Published in final edited form as:

Biol Psychiatry. 2011 September 15; 70(6): 553–560. doi:10.1016/j.biopsych.2011.05.008.

AN INITIAL STUDY OF NEURAL RESPONSES TO MONETARY INCENTIVES AS RELATED TO TREATMENT OUTCOME IN COCAINE DEPENDENCE

Zhiru Jia^{*,^}, Patrick D. Worhunsky^{*}, Kathleen M. Carroll, Bruce J. Rounsaville, Michael C. Stevens, Godfrey D. Pearlson, and Marc N. Potenza

Department of Psychiatry (ZJ, PDW, KMC, BJR), Yale University School of Medicine and Veteran Affairs Connecticut Healthcare System, West Haven, Connecticut; Department of Psychiatry (MCS, GDP), Yale University School of Medicine and Olin Research Center Institute of Living/Hartford Hospital, Hartford, Connecticut; Department of Psychiatry, Child Study Center and Neurobiology (MNP), Yale University School of Medicine, New Haven, Connecticut.

Abstract

Background—Although cocaine dependence involves abnormalities in drug-related reward-based decision-making, it is not well understood whether these abnormalities generalize to non-drug-related cues and rewards, and how neural functions underlying reward processing in cocaine abusers relate to treatment outcome.

Methods—Twenty cocaine dependent (CD) patients before treatment and 20 matched healthy control (HC) subjects participated in fMRI while performing a Monetary Incentive Delay Task (MIDT). Outcomes through eight weeks were assessed via percent cocaine-negative urine toxicology, self-reported cocaine abstinence, and treatment retention.

Results—Amongst the whole sample, anticipation of working for monetary reward (i.e., reward anticipation) was associated with activation in the ventral striatum (VS), medial frontal gyrus, thalamus, right subcallosal gyrus, right insula, and left amygdala. CD as compared with HC participants exhibited greater activation during notification of rewarding outcome (i.e., reward receipt) in left and right VS, right caudate, and right insula. In CD participants during reward

© 2011 Society of Biological Psychiatry. Published by Elsevier Inc. All rights reserved.

Corresponding author: Marc N. Potenza, MD, PhD, Yale School of Medicine, Connecticut Mental Health Center, Room S-104, 34 Park Street, New Haven, CT 06517, marc.potenza@yale.edu, Phone: 203 974-7356, Fax: 203 974-7366.

^{*}These authors contributed equally to the generation of this manuscript.

[^]Current address: Department of Psychiatry, Weill Cornell Medical College, White Plains, New York

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

DISCLOSURES

The authors report that they have no biomedical financial interests or potential conflicts of interest with respect to the content of this manuscript.

Dr Potenza has received financial support or compensation for the following:

Dr Potenza consults for and is an advisor to Boehringer Ingelheim; has consulted for and has financial interests in Somaxon; has received research support from the National Institutes of Health, Veteran's Administration, Mohegan Sun Casino, the National Center for Responsible Gaming and its affiliated Institute for Research on Gambling Disorders, and Forest Laboratories, Psyadon, Ortho-McNeil, Oy-Control/Biotie and Glaxo-SmithKline pharmaceuticals; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse control disorders or other health topics; has consulted for law offices and the federal public defender's office in issues related to impulse control disorders; provides clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; has performed grant reviews for the National Institutes of Health and other agencies; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts.

anticipation, activation in left and right thalamus and right caudate correlated negatively with percent cocaine-negative urine toxicology, activation in thalamus bilaterally correlated negatively with self-reported abstinence measures, and activation in left amygdala and parahippocampal gyrus correlated negatively with treatment retention. During reward notification, activation in right thalamus, right VS and left culmen correlated negatively with abstinence and with urine toxicology.

Conclusions—These findings suggest that in treatment-seeking CD participants, cortico-limbic reward circuitry is relatively over-activated during MIDT performance and specific regional activations related to reward processing may predict aspects of treatment outcome and represent important targets for treatment development in CD.

Keywords

Cocaine Dependence; Reward Circuitry; Monetary Incentive Delay Task; Anticipation; fMRI; Treatment Outcome

INTRODUCTION

Cocaine dependence (CD) is a public health concern associated with a significant rate of relapse (1). Cocaine activates meso-cortico-limbic circuitry including the ventral striatum (VS), amygdala, and regions of the prefrontal cortex (PFC), including the orbital frontal cortex (OFC), ventromedial prefrontal cortex (vmPFC) and anterior cingulate cortex (ACC) (2–3). As a similar network of regions is implicated in reward processing, difficulties in developing effective treatments for CD may derive in part from cocaine's activation of reward circuitry (4, 5). Several behavioral therapies have demonstrated efficacy and durability among CD populations (6). However, there remains variability in treatment response, and identification of consistent predictors of treatment outcome has been elusive (7). Neuroimaging techniques examining brain function related to specific neurocognitive features hypothesized to underlie important aspects of addiction (e.g., reward processing) may aid in this endeavor.

While individuals with substance addictions display a hypersensitivity of reward processes in response to drug-related cues (8), evidence of hypersensitivity to non-drug-related reward processing in addiction is mixed. Although tobacco smokers display similar responses to cigarette-related and monetary incentives (9), alcoholic samples display relatively diminished activation of VS during reward anticipation, with degree of activation correlating inversely with alcohol craving and impulsivity measures (10–11). However, a sample of alcohol-dependent patients with frequent co-occurring CD demonstrated increased meso-cortico-limbic activation during reward processing, particularly during reward receipt (12), consistent with other findings that individuals with CD show relatively increased cortico-limbic activations in response to promotivational or rewarding stimuli (13). Additionally, increased VS activity during monetary reward anticipation has been reported in other drug (e.g., cannabis) users relative to healthy control comparison subjects (14). To date, neural responses during reward anticipation and receipt have not been examined in treatment-seeking CD patients with respect to treatment outcome measures.

Neuroimaging approaches including fMRI have investigated neural correlates of treatment outcomes in patients with cocaine or other stimulant dependence (15–18) or alcoholism (19). We previously reported (18) in CD patients that during fMRI Stroop performance, activation of vmPFC, left posterior cingulate cortex (PCC), and right dorsal striatum correlated positively with cocaine abstinence and activation of dorsolateral prefrontal cortex (dlPFC)

correlated inversely with treatment retention. Although important, this study investigated one neurocognitive construct (cognitive control) and lacked a control comparison group.

Here we extend this earlier work by using a Monetary Incentive Delay Task (MIDT) to investigate in the same CD sample the neural correlates of reward processing, how they differ in CD and healthy control (HC) participants, and how these brain measures relate to treatment outcome. The MIDT dissects reward processing into anticipatory and outcome phases related to receiving reward or avoiding punishment (20, 21). An activation likelihood estimate (ALE) meta-analysis of fMRI MIDT studies (21) found increased activation of the VS, thalamus, insula, medial PFC, and culmen during anticipation of working for monetary reward (hereafter termed reward anticipation) in gain versus non-gain conditions. The same meta-analysis identified activation in caudate, VS, subcallosal gyrus, amygdala, and parahippocampal gyrus during notification of a rewarding outcome (hereafter termed reward receipt) in gain vs. non-gain conditions. The current study aimed to investigate brain activity in these regions in CD patients as compared to HC subjects, and in relation to treatment outcome.

We hypothesized that: (1) both groups of participants would show activation of VS, thalamus, insula, medial PFC, and culmen during reward anticipation and activation of caudate, VS, subcallosal gyrus, amygdala, and parahippocampal gyrus during reward receipt; (2) CD as compared to HC participants would show increased regional brain activations during reward anticipation and outcome; and (3) increased regional brain activation during phases of reward processing in CD patients at treatment onset would correlate with poor treatment outcome abstinence and retention measures.

METHODS

PARTICIPANTS AND TREATMENTS

Participants included 20 treatment-seeking CD patients as described previously (18) and 20 HC participants matched on age, gender, and race (Table 1) who all spoke English as their first language and were right-handed. CD participants were recruited for the treatment studies from community health facilities, and all CD patients enrolled in treatment were afforded the option to participate in fMRI. HC participants were recruited through local advertisements, and while matching efforts resulted in HC subjects on average participating at a later date, all scanning occurred over a two-year period during which standard and frequent quality assurance measures were employed to maintain magnet stability and reliability. Motivations for fMRI participation may have involved monetary reimbursement for time related to involvement, and possibly other factors (e.g., motivation to advance understandings of addictions). The MIDT fMRI scanning was performed before the first treatment session in the CD group. Prolonged abstinence from cocaine was not required for CD patients given the treatment-seeking nature of the sample and need to be actively using cocaine to participate in treatment. At the scanning session, all CD participants denied using earlier that day. Two of 22 CD patients scanned were excluded due to head motion exceeding 4 mm. All CD participants met DSM-IV criteria for CD as determined via Structured Clinical Interview for DSM-IV (SCID;24) and were involved in one of two clinical trials being conducted in community health clinics as described previously (17). Briefly, Study 1 (N = 8) compared a computer-assisted version of CBT to a standard community-based drug treatment program as described elsewhere (23). Participants received either weekly individual plus group sessions (treatment as usual TAU; N=3) or TAU plus a multimedia computer-assisted version of CBT to which patients had access twice weekly during eight weeks of treatment (N=5). Study 2 (n = 12) was a randomized clinical trial of cocaine users randomized to weekly individual CBT in conjunction with one of four conditions: a) placebo (N=4), b) disulfiram (N=4), c) contingency management + placebo

(N=3) or d) contingency management + disulfiram (N=1). Contingency management in Study 2 consisted of providing positive reinforcement for cocaine-free urines. The outcome measures examined are frequently used in randomized clinical trials and have been employed previously when examining fMRI correlates of treatment outcome in CD (6, 18). The measures included longest duration of self-reported continuous abstinence, percent (of at least twice-weekly) cocaine-negative urine toxicology screens, and weeks of treatment completed. Additional information on CD participants has been published previously (18). The study was approved by the Yale Human Investigation Committee. All participants provided written informed consent

MONETARY INCENTIVE DELAY TASK (MIDT)

The present study used a revised MIDT following the protocol described previously (20, 21, 25–27) with modifications described briefly in the Supplement.

IMAGE ACQUISITION AND ANALYSIS

Image acquisition methods used previously described approaches (25–30) as detailed in the Supplement. MRI data were analyzed in two ways. A region of interest (ROI) approach was used initially to test our hypotheses, as described below. Subsequent whole-brain statistical parametric analyses were also conducted to examine regional activations associated with reward-processing and between-diagnostic-group differences. Whole-brain analyses were conducted using voxel-level family-wise error (FWE) corrected thresholds and also at less stringent conjoint thresholds of uncorrected $p < 0.001$ or $p < 0.005$ with cluster extent $k > 20$ voxels. Due to group differences in IQ and education, these were included as covariates in the two-sample t-tests.

REGION OF INTEREST (ROI) ANALYSIS

Group-level random-effects models were investigated using the Small Volume Correction (SVC) tool in SPM2. Regions of interest (ROIs) were derived from an ALE meta-analysis study (22) that included 21 MIDT studies with 20 contributing to anticipation and 12 to outcome processing. The 15 total locations reported for analogous contrasts (gain vs non-gain) during anticipatory and outcome phases were first transformed into MNI space using tal2mni (Matthew Brett, <http://imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/tal2mni.m>). For anatomical accuracy, we have used the term “VS” for the regions labeled as “nucleus accumbens” in the meta-analysis. Search volumes were then defined as spheres with 4mm radii centered on the MNI coordinates. Each of the eight anticipation-related volumes and seven outcome-related volumes (Figure S2 in the Supplement) were applied to a one-sample t-test of the entire study sample, a between-groups two-sample t-test, and correlational analyses investigating the relationship between brain activation and treatment outcome in the CD group. FWE corrected p-values (pFWE) were used in all SVC ROI analyses at a threshold of $pFWE < 0.05$.

RESULTS

SAMPLE CHARACTERISTICS AND BEHAVIORAL DATA

CD and HC participants did not differ on measures of age, gender, race, or MIDT performance (total earnings, hit rate and reaction time, Table 1). More CD participants were daily tobacco smokers (85%) than HC participants (10%) ($\chi^2=22.56$, $DF=1$, $p < 0.00001$). CD participants had slightly lower overall years of education ($t = -2.42$, $p < 0.05$) and estimated IQ levels ($t = -3.06$, $p < 0.01$) than did HC participants. However, both groups' mean education and IQ estimates were within the average range. The CD sample reported an average of 12.30 (SD = 9.49) days of cocaine use in the 28 days prior to treatment and an

average of 11.05 (SD = 7.86) years of lifetime cocaine use. On average, patients reported last using cocaine 5.4 (SD=5.7) days prior to scanning (although the precise timing was not objectively verified), remained in treatment 5.5 (SD=3.1) weeks, reported 32.0 (SD=21.4) consecutive days of abstinence, and provided 58.4% (SD=46.8) cocaine-free urine samples. Co-occurring conditions and non-cocaine substance use of the CD patients are shown in Table S1 in the Supplement. Controlling for days of use prior to entering treatment, there was no significant relationship between intervention received and treatment outcome measures or brain activations or correlations in regions of interest (all $p>0.1$).

REWARD ANTICIPATION AND OUTCOME—Results of the ROI analyses for the one-sample and between-group tests are listed in Table 2. For the one-sample t-test (N=40), significant activation during anticipation was observed in six of the eight anticipation-related ROIs (Table 2), including bilaterally in the VS, right insula, two left thalamus ROIs and medial frontal gyrus. Significant anticipatory activation was also observed in four of the outcome-related ROIs (Table 2), including right and left VS, right subcallosal gyrus, and left amygdala. No significant activations were observed in any of the ROIs during reward outcomes. There were also no between-group differences during anticipation in any of the ROIs; however, CD participants displayed greater activation in comparison to HC participants in the left VS reward-outcome-related ROI (Table 2). CD participants also displayed significantly greater activation than HC participants during outcome in three of the reward-anticipation related ROIs including bilateral VS and right insula, (Table 2).

The one-sample (20 CD + 20 HC participants) whole-brain FWE corrected analysis showed significant activation during reward anticipation (gain versus non-gain) in medial frontal gyrus/anterior cingulate, right putamen, and bilaterally in fusiform gyrus, lingual gyrus, and cuneus ($p_{FWE}<0.05$; Table S2 & Figure S3A in the Supplement). During outcome in gain versus non-gain contrasts across all participants, increased activation was observed in right parahippocampal gyrus/amygdala (Table S2 & Figure S3B in the Supplement). Within- and between-group analyses did not survive whole-brain FWE correction at $p_{FWE}<0.05$; however, the whole-brain results at a less stringent conjoint threshold of uncorrected $p<0.001$ or $p<0.005$ and cluster extent $k>20$ voxels are displayed in Figure 1 and listed in Table S3 in the Supplement. Briefly, the within- and between-group whole brain analyses confirm ROI findings of increased striatal activation during anticipation in both groups that was greater in CD patients as compared to HC ones, and increased striatal activation in response to reward outcomes in CD versus HC subjects.

REWARD PROCESSING CORRELATION WITH TREATMENT OUTCOME

Table 3 lists the regions displaying significant association between reward processing and treatment outcome in CD participants. For reward-anticipation related ROIs (Table 3), activation of left and right thalamus during anticipation in the CD group correlated inversely with self-reported abstinence and negative urine toxicology. Activation of right thalamus during outcome was also negatively associated with self-reported abstinence and with negative urine toxicology. Activation of the culmen during outcome correlated inversely with self-reported abstinence and negative urine toxicology. For reward-outcome related ROIs (Table 3), activation of left amygdala and left parahippocampal gyrus during anticipation was inversely correlated with treatment retention. Activation of right VS during outcome was negatively associated with self-reported abstinence and negatively with urine toxicology. No correlation survived whole-brain FWE correction at $p_{FWE}<0.05$, though results at a conjoint threshold of uncorrected $p<0.005$ and cluster extend $k>20$ (Table S4, and Figure S4 in the Supplement) show the general trends of correlations of MIDT activation with treatment outcome measures.

DISCUSSION

To our knowledge, this is the first study to compare cocaine abusers and healthy controls using the MIDT and the first to investigate the neural correlates of reward processing in relation to treatment outcome in CD. Consistent with our first hypothesis, the MIDT engaged VS and thalamus across all participants during reward anticipation, demonstrating the effectiveness of the modified task activating reward-processing-related brain regions, as observed in previous studies (20–22, 25–27). Consistent with our second hypothesis, CD patients relative to HC subjects showed relatively increased activation during reward receipt in bilateral VS, right caudate, and right insula. In support of the third hypothesis, pre-treatment MIDT activations in the CD group correlated with treatment outcome measures, with activation during anticipation in left and right thalamus correlating inversely with abstinence measures, activation during anticipation in left amygdala and left parahippocampal gyrus correlating inversely with treatment retention, and activation during outcome in right thalamus, right caudate and culmen correlating inversely with abstinence measures. These findings suggest that specific neural abnormalities involved in reward processing and present prior to treatment in CD may underlie CD patients' abilities to remain abstinent. Thus, reward processing and its related neuropathology in CD may represent important targets for treatment development.

REGIONAL BRAIN ACTIVATIONS DURING REWARD PROCESSING – SAMPLE-WIDE FINDINGS

The present finding of VS activation during the anticipatory and outcome phases of reward processing is consistent with prior results using the MIDT (20, 25). Similarly, other regions activated during the anticipation of working for monetary reward have been implicated in specific aspects of reward processing (e.g., anterior insula and thalamus in reward-based decision-making) (31). Amygdala activation during reward anticipation is consistent with its role in processing emotionally-salient stimuli and monetary rewards (29, 32). Together, these findings suggest that the MIDT is appropriately activating reward circuitry during anticipatory phases in our experiment.

FMRI OF REWARD PROCESSING IN COCAINE DEPENDENCE

Reward-related processes are central to drug dependence, with anticipation theoretically representing an important phase of incentive processing guiding subsequent engagement in hedonic behaviors. Incentive salience (32) or impulsivity (34) theories of drug addiction suggest that reward or drug cue responses may be more robust in addicted individuals, whereas a reward deficiency syndrome theory (RDS) of addiction (35) suggests diminished recruitment of reward circuitry. A possible drug-sensitized brain reward circuit where heightened drug motivation may 'spillover' to non-drug rewards (36) is supported by evidence from animal studies that drug sensitization can increase the incentive value of other rewards, such as sucrose or other foods (37). Human studies also suggest that some cocaine-addicted individuals are hypersexual (38) and some substance dependent individuals may be hyper-responsive to money rewards (39). While the incentive sensitization hypothesis pertains strictly to drug-associated cues, the present results demonstrated relatively increased activation of brain reward circuitry (e.g., in VS, caudate, thalamus, amygdala, and insula) during both reward anticipation and receipt. Similarly, a study of adolescents with externalizing disorders and at risk for substance use disorders showed increased VS activation in response to reward outcomes during a MIDT (40). These findings suggest impairments that may reflect greater salience, reward hypersensitivity, inefficient processing, or perhaps some other possibilities or combinations thereof (25). The extent to which these findings represent brain changes related to cocaine exposure (41) as compared with pre-existing characteristics requires further investigation.

During reward processing, CD participants showed more robust regional activations than did HC participants in several regions including bilateral VS, right caudate, and right insula during reward receipt. Increased activation of subcortical structures (e.g., VS and caudate) and PFC have been observed frequently during drug cue processing in CD (42, 43). A prior study of reward processing in cocaine abusers using a forced choice task under monetary conditions (3) found relatively decreased brain activations in PFC and cerebellum in response to monetary rewards. The 16 cocaine abusers in (3) included only 9 who were dependent on cocaine at the time of the study. Furthermore, the cocaine abusers were not seeking treatment and were compared with 13 control subjects. The task in (3) applied fixed durations for monetary reward cues and fixed periods before and after the cue display, as well as fixed task difficulty and varied hit rates. Perhaps due to methodological differences in the tasks employed and characteristics of the samples with respect to illness severity and treatment-seeking status, the present study found relatively increased activation of the cerebellum in cocaine users, a region implicated in reward processing during MIDT performance (25). The extent to which these findings relate to neurobiological vulnerabilities prior to drug exposure, the influence of chronic cocaine exposure on brain circuitry, or other factors requires additional investigation.

The current study also implicates other brain regions relevant to addiction and its treatment. For example, more robust activation of the insula in CD participants as compared to HC during reward receipt may reflect differences in integrating interoceptive states generated during risk/reward processes (44, 45). Knutson & Greer's anticipatory affect model (22) suggests that VS activation promotes approach towards uncertain outcomes, while anterior insula activation promotes avoidance of uncertain outcomes, implicating a nascent model of the influence of anticipatory affect on choice. As these brain regions have also been linked to impaired impulse control and treatment outcome in addictions (46), future prospective investigations appear warranted to determine the extent to which specific treatments might "normalize" function within these and possibly other brain regions.

BRAIN ACTIVATIONS ASSOCIATED WITH TREATMENT OUTCOME AND RELATIONSHIP WITH PREVIOUS FINDINGS

In the present study, reduced brain activity in reward processing circuits (namely the VS and culmen in response to reward outcome and thalamus during reward anticipation) at treatment onset was associated with greater abstinence during treatment while relatively decreased amygdalar and parahippocampal activation during reward anticipation were associated with better treatment retention. Importantly, some of the same brain regions showing increased activation during reward processing were those that are inversely correlated with treatment outcome. For example, CD as compared to HC participants demonstrated relatively increased activations of VS and insula during reward anticipation, and activation within these brain regions during reward receipt correlated inversely with percent cocaine-negative urine toxicology results. These findings in conjunction with the previous report involving the same CD patients performing a Stroop task (18) seem to highlight contributions of distinct and complementary components of neural systems in treatment prediction. In the prior study, activation of vmPFC, striatum and PCC during a cognitive control task correlated positively with abstinence measures. In the current study, relatively reduced activity in overlapping circuitry was associated with a positive response to behavior therapy. It could be postulated that in CD patients, monetary rewards were increased over HC subjects as money acted as a secondary reinforcer toward substance use, and thus increased anticipation and outcome responses indicated a dysfunction in reward mechanisms more resistant to intervention. Together, these findings suggest that relatively increased activation related to 'top-down' processes and relatively decreased activation in 'bottom-up' processes may be predictive of better outcomes in the same sample. This

conceptualization of top-down and bottom-up processes in conjunction with an improved understanding of their neural underpinnings may aid in the development of improved behavioral and pharmacological treatments for addictions (47). With regard to the current study, findings suggest abnormal reward processing, detectable at the neural level, may represent an important target related to treatment in CD. Previous research indicates neurocognitive training from a top-down level may influence bottom-up delay-discounting deficits in stimulant abusers (48), and similar approaches may prove useful in augmenting traditional treatment interventions for substance dependence (49).

STRENGTHS, LIMITATIONS AND FUTURE DIRECTIONS

Strengths of the present study include a sample of patients and controls where selection criteria, assessments, and treatment outcomes (for CD patients) were well defined and validated and the use of a non-drug reward paradigm (MIDT) that probes phases of reward processing. The findings offer a potential resolution of mixed findings on MIDT and drug dependence, where CD may be associated with enhanced cortico-limbic activations and alcohol dependence in the absence of CD with relatively diminished cortico-limbic activations. Limitations include a relatively small sample of CD patients, and future studies utilizing larger samples may be able to employ more stringent statistical thresholds including whole-brain correction procedures across all analyses and correction for multiple comparisons of correlational analyses. Future studies may also investigate the possible influences of different value magnitudes on reward processing in CD in relation to treatment outcome. The use of SVC is one of multiple methodological approaches that exist for examining brain activity in regions of interest derived from previous studies, and while the current findings are supported by subsequent whole-brain analysis, alternate methods may yield slightly different results (50). HC participants were not ideally matched to CD patients on education, IQ, and non-cocaine substance use, particularly daily tobacco smoking. However, findings persisted when controlling for IQ and education differences between CD and HC groups and the estimated IQ for both groups was within the average range, which mitigates against the possibility that neurobiological factors related to widely different intellectual abilities that have been found in several previous studies represents a meaningful confound. As the time of last cocaine use prior to scanning was not objectively verified, differences may exist between reported and actual last use of drug. These differences may have an influence on fMRI findings and are a limitation of the current study. Most CD patients and very few HC participants were daily tobacco smokers, and this group difference could not be controlled for statistically (51–52). The percentage of tobacco smokers in our CD sample reflects the rates observed in previous research of individuals with cocaine dependence (see 53), though as nicotine dependent smokers display non-differential reward sensitivity in response to cigarette-related and monetary incentives and less VS activation during reward anticipation compared to occasional smokers (9), future studies should more directly examine the effects of nicotine on reward processes in cocaine dependence. Half of the cocaine subjects reported life-time alcohol dependence and one fifth were using alcohol around the time of the study. Although alcohol dependent subjects have shown relatively diminished VS activation during reward anticipation (10–11), the current findings are consistent with previous reports of greater VS activation by reward deliveries in alcoholics who also used other drugs including cocaine (12). Future studies should directly examine the potential influences of tobacco, alcohol, and other substances in CD reward processing.

The present study provides evidence that approach-related (monetary reward) activation inversely correlates with therapeutic outcome measures, and these findings differ from those in the same CD subjects performing an fMRI Stroop task in which positive correlations between cognitive control task activation and treatment outcome measures were observed. Future research examining the association between the neural mechanisms underlying

cognitive control and reward-processing within individuals may provide insight into how the relationship between systems may influence clinical outcome. In line with the findings that immediate monetary reward availability in delay discounting tasks recruits VS, but not choices between deferred rewards (54), the increased VS activation by the ‘now-ish’ rewards converges on how CD subjects that are over-responsive to ‘right-now’ (salient) rewards may be at particular risk of relapse. Future investigations should address the study limitations and investigate the extent to which specific therapies (e.g., those specifically linked to reward processing such as contingency management or cognitive enhancing approaches shown to modify delay discounting (48)) might effectively target specific neural abnormalities that underlie specific aspects of CD and other addictions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support was provided by the following Grants: National Institutes of Health grants P50-DA09241, P50-AA012870, R01-DA020908, R01-DA020709, R01-AA016599, R37-DA15969, K05-DA00457, and the Veterans Integrated Service Network 1 Mental Illness Research, Education, and Clinical Center (MIRECC).

REFERENCES

1. Yuferov V, Butelman ER, Kreek MJ. Biological clock: biological clocks may modulate drug addiction. *Eur J Hum Genet.* 2005; 13(10):1101–1103. [PubMed: 16094306]
2. Volkow ND, Wang GJ, Ma Y, Fowler JS, Wong C, Ding YS, et al. Activation of orbital and medial prefrontal cortex by methylphenidate in cocaine-addicted subjects but not in controls: relevance to addiction. *J Neurosci.* 2005; 25(15):3932–3939. [PubMed: 15829645]
3. Goldstein RZ, Alia-Klein N, Tomasi D, Zhang L, Cottone LA, Maloney T, et al. Is decreased prefrontal cortical sensitivity to monetary reward is associated with impaired motivation and self-control in cocaine addiction? *Am J Psychiatry.* 2007; 164(1):43–51. [PubMed: 17202543]
4. Chau DT, Roth RM, Green AI. The neural circuitry of reward and its relevance to psychiatric disorders. *Curr Psychiatry Rep.* 2004; 6:391–399. [PubMed: 15355762]
5. Gorelick DA. Neurobiology and treatment of cocaine dependence. *Eur Psychiatry.* 2008; 23(2):16.
6. Carroll KM, Onken LS. Behavioral therapies for drug abuse. *Am J Psychiatry.* 2005; 162:1452–1460. [PubMed: 16055766]
7. Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW. A meta-analytic review of psychosocial interventions for substance use disorders. *Am J Psychiatry.* 2008; 165:179–187. [PubMed: 18198270]
8. Volkow ND, Wang G-J, Fowler JS, Tomasi D, Telang F, Baler R. Addiction: Decreased reward sensitivity and increased expectation sensitivity conspire to overwhelm the brain's control circuit. *Bioessays.* 2010; 32:748–755. [PubMed: 20730946]
9. Buhler M, Vollstadt-Klein S, Kobiella A, Budde H, Reed LJ, Braus DF, et al. Nicotine dependence is characterized by disordered reward processing in a network driving motivation. *Biol Psychiatry.* 2010; 67:745–752. [PubMed: 20044075]
10. Beck A, Schlagenhauf F, Wüstenberg T, Hein J, Kienast T, Kahnt T, et al. Ventral striatal activation during reward anticipation correlates with impulsivity in alcoholics. *Biol Psychiatry.* 2009; 66:734–742. [PubMed: 19560123]
11. Wrase J, Schlagenhauf F, Kienast T, Wüstenberg T, Bermpohl F, Kahnt T, et al. Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics. *Neuroimage.* 2007; 35:787–794. [PubMed: 17291784]
12. Bjork JM, Smith AR, Hommer DW. Striatal sensitivity to reward deliveries and omissions in substance dependent patients. *Neuroimage.* 2008; 42(4):1609–1621. [PubMed: 18672069]

13. Potenza MN, Hong KA, Lacadie CM, Fulbright RK, Bergquist KL, Sinha R. Neural correlates of stress-induced and cue-induced craving: Influences of gender and cocaine dependence. *Am J Psychiatry*. (under review).
14. Nestor L, Hester R, Garavan H. Increased ventral striatal BOLD activity during non-drug reward anticipation in cannabis users. *Neuroimage*. 2010; 49(1):1133–1143. [PubMed: 19631753]
15. Paulus MP, Tapert SF, Schuckit MA. Neural activation patterns of methamphetamine-dependent subjects during decision making predict relapse. *Arch Gen Psychiatry*. 2005; 62:761–768. [PubMed: 15997017]
16. Kosten TR, Scanley BE, Tucker KA, Oliveto A, Prince C, Sinha R, et al. Cue-induced brain activity changes and relapse in cocaine-dependent patients. *Neuropsychopharmacology*. 2006; 31:644–650. [PubMed: 16123763]
17. Moeller FG, Steinberg JL, Schmitz JM, Ma L, Liu S, Kjöme KL, et al. Working memory fMRI activation in cocaine-dependent subjects: association with treatment response. *Psychiatry Res*. 2010; 181:174–182. [PubMed: 20153142]
18. Brewer JA, Worhunsky PD, Carroll KM, Rounsaville BJ, Potenza MN. Pretreatment brain activation during stroop task is associated with outcomes in cocaine-dependent patients. *Biol Psychiatry*. 2008; 64(11):998–1004. [PubMed: 18635157]
19. Grusser SM, Wrase J, Klein S, Hermann D, Smolka MN, Ruf M, et al. Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. *Psychopharmacology*. 2004; 175:296–302. [PubMed: 15127179]
20. Knutson B, Fong GW, Adams CM, Varner JL, Hommer D. Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport*. 2001; 12:3683–3687. [PubMed: 11726774]
21. Andrews MM, Medo SA, Thomas AD, Potenza MN, Krystal JH, Worhunsky P, et al. Individuals Family History Positive for Alcoholism Show Functional Magnetic Resonance Imaging Differences in Reward Sensitivity That Are Related to Impulsivity Factors. *Biol Psychiatry*. (in press).
22. Knutson B, Greer SM. Anticipatory affect: neural correlates and consequences for choice. *Philos Trans R Soc Lond B Biol Sci*. 2008; 363:3771–3786. [PubMed: 18829428]
23. Carroll KM, Ball SA, Martino S, Nich C, Babuscio TA, Nuro KF, et al. Computer-assisted delivery of cognitive-behavioral therapy for addiction: A randomized trial of CBT4CBT. *Am J Psychiatry*. 2008; 165(7):881–888. [PubMed: 18450927]
24. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders. Research Version, Patient Edition (SCID-I/P). New York: Biometrics Research, New York State Psychiatric Institute; 2002.
25. Knutson B, Westdorp A, Kaiser E, Hommer D. FMRI visualization of brain activity during a monetary incentive delay task. *Neuroimage*. 2000; 12:20–27. [PubMed: 10875899]
26. Knutson B, Bjork JM, Fong GW, Hommer D, Mattay VS, Weinberger DR. Amphetamine modulates human incentive processing. *Neuron*. 2004; 43:261–269. [PubMed: 15260961]
27. Dillon DG, Holmes AJ, Jahn AL, Bogdan R, Wald LL, Pizzagalli DA. Dissociation of neural regions associated with anticipatory versus consummatory phases of incentive processing. *Psychophysiology*. 2008; 45(1):36–49. [PubMed: 17850241]
28. Freire L, Roche A, Mangin JF. What is the best similarity measure for motion correction in fMRI time series? *IEEE Trans Med Imaging*. 2002; 21:470–484. [PubMed: 12071618]
29. Breiter HC, Aharon I, Kahneman D, Dale A, Shizgal P. Functional imaging of neural responses to expectancy and experience of monetary gains and losses. *Neuron*. 2001; 30:619–639. [PubMed: 11395019]
30. Calhoun VD, Stevens MC, Pearlson GD, Kiehl KA. fMRI analysis with the general linear model: Removal of latency-induced amplitude bias by incorporation of hemodynamic derivative terms. *Neuroimage*. 2004; 22:252–257. [PubMed: 15110015]
31. Bush G, Vogt BA, Holmes J, Dale AM, Greve D, Jenike MA, et al. Dorsal anterior cingulate cortex: A role in reward-based decision making. *Proc Natl Acad Sci USA*. 2002; 99:523–528. [PubMed: 11756669]
32. Canli T, Sivers H, Whitfield SL, Gotlib IH, Gabrieli JE. Amygdala response to happy faces as a function of extraversion. *Science*. 2002; 296(5576):2191. [PubMed: 12077407]

33. Robinson TE, Berridge KC. The incentive sensitization theory of addiction: some current issues. *Philos Trans R Soc Lond B Biol Sci.* 2008; 363:3137–3146. [PubMed: 18640920]
34. Hommer DW, Bjork JM, Gilman JM. Imaging brain response to reward in addictive disorders. *Ann NY Acad Sci.* 2011; 1216:50–61. [PubMed: 21272010]
35. Blum K, Braverman ER, Holder JM, Lubar JF, Monastra VJ, Miller D, et al. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. *J Psychoactive Drugs.* 2000; 32 Suppl((i-iv)):1–112.
36. Robinson TE, Berridge KC. Addiction. *Annu Rev Psychol.* 2003; 54:25–53. [PubMed: 12185211]
37. Wyvell CL, Berridge KC. Incentive sensitization by previous amphetamine exposure: increased cue-triggered "wanting" for sucrose reward. *J Neurosci.* 2001; 21:7831–7840. [PubMed: 11567074]
38. Washton AM, Stone-Washton N. Outpatient treatment of cocaine and crack addiction: a clinical perspective. *NIDA Res Monogr.* 1993; 135:15–30. [PubMed: 8289894]
39. Bechara A, Dolan S, Hindes A. Decision-making and addiction (part II): myopia for the future or hypersensitivity to reward. *Neuropsychologia.* 2002; 40:1690–1705. [PubMed: 11992657]
40. Bjork JM, Chen G, Smith AR, Hommer DW. Incentive-elicited mesolimbic activation and externalizing symptomatology in adolescents. *Journal of Child Psychology and Psychiatry.* 2010; 51(7):827–837. [PubMed: 20025620]
41. Beveridge TJR, Gill KE, Hanlon CA, Porrino LJ. Parallel studies of cocaine-related neural and cognitive impairment in humans and monkeys. *Philos Trans R Soc Lond B Biol Sci.* 2008; 363:3257–3266. [PubMed: 18640916]
42. Childress A, Mozely PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP. Limbic activation during cue-induced cocaine craving. *Am J Psychiatry.* 1999; 156:11–18. [PubMed: 9892292]
43. Wexler B, Gottschalk CH, Fulbright RF, Prohovnik I, Lacadie CM, Rounsaville BJ, Gore JC. fMRI of Cocaine Craving. *Am J Psychiatry.* 2001; 158:86–95. [PubMed: 11136638]
44. Craig AD. How do you feel? Interoception: The sense of the physiological condition of the body. *Nature Rev Neurosci.* 2002; 3:655–666. [PubMed: 12154366]
45. Naqvi NH, Bechara A. The hidden island of addiction: the insula. *Trends Neurosci.* 2009; 32(1): 56–67. [PubMed: 18986715]
46. Chamberlain SR, Sahakian BJ. The neuropsychiatry of impulsivity. *Curr Opin Psychiatry.* 2007; 20:255–261. [PubMed: 17415079]
47. Potenza MN, Sofuoglu M, Carroll KM, Rounsaville BJ. Neuroscience of behavioral and pharmacological treatments for addictions. *Neuron.* (in press).
48. Bickel WK, Yi R, Landes RD, Hill PF, Baxter C. Remember the future: working memory training decreases delay discounting among stimulant addicts. *Biol Psychiatry.* 2011; 69:260–265. [PubMed: 20965498]
49. Wexler BE. Computerized cognitive remediation treatment for substance abuse disorders. *Biol Psychiatry.* 2011; 69:197–198. [PubMed: 21199708]
50. Poldrack RA. Region of interest analysis for fMRI. *Soc Cogn Affect Neur.* 2007; 2:67–70.
51. Miller GA, Chapman JP. Misunderstanding Analysis of Covariance. *J Abnorm Psychology.* 2001; 1:40–48.
52. Bowerman, BL.; O'Connell, RT. *Linear statistical models: An applied approach.* 2nd edition. Belmont, CA: Duxbury; 1990.
53. Kalman D, Morissette SB, George TP. Co-morbidity of smoking in patients with psychiatric and substance use disorders. *Am J Addiction Psychiat.* 2005; 14:106–123.
54. McClure SM, Laibson DI, Loewenstein G, Cohen JD. Separate neural systems value immediate and delayed monetary rewards. *Science.* 2004; 306:503–507. [PubMed: 15486304]

Figure 1. Within- and between-group whole-brain activation during anticipation (A) and outcome (B) in gain versus non-gain contrasts displayed on axial slices (numbers indicate MNI z-coordinate for each row of slices). CD = cocaine dependent group; HC = healthy control group. L = left; * $p < 0.005$, $k > 20$; ** $p < 0.001$, $k > 20$

Table 1

Sample characteristics and behavioral performance

	CD (N = 20)	HC (N = 20)	p-values
Demographics			
Age, yrs (SD)	38.6 (9.29)	35.25 (10.19)	$t = -1.09$, $p = 0.14$
Gender, % female	40	40	$\chi^2 = 0.00$, $p = 1.00$
Race, %			
Caucasian	30	60	$\chi^2 = 3.81$, $p = 0.15$
African American	50	25	
Other	20	15	
Education, yrs (SD)	12.7 (1.13)	14.2 (2.43)	$t = -2.42$, $p = 0.01$
Estimated IQ, IQ (SD)	90.35 (12.77)	102.95 (13.23)	$t = -3.06$, $p < 0.01$
MIDT Performance			
Total earnings: \$ (SD)	33.45 (19.53)	35.83 (13.50)	$t = -0.45$, $p = 0.33$
Hit Rate: % (SD)	75.27 (11.02)	76.82 (10.89)	$t = -0.45$, $p = 0.33$
Reaction Time: ms (SD)	270.22 (79.91)	275.07 (177.66)	$t = -0.11$, $p = 0.46$

CD = cocaine dependent group. HC = healthy control group.

Table 2

Region of interest analysis for one-sample and between-group tests

Region	CD + HC						CD vs HC			
	x	y	x	t	AN	OC	t	AN	OC	t
Gain vs non-gain anticipation										
R Ventral striatum	10	8	3	3.90***	0.07			-0.69		2.41*
R Thalamus	4	-11	12	1.26	-0.75			0.45		0.94
L Ventral striatum	-12	10	-2	4.68***	2.30			0.34		2.64*
R Insula (BA 47)	32	19	1	2.93**	0.59			1.10		2.65*
L Thalamus	-6	-23	5	3.73***	-0.93			-1.01		1.67
L Thalamus	-2	-23	10	2.93*	1.11			-0.97		1.21
Medial frontal gyrus (BA 6)	0	-5	52	6.20***	0.29			1.05		1.51
Culmen	0	-61	-11	1.82	1.06			1.68		2.41
Gain vs non-gain outcome										
R Caudate	8	16	3	1.66	0.39			0.14		1.99
R Ventral striatum	12	11	-7	4.98***	1.15			-0.75		1.77
R Subcallosal gyrus	8	2	-9	4.38***	2.22			1.21		1.81
L Amygdala	-16	-2	-12	4.16***	0.89			0.52		0.90
L Ventral striatum	-8	6	-4	3.50***	1.36			0.25		2.31*
L Parahippocampal gyrus (BA 28)	-18	-27	-6	1.60	1.78			1.80		1.38
R Parahippocampal gyrus (BA 28)	22	-22	-6	2.07	1.44			2.41		1.82

SVC results of group analysis for gain vs non-gain ROIs derived from Knutson & Greer, 2008 (anticipation and outcome). CD = cocaine dependent group (N=20); HC = healthy control group (N=20); AN = anticipation; OC = outcome. MNI coordinates and t-scores listed for each region during each period for CD+HC and CD vs HC analyses. Negative t-scores indicate regions of deactivation for the CD + HC analysis and regions where CD display less activation (or more deactivation) than HC for CD vs HC analysis. Family-wise error (FWE) corrected p values marked:

* pFWE<0.05;

** pFWE<0.01;

*** pFWE<0.005.

Table 3

Regions of interest displaying significant MIDT activation correlation with treatment outcome measures

Region	Anticipation						Outcome					
	x	y	z	MDA	Utox	Weeks	MDA	Utox	Weeks	t	t	t
Gain vs non-gain anticipation												
R Thalamus	4	-11	12	-2.34*	-2.36*	0.57	-2.36*	-2.46*	-0.83			
L Thalamus	-2	-23	10	-3.00*	-3.46**	1.28	-0.48	-1.23	-0.59			
L Culmen	0	-61	-11	-1.57	-1.69	1.96	-3.15**	-2.39*	0.41			
Gain vs non-gain outcome												
R Caudate	8	16	3	-1.63	-2.90**	-1.43	-1.35	-1.97	-1.16			
R Ventral striatum	12	11	-7	-1.32	-1.25	-0.74	-2.54*	-2.35*	2.14			
L Amygdala	-16	-2	-12	1.29	1.15	-2.18*	1.26	1.28	-0.20			
L Parahippocampal gyrus (BA 28)	-18	-27	-6	-0.84	-1.35	-3.10*	-1.50	-0.98	-1.33			

SVC results of correlational analysis for gain vs non-gain ROIs derived from Knutson & Greer, 2008 (anticipation and outcome). MNI coordinates and t-scores listed for those regions displaying significant correlation with treatment outcome (MDA = maximum duration of contiguous abstinence; Utox = percent cocaine-negative urine toxicology; Weeks = weeks in treatment). Negative t-scores indicate inverse correlations.

^aAnalyses covaried for between-group IQ and education differences. Family-wise error (FWE) corrected p values marked:

* pFWE<0.05;

** pFWE<0.01;