample in the current study demonstrated high internal consistency (α=0.96 at the baseline assessment, α=0.95 at the one-month follow-up, and α=0.94 at the three-month follow-up).

Environmental reward. The Reward Probability Index (RPI; Carvalho et al., 2011) is a 20-item self-report questionnaire administered to all participants at the baseline, one-month, and three-month follow-ups to assess availability of environmental reward. The RPI has two subscales: Reward Probability Index, 11 items assessing potential to obtain reinforcement through instrumental behaviors and Environmental Suppressors Index, 9 items assessing availability of potential environmental reinforcers and aversive stimuli; however, the total score was used in the current study, with higher scores reflecting greater self-reported availability of environmental reward. Items are rated on a 4-point Likert scale ranging from 1 (not at all) to 4 (extremely). The RPI for the total sample in the current study demonstrated high internal consistency (α=0.90 at the baseline assessment, α=0.92 at the one-month follow-up, and α=0.88 at the three-month follow-up).

Substance use. The Timeline Followback (TLFB; Sobell & Sobell, 1992) is a widely used tool to obtain self-reported estimates of frequency of substance use across drug classes over a targeted time interval using a calendar method and other recall-enhancing techniques (identification of use surrounding personally meaningful events). It was administered to all

participants at the baseline, one-month, and three-month follow-up assessments to assess for frequency of substance use, defined as the number of days individuals used one or more substances during the 30 days prior to the assessment.

Anhedonia. Anhedonia symptoms will be measured by the sum of BDI-II (Beck, Steer, & Brown, 1996) items #4 (loss of pleasure), #12 (loss of interest), and #21 (loss of interest in sex), with higher scores indicating greater severity of anhedonia symptoms (Joiner et al., 2003; Pizzagalli et al., 2005). Anhedonia for the total sample in the current study demonstrated high internal consistency at the baseline assessment (α=0.80) and one-month follow-up (α=0.79), but poor internal consistency at the three-month follow-up (α=0.49).

Covariates.

Demographics. At the baseline assessment, participants reported their age, ethnicity/race, and years of education.

Motivation for substance use treatment. The Circumstances, Motivation, and Readiness Scales (CMRS) for Substance Abuse Treatment (De Leon et al., 1994) is an 18-item self-report questionnaire administered to OUDD participants at the baseline assessment to assess an individual's perceptions of one's motivation and readiness for substance use treatment. The Motivation subscale, consisting of 5 items rated on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree), was used as it assesses for positive and negative inner reasons for personal change. Higher scores indicate greater motivation for substance use treatment. Motivation for the total sample in the current study demonstrated high internal consistency at the baseline assessment (α=0.89).

Other measures.

Image ratings. In order to assess how rewarding participants found the presented substance-free activity images during the AID task, arousal and valence of 40 substance-free activity images using the Self-Assessment Manikin (SAM) scale (Bradley & Lang, 1994) on 5-point Likert scales ranging from 1 (more positive/aroused) to 5 (less positive/aroused). Likelihood of engaging in the depicted substance-free activity was rated on a 10-point Likert scale ranging from 1 (not at all likely) to 10 (extremely likely). Twenty (50%) of the images were substance-free activity engagement images that were not included in the AID task to reduce the potential impact of familiarity on image ratings.

Behavioral Data Acquisition and Analysis

Acquisition. Behavioral data for the Activity Incentive Delay (AID) and Monetary Incentive Delay (MID) tasks were collected using E-Prime Version 2.0 (Schneider, Eschman, & Zuccolotto, 2002).

Analysis. Response time was extracted and meaned by Group (OUDD, HC), Trial Type (Reward, Non-Reward), and Run (Run 1, Run 2) for the AID and MID tasks in E-Prime 2.0 Data Aid, and entered into SPSS Version 23 (IBM Corp, 2015). Response time was analyzed with Group (OUDD vs. HC) x Trial Type (Reward vs. Non-Reward) x Run (Run 1 vs. Run 2) repeated measures MANOVAs with Group as a between-subjects factor and Reward Type and Run as within-subjects factors for each task. Significant interactions were probed with repeated measures ANOVAs.

Imaging Data Acquisition and Analysis

Acquisition. Anatomical and functional images were collected on a Siemens 7-Tesla Magnetom scanner (Siemens, Erlangen, Germany) equipped with a 32-channel head coil. High resolution, whole-brain, T1-weighted anatomical images (MPRAGE) were acquired with 160

sagittal slices using a single-shot gradient-echo-planar imaging (EPI) sequence (voxel size=1x1x1 mm, repetition time (TR)=2200 ms, echo time (TE)=2.78 ms, FA=7 degrees, and field of view (FOV)=220x220 mm) for normalization and co-registration with functional data. Whole-brain functional images were acquired with 70 transverse slices using a single shot, T2*-weighted gradient-echo, echo planar imaging (EPI) sequence (voxel size=1.5x1.5x1.5 mm, TR=2000 ms, TE=22 ms, FOV=220x220 mm, flip angle (FA)=80 degrees).

Pre-processing. Functional data were pre-processed using Oxford Centre for Functional Magnetic Resonance Imaging of the Brain's (FMRIB) Software Library (FSL) Version 5.0.9. (Oxford University, UK). FSL-compatible stimulus timing files were created by extracting onset times of events of interest to model whole-brain response for each type of response in each reward phase (Anticipation: Reward, Non-Reward; Receipt: Win, Non-Win) for each task (AID, MID). Pre-processing was conducted as follows: (1) brain extraction for non-brain removal using the Brain Extraction Tool (BET; Smith, 2002), (2) motion correction using motion correction FMRIB's Linear Image Registration Tool (MCFLIRT; Jenkinson, Bannister, Brady, & Smith, 2002), (3) spatial smoothing using a Gaussian kernel of full-width half-maximum (FWHM) 5 mm, (4) grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, and (5) high-pass temporal filtering (Woolrich et al., 2001). Functional images were registered to anatomical images, and anatomical images were normalized to the 1 mm Montreal Neurological Institute (MNI) standard-space template using FLIRT with an affine transformation with 12 degrees of freedom. Estimation and correction of voxel-wise temporal autocorrelation used FMRIB's Improved Linear Model (FILM; Smith et al., 2004). To remove residual effects of motion remaining after MCFLIRT motion correction, time points with high frame displacement (75^{th} percentile + 1.5 times the interquartile range [IQR]), as detected by FSL's Motion Outliers

Detection Tool, were censored (Siegel et al., 2014) by entering these time points as confound regressors within first-level, participant-specific analyses.

Identification of Covariates

Aim 1.

Region-of-interest analyses. Age was tested as a potential covariate for inclusion in region-of-interest (ROI) analyses testing group differences in attenuation of neural response. Pearson's (*r*) correlations were conducted between age and mean parameter estimates for each ROI for each task phase. If significant correlations ($p<0.05$) were found, age was included as a covariate in the repeated-measures MANCOVA models for the specific ROI.

Supplementary analyses. Given the documented impact of age on neural activation during reward processing (e.g., Eppinger et al., 2013; Vink et al., 2015), age was tested as a potential covariate for inclusion in whole-brain analyses testing group differences in attenuation of neural response. A whole-brain general linear model (GLM) was conducted to test attenuation of neural response across the total sample with age, demeaned across the total sample, as the sole regressor for each task phase (whole-brain method is discussed later in more detail). If significant activation clusters were yielded on whole-brain activation maps thresholded at $z>2.3$ with a corrected cluster significance of $p<0.05$, age was included as a covariate in the third level of the whole-brain GLM analyses for the specific task phase.

Aim 2. Age was tested as a potential covariate for inclusion in functional connectivity analyses testing group differences in global connectivity and attenuation of functional connectivity between reward-related and prefrontal cortical regions. Generalized psychophysiological interaction (gPPI) analyses were conducted to test functional connectivity and attenuation of functional connectivity across the total sample with age, demeaned across the

total sample, as the sole regressor for each task phase (gPPI method is discussed later in more detail). If significant activation clusters were yielded on PPI maps thresholded at $z>2.3$ with a corrected cluster significance of $p<0.05$, age was included as a covariate in the third level of the gPPI analyses.

Aim 3. Motivation for substance use treatment was tested as a potential covariate for inclusion in hierarchical regression analyses testing whether attenuation of neural response predicted reward-related clinical correlates (i.e., anhedonia, substance use) and mechanisms (i.e., behavioral activation, environmental reward) at the one- and three-month follow-ups. If significant correlations ($p<0.05$) were found, motivation for substance use treatment was included as a covariate in the regression model(s) specifically predicting the clinical correlate and/or mechanism of interest.

Aim Analyses

Aim 1. In order to test attenuation of neural response in reward-related regions in the OUDD participants relative to HC, a region-of-interest (ROI) approach was utilized. *A priori* regions-of-interest (ROIs) were selected based on their theory- and empirically-based involvement in reward processing, informed by an activation likelihood estimation (ALE) meta-analysis of studies examining cued responses to monetary reward (Knutson & Greer, 2008). Reports of group differences between individuals with major depressive disorder and healthy controls in attenuation of neural response to reward (Carl et al., 2016), as well as differences between individuals with opiate use disorder and moderate depressive symptoms and healthy controls in neural response to reward (Yi et al., 2019), were cross-referenced to further inform selection of reward-related ROIs. *A priori* regions-of-interest (ROIs) included the nucleus accumbens (NAcc), putamen, insular cortex, caudate, orbitofrontal cortex (OFC), and anterior

cingulate cortex (ACC), all of which were lateralized and defined using anatomical masks from the Harvard Oxford cortical and subcortical probabilistic atlases in FSLView, Version 3.2.0. For each task phase and ROI, participant- and run-specific mean parameter estimates were extracted using FSL's featquery tool with Reward>Non-Reward as the contrast of interest for anticipation task phases and Win>Non-Win as the contrast of interest for receipt task phases. Mean parameter estimates were analyzed with a 2 (Group: OUDD, HC) x 2 (Run: Run 1, Run 2) repeated measures mixed analyses of variance (MANOVAs) or analyses of covariance (MANCOVAs) for each ROI to examine potential Group x Run interactions and main effects of Group and Run, if interactions were non-significant using a significance level of $p<0.05$.

Supplementary analyses. Supplementary whole-brain analyses were also conducted to provide a more data-driven approach with the inclusion of all imaged voxels; however, these analyses were not included as primary results given the small sample size and concerns of low power to detect significant clusters of activation reflecting attenuation of neural response to reward. Whole-brain general linear model (GLM) activation analyses were conducted using FSL's Expert Analysis Tool (FEAT; Woolrich et al., 2001; 2004a; 2004b) for each task phase. First level analyses using FILM GLM were conducted for run-specific time-series analyses of each participant's raw 4D fMRI data by modeling the contrast, Reward>Non-Reward, to yield specifically reward-related activation. Second level analyses using FMRIB's Local Analysis of Mixed Effects (FLAME) with fixed effects (FE) higher-level modeling estimated the inter-run component of the mixed-effects variance (Run 1>Run 2), reflecting neural response attenuation for each participant. Third level analyses were conducted with mixed effects modeling FLAME stage 1 (Woolrich et al., 2001; Smith et al., 2004) to test group differences in attenuation of neural response between the OUDD and HC groups, specifically with the contrasts of

OUDD>HC and OUDD<HC. Within- (OUDD, HC) and between-group (OUDD vs. HC) whole-brain activation maps were generated and Z (Gaussianized T/F) statistic images were thresholded at $z>2.3$ with 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 in FSLView.

Aim 2. Building upon findings from Aim 1, Aim 2 was conducted to further test group differences in attenuation of neural response to reward, but more specifically focusing on functional connectivity to measure temporally-based correlations between reward-related and prefrontal cortical regions. Task-based functional connectivity was tested using a generalized psychophysiological interaction (gPPI) approach (Cisler et al., 2014). The seed ROI was identified if there was observed attenuation of neural response in the OUDD group, HC group, and/or between-group comparisons. For each participant, mean fMRI timecourses (physiological regressors) were extracted from the seed regions for each task run using FSL's fslmeants command-line utility and multiplied by the psychological regressors of interest, consisting of Reward or Non-Reward for the anticipation task phases and Win or Non-Win for the receipt task phases, to form the PPI interaction terms. The contrasts of interest tested the difference in functional connectivity during Reward vs. Non-Reward trials (Reward>Non-Reward) for anticipation task phases and Win vs. Non-Win trials (Win>Non-Win) for receipt task phases.

Functional connectivity was estimated by calculating the timeseries correlation between the seed region and the identified cluster. Within- and between-group differences in functional connectivity were modeled in two ways, based on the approach taken by Walsh and colleagues (2017): (1) *global connectivity*, defined as seed-based connectivity across both task runs and (2)

connectivity attenuation, defined as changes in seed-based connectivity from Run 1 to Run 2 or more specifically, reductions in seed-based connectivity from Run 1 to Run 2, for each task phase. Within- and between-group whole-brain activation maps for each task phase were generated with Bayesian estimation techniques using FMRIB's Local Analysis of Mixed Effects (FLAME; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). Resulting images were thresholded at $z>2.3$ and a corrected cluster significance of $p<0.05$. Significant clusters generated by the PPI were localized using the Harvard-Oxford cortical and subcortical structural atlases, set at 10% and overlaid on the MNI standard-space T1-weighted structural template image in FSLView, Version 3.2.0.

Aim 3. Extending findings from Aims 1 and 2, hierarchical linear regression models tested whether significant attenuation of functional connectivity predicted anhedonia, behavioral activation, environmental reward, and substance use at one- and three-month follow-ups among OUDD participants. In step 1, baseline values of the clinical or mechanism measure and covariates (if applicable) were entered. In step 2, parameter estimates from the clusters that reflected significant group differences in attenuation of functional connectivity from Run 1 to Run 2 in the AID and/or MID tasks from Aim 2 were entered. A separate model was run for each clinical or mechanism measure, cluster, and timepoint.

Analytic Design Considerations

A psychophysiological interaction (PPI) approach was utilized as it allows for the examination of how neural regions interact with psychological factors elicited by the experimental context (Friston et al., 1997; Cisler, Bush, & Steele, 2014). For the current study, it allowed for the potential to uncover changes in patterns of information processing among reward-related and prefrontal cortical regions when individuals are anticipating and receiving

reward. More specifically, a *generalized* PPI (gPPI) approach was utilized to analyze changes in task-based functional connectivity given its ability to more accurately estimate psychophysiological interactions compared to a standard PPI (sPPI) approach, as evidenced by improved model fit, based on Akaike Information Criterion [AIC] when comparing gPPI and sPPI methods tested on both simulated and empirical data. A detailed discussion of the advantages of using a gPPI is presented by McLaren and colleagues (2012) and Cisler and colleagues (2014); however, in general, a gPPI approach allows for modeling of the entire experimental space by including all possible inter-relationships between experimental, resulting in improved sensitivity to uncover neural regions of context-dependent connectivity and in turn, model fit.

RESULTS

Sample Characteristics

Sample characteristics are reported in **Table 1** and measures of clinical correlates and mechanisms are reported in **Table 2**. OUDD participants were significantly older and were less likely to be African American/Black. There were no significant group differences in frequency of Caucasian/White, Native American/American Indian, or Hispanic/Latino participants. The majority of both OUDD participants and HC were single, followed by in a relationship, and living with a partner. Additionally, there were no significant group differences in the number of years of education and WRAT reading score.

On average, OUDD participants were abstinent for 3.38 days (*SD*=1.31 days) days before undergoing the fMRI scan and had been on the inpatient detoxification for a 2.38 days (*SD*=1.20 days). OUDD participants predominantly used heroin in the 30 days before the scan, but also reported use of alcohol, cocaine, marijuana, painkillers (not prescribed, amphetamines, and benzodiazepines (not prescribed). HC reported low use of alcohol and marijuana in the 30 days before the scan. OUDD participants reported significantly higher levels of depressive symptoms and anhedonia, as well as lower levels of behavioral activation and environmental reward than HC.

Task Performance during Substance-Free Activity and Monetary Reward

Substance-free activity reward. The repeated measures MANOVA on response time did not reveal significant Group x Trial Type x Run, Group x Run, Group x Trial Type, or Trial Type x Run interactions (**Table 3**). The main effect of Trial Type was significant with faster

response times for reward trials relative to non-reward trials across both groups. The main effects of Run and Condition on response time were not significant.

Monetary reward. The repeated measures MANOVA on response time did not reveal a significant Group x Trial Type x Run interaction (**Table 3**). The interaction effect of Trial Type x Run was significant with post-hoc tests revealing significantly slower response times during Run 1 (M=198.42, SD=22.56) relative to Run 2 (M=190.36, SD=20.77) during reward trials, $F(1,32)=11.58$, $p<0.01$, but no significant difference in response times between Run 1 (M=208.42, SD=28.46) and Run 2 (M=211.53, SD=37.43) during non-reward trials, $F(1,32)=0.47$, $p=0.55$, across both groups.

Attenuated Neural Response during Anticipation and Receipt of Substance-Free Activity and Monetary Reward

Substance-free activity reward.

Anticipation. Repeated measures MAN(C)OVAs did not reveal any significant interaction effects of Run x Group on neural response in any of the ROIs (**Table 4**). A significant main effect of Run was found on neural response in the right anterior cingulate cortex (ACC) with greater neural response in Run 1 relative to Run 2 across both groups. Additionally, significant main effects of Group on neural response were found for the left ACC, right ACC, left and right caudate, and left orbitofrontal cortex (OFC) with greater neural response in HC relative to the OUDD group across runs. There were no other significant interaction or main effects on neural response in any other ROIs.

Receipt. Repeated measures MAN(C)OVAs did not reveal any significant interaction effects of Run x Group or main effects of Run or Group on neural response in any of the ROIs (**Table 4**).

Monetary reward.

Anticipation. Repeated measures MAN(C)OVAs did not reveal any significant interaction effects of Run x Group or main effects of Run on neural response in any of the ROIs (**Table 4**). A significant main effect of Group on neural response in the right OFC was found with greater neural response in HC relative to the OUDD group across runs. There were no other significant interaction or main effects on neural response for any other ROIs.

Receipt. Repeated-measures MAN(C)OVAs did not reveal any significant interaction effects of Run x Group or main effects of Run or Group on neural response in any of the ROIs (**Table 4**).

Global Functional Connectivity during Anticipation and Receipt of Substance-Free Activity and Monetary Reward

Substance-free activity reward.

Anticipation. Between-group analyses yielded two significant clusters in which the OUDD group demonstrated significantly reduced functional connectivity with the right ACC relative to the HC group in the left precentral gyrus and right planum temporale (**Table 5, Figure 2**). The OUDD group did not demonstrate significantly greater functional connectivity relative to the HC group in any clusters of connectivity.

Receipt. Between-group analyses yielded two significant clusters in which the OUDD group demonstrated significantly reduced functional connectivity with the right ACC relative to the HC group in the left superior parietal lobule (SPL) and right putamen (**Table 5, Figure 2**). Additionally, the OUDD group demonstrated significantly greater functional connectivity in relative to the HC group in one significant cluster, the right frontal operculum cortex/inferior frontal gyrus (IFG).

Monetary reward.

Anticipation. Between-group analyses yielded five significant clusters in which the OUDD group demonstrated significantly reduced functional connectivity with the right ACC relative to the HC group in the left SPL, left precentral gyrus, left juxtapositional lobule cortex, right supracalcaine cortex, and right juxtapositional lobule cortex (**Table 6, Figure 3**). Additionally, the OUDD group demonstrated significantly greater functional connectivity in relative to the HC group in one significant cluster, the right frontal operculum cortex/IFG/insular cortex.

Receipt. Between-group analyses yielded one significant cluster in which the OUDD group demonstrated significantly reduced functional connectivity with the right ACC relative to the HC group in the SPL (**Table 6, Figure 3**). Additionally, the OUDD group demonstrated significantly greater functional connectivity in relative to the HC group in one significant cluster, the right frontal operculum cortex/IFG/OFC.

Attenuated Functional Connectivity during Anticipation and Receipt of Substance-Free Activity and Monetary Reward

Substance-free activity reward.

Anticipation. Between-group analyses yielded two significant clusters of activation in which the OUDD group demonstrated significantly greater attenuation of functional connectivity with the right ACC relative to the HC group in the right posterior supramarginal gyrus and the left anterior supramarginal gyrus (**Table 7, Figure 4**).

Receipt. Between-group analyses yielded one significant cluster of activation in which the OUDD group demonstrated significantly greater attenuation of functional connectivity with the right ACC relative to the HC group in the left precentral gyrus/middle frontal gyrus (MFG) (**Table 7, Figure 4**).

Monetary reward.

Anticipation. Within-group analyses for the OUDD group of attenuation of functional connectivity with the right ACC during anticipation of monetary reward yielded four significant clusters in the right central opercular cortex/IFG (pars opercularis), left precentral gyrus, left superior frontal gyrus (SFG)/MFG, and the right MFG/SFG (**Table 8, Figure 5**). Within-group analyses for the HC group yielded two significant clusters in the right paracingulate gyrus and left putamen. Between-group analyses yielded six significant clusters in which the OUDD group demonstrated significantly greater attenuation of functional connectivity with the right ACC relative to the HC group in the right precentral gyrus, left middle temporal gyrus (temporoccipital part), right central opercular cortex/IFG (pars opercularis), right occipital fusiform gyrus, right frontal pole/MFG/IFG (pars triangularis), and right MFG/SFG.

Receipt. Within-group analyses for the OUDD group of attenuation of functional connectivity with the right ACC during anticipation of monetary reward yielded two significant clusters in the right SFG and left paracingulate gyrus (**Table 8, Figure 5**). Within group analyses for the HC group and between-group analyses did not yield any significant clusters of connectivity.

Attenuation of Functional Connectivity as Predictor of Anhedonia, Behavioral Activation, Environmental Reward, and Substance Use

The final model testing the effect of attenuation of functional connectivity between the right ACC and left MFG on substance use at the one-month follow-up was significant with greater attenuation of functional connectivity predicting a greater number of days of substance use in the 30 days before the one-month follow-up, while controlling for the number of days of substance use in the 30 days before the baseline **(Table 9, Figure 6).** Models testing the effect of attenuation of functional connectivity between the right ACC and the left MFG during the anticipation of substance-free activity image reward on anhedonia, behavioral activation, or

environmental reward at the one-month follow-up (**Table 9**) and anhedonia, behavioral activation, environmental reward, or substance use at the three-month follow-up (**Table 10**) were not significant. Additionally, models testing the effect of attenuation of functional connectivity between the right ACC and the right MFG during the anticipation of monetary reward on anhedonia, behavioral activation, environmental reward, or substance use at the one-month follow-up **(Table 9)** or three-month follow-up **(Table 10)** were not significant**.**

DISCUSSION

The current study tested differences in the attenuation of neural response during both anticipation and receipt of substance-free activity and monetary reward between individuals with opiate use disorder and co-occurring moderate depressive symptoms (OUDD) and healthy controls (HC). Contrary to expectation, the OUDD and HC groups did not demonstrate significant differences in neural ROI attenuation. However, hypothesized group differences in functional connectivity were observed.

Contrary to our hypothesis, significant group differences in attenuation of neural response during anticipation and receipt of either type of reward were not found in *a priori* ROIs. Rather, significant attenuation of neural response in the right ACC was found across both groups during anticipation of substance-free activity reward. When encountering positively-valenced stimuli or stimuli with the potential to elicit pleasure and related feelings of enjoyment, it is hypothesized that individuals need to successfully engage in effective up- and down-regulation of positive emotion in order to experience positive affect over time (Tomarken & Keener, 1998). It is further suggested that bias signaling initiated in prefrontal cortical regions, including the ACC, to the NAcc are critical for this regulation of positive emotion (Kim & Hamann, 2007; Wager et al., 2008). In particular, the ACC has been consistently linked to the representation of expected reward values (Amiez, Joseph, & Procyk, 2006), as well as active performance monitoring during goal-oriented behavior (Holdroyd & Coles, 2002; Kerns et al., 2004). Moreover, specific to the context of processing positively valenced and reward stimuli, such as substance-free activity images, the ACC has been implicated in the assessment of the saliency of incoming

emotional information and subsequent regulation of emotional responses (Bush, Luu, & Posner, 2000). Although the current study did not test functional subdivisions of the ACC, previous studies suggest that the rostral ACC may be particularly relevant to the regulation of emotional responses while attending to positively or negatively valenced stimuli (Bush et al., 2000). Attenuation of right ACC activation over time may reflect difficulties in sustained recruitment and engagement of the ACC to represent and/or signal reward value associated with substance-free activity images from the first to the second half of the Activity Incentive Delay (AID) task across both OUDD and HC groups. Importantly, these difficulties were observed during anticipation, but not receipt of substance-free activity reward, suggesting difficulties in incentive processing of reward stimuli as opposed to the related, but distinct ability to receive reward feedback and to respond accordingly (e.g., sustain positive affect).

One possibility contributing to the attenuation of neural response in the right ACC during anticipation of substance-free activity reward across both OUDD and HC groups may be attentional and/or motivational disengagement from AID task demands over time. However, examination of AID task performance data suggest attentional disengagement is a less plausible explanation as both groups demonstrated similar mean response times in the first half compared to the second half of the task. Therefore, it is likely that both OUDD and HC groups remained engaged throughout the task. Additionally, previous data published from the same samples of OUDD and HC as the current study support the notion that participants were not motivationally disengaged as both groups rated the substance-free activity engagement images presented in the AID task as positively valenced, arousing, and representative of activities in which they would likely engage (Yi et al., 2019).

The second aim of the current study tested group differences in global functional connectivity (across both task runs) during the anticipation and receipt of substance-free activity and monetary reward. Compared to the ROI approach, this connectivity approach allows for the consideration of how spatially distinct reward and prefrontal cortical regions are coupled or functionally integrated to perform specific functions (Friston, 2011; Rogers et al., 2007; Smith et al., 2012), such as the representation of expected reward values, active performance monitoring during goal-directed activity, and regulation of positive affect. The right ACC was chosen as the seed ROI given the findings of right ACC neural attenuation across both OUDD and HC groups.

In support of our hypothesis, OUDD participants demonstrated significantly reduced global connectivity between the right ACC and the left precentral gyrus and the right planum temporale during anticipation of substance-free activity reward. In addition, OUDD participants demonstrated significantly reduced global connectivity between the right ACC and the left SPL, precentral gyrus, juxtapositional lobule cortex, right supracalcarine cortex, and juxtapositional lobule cortex during anticipation of monetary reward. One of the central functions of the precentral gyrus is the execution of stimulus-response associations with coordinated activity in motor regions such as the juxtapositional lobule and the superior parietal lobule (SPL) for sensorimotor integration (Brass et al., 2009). Moreover, OUDD participants demonstrated significant reduced global connectivity between the right ACC and the left SPL and right putamen during receipt of substance-free activity reward and between the right ACC and left SPL during receipt of monetary reward relative to HC, further supporting the proposed notion of weaker reward stimulus-response associations among OUDD. Namely, the putamen's anatomical connections with sensorimotor regions, such as the primary and premotor cortices support its function in evaluating reward stimuli and feedback (Haruno & Kawato, 2006), while

the parietal lobule is implicated in the integration of sensory and reward information (Summerfield & Koechlin, 2010). Together, reduced global functional connectivity of the right ACC with these regions may reflect weaker generation of reward stimulus-response associations during both anticipation and receipt of substance-free activity and monetary reward among OUDD participants relative to HC further attributed to substance-free reward and goal devaluation among individuals with substance use disorder (Montague, Hyman, & Cohen, 2004).

Unexpectedly, OUDD participants demonstrated significantly greater global connectivity between the right ACC and right frontal operculum cortex/inferior frontal gyrus (IFG) during anticipation of substance-free activity reward. The right IFG is well understood to be a critical region for emotion regulation, in both healthy and clinical populations, including individuals with depressive symptoms (Johnstone et al., 2007). At rest, increased functional connectivity between the right ACC and right IFG has been found to be associated with increased severity of depressive symptoms among individuals with subclinical depression (Philippi et al., 2015). However, under task demands, increased functional connectivity between the right ACC and right IFG may reflect compensatory recruitment and engagement among OUDD participants to engage in the same degree of integration of attentional engagement and positive emotion regulation as HC. Similarly, OUDD participants also demonstrated significantly greater global connectivity between the right ACC and right frontal operculum cortex/IFG/OFC during receipt of substance-free activity reward relative to HC, further suggesting compensatory recruitment and engagement of attentional processes when receiving reward feedback, not only when anticipating reward.

The second aim of the current study also tested attenuation of functional connectivity (reduction from the first to the second task run) during the anticipation and receipt of substance-

free activity and monetary reward. OUDD participants demonstrated significantly greater attenuation of functional connectivity between the right ACC and right posterior supramarginal gyrus and left anterior supramarginal gyrus during the anticipation of substance-free activity reward. OUDD participants also demonstrated significantly greater attenuation of functional connectivity between the right ACC and left middle temporal gyrus, right central opercular cortex/IFG, occipital fusiform gyrus, frontal pole/MFG/IFG, precentral gyrus, and MFG/SFG during anticipation of monetary reward. Connectivity between the right ACC and bilateral MFG is particularly relevant as numerous reciprocal connections between these regions have been documented and deemed critical for monitoring of incoming information gathered from lower level stimuli detection, processing of this information, and executing cognitive control when competing demands or response plans arise (MacDonald et al., 2000; Sohn et al., 2007). Further distinguishing the distinct contributions of these two prefrontal regions, performance monitoring, self-evaluation, and detection of emotional salience can most readily be attributed to the ACC, in turn, prompting the MFG to initiate behavioral adjustments and regulatory behavior as necessary (Cieslik et al., 2012; Pizzagalli, 2011). Specifically, attenuation of the connectivity between the right ACC and left MFG during receipt of substance-free activity reward may indicate challenges among OUDD participants to adjust regulatory behavior, such as up-regulation of positive affect related to processing the receipt of substance-free activity reward. This is consistent with theory and empirical findings of disturbances in the reward system among individuals with substance use disorders contributing to the biasing of emotional processing away from substance-free rewards (Murphy, Taylor, & Elliott, 2012). This is also consistent with similar findings among depressed populations with disordered emotional processing of positive affect and reward (Heller et al., 2009; Tomarken & Keener, 1998). Interestingly, greater attenuation of functional

connectivity between the right ACC and MFG was also found for OUDD participants relative to HC during anticipation of monetary reward, as opposed to receipt of monetary reward. Therefore, it is important to consider how dysfunctional reward processing may look different depending on the type of reward stimuli. For instance, OUDD participants may have greater challenges with regulating responses to monetary stimuli when anticipating its receipt, rather than during and after the delivery of monetary reward.

In line with findings during the anticipation of reward, OUDD participants demonstrated and between the right ACC and left precentral gyrus/middle frontal gyrus (MFG) during receipt of substance-free activity reward relative to HC, as well as between the right ACC and left paracingulate gyrus and right SFG during receipt of monetary reward relative to HC. Difficulties among OUDD participants to engage in goal-oriented performance monitoring and adjustment of regulatory behavior appear to be consistent throughout both the anticipation and receipt of reward, suggesting more of an overall, as opposed to a cue or feedback prompted deficit. Taken together, although attenuation of right ACC activation during anticipation of substance-free activity reward was found across both OUDD and HC groups, significant group differences in both global functional connectivity and attenuation of functional connectivity suggest differential mechanistic contributors to ACC activation when temporal relationships and information processing between spatially distinct regions are considered.

Several previous studies report greater attenuation of connectivity during reward processing among individuals with major depressive disorder (MDD) relative to HC; however, they found reduced connectivity between the right ACC and other reward-related regions. For instance, MDD outpatients demonstrated greater attenuation of functional connectivity between the right ACC and the right OFC and left frontal pole during anticipation of monetary reward

(Walsh et al., 2017). Additionally, MDD outpatients demonstrated greater attenuation of functional connectivity between striatal seeds and bilateral OFC and right frontal pole. The OFC is well-documented to have numerous connections with limbic areas, such as the amygdala, thalamus, and insula (Peters & Buchel, 2010) allowing for associative information between reward cues and receipt to be encoded in representational memory (Schoenbaum & Roesch, 2005). Thus, attenuation of functional connectivity between these regions may reflect difficulties in associative learning and subsequent generation of reward expectancies. Contrastingly, attenuation of functional connectivity between the right ACC and bilateral MFG may differently reflect difficulties in the actual execution of positive emotion regulation.

Lastly, in partial support of our third hypothesis, greater attenuation of functional connectivity between the right ACC and left MFG during anticipation of substance-free activity reward significantly predicted greater frequency of substance use one month later, while it did not significantly predict anhedonia, environmental reward, or reward availability. Interestingly, the ACC and MFG are recognized as major hubs of large-scale networks (Menon, 2011). More specifically, the salience network (SN), primarily involved in the detection and integration of interoceptive and emotional information and stimuli, is anchored in the ACC. The central executive network (CEN), responsible for active maintenance and manipulation of information in the context of goal-directed behavior, is anchored in the MFG. Coordination between these large-scale networks is critical for the detection of task-related stimuli to inform regulatory behavior, such as up- and down-regulation of positive affect. Thus, in the context of substance use, greater attenuation of functional connectivity between these regions and networks may reflect inadequate detection and integration of potentially rewarding stimuli (i.e., substance-free activity images), in turn leading to dysfunctional regulation of positive affect and reward

responsivity. This is in line with conceptualizations of substance use among individuals with substance use disorder as a loss of control over regulatory behavior when processing reward stimuli (Everitt & Robbins, 2005; Koob & Volkow, 2010). Importantly, attenuation of functional connectivity during the anticipation of substance-free reward may serve as a useful biomarker of substance use outcomes, such as frequency of prospective substance use.

Limitations and Future Directions

Findings should be interpreted considering several limitations. Current findings were reported using a relatively liberal statistical threshold and small sample size. Additionally, given the current OUDD group was male and recruited from an inpatient detoxification facility, findings may not generalize to other substance use populations (e.g., female, outpatient treatment, substance use disorders other than opiate use disorder). Accordingly, future studies should seek to replicate these findings in other samples prior to generalizing these findings. It is also important to note that the current study did not aim to test any casual pathways among neural indicators of reward processing and clinical and mechanistic measures. Rather, findings suggest these neural indicators of reward processing may be potential biomarkers of opiate use disorder and co-occurring moderate depressive symptoms.

Despite these limitations, these findings broaden our understanding of reward-related deficits in individuals with opiate use disorder and co-occurring moderate depressive symptoms in several ways. The large majority of studies examining reward processing in healthy and clinical populations have utilized monetary reward, understandably, given its widely learned extrinsic value and motivational potential (Forbes, 2009). However, it is important to expand our investigations to different types of reward, such as substance-free activity reward, that are more directly relevant to mechanisms theoretically conceptualized and empirically evidenced to

contribute to the maintenance of opiate use disorder and co-occurring moderate depressive symptoms and treatments developed to target such mechanisms. Furthermore, studies have predominately examined mean neural response to reward across subgroups of trials types (e.g., reward, non-reward) and/or across the whole length of reward tasks. Yet, given symptom presentations such as anhedonia, it may be worth continuing to examine the nature of these reward deficits among clinical populations, including questions surrounding the temporal characteristics of reward dysfunction (e.g., are these deficits sustained over the course of a task and/or after treatment?) as well as the temporal dynamics and integration among neural regions involved in reward processing, such as canonical regions as well as prefrontal cortical regions, and more largely, higher order, goal-oriented processing. A compelling next step will be to examine whether substance use treatments targeting reward deficits (e.g., behavioral activation [BA]), or neuromodulation techniques (e.g., transcranial current stimulation [tACS/tDCS]) can improve individuals' capacity to sustain functional connectivity between reward and prefrontal cortical regions during processing of substance-free activity image and monetary reward to ideally improve post-treatment substance use outcomes.

Table 1. *Sample characteristics*

	OUDD (*n*=16)	**HC (*n*=17)**	**Statistic**
	Mean (SD)		
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)	$t(31)=1.80$
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)	0.00 (0.00)	$t(31)=-1.91$
Marijuana	1.06 (2.41)	0.76 (1.48)	$t(31)=-0.43$
Heroin	19.25 (9.07)	0.00 (0.00)	$t(31)=24.65$**
Painkillers (not prescribed)	1.06 (2.52)	0.00 (0.00)	$t(31)=-1.74$
Amphetamines	0.25 (1.00)	0.00 (0.00)	$t(31)=-1.03$
Benzodiazepines (not prescribed)	1.06 (2.41)	0.00 (0.00)	$t(31)=-1.82$

Note: *$p<0.05$, **$p<0.001$.

Table 2. *Clinical correlates and mechanisms*

	OUDD (*n*=16)	**HC (*n*=17)**	**Statistic**
	Mean (SD)		
TLFB			
# days used any substance in past 30 days			
Baseline	22.25 (7.51)	--	--
1-month follow-up	2.00 (2.37)	--	--
3-month follow-up	5.87 (10.29)	--	--
# days used heroin in past 30 days			
Baseline	19.25 (9.07)	--	--
1-month follow-up	1.50 (2.58)	--	--
3-month follow-up	1.40 (3.20)	--	--
# days used painkillers in past 30 days			
Baseline	1.06 (2.52)	--	--
1-month follow-up	0.06 (0.25)	--	--
3-month follow-up	0.47 (1.13)	--	--
BDI			
Baseline	23.56 (7.13)	3.00 (3.30)	$t(31)=-10.74^{**}$
1-month follow-up	12.21 (11.00)	--	--
3-month follow-up	13.33 (9.96)	--	--
Anhedonia			
Baseline	3.38 (1.67)	0.29 (0.47)	$t(31)=-7.32^{**}$
1-month follow-up	1.50 (1.99)	--	--
3-month follow-up	1.73 (1.39)	--	--
BADS			
Baseline	33.20 (9.78)	62.00 (7.16)	$t(29)=9.40^{**}$
1-month follow-up	50.08 (14.82)	--	--
3-month follow-up	50.87 (12.85)	--	--
RPI			
Baseline	52.40 (4.29)	66.31 (5.83)	$t(29)=7.53^{**}$
1-month follow-up	57.46 (10.49)	--	--
3-month follow-up	57.47 (8.98)	--	--

Note: $^{*}p<0.05$, $^{**}p<0.001$.

Table 3. *Repeated measures MANOVAs on response time for the AID and MID tasks*

Source	SS	df	MS	*F*	*p*
AID					
Within-Subject Effects					
Run	81.19	1	81.19	0.23	0.64
Group x Run	594.435	1	594.435	1.67	0.21
Trial Type	4654.92	1	4654.92	11.88	0.002
Group x Trial Type	34.24	1	34.24	0.09	0.77
Trial Type x Run	316.639	1	316.639	1.40	0.25
Group x Trial Type x Run	94.36	1	94.36	0.42	0.52
Between-Subject Effects					
Condition	4316.37	1	4316.37	1.72	0.20
MID					
Within-Subject Effects					
Run	230.91	1	230.91	0.77	0.34
Group x Run	661.57	1	661.57	2.19	0.15
Trial Type	8196.80	1	8196.80	25.89	<0.001
Group x Trial Type	577.235	1	577.235	1.82	0.19
Trial Type x Run	968.880	1	968.880	7.85	0.009
Group x Trial Type x Run	215.281	1	215.281	1.74	0.20
Between-Subject Effects					
Condition	9256.50	1	9256.50	4.19	0.05

Table 4. *Group x Run MANOVAs on parameter estimates for a priori ROIs during anticipation and receipt of substance-free activity reward (AID) and monetary reward (MID)*

ROI	AID					
	Anticipation			Receipt		
	Main Effect of Run	Main Effect of Group	Group x Run	Main Effect of Run	Main Effect of Group	Group x Run
L NAcc	0.08	0.26	1.58	0.80	0.09	0.01
R NAcc	0.11	0.06	1.29	1.08	2.03	0.07
L ACC	3.67	4.30*	0.10	1.18	0.00	0.03
R ACC	4.32*	6.59*	0.09	1.51	0.05	0.01
L Cau	0.31	7.80**	0.83	0.31	0.04	0.05
R Cau	1.06	8.59**	0.14	1.49	0.01	0.02
L OFC	0.50	4.22*	0.40	0.00	0.66	0.36
R OFC	1.09	1.72	0.44	0.24	0.07	0.19
L Put	1.46	3.07	3.21	1.10	0.06	0.17
R Put	0.42	2.15	1.11	1.01	0.08	0.09
L Ins	1.89	2.51	4.02	0.19	0.01	3.48
R Ins	3.10	1.11	1.50	0.31	0.07	1.85
ROI	**MID**					
	Anticipation			Receipt		
	Main Effect of Run	Main Effect of Group	Group x Run	Main Effect of Run	Main Effect of Group	Group x Run
L NAcc	0.27	0.28	0.01	0.03	0.12	0.32
R NAcc	0.01	0.94	0.05	1.68	0.18	0.29
L ACC	0.09	0.20	0.08	2.12	0.49	0.20
R ACC	0.00	1.31	0.12	1.58	0.64	0.69
L Cau	1.35	3.27	0.08	2.31	0.01	0.56
R Cau	0.78	3.85	0.19	1.17	0.04	0.69
L OFC	0.47	1.85	0.00	0.05	0.31	0.03
R OFC	0.00	6.56*	0.16	0.21	0.60	0.12
L Put	1.04	1.56	0.03	3.27	0.01	1.41
R Put	0.40	2.95	0.45	1.18	0.10	0.34
L Ins	3.34	0.56	1.95	0.98	1.81	0.67
R Ins	1.70	0.95	1.72	0.53	3.23	0.39

Note: *p<0.05, **p<0.01. L=left, R=right. Presented values indicate F-values with df=(1,31).

Table 5. *Group differences in global connectivity of rACC functional connectivity during anticipation and receipt of substance-free activity reward (AID)*

Regions	Cluster Size	X	Y	Z	*p*
Anticipation ([Reward]-[Non-Reward])					
OUDD>HC					
None					
OUDD<HC					
L. precentral gyrus *L. postcentral gyrus*	1504	-31	-19	43	2.42×10^{-2}
R. planum temporale *R. parietal operculum cortex*	1484	31	-31	16	2.61×10^{-2}
Receipt ([Win]-[Non-Win])					
OUDD>HC					
R. frontal operculum cortex *R. inferior frontal gyrus (pars triangularis), R. inferior frontal gyrus (pars opercularis), R. frontal orbital cortex*	1331	46	23	4	4.50×10^{-2}
OUDD<HC					
L. superior parietal lobule *L. supramarginal gyrus (posterior division), L. lateral occipital cortex (superior division), L. precuneous cortex*	1925	-27	-51	42	4.81×10^{-3}
R. putamen	1529	28	-10	-3	2.08×10^{-2}

Table 6. *Group differences in global connectivity of rACC functional connectivity during anticipation and receipt of monetary reward (MID)*

Regions	Cluster Size	X	Y	Z	*p*
Anticipation ([Reward]-[Non-Reward])					
OUDD>HC					
R. frontal operculum cortex *R. inferior frontal gyrus (pars triangularis), R. inferior frontal gyrus (pars opercularis), R. frontal orbital cortex, R. insular cortex*	2791	46	23	4	1.97×10^{-6}
OUDD<HC					
L. superior parietal lobule *L. lateral occipital cortex (superior division), L. supramarginal gyrus (posterior division)*	1744	-22	-53	42	3.00×10^{-4}
L. precentral gyrus	1414	-13	-26	55	1.78×10^{-3}
L. juxtapositional lobule cortex	1107	-14	-1	50	1.05×10^{-2}
R. supracalcarine cortex *R. precuneous cortex*	1102	29	-53	17	1.08×10^{-2}
R. juxtapositional lobule cortex *R. precentral gyrus*	902	11	-3	54	3.74×10^{-2}
Receipt ([Win]-[Non-Win])					
OUDD>HC					
R. frontal operculum cortex *R inferior frontal gyrus (pars triangularis), R. inferior frontal gyrus (pars opercularis), R. frontal orbital cortex*	2365	45	23	5	1.04×10^{-3}
OUDD<HC					
L. superior parietal lobule *L. lateral occipital cortex (superior division), L. supramarginal gyrus (posterior division)*	1745	-23	-54	45	9.18×10^{-3}

Table 7. *Group differences in attenuation of rACC functional connectivity during anticipation and receipt of substance-free activity reward (AID)*

Regions	Cluster Size	X	Y	Z	*p*
Anticipation ([Reward]-[Non-Reward])					
OUDD>HC					
R. supramarginal gyrus (posterior division) *R. superior parietal lobule, R. angular gyrus, R. postcentral gyrus, R. supramarginal gyrus (anterior division), R. precentral gyrus*	3280	45	-40	50	3.21×10^{-5}
L. supramarginal gyrus (anterior division) *L. supramarginal gyrus (posterior division), L. angular gyrus, L. superior parietal lobule, L. parietal operculum cortex, L. postcentral cortex*	3277	-51	-39	40	3.23×10^{-5}
OUDD<HC					
None					
Receipt ([Win]-[Non-Win])					
OUDD>HC					
L. precentral gyrus *L. middle frontal gyrus, L. postcentral gyrus*	2783	-41	-5	56	2.13×10^{-4}
OUDD<HC					
None					

Table 8. *Group differences in attenuation of rACC functional connectivity during anticipation and receipt of monetary reward (MID)*

Regions	Cluster Size	X	Y	Z	*p*
Anticipation ([Reward]-[Non-Reward])					
OUDD>HC					
R. precentral gyrus *R. superior frontal gyrus, R. juxtapositional lobule cortex*	2177	19	-16	57	2.50×10^{-6}
L. middle temporal gyrus (temporoccipital part) *L. lateral occipital cortex (inferior division), L. inferior temporal gyrus (temporoccipital part), L. angular gyrus*	1125	-49	-60	3	1.93×10^{-3}
R. central opercular cortex *R. inferior frontal gyrus (pars opercularis)*	1098	45	-2	17	2.34×10^{-3}
R. occipital fusiform gyrus *R. lingual gyrus*	820	29	-74	1	1.88×10^{-2}
R. frontal pole *R. middle frontal gyrus, R. inferior frontal gyrus (pars triangularis)*	819	39	35	14	1.89×10^{-2}
R. middle frontal gyrus *R. precentral gyrus, R. superior frontal gyrus*	735	27	3	43	3.68×10^{-2}
OUDD<HC					
None					
Receipt ([Win]-[Non-Win])					
OUDD>HC					
None					
OUDD<HC					
None					

Table 9. *Hierarchical linear regression models predicting anhedonia, behavioral activation, environmental reward, and substance use at the 1-month follow-up*

Predictor	*B*	*SE*	95% CI
Anhedonia			
R. ACC-R.MFG, Model R_2=0.04, F(2,13)=0.23, p=0.80			
Anhedonia (baseline)	-0.05	0.36	[-0.84, 0.74]
R. ACC-R. MFG	0.19	0.28	[-0.43, 0.81]
R. ACC-L.MFG, Model R_2=0.10, F(2,13)=0.60, p=0.57			
Anhedonia (baseline)	0.14	0.36	[-0.66, 0.94]
R. ACC-L. MFG	2.81	2.56	[-2.83, 8.45]
Behavioral Activation			
R. ACC-R.MFG, Model R_2=0.09, F(3,11)=0.27, p=0.85			
Behavioral activation (baseline)	-0.51	0.76	[-2.27, 1.26]
Motivation (baseline)	-0.64	0.94	[-2.81, 1.52]
R. ACC-R. MFG	-0.43	2.60	[-6.43, 5.57]
R. ACC-L.MFG, Model R_2=0.10, F(3,11)=0.28, p=0.84			
Behavioral activation (baseline)	-0.49	0.75	[-2.22,1.25]
Motivation (baseline)	-0.68	0.87	[-2.67, 1.32]
R. ACC-L. MFG	-5.73	23.05	[-58.88, 47.42]
Environmental Reward			
R. ACC-R.MFG, Model R_2=0.14, F(2,11)=0.70, p=0.52			
Environmental reward (baseline)	0.27	0.80	[-1.53, 2.08]
R. ACC-R. MFG	-1.56	1.61	[-5.20, 2.08]
R. ACC-L.MFG, Model R_2=0.06, F(2,11)=0.27, p=0.77			
Environmental reward (baseline)	0.54	0.79	[-1.26, 2.33]
R. ACC-L. MFG	5.07	14.38	[-27.46, 37.59]
Substance Use			
R. ACC-R.MFG, Model R_2=0.13, F(2,15)=0.96, p=0.41			
Substance use (baseline)	0.34	0.25	[-0.20, 0.87]
R. ACC-R. MFG	-0.05	0.08	[-0.21, 0.13]
R. ACC-L.MFG, Model R_2=0.39, F(2,15)=4.13, p=0.04			
Substance use (baseline)	0.34	0.20	[-0.09, 0.78]
R. ACC-L. MFG	1.39*	0.57	[0.16, 2.62]

Note: *p<0.05.

Table 10. *Hierarchical linear regression models predicting anhedonia, behavioral activation, environmental reward, and substance use at the 3-month follow-up*

Predictor	B	SE	95% CI
Anhedonia			
R. ACC-R.MFG, Model R_2=0.21, F(2,14)=1.60, p=0.24			
Anhedonia (baseline)	-0.22	0.22	[-0.74, 0.21]
R. ACC-R. MFG	0.26	0.17	[-0.11, 0.63]
R. ACC-L.MFG, Model R_2=0.06, F(2,14)=0.38, p=0.69			
Anhedonia (baseline)	-0.22	0.25	[-0.76, 0.32]
R. ACC-L. MFG	-0.39	1.75	[-4.19, 3.42]
Behavioral Activation			
R. ACC-R.MFG, Model R_2=0.10, F(3,13)=0.38, p=0.77			
Behavioral activation (baseline)	-0.60	0.59	[-1.91, 0.71]
Motivation (baseline)	-0.64	0.72	[-2.25, 0.98]
R. ACC-R. MFG	0.42	2.00	[-4.05, 4.89]
R. ACC-L.MFG, Model R_2=0.10, F(3,13)=0.37, p=0.78			
Behavioral activation (baseline)	-0.52	0.58	[-1.82, 0.78]
Motivation (baseline)	-0.56	0.67	[-2.06, 0.93]
R. ACC-L. MFG	-2.45	17.83	[-42.173, 37.26]
Environmental Reward			
R. ACC-R.MFG, Model R_2=0.16, F(2,13)=1.07, p=0.38			
Environmental reward (baseline)	0.48	0.61	[-0.86, 1.81]
R. ACC-R. MFG	-1.14	1.23	[-3.84, 1.56]
R. ACC-L.MFG, Model R_2=0.10, F(2,13)=0.59, p=0.57			
Environmental reward (baseline)	0.65	0.31	[-0.67, 1.97]
R. ACC-L. MFG	-0.64	-0.02	[-24.62, 23.33]
Substance Use			
R. ACC-R.MFG, Model R_2=0.05, F(2,14)=0.29, p=0.76			
Substance use (baseline)	0.40	0.57	[-0.83, 1.64]
R. ACC-R. MFG	-0.08	0.18	[-0.47, 0.32]
R. ACC-L.MFG, Model R_2=0.05, F(2,14)=0.34, p=0.72			
Substance use (baseline)	0.37	0.54	[-0.82, 1.55]
R. ACC-L. MFG	0.84	1.55	[-2.55, 4.22]

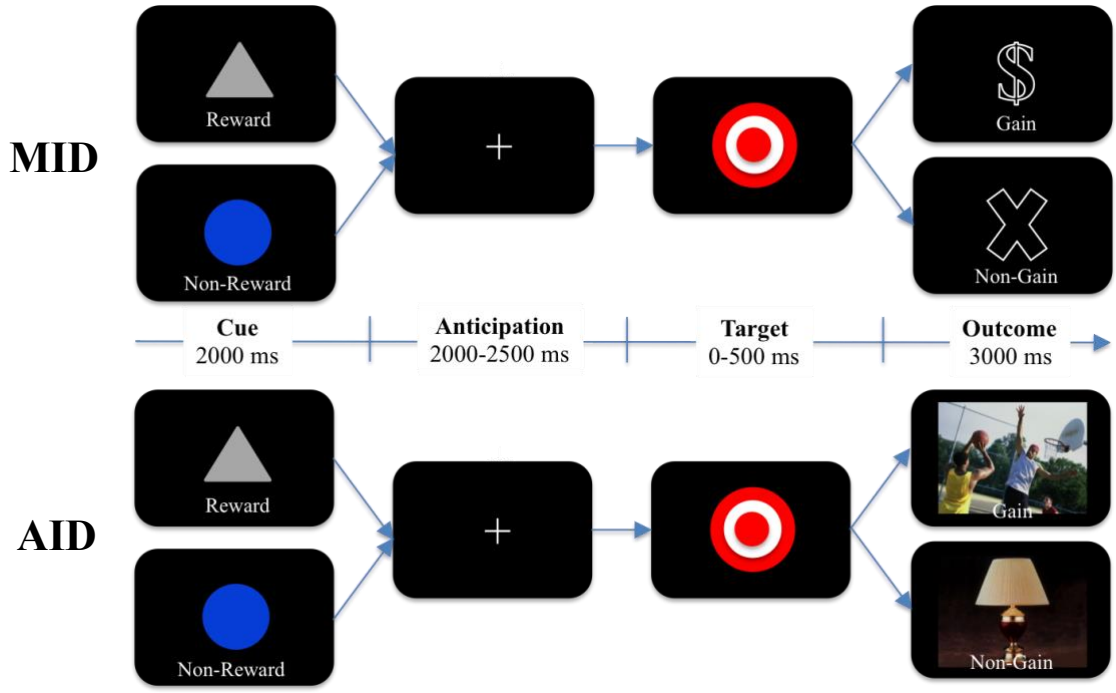

Figure 1. Trial structure of the MID and AID tasks.

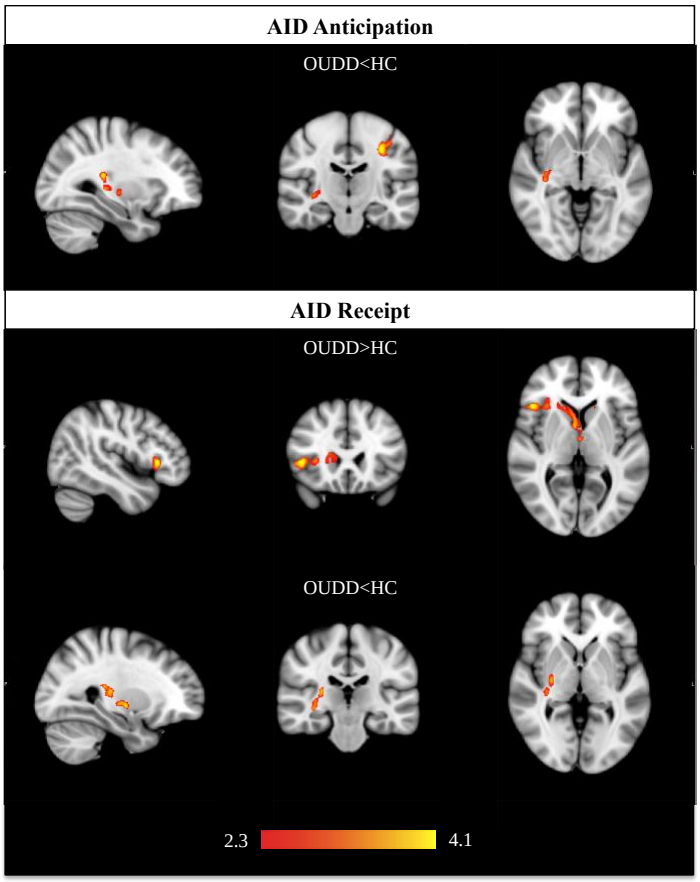

Figure 2. PPI results for global connectivity with the rACC during anticipation and receipt substance-free activity image reward (AID task).

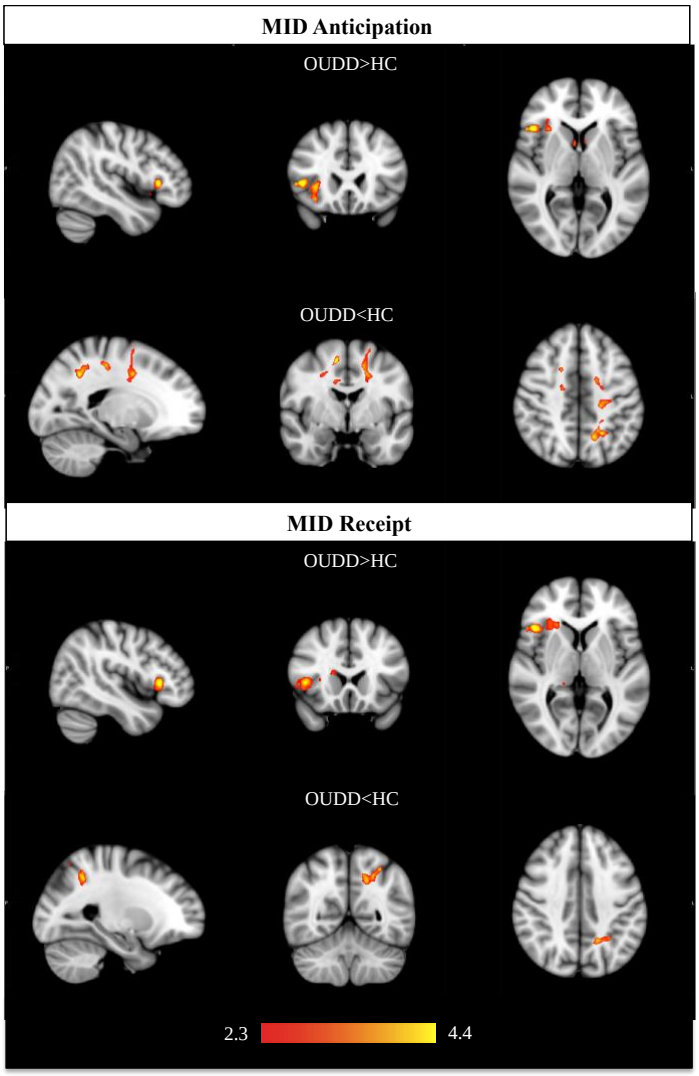

Figure 3. PPI results for global connectivity with the rACC during anticipation and receipt of monetary reward (MID task).

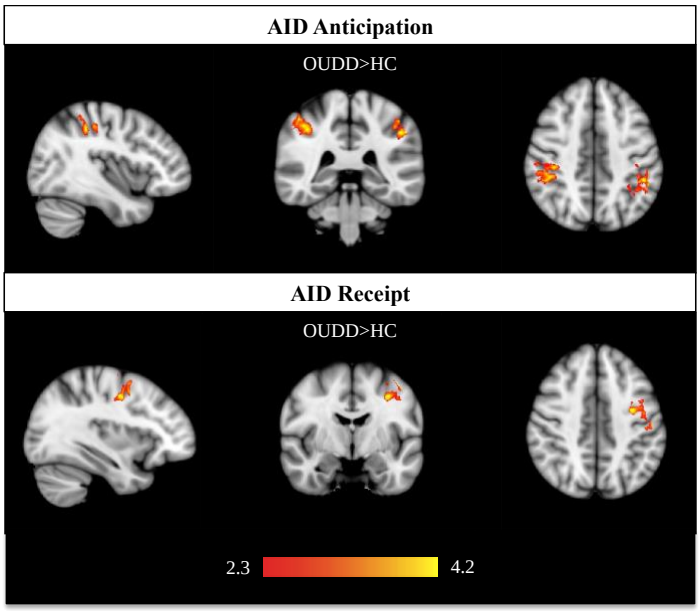

Figure 4. PPI results for attenuation of connectivity (Run 1>Run 2) with the rACC during anticipation and receipt of substance-free activity image reward (AID task).

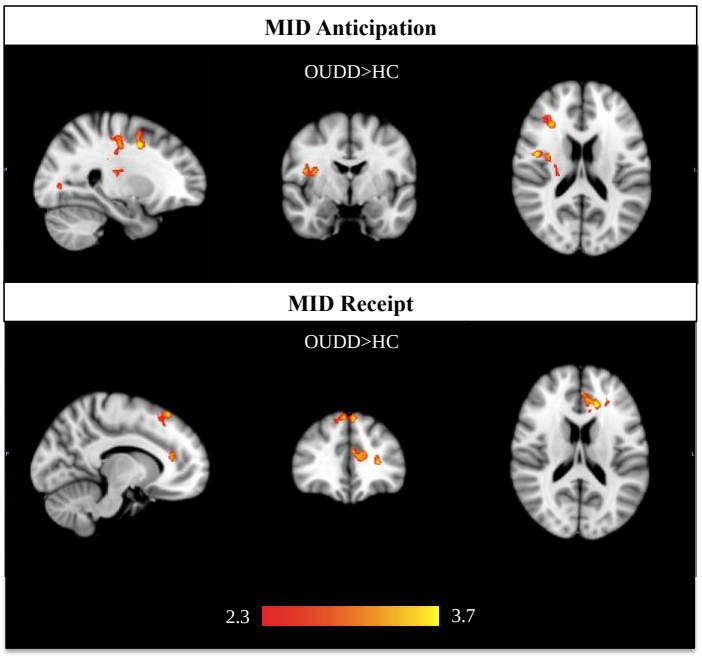

Figure 5. PPI results for attenuation of connectivity (Run 1>Run 2) with the rACC during anticipation and receipt of monetary reward (MID task).

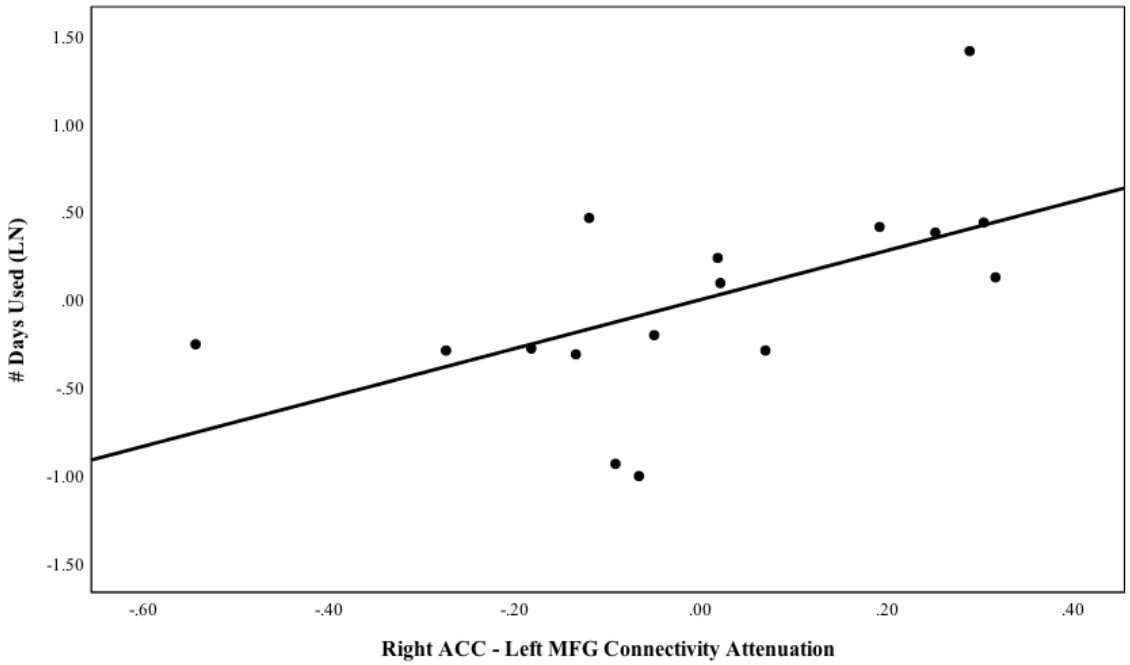

Figure 6. Partial regression plot for connectivity attenuation between the right ACC and left MFG during receipt of substance-free activity image reward (AID task) and number of days used of any substance during the 30 days before the 1-month follow-up, after controlling for number of days used of any substance during the 30 days before baseline.

APPENDIX 1: SUPPLEMENTARY TEXT

Results for Identification of Covariates

Aim 1.

Whole-brain analyses. Whole-brain analyses with age as a predictor did not yield any significant clusters of activation for either phase (anticipation, receipt) of either task (AID, MID). Age was not included as a covariate in whole-brain analyses.

Region-of-interest analyses. As shown in **Table S1**, age was significantly correlated to neural response in the left and right anterior cingulate cortices, and right insular cortex during the anticipation phase of Run 1 of the AID task, right nucleus accumbens during the receipt phase of Run 1 of the AID task, and left and right insular cortices during the anticipation phase of Run 1 of the MID task. Accordingly, age was included as a covariate in repeated measures MANCOVAs specific to the left and right anterior cingulate cortices, left and right insular cortices, and right nucleus accumbens.

Aim 2.

Global functional connectivity. PPI analyses with age as a predictor yielded two significant clusters of connectivity with the right anterior cingulate cortex in the left middle frontal gyrus/frontal pole and right precentral gyrus/middle frontal gyrus/superior frontal gyrus during anticipation of substance-free activity image reward and two significant clusters in the left middle frontal gyrus/superior frontal gyrus and right precentral gyrus during receipt of substance-free activity reward (**Table S2, Figure S1**). In addition, PPI analyses yielded three clusters in the left posterior cingulate gyrus and left frontal pole/middle frontal gyrus during anticipation of monetary reward and no clusters during receipt of monetary reward (**Table S3,**

Figure S1). Accordingly, age was included as a covariate in PPI analyses for the anticipation and receipt phases of substance-free activity reward and anticipation phase of monetary reward.

Attenuation of functional connectivity. PPI analyses with age as a predictor did not yield any significant clusters of connectivity with the right anterior cingulate cortex during anticipation of substance-free activity image reward (**Table S4, Figure S2**). PPI analyses yielded one significant cluster in the left superior parietal lobule during receipt of substance-free activity image reward. Additionally, PPI analyses yielded three significant clusters in the right angular gyrus, right Heschl's gyrus/insular cortex, and left parietal operculum during anticipation of monetary reward, and one significant cluster in the right superior lateral occipital cortex during receipt of monetary reward (**Table S5, Figure S2**). Accordingly, age was included as a covariate for PPI analyses of the receipt phase of substance-free activity image reward, and anticipation and receipt phases of monetary reward.

Aim 3. As shown in **Table S6**, motivation for substance use treatment was significantly correlated to behavioral activation measured at baseline. Accordingly, motivation for substance use treatment was included as a covariate in the regression models predicting behavioral activation.

Whole Brain Analysis of Attenuated Neural Response during Anticipation and Receipt of Substance-Free Activity and Monetary Reward

Substance-free activity reward.

Anticipation. Within-group analyses for the HC group of attenuation of neural response during anticipation of substance-free activity reward yielded one significant cluster of activation in the right subcallosal cortex/anterior cingulate gyrus (**Table S7, Figure S3**). Within-group analyses for the OUDD group did not yield any significant clusters of activation. Between-group analyses yielded two significant clusters of activation in which the OUDD group demonstrated significantly less attenuation of neural response relative to the HC group in the right planum temporale and right superior frontal gyrus.

Receipt. Within-group analyses for the OUDD and HC groups of attenuation of neural response during receipt of substance-free activity reward did not yield any significant clusters of activation (**Table S7**). Between-group analyses yielded one significant cluster of activation in which the OUDD group demonstrated significantly less attenuation of neural response relative to the HC group in the left opercular cortex/insular cortex (**Figure S3).**

Monetary reward.

Anticipation. Within- and between-group analyses for the OUDD and HC groups of attenuation of neural response during anticipation of monetary reward did not yield any significant clusters of activation.

Receipt. Within- and between-group analyses for the OUDD and HC groups of attenuation of neural response during receipt of monetary reward did not yield any significant clusters of activation.

APPENDIX 2: SUPPLEMENTARY TABLES

Table S1. *Pearson's (r) correlations between age and parameter estimates of a priori ROIs during anticipation and receipt of substance-free activity reward (AID) and monetary reward (MID)*

		L NAcc	R NAcc	L ACC	R ACC	L Cau	R Cau	L OFC	R OFC	L Put	R Put	L Ins	R Ins
AID Anticipation													
Age													
	Run 1	-0.16	-0.23	-0.45**	-0.43	-0.11	-0.06	-0.16	-0.22	-0.33	-0.32	-0.34	-0.40*
	Run 2	-0.06	-0.04	-0.09	-0.04	0.06	-0.05	0.07	0.11	0.22	0.03	0.20	0.17
AID Receipt													
Age													
	Run 1	-0.31	-0.36*	-0.01	-0.05	-0.08	-0.09	-0.20	-0.05	-0.18	-0.23	-0.12	-0.15
	Run 2	-0.05	-0.04	-0.25	-0.21	-0.01	-0.09	-0.05	-0.09	0.02	0.03	0.03	-0.07
MID Anticipation													
Age													
	Run 1	-0.07	0.02	0.13	0.20	0.19	0.16	0.09	0.31	0.16	0.08	0.42*	0.40*
	Run 2	0.04	-0.01	0.19	0.08	-0.14	-0.03	0.19	0.14	-0.17	-0.07	0.17	0.29
MID Receipt													
Age													
	Run1	0.06	0.20	0.14	0.22	-0.03	0.05	0.29	0.33	0.10	0.10	0.08	0.12
	Run 2	0.09	0.21	-0.14	-0.21	-0.09	0.09	0.15	0.01	-0.02	-0.01	-0.21	-0.20

Note: *p<0.05, **p<0.01.

Table S2. *Global functional connectivity with the rACC during anticipation and receipt of substance-free activity reward (AID) for the total sample predicted by age*

Regions	Cluster Size	X	Y	Z	*p*
Anticipation ([Reward]-[Non-Reward])					
L. middle frontal gyrus *L. frontal pole*	4522	-35	30	41	1.97×10^{-6}
R. precentral gyrus *R. middle frontal gyrus, R. superior frontal gyrus*	1892	40	0	46	5.79×10^{-3}
Receipt ([Win]-[Non-Win])					
L. middle frontal gyrus *L. superior frontal gyrus*	2817	-25	10	50	2.43×10^{-4}
R. precentral gyrus *R. juxtapositional lobule cortex*	1514	16	-21	50	2.20×10^{-2}

Table S3. *Global functional connectivity with the rACC during anticipation and receipt of monetary reward (MID) for the total sample predicted by age*

Regions	Cluster Size	X	Y	Z	*p*
Anticipation ([Reward]-[Non-Reward])					
L. posterior cingulate gyrus *L. precentral gyrus*	22467	-2	-20	42	7.71×10^{-31}
L. frontal pole *L. middle frontal gyrus*	6056	-19	45	36	6.74×10^{-12}
L. frontal pole *L. middle frontal gyrus*	1122	-31	42	23	9.61×10^{-3}
Receipt ([Win]-[Non-Win])					
None					

Table S4. *Attenuation of rACC functional connectivity during anticipation and receipt of substance-free activity reward (AID) for the total sample predicted by age*

Regions	Cluster Size	X	Y	Z	*p*
Anticipation ([Reward]-[Non-Reward])					
None					
Receipt ([Win]-[Non-Win])					
L. superior parietal lobule					
L. postcentral gyrus, L. supramarginal gyrus (anterior & divisions), L. angular gyrus	3120	-29	-41	41	7.28×10^{-5}

Table S5. *Attenuation of rACC functional connectivity during anticipation and receipt of monetary reward (MID) for the total sample predicted by age*

Regions	Cluster Size	X	Y	Z	*p*
Anticipation ([Reward]-[Non-Reward])					
R. angular gyrus *R. supramarginal gyrus (posterior division)*	1760	59	-50	26	2.97×10^{-5}
R. Heschl's gyrus *R, planum temporale, R. parietal operculum cortex, R. insular cortex, R. central opercular cortex*	1289	48	-24	10	6.17×10^{-4}
L. parietal operculum *L. planum temporale, L. Heschl's gyrus, L. supramarginal gyrus (anterior division)*	928	-48	-32	16	8.17×10^{-3}
Receipt ([Win]-[Non-Win])					
R. lateral occipital cortex (superior division) *R. angular gyrus, R. lateral occipital cortex (inferior division), R. middle temporal gyrus (temporoccipital part)*	2727	-50	4	2	6.52×10^{-3}

Table S6. *Pearson's (r) correlations between anhedonia, behavioral activation, environmental reward, and substance use at the 3-month follow-up*

	Motivation
Anhedonia	
FU1	0.44
FU3	0.19
BADS	
FU1	-0.21
FU3	-0.04
RPI	
FU1	-0.06
FU3	0.20
Substance Use	
FU1	0.33
FU3	0.10

Table S7. *Whole-brain results for significant clusters of attenuation 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					
R. subcallosal cortex					
R. anterior cingulate gyrus, R. paracingulate gyrus, L. frontal medial cortex, L. frontal pole	2194	4	27	-4	2.39×10^{-2}
OUDD>HC					
None					
OUDD<HC					
R. planum temporale					
R. superior temporal gyrus (posterior division), R. supramarginal gyrus (posterior division), R. parietal operculum cortex, R. middle temporal gyrus (posterior)	3140	62	-33	15	4.94×10^{-3}
R. superior frontal gyrus					
R. juxtapositional lobule cortex, L. precentral gyrus	2149	7	13	62	4.25×10^{-2}
Receipt ([Win]-[Non-Win])					
OUDD					
None					
HC					
None					
OUDD>HC					
None					
OUDD<HC					
L. central opercular cortex					
L. precentral gyrus, L. temporale pole, L. inferior frontal gyrus (pars opercularis), L. frontal operculum cortex, L. insular cortex, L. planum polare	2727	-50	4	2	6.52×10^{-3}

APPENDIX 3: SUPPLEMENTARY FIGURES

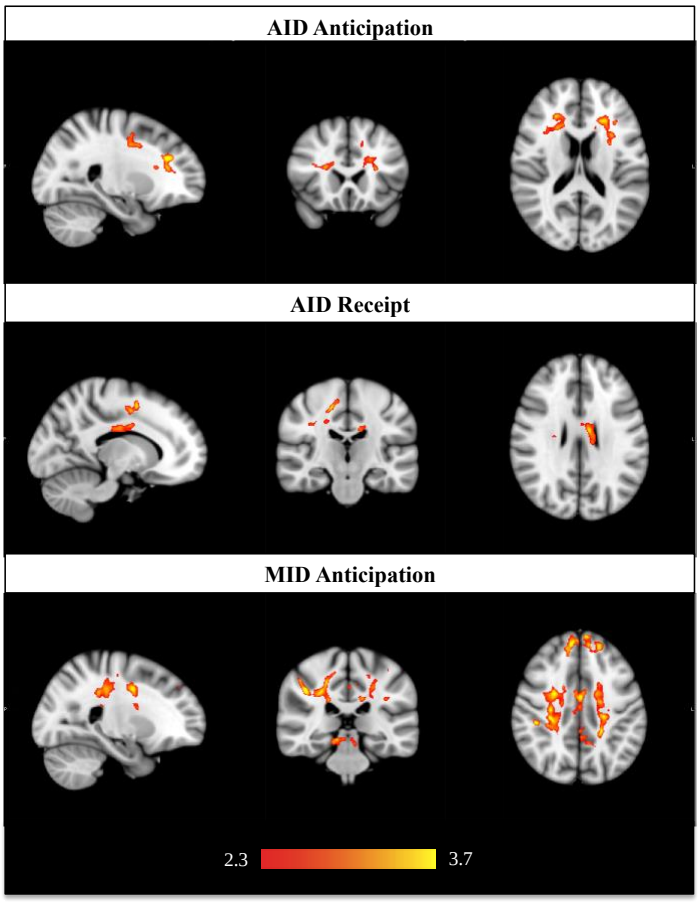

Figure S1. PPI results for global connectivity with rACC during anticipation and receipt of substance-free activity image (AID) and monetary reward (MID) with age as a predictor.

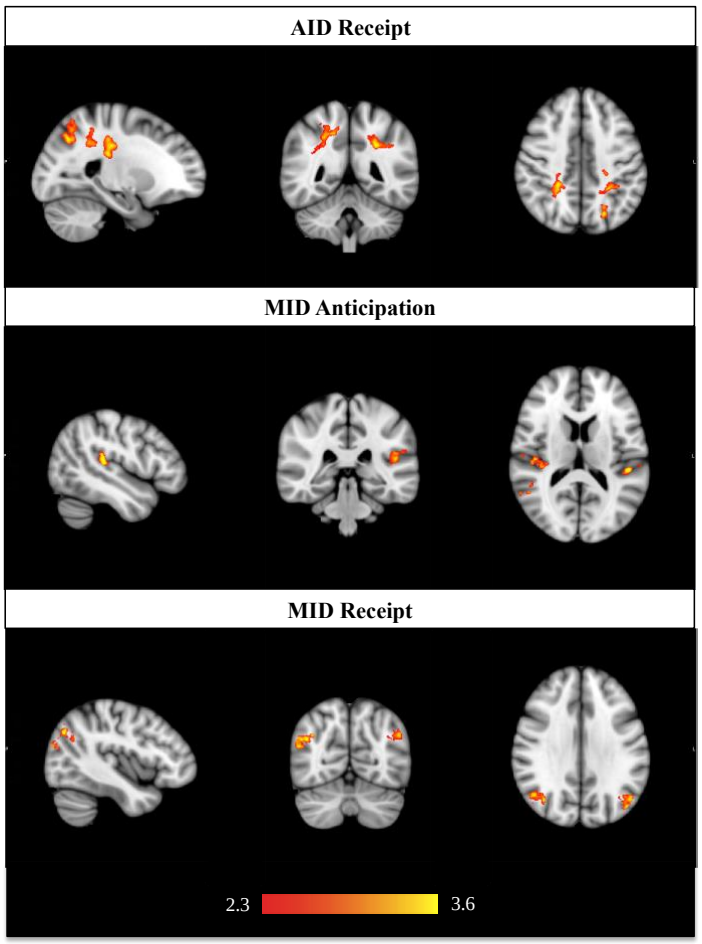

Figure S2. PPI results for attenuation of connectivity (Run 1>Run2) with rACC during anticipation and receipt of substance-free activity image (AID) and monetary reward (MID) with age as a predictor.

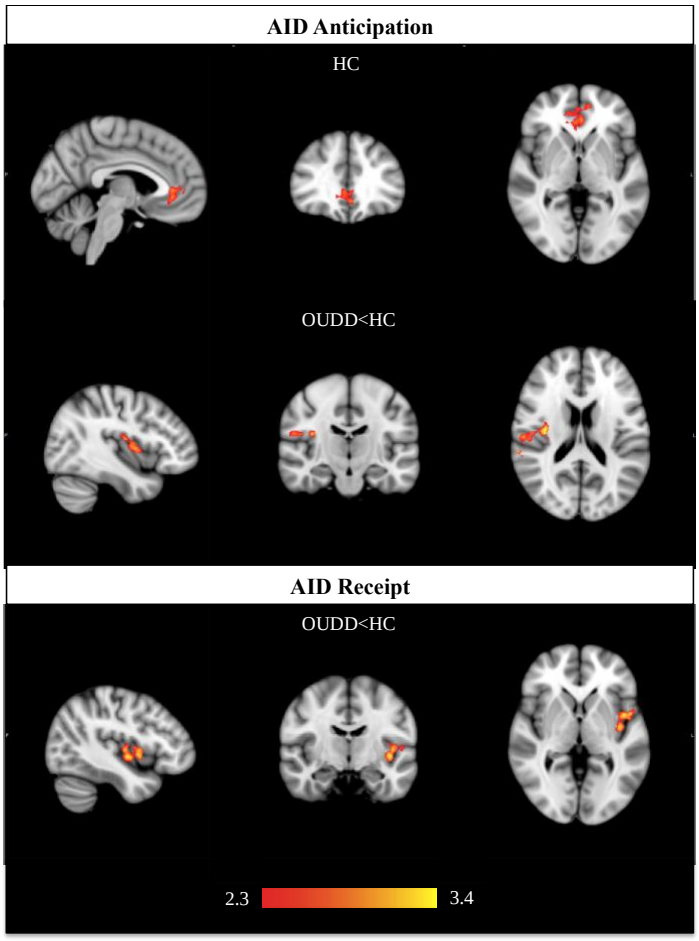

Figure S3. Whole-brain results for attenuation of connectivity (Run 1>Run2) during anticipation and receipt of substance-free activity image reward (AID).

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