Drug and Alcohol Dependence 166 (2016) 134–142

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Anticipatory reward processing among cocaine-dependent individuals with and without concurrent methadone-maintenance treatment: Relationship to treatment response

Sarah W. Yip[a,b,*], Elise E. DeVito[b], Hedy Kober[b], Patrick D. Worhunsky[b,c], Kathleen M. Carroll[b], Marc N. Potenza[a,b,d,e]

[a] National Center on Addiction and Substance Abuse, Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA
[b] Division of Substance Abuse, Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA
[c] Diagnostic Radiology, Yale University School of Medicine, New Haven, CT, USA
[d] Department of Neuroscience, Yale University School of Medicine, New Haven, CT, USA
[e] Yale Child Study Center, Yale University School of Medicine, New Haven, CT, USA

ARTICLE INFO

Article history:
Received 4 March 2016
Received in revised form 21 June 2016
Accepted 4 July 2016
Available online 16 July 2016

Keywords:
Medication
Cocaine
Heroin
Opioids
Methadone
Polysubstance use

ABSTRACT

Background: Cocaine dependence among opioid-dependent methadone-maintained individuals is a significant public health problem and is particularly challenging to treat. The neurobiology of this clinically complex population has not been previously assessed using fMRI.
Methods: fMRI data from cocaine-dependent, methadone-maintained (CD-MM) patients (n = 24), cocaine-dependent (CD) patients (n = 20) and healthy comparison (HC) participants (n = 21) were acquired during monetary incentive delay task performance. All patients were scanned prior to treatment for cocaine dependence. Between-group differences in anticipatory reward and loss processing were assessed using whole-brain ANOVAs in SPM12 (pFWE < 0.05). Correlations between durations of abstinence during treatment and BOLD responses within the insula and caudate were also explored.
Results: Main effects of diagnostic group, primarily involving decreased BOLD responses among CD-MM patients in comparison to HCs, were observed during anticipatory reward and loss processing within regions of posterior cingulate cortex, precuneus, inferior frontal gyrus and dorsolateral prefrontal cortex. BOLD responses within the right caudate were negatively associated with percentage of cocaine-negative urines during treatment among CD-MM patients, but not among non-methadone-maintained CD patients.
Conclusions: These data suggest neurofunctional differences that may be related to treatment outcomes for behavioral therapies between cocaine-dependent individuals with and without methadone-maintenance treatment. These findings may relate to differences in treatment efficacies and to the elevated relapse rates observed in methadone-maintained populations.

1. Introduction

1.1. Cocaine dependence among methadone-maintained individuals

Cocaine abuse or dependence is common among opiate-dependent individuals receiving methadone-maintenance treatment (Kolar et al., 1990; Dobler-Mikola et al., 2005); *e.g.*, approximately 58% of patients admitted for methadone-maintenance treatment also meet criteria for cocaine dependence; *reviewed in* (Kosten et al., 2003). Cocaine use in this population is associated with numerous negative factors including high-risk sexual behaviors (Tross et al., 2009), illegal activities (Hunt et al., 1986), poorer treatment outcomes (Schottenfeld et al., 2005; Williamson et al., 2006) and greater societal costs (Hunt et al., 1986; Carroll et al., 2014a,b). While clinically recognized for a number of years (Kolar et al., 1990), very little is known about the neurobiology of this treatment refractory population. In addition, despite significant progress in the development of effective intervention strategies, the treatment of cocaine dependence among

* Corresponding author at: 1 Church Street, 7th Floor, Room 730, New Haven, CT 06510-3330, USA.
E-mail address: sarah.yip@yale.edu (S.W. Yip).

http://dx.doi.org/10.1016/j.drugalcdep.2016.07.006
0376-8716/

methadone-maintained individuals remains particularly challenging (Carroll et al., 2014a,b).

1.2. Neural function and treatment response

Studies conducted in non-methadone-maintained populations suggest that individual variability in response to treatment interventions for cocaine dependence is related to variation in neural functional responses in regions including the striatum, cingulate and the prefrontal cortex (PFC; *e.g.*, Brewer et al., 2008; Marhe et al., 2013; Clark et al., 2014). Alterations in both reward-processing-related neurocircuitry (*e.g.*, striatum, insula) and in fronto-parietal regions (*e.g.*, dorsolateral prefrontal and orbitofrontal cortices, posterior cingulate cortex (PCC), cuneus and precuneus) have been reported both among individuals with cocaine dependence (Brewer et al., 2008; Potenza et al., 2012; Patel et al., 2013; Clark et al., 2014) and among non-cocaine-dependent, methadone-maintained individuals (Langleben et al., 2008; Jiang et al., 2011; Gradin et al., 2014). However, given differences in treatment responses between individuals with cocaine dependence with and without methadone-maintenance treatment – in addition to the relatively diffuse action of methadone on multiple neurotransmitter systems (*e.g.*, μ-opioid, dopamine and acetylcholine systems; Merali et al., 1974; Koob, 1992) – it is possible that the functional neurobiology underlying treatment responses may differ between these two groups. Elucidation of the functional neurobiology of this difficult-to-treat population may provide important mechanistic knowledge (Balodis and Potenza, 2015) that may eventually aid in the development of novel therapies or in the improvement of current interventions and may represent an important first-step toward *a priori* assignment of patients with appropriate interventions on an individual level (*e.g.*, Feldstein Ewing and Chung, 2013).

1.3. Anticipatory reward and loss processing in addiction

Monetary incentive delay (MID) tasks (Knutson et al., 2000; Andrews et al., 2011) allow for assessment of anticipatory reward and loss processing and have been widely used to study neural responses among individuals with a range of addictions (for a recent review, see Balodis and Potenza, 2015). Findings from studies employing MID tasks generally suggest alterations in reward-related neurocircuitry during anticipatory processing among individuals with addictions. However, multiple inconsistencies exist and findings have not been the same for all drugs-of-abuse (Balodis and Potenza, 2015). While some MID studies of cocaine dependence have include methadone-maintained individuals (*e.g.*, Patel et al., 2013), these and other possible drug effects have not always been controlled for (*reviewed in* Balodis and Potenza, 2015). Direct comparison of subgroups of addicted individuals (*e.g.*, cocaine-dependent individuals with and without methadone maintenance treatment) can provide needed insight into seemingly inconsistent findings from some previous studies (*e.g.*, Patel et al., 2013; Bustamante et al., 2014), and inform current understanding of an understudied clinical population – methadone-maintained, cocaine-dependent individuals.

1.4. Study overview and hypotheses

In this study we assessed neural responses associated with anticipatory reward and loss processing during performance of a MID task (Knutson et al., 2000; Andrews et al., 2011). Neural responses were compared between: (i) cocaine-dependent, methadone-maintained (CD-MM) patients (n = 24); (ii) cocaine-dependent (CD) patients *not* maintained on methadone (n = 20); and (iii) healthy comparison (HC) participants (n = 21). All patients were scanned prior to behavioral treatment for cocaine dependence. Correlational analyses were conducted to explore associations between BOLD responses and durations of abstinence during treatment.

Based on previous findings (reviewed above) of alterations within cortico-striatal and fronto-parietal regions among individuals with cocaine and opioid dependence, separately (Brewer et al., 2008; Langleben et al., 2008; Jiang et al., 2011; Potenza et al., 2012; Patel et al., 2013; Clark et al., 2014; Gradin et al., 2014), we hypothesized: (i) a significant main effect of diagnostic group on neural responses during anticipatory reward and loss processing within cortico-striatal and fronto-parietal networks. Based on previous reports of decreased BOLD responses during reward (Bustamante et al., 2014) and loss (Patel et al., 2013) anticipation among individuals with cocaine dependence, we further hypothesized that this would involve decreased BOLD responses during anticipatory reward and loss processing among CD-MM and CD participants, in comparison to HC participants. Given methadone's inhibitory effects on μ-opioid, cholinergic and dopaminergic systems (Merali et al., 1974; Koob, 1992), we further hypothesized that: (ii) reductions in BOLD response would be most pronounced among CD participants also receiving methadone-maintenance therapy; and (iii) there would be a negative association between BOLD responses and daily methadone dose (mg/day) in this patient group.

Several recent studies conducted in non-methadone-maintained populations suggest a negative association between insular functioning and subsequent relapse. Specifically, reduced insular BOLD responses (Clark et al., 2014) and reduced insular-striatal connectivity (McHugh et al., 2013) have been positively associated with subsequent relapse to stimulants. In addition, increased caudate BOLD response has been found to be positively associated with treatment retention among individuals with cocaine dependence (Bustamante et al., 2014). Based on these data, a final exploratory hypothesis (iv) was that neural responses within the caudate and insula during anticipatory reward and loss processing would be positively associated with better treatment outcomes (maximum days of consecutive abstinence) among both CD-MM and CD patients.

2. Methods

2.1. Participants and recruitment

Treatment-seeking CD-MM participants (n = 24), treatment-seeking CD patients (n = 20) and demographically similar HC participants (n = 21) were included in this study. All patients were recruited from randomized clinical trials (RCTs) of behavioral interventions for cocaine dependence (details in Supplemental Materials). Inclusion criteria for all RCTs included a diagnosis of DSM-IV cocaine dependence, as assessed using structured clinical interview (SCID; First et al., 1995) and willingness to commit to eight weeks of treatment. Data from the CD patient group have been published previously and were collected as part of a separate study (Jia et al., 2011); however, this patient group is included here as a comparison group in order to allow for assessment of neural responses specifically related to methadone-maintenance treatment among individuals with cocaine dependence. Importantly, this earlier publication (Jia et al., 2011) did not include data relating to the anticipatory phase (A2 phase) of the MID task that is focus of the current manuscript.

HC participants were recruited from the community via advertisement. Exclusion criteria for HC participants included current or past use of any psychotropic medication, and any current or past Axis-I disorder (including lifetime alcohol- or other substance-use disorder with the exception of nicotine dependence) as assessed using a SCID (First et al., 1995).

2.2. Demographic and clinical characteristics

Demographic, clinical and cocaine-use characteristics are shown in Table 1. In comparison to both CD-MM and CD participants, HC participants had significantly more years of education ($p < 0.001$), but did not differ in age or gender (Table 1). CD-MM and CD participants did not differ in years of education, age or gender.

CD-MM and CD participants did not differ in years of pretreatment cocaine use or days of cocaine use in the month prior to treatment (p's > 0.05; Table 1). However, consistent with the general literature, CD-MM participants had significantly higher pretreatment Addiction Severity Index (ASI) scores ($p=0.005$) and achieved significantly less days of abstinence from cocaine during treatment than did non-methadone-maintained CD participants ($p < 0.001$). CD-MM and CD participants did not differ in rates of tobacco-smoking, alcohol-use, mood, anxiety or personality disorders (Table 1).

2.3. Monetary incentive delay task

The modified MID task used in this study has been previously described (Andrews et al., 2011); Supplemental Fig. 1. At the start of each trial participants were presented with a cue for 1000msec, indicating the amount of money to be won or lost on that trial (*e.g.*, 'WIN $1′, 'LOSE $1′), followed by a fixation cross (prospect of reward; A1 phase; variable duration). Participants were then presented with a target stimulus for a variable 3–5 s duration. In order to win (on 'Win' trials), or avoid losing (on 'Loss' trials) money on each trial, participants responded with a button press while the target was on the screen. Following the target stimulus, a fixation cross was again presented (anticipation of reward or loss phase; A2; variable 3–5 s duration). Finally, participants were given feedback on the outcome of the trial based on whether they successfully hit the target (*e.g.*, 'WON $1′; 'DID NOT WIN $1′; 'LOST $1′; 'DID NOT LOSE $1′). Further details (duration, subject payment) are provided in the Supplemental Materials.

2.4. Image acquisition, spatial processing and subject-level statistics

CD participants were recruited and scanned between 2006 and 2007. CD-MM participants were recruited and scanned between 2008 and 2009. All imaging data were acquired using the same Siemens Trio 3T scanner (Siemens AG, Erlangen, Germany). Further details of image acquisition, spatial processing and comparison of subject motion are presented in the Supplemental Materials. Onsets of task events were convolved with the hemodynamic response function in SPM12. Models were high-pass filtered at 128 s and included additional motion regressors from realignment. All events were modelled with temporal derivatives. Given debate regarding the significance of a neutral comparison (*e.g.*, 'WIN $0) condition (Balodis and Potenza, 2015), events of interest were compared to implicit (non-modelled) baseline activity, consistent with previous studies (*e.g.*, Andrews et al., 2011).

2.5. Group-level statistics

A single multi-level voxel-wise ANOVA including the between-subjects factor of group (CD-MM, CD, HC) and the within-subjects factor of trial type (win/loss) was used to test the primary study hypothesis of a significant main effect of diagnostic group on neural responses during anticipatory processing. In order to determine the direction of the identified main effects, post-hoc group-wise comparisons were conducted using voxel-wise *t*-tests. All statistical maps were voxel-level thresholded at $p < 0.001$ prior to undergoing cluster-based family-wise-error (FWE) correction ($pFWE < 0.05$). Associations between daily methadone dose and BOLD responses within the identified clusters were assessed using Pearson's r.

2.6. Exploratory correlational analyses related to abstinence during treatment

As described in the introduction, the insula and caudate were selected as *a priori* ROIs for correlational analyses with days of abstinence during treatment (details below), based on findings from previous studies of cocaine dependence (*e.g.*, Marhe et al., 2013; McHugh et al., 2013; Clark et al., 2014), and methadone-maintained opioid-dependence (*e.g.*, Langleben et al., 2008; Gradin et al., 2014). Previous MID studies of cocaine dependence have differed with respect to the functional coordinates used to define the caudate (*reviewed in* Balodis and Potenza, 2015) and both the anterior and posterior aspects of the insula are implicated in cocaine dependence (*e.g.*, Kilts et al., 2001; McHugh et al., 2013). Given this lack of specificity, both ROIs were defined anatomically (see Fig. S2). Bilateral anatomical ROIs were defined using the automatic anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). Comparisons of BOLD signal within these ROIs were conducted using small volume correction (SVC) as implemented in SPM12 ($pFWE < 0.05$). Average BOLD signal values for each ROI were extracted from individual participant contrast images and entered into SPSS for correlational analyses with methadone dose (CD-MM group only) and percentage of cocaine-negative urines during treatment (all patients) and were conducted using Pearson's r, two-tailed $\alpha = 0.05$.

3. Results

3.1. Task performance

The modified MID task utilizes an individual calibration method (based on participants' out-of-scanner reaction times) to ensure relatively equal numbers of 'hits' (successful wins on win trials and successful avoidance of losses on loss trials) across participants (Andrews et al., 2011). Consistent with this calibration method, neither hit rates nor total amounts of money won differed significantly across participant groups (Table 1). In addition, groups did not differ on overall reaction times for either win or loss trials (Table 1).

3.2. Whole-brain effects of group

Whole-brain ANOVAs indicated significant main effects of group on neural responses during anticipatory reward and loss processing (A2 phase of the MID task) within nine clusters (Table 2; Fig. 1). The first cluster included regions of the left posterior cingulate, cuneus, precuneus, visual cortex and parahippocampal gyrus. The second cluster included regions of the left dorsolateral prefrontal cortex (DLPFC) and left inferior and middle frontal gyri. Together, clusters three, four, five and six included regions of the right lingual, fusiform and inferior temporal gyri, of the left medial frontal gyrus and of bilateral middle and superior temporal gyri. The seventh cluster was located in the right putamen. The eighth cluster was located in the right preuneus and the ninth cluster in the right cuneus.

3.3. Groupwise comparisons

Findings from whole-brain-corrected post-hoc groupwise comparisons related to effects of group on neural responses during anticipatory reward and loss processing are described below and are shown in Fig. 1 and Table 3.

Table 1
Demographic and clinical characteristics for healthy comparison (HC) participants, cocaine-dependent, methadone-maintained (CD-MM) participants and non-methadone-maintained, cocaine-dependent (CD) participants.

	HCs (n = 21)		CD-MMs (n = 24)		CDs (n = 20)		x2	p	df
	n	%	n	%	n	%			
Gender (male)	9	42.86	8	33.33	12	57.14	3.18	0.20	2
	Mean	St. Dev.	Mean	St. Dev.	Mean	St. Dev.	F	p	df
Age	34.57	11.99	40.75	10.18	38.6	9.29	1.95	0.15	62
Education (years)	14.57	2.09	12.04	2.18	12.70	1.13	10.62	<0.001[a]	62
Monetary Incentive Delay task (MIDt) performance									
Win reaction time	257.52	60.85	308.80	140.59	252.47	76.91	2.13	0.13	62
Loss reaction time	261.01	75.54	319.35	137.45	264.67	84.57	2.20	0.12	62
Hit Rate[b]	75.67	12.21	70.23	10.80	75.27	11.02	1.63	0.20	62
Money Earned[c]	33.71	16.50	27.69	16.86	33.45	19.53	0.85	0.43	62
Pre-treatment cocaine-use variables									
Pre-treatment past month cocaine use (days)			15.42	10.14	12.30	9.49	1.09	0.30	42
Years pre-treatment cocaine use			11.71	8.08	11.05	7.86	0.08	0.79	42
Addiction Severity Index – Cocaine			0.69	0.28	0.42	0.34	8.74	<0.01	42
Days of cocaine abstinence during 56-day Tx			8.63	8.51	31.95	21.42	24.00	<0.001	42
Co-occurring disorders			n	%	n	%	x2	p	df
Current Depressive Disorder			1	4.17	0	0.00	0.01	0.92	1
Lifetime Depressive Disorder			6	25.00	10	50.00	1.97	0.16	1
Anti-Social Personality Disorder			0	0.00	4	20.00	3.14	0.08	1
Daily Tobacco Smoker			24	100.00	17	85.00	1.86	0.17	1
Current Alcohol Dependence/Abuse			2	8.33	4	20.00	0.46	0.50	1
Lifetime Alcohol Dependence/Abuse			14	58.33	11	55.00	0.01	0.92	1

[a] Post-hoc comparisons indicated significantly fewer years of education among both patient groups, in comparison to HCs; Methadone-maintained, cocaine-dependent patients and non-methadone-maintained, cocaine-dependent patients did not differ in years of education.
[b] percent trials on which participant successfully 'hit' the target.
[c] Mean amount of money ($) earned per run of the MID task; Tx = treatment.

3.3.1. *Reward anticipation.*

3.3.1.1. HCs vs. CD-MM. In comparison to HC participants, CD-MM participants exhibited reduced activity during anticipatory reward processing within two clusters: The first cluster included bilateral regions of the cuneus and precuneus and extended anteriorly into the posterior cingulate cortex (PCC). The second cluster included regions of the left DLPFC and left inferior frontal gyrus (IFG). These findings remained after controlling for years of education (Supplemental Materials).

Correlational analyses indicated a significant negative association between daily methadone dose and BOLD responses within both clusters (DLPFC/IFG: $r_{(df=22)} = -0.42$, $p = 0.040$; PCC/precuneus/cuneus: $r_{(df=22)} = -0.43$, $p = 0.036$; Fig. 1A) such

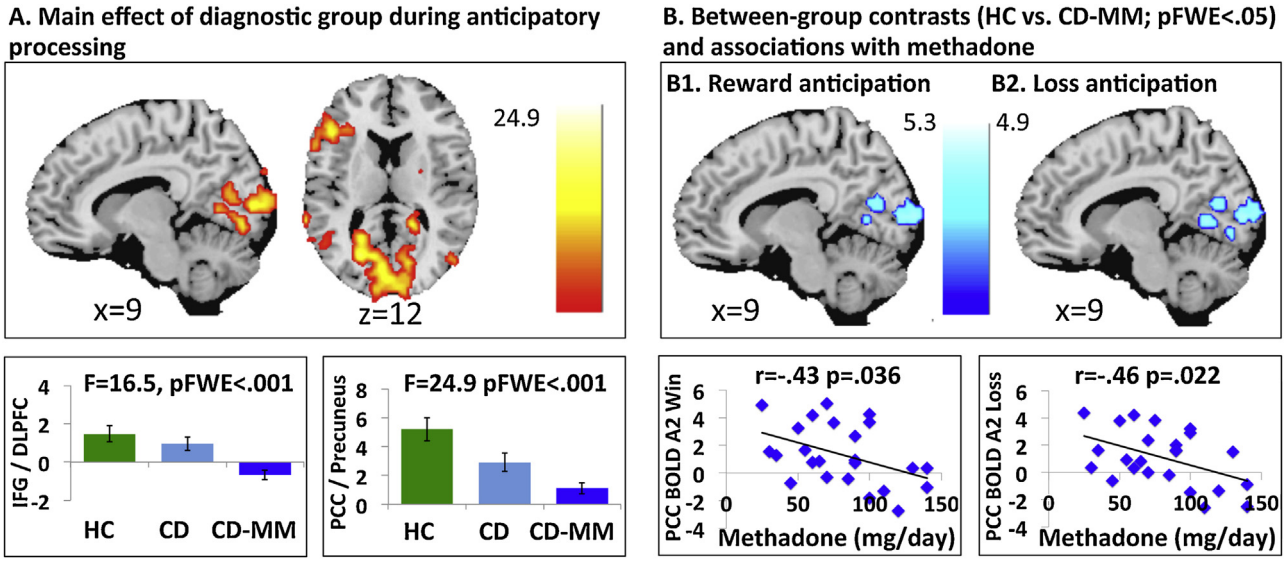

Fig. 1. Findings from whole-brain ANOVA and groupwise analyses of BOLD responses during anticipatory reward and loss processing. Panel A (top) shows main effects of diagnostic group on BOLD responses during anticipatory reward/loss processing (voxel-level p = 0.001, pFWE < 0.05, df = 63). Panel A (bottom) shows mean ± standard error BOLD signals for diagnostic groups separately within selected clusters identified in the whole-brain ANOVA. Panel B (top) shows findings from whole-brain *t*-tests of healthy comparison (HC) *versus* cocaine-dependent, methadone-maintained (CD-MM) participants (voxel-level p = 0.001, pFWE < 0.05, df = 43). Blue – light blue indicates reduced activity among CD-MM participants. Panel B (bottom) shows associations between BOLD signal within the PCC/precuneus clusters identified in the whole-brain *t*-tests and daily methadone dose among CD-MM participants. IFG = inferior frontal gyrus; DLPFC = dorsolateral prefrontal cortex; PCC = posterior cingulate cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

that those with the highest methadone dose showed the lowest recruitment of these regions. These associations remained significant after controlling for ASI scores, years of cocaine use and years of opioid use (Supplemental Materials).

3.3.1.2. CD-MM vs. *CDs.* No significant whole-brain between-group differences in neural responses during anticipatory reward processing were observed between CD-MM *versus* CD participants (pFWE > 0.05)

3.3.1.3. CDs vs. *HCs.* No significant whole-brain between-group differences in neural responses during anticipatory reward processing were observed between CD *versus* HC participants (pFWE > 0.05)

3.3.2. Loss anticipation.

3.3.2.1. CD-MM vs. *HCs.* In comparison to HC participants, CD-MM participants exhibited reduced activity during anticipatory loss processing within three clusters, including one precuneal/cuneal cluster that extended into the PCC, one left IFG and DLPFC cluster, and a third lingual gyrus cluster (Table 3). These findings remained after controlling for years of education (Supplemental Materials).

Correlational analyses indicated a significant negative association between daily methadone dose and BOLD responses within the PCC/precuneus/cuneus cluster during anticipatory loss processing ($r_{(df=22)} = -0.46$, p=0.022; Fig. 1B). Associations between daily methadone dose and BOLD responses within this cluster remained significant after controlling for ASI scores, years of cocaine use and years of opioid use (details in Supplemental Materials).

3.3.2.2. CD-MM vs. *CDs.* In comparison to CD participants, CD-MM participants exhibited reduced activity during anticipatory loss processing within two clusters, including a left IFG cluster and a second cluster including regions of the angular gyrus and middle and superior temporal gyri (Table 3 and Fig. S3).

3.3.2.3. CDs vs. *HCs.* No significant whole-brain between-group differences in neural responses during anticipatory loss processing were observed between CD *versus* HC participants (pFWE > 0.05)

3.3.3. ROI-based analyses. ROI-based analyses (conducted to allow for comparisons with previously published MID studies of cocaine dependence which have utilized ROI-based approaches; *reviewed in* Balodis and Potenza, 2015) indicated significant main effects of diagnostic group on neural responses within the bilateral caudate and insula ROIs (pFWE < 0.05). For the caudate ROI, SVC analyses identified a single peak located in the left caudate (F = 10.30, pFWE = 0.018, df = 63; peak[x,y,x] = [−18, −25, 25]). For the insula ROI, SVC analyses identified two peaks, one in the left insula (F = 12.94, pFWE = 0.007, df = 63; peak = [−42, −7, 1]) and one in the right posterior insula (F = 14.72, pFWE = 0.002, df = 63; peak = [45,−22, 22]).

Subsequent groupwise SVC comparisons indicated significantly reduced right insula activity among CD-MM patients in comparison to HC participants (t = 4.50, pFWE = 0.018, df = 43; peak = [36,−13, 22]) and in comparison to CD patients (t = 4.97, pFWE = 0.006, df = 42; peak = [45,−22, 22]) during anticipatory loss (but not win) processing.

Groupwise comparisons further indicated significantly reduced activity among CD patients in comparison to HCs within the left caudate body (t = 3.90, pFWE= 0.037, df = 39; peak = [−12, 17, 10]) during anticipatory loss processing, but no differences in caudate activity between CD-MM patients and HC participants.

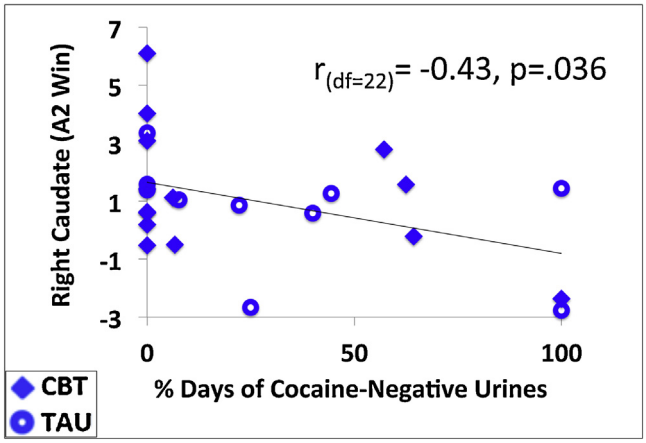

Fig. 2. Association between caudate activity during anticipatory win processing and abstinence during treatment among methadone-maintained, cocaine-dependent individuals. Scatterplot shows the negative associations between pretreatment right caudate (defined anatomically using the automatic anatomical labeling (AAL) atlas in SPM12) activation during anticipatory win processing and percentage of cocaine-negative urines during treatment for cocaine dependence among cocaine-dependent, methadone-maintained patients. No significant associations between durations of abstinence during treatment and caudate activity were observed among non-methadone-maintained, cocaine-dependent patients. Statistical comparisons indicated significant differences in r-values between patient groups (Z = −1.82, p= 0.034). CBT = computer-based cognitive behavioral therapy; TAU = treatment-as-usual.

3.4. Exploratory correlational analyses related to abstinence during treatment

Among CD-MM patients, there was a significant negative association between treatment response (percentage of cocaine-negative urines during treatment) and pretreatment BOLD responses during win anticipation (A2 phase) within the right caudate ($r_{(df=22)} = -0.43$, p= 0.036; Fig. 2). This relationship remained significant after controlling for current methadone dose ($r_{(df=21)} = -0.41$, p= 0.0496) and was not observed among non-methadone-maintained CD patients ($r_{(df=18)} = 0.13$, p= 0.573). Comparison of r-values using Fisher's r-to-z transformation indicated significant differences in the strength of the correlations between days of consecutive abstinence and BOLD responses within the caudate among CD-MM *versus* CD patients (Z = −1.82, one-tailed p= 0.034). Follow-up comparisons controlling for treatment group confirmed these findings and are presented in Table S2.

4. Discussion

This study compared neural responses during anticipatory reward and loss processing between cocaine-dependent patients with and without current methadone-maintenance treatment, and relative to a group of healthy comparison participants. Consistent with our primary hypothesis, whole-brain analyses indicated a significant main effect of diagnostic group on neural responses within fronto-parietal-limbic regions, including components of the putamen, parahippocampal gyrus, PCC, precuneus, cuneus, IFG and DLPFC. Subsequent analyses indicated that these effects primarily involved reduced activity within fronto-parietal regions among CD-MM patients in comparisons to HCs, and that activation within these regions was associated with daily methadone dose in CD-MM patients. *A priori* ROI-based analyses further indicated significant effects of diagnostic group on neural responses within the insula and caudate, involving decreased insula responses among CD-MM patients and decreased caudate responses among CD patients during anticipatory loss processing. Among CD-MM patients only,

Table 2
Whole-brain effects of diagnostic group on neural responses during anticipatory reward/loss processing (pFWE < 0.05).

	BA	k	Cluster Peak				pFWE
			x	y	z	F	
L Posterior Cingulate/Cuneus/Precuneus/Parahippocampal Gyrus	17, 18, 19, 30, 31	867	−24	−70	7	24.94	<0.001
L Inferior Frontal Gyrus/Middle Frontal Gyrus/DLPFC	9, 36, 45	255	−45	29	16	16.48	<0.001
R Lingual Gyrus/Fusiform Gyrus	18, 19	111	33	−76	−8	14.28	0.001
L Middle Temporal Gyrus/Superior Temporal Gyrus	22	83	−57	−49	4	16.73	0.003
L Superior Frontal Gyrus/Medial Frontal Gyrus	8	63	−9	20	55	12.70	0.013
R Middle Temporal Gyrus/Inferior Temporal Gyrus/Fusiform Gyrus	37	59	48	−64	−5	13.49	0.017
R Putamen		57	27	2	−2	18.22	0.020
R Precuneus		50	18	−46	10	16.07	0.034
R Cuneus	19	47	24	−88	34	11.58	0.044

Findings from whole-brain ANOVA comparing neural responses during anticipatory processing among healthy comparison (HC), cocaine-dependent methadone-maintained (CD-MM) and non-methadone-maintained, cocaine-dependent (CD) participants. Voxel-level p < 0.001; cluster-level-corrected for family-wise-error (FWE) at pFWE < 0.05.
L = left; R = right; BA = Brodmann Area; k = cluster size; FWE = family-wise-error.

Table 3
Findings from whole-brain, groupwise *t*-tests of BOLD responses during anticipatory reward and loss processing (voxel-level p < 0.001; pFWE < 0.05).

Win Anticipation	BA	k	Cluster Peak				df	pFWE
			x	y	z	t		
Healthy comparison > Cocaine-dependent, methadone-maintained								
Cuneus/Precuneus/Posterior Cingulate/Middle Occipital Gyrus/Lingual Gyrus	17, 18, 30, 31	600	−9	−79	16	4.98	43	<0.001
L Inferior Frontal Gyrus/DLPFC	46	128	−45	26	13	5.33	43	0.002
Loss Anticipation								
Healthy comparison > Cocaine-dependent, methadone-maintained								
Cuneus/Precuneus/Posterior Cingulate/Middle Occipital Gyrus/Lingual Gyrus	17, 18, 19, 30, 31	731	−24	−70	16	4.75	43	<0.001
L Inferior Frontal Gyrus/DLPFC	45, 46	108	−45	26	10	4.86	43	0.004
L Lingual Gyrus		60	−30	−76	−11	4.60	43	0.047
Cocaine dependent > Cocaine-dependent, methadone-maintained								
L Middle Temporal Gyrus/Superior Temporal Gyrus Angular Gyrus	22, 39	101	−60	−49	4	5.38	42	0.002
L Inferior Frontal Gyrus		57	−45	23	−2	4.75	42	0.035

Findings from whole-brain *t*-tests comparing neural responses during anticipatory reward and loss processing among healthy comparison (HC), cocaine-dependent methadone-maintained (CD-MM) and non-methadone-maintained, cocaine-dependent (CD) participants. Voxel-level p < 0.001; cluster-level-corrected for family-wise-error (FWE) at pFWE < 0.05.
L = left; R = right; BA = Brodmann Area; k = cluster size; df = ◦ of freedom; FWE = family-wise-error; DLPFC = dorsolateral prefrontal cortex.

pretreatment BOLD response in the caudate was negatively associated with abstinence during treatment. The clinical significance of these findings is discussed below.

4.1. Whole-brain between-group differences

During anticipatory reward and loss processing, CD-MM individuals exhibited significantly decreased activity within fronto-parietal regions implicated in cognitive processes including aspects of working memory, cognitive control and sustained attention (Owen et al., 2005; Swick et al., 2008), but not within reward-related neurocircuitry (*e.g.*, caudate), as has been previously reported in some studies of cocaine dependence (*e.g.*, Bustamante et al., 2014). All previous MID studies conducted in cocaine dependence have employed ROI-based approaches focusing primarily on reward-related regions (*e.g.*, none included the IFG or PCC; Jia et al., 2011; Patel et al., 2013; Bustamante et al., 2014). Thus, the extent to which MID task performance is associated with alterations within the identified regions among individuals with cocaine dependence has not been assessed previously. These data suggest that augmentation of current treatments with interventions specifically targeting fronto-parietal attentional networks (*e.g.*, neurocognitive training, cholinergic enhancement; Sofuoglu et al., 2013) may be beneficial among cocaine-dependent individuals who are maintained on methadone.

The PCC and precuneus regions identified in our main effects analyses are central hubs of the default mode network, which is typically deactivated during cognitive task performance (Raichle et al., 2001). Thus, greater deactivations within these regions during reward task performance may relate to default mode functional connectivity alterations previously reported in both opioid- and cocaine-dependent populations (*e.g.*, Upadhyay et al., 2010; Konova et al., 2015). Similarly, decreased IFG activity may relate to alterations within cognitive control and/or salience networks (Sharp et al., 2010). However, further research using network-based analysis approaches (*e.g.*, independent component analysis; ICA) is needed to test this hypothesis.

The precuneus, PCC and IFG are implicated in multiple addiction-related processes including drug-cue reactivity (Wilcox et al., 2011; Courtney et al., 2014), craving (Garavan et al., 2000; Brody et al., 2007) and vulnerabilities to relapse (Clark et al., 2014; Stewart et al., 2014). Alterations within the primary visual cortex (also identified in the main effects and post-hoc analyses) have been previously reported among individuals with a range of addictions, including opioid addiction (Gradin et al., 2014), and may relate to impairments in visual memory noted in this population (Darke et al., 2000). Our findings are further consistent with recent meta-analytic data indicating robust effects of both pharmacological and behavioral treatment interventions for addictions on neurofunctional responses within the precuneus, PCC, IFG and primary visual cortex (Konova et al., 2013). As such, our findings of methadone-related reductions in neural responses within these regions add to an emerging body of literature highlighting the role of fronto-parietal neurocircuitry in the development, maintenance and treatment of addictions (Courtney et al., 2014). Our correlational analyses suggest that BOLD signal reductions within the IFG and precuneus may be related to methadone in a dose dependent fashion. These data are consistent with methadone's indirect

effects on multiple neurotransmitter systems including (in addition to the μ-opioid system) those involved in attentional control and reward-related processes; *e.g.*, acetyl-cholinergic, dopaminergic (Merali et al., 1974; Koob, 1992).

4.2. ROI analyses

Although not detected in our whole-brain analyses, *a priori* ROI-based analyses further indicated a significant effect of diagnostic group on neural responses within the insula and caudate during anticipatory processing. For the insula, groupwise comparisons indicated that this involved decreased responses among CD-MM patients in comparison to both CD and HC participants. This finding is consistent with a recent report of decreased insula activation during reward anticipation among opiate-dependent individuals maintained on methadone (Gradin et al., 2014), as well as with structural MRI findings suggesting differences in insular cortex activity between cocaine- and opiate-dependent individuals (Lyoo et al., 2004). Given the central role of the insula in a range of interoceptive and reward-related processes (*e.g.*, approach behaviors, drug cue-reactivity; Paulus and Stewart, 2014) one possible interpretation of these findings is that methadone's efficacy in reducing opioid use might involve a reduction in drug cue-reactivity and associated approach behaviors via attenuation of insular activity during anticipatory processing. While further research is needed to support this hypothesis, further research into treatments specifically targeting insular function in this and other addicted populations appears warranted (Paulus and Stewart, 2014).

The main effect of diagnostic group within the caudate was primarily driven by relatively decreased activity during loss anticipation among the CD group when compared to the HC group. Previous studies using variations of the MID task to study anticipatory reward and loss processing have yielded somewhat mixed findings, with both increases, decreases and no alterations in caudate activity reported among individuals with cocaine dependence (Jia et al., 2011; Patel et al., 2013; Bustamante et al., 2014). Seemingly discrepant findings may relate to between-study differences in the clinical characteristics of patients or to within-study heterogeneity, as previous studies have not consistently assessed the effects of current medication status (*e.g.*, methadone) on neural responses among individuals with cocaine dependence (Patel et al., 2013; Balodis and Potenza, 2015).

4.3. Associations with abstinence

Partially contrary to our exploratory hypothesis, no significant associations between neural responses within the insula and durations of abstinence were observed within either patient group. Among CD-MM patients, neural responses within the right caudate were negatively associated with abstinence during treatment (percent days of cocaine-negative urines). This relationship was not observed among non-methadone-maintained CD patients. Statistical comparison of r-values confirmed a differential relationship between caudate activity and abstinence between the two patient groups, which remained after controlling for the type of treatment received. Individual variations in pretreatment neural responses relate to differences in response to treatments for cocaine dependence (*e.g.*, Brewer et al., 2008; Marhe et al., 2013). However to our knowledge, this is the first report of a differential relationship between pretreatment neural activity among individuals with and without methadone-maintenance treatment. While preliminary, these data support the hypothesis that individual differences in pretreatment neural function and neurochemistry relate to heterogeneities in treatment responses for addictions (Martinez et al., 2011). They further demonstrate the importance of assessing the relationship between neural function and treatment responses among different sub-populations of disorders (*e.g.*, methadone-maintained, cocaine-dependent individuals).

4.4. Strengths, limitations and conclusions

To our knowledge, this is the first study to compare neural responses between individuals with cocaine dependence with and without methadone-maintenance treatment, and in comparison to HC participants. This study's strengths include recruitment of a difficult-to-treat population, the use of a well-validated MID task, and the relatively close matching of CD individuals in the outpatient *versus* the methadone samples. Study findings should nonetheless be considered within the context of some limitations, including the absence of a non-cocaine-dependent, methadone-maintained comparison group. Based on our *a priori* hypotheses, we constrained our analyses to the anticipatory (A2) phase of the MID task. This phase was selected given the particular relevance of anticipatory processing to action selection and to addictive behaviors more generally (Balodis and Potenza, 2015). However, future studies assessing other aspects of reward-processing (*e.g.*, consummatory processing of reward outcomes) are warranted. In particular, studies employing computational modeling techniques to assess more nuanced aspects of reward and loss processing (*e.g.*, prediction errors) within different subdivisions of the striatum during MID task performance in this and other addicted populations are needed (Robinson et al., 2010; Balodis and Potenza, 2015).

This study did not include assessment of some clinical factors which could have influenced treatment responses; *e.g.*, trauma history (Heffner et al., 2011), neurocognitive factors (Aharonovich et al., 2006). Thus we cannot exclude possible effects of these variables on study findings. Several patients met criteria for past or current depression, which may influence neural reward responses (Hagele et al., 2015). While we were not sufficiently powered to assess between-group differences in neural responses based on depression variables, the CD-MM and CD groups did not differ in rates of past or current depression. Similarly, while our inclusion of only treatment-seeking, cocaine-dependent individuals allowed for correlational analyses with treatment outcomes, the behavioral treatments delivered differed across patients and we were not sufficiently powered to explore group-by-therapy (*e.g.*, CBT4CBT *vs.* TAU) interactions. While correlational findings remained unchanged after controlling for the type of therapy received, caution is warranted when interpreting these data. Thus, further studies in larger samples are needed to adequately assess relationships with treatment.

Previous research suggests neurostructural differences (as assessed via quantification of white matter hyperintensities) between opiate- and cocaine-dependent individuals within regions including the insular cortex (Lyoo et al., 2004). Neural structural factors within regions including the caudate and hippocapmus are related to treatment outcomes among individuals with addictions (Xu et al., 2014; Yip et al., 2014). In addition, individual variability in neurofunctional responses during MID task performance has been linked to neurostructural variability (Yip et al., 2015). Thus, a final limitation of this study is the absence of accompanying structural (*e.g.*, T1- or diffusion-weighted) data analyses, as would be required to explore the effects of these factors on functional neural responses in this population.

These data nonetheless suggest significant neurofunctional differences between individuals with cocaine dependence who are also maintained on methadone for opioid dependence, in comparison to those who are not. Consistent with previous findings of methadone-associated attenuation of neural responses (Langleben et al., 2008) – and with methadone's general inhibitory effects on neurotransmitter systems including μ-opioid, cholinergic and

dopaminergic systems (Merali et al., 1974; Koob, 1992) – negative associations between daily methadone dose and BOLD responses were observed. These associations remained after controlling for addiction severity measures. Thus, differences in neural responses observed between cocaine-participant groups in this study may relate specifically to methadone dosing. These data highlight the importance of comparing functional responses between different subgroups of addicted populations, particularly as these responses link to treatment-related variables.

Role of funding source

This study was supported by National Institute on Drug Abuse grants R37-DA 015969, P50-DA09241, R01 DA035058, R01020908, R01-DA020709, K01DA039299, K05-DA00457, T32 AA015496, T32 AA015496, T32 DA022975, the Connecticut Mental Health Center, the Connecticut State Department of Mental Health and Addiction Services and the National Center on Addiction and Substance Abuse.

Contributors

Drs. Potenza and Carroll designed the protocol and study. Dr. Yip conducted statistical analyses and wrote the first draft of the manuscript. Drs. DeVito, Kober and Worhunsky assisted in compiling and coordinating data and contributed to statistical analyses. All authors consulted on the interpretation of the analyses and data and have provided critical feedback on the manuscript.

Conflict of interest

Dr. Carroll has received grant support from NIH and is a member of CBT4CBT LLC, which makes CBT4CBT available to qualified clinical providers and organizations on a commercial basis. Dr. Carroll works with Yale University to manage any potential conflicts of interest. Dr. Potenza has: consulted for and advised Ironwood, Lundbeck, INSYS, Shire, RiverMend Health, Opiant/Lakelight Therapeutics and Pfizer; has received research support from Mohegan Sun Casino, the National Center for Responsible Gaming, and Pfizer; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse-control disorders or other health topics; has consulted for gambling and legal entities on issues related to impulse-control and addictive 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 edited journals or journal sections; 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. Drs. Yip, DeVito, Kober and Worhunsky report no potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2016.07.006.

References

Aharonovich, E., Hasin, D.S., Brooks, A.C., Liu, X., Bisaga, A., Nunes, E.V., 2006. Cognitive deficits predict low treatment retention in cocaine dependent patients. Drug Alcohol Depend. 81, 313–322.

Andrews, M.M., Meda, S.A., Thomas, A.D., Potenza, M.N., Krystal, J.H., Worhunsky, P., Stevens, M.C., O'Malley, S., Book, G.A., Reynolds, B., Pearlson, G.D., 2011. Individuals family history positive for alcoholism show functional magnetic resonance imaging differences in reward sensitivity that are related to impulsivity factors. Biol. Psychiatry 69, 675–683.

Balodis, I.M., Potenza, M.N., 2015. Anticipatory reward processing in addicted populations: a focus on the Monetary Incentive Delay Task. Biol. Psychiatry 77, 434–444.

Brewer, J.A., Worhunsky, P.D., Carroll, K.M., Rounsaville, B.J., Potenza, M.N., 2008. Pretreatment brain activation during stroop task is associated with outcomes in cocaine-dependent patients. Biol. Psychiatry 64, 998–1004.

Brody, A.L., Mandelkern, M.A., Olmstead, R.E., Jou, J., Tiongson, E., Allen, V., Scheibal, D., London, E.D., Monterosso, J.R., Tiffany, S.T., Korb, A., Gan, J.J., Cohen, M.S., 2007. Neural substrates of resisting craving during cigarette cue exposure. Biol. Psychiatry 62, 642–651.

Bustamante, J.C., Barros-Loscertales, A., Costumero, V., Fuentes-Claramonte, P., Rosell-Negre, P., Ventura-Campos, N., Llopis, J.J., Avila, C., 2014. Abstinence duration modulates striatal functioning during monetary reward processing in cocaine patients. Addict. Biol. 19, 885–894.

Carroll, K.M., Kiluk, B.D., Nich, C., DeVito, E.E., Decker, S., LaPaglia, D., Duffey, D., Babuscio, T.A., Ball, S.A., 2014a. Toward empirical identification of a clinically meaningful indicator of treatment outcome: features of candidate indicators and evaluation of sensitivity to treatment effects and relationship to one year follow up cocaine use outcomes. Drug Alcohol Depend. 137, 3–19.

Carroll, K.M., Kiluk, B.D., Nich, C., Gordon, M.A., Portnoy, G.A., Marino, D.R., Ball, S.A., 2014b. Computer-assisted delivery of cognitive-behavioral therapy: efficacy and durability of CBT4CBT among cocaine-dependent individuals maintained on methadone. Am. J. Psychiatry 171, 436–444.

Clark, V.P., Beatty, G.K., Anderson, R.E., Kodituwakku, P., Phillips, J.P., Lane, T.D., Kiehl, K.A., Calhoun, V.D., 2014. Reduced fMRI activity predicts relapse in patients recovering from stimulant dependence. Hum. Brain Mapp. 35, 414–428.

Courtney, K.E., Ghahremani, D.G., London, E.D., Ray, L.A., 2014. The association between cue-reactivity in the precuneus and level of dependence on nicotine and alcohol. Drug Alcohol Depend. 141, 21–26.

Darke, S., Sims, J., McDonald, S., Wickes, W., 2000. Cognitive impairment among methadone maintenance patients. Addiction 95, 687–695.

Dobler-Mikola, A., Hattenschwiler, J., Meili, D., Beck, T., Boni, E., Modestin, J., 2005. Patterns of heroin, cocaine, and alcohol abuse during long-term methadone maintenance treatment. J. Subst. Abuse Treat. 29, 259–265.

Feldstein Ewing, S.W., Chung, T., 2013. Neuroimaging mechanisms of change in psychotherapy for addictive behaviors: emerging translational approaches that bridge biology and behavior. Psychol. Addict. Behav. 27, 329–335.

First, M., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1995. Structured Clinical Interview for DSM-IV, Patient edition. American Psychiatric Press, Inc, Washington, DC.

Garavan, H., Pankiewicz, J., Bloom, A., Cho, J.-K., Sperry, L., Ross, T.J., Salmeron, B.J., Risinger, R., Kelley, D., Stein, E.A., 2000. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. Am. J. Psychiatry 157, 1789–1798.

Gradin, V.B., Baldacchino, A., Balfour, D., Matthews, K., Steele, J.D., 2014. Abnormal brain activity during a reward and loss task in opiate-dependent patients receiving methadone maintenance therapy. Neuropsychopharmacology 39, 885–894.

Hagele, C., Schlagenhauf, F., Rapp, M., Sterzer, P., Beck, A., Bermpohl, F., Stoy, M., Strohle, A., Wittchen, H.U., Dolan, R.J., Heinz, A., 2015. Dimensional psychiatry: reward dysfunction and depressive mood across psychiatric disorders. Psychopharmacology (Berl.) 232, 331–341.

Heffner, J.L., Blom, T.J., Anthenelli, R.M., 2011. Gender differences in trauma history and symptoms as predictors of relapse to alcohol and drug use. Am. J. Addict. 20, 307–311.

Hunt, D., Spunt, B., Lipton, D., Goldsmith, D., Strug, D., 1986. The costly bonus: cocaine related crime among methadone treatment clients. Adv. Alcohol Subst. Abuse 6 (2), 107–122.

Jia, Z., Worhunsky, P.D., Carroll, K.M., Rounsaville, B.J., Stevens, M.C., Pearlson, G.D., Potenza, M.N., 2011. An initial study of neural responses to monetary incentives as related to treatment outcome in cocaine dependence. Biol. Psychiatry 70, 553–560.

Jiang, G.H., Qiu, Y.W., Zhang, X.L., Han, L.J., Lv, X.F., Li, L.M., Lin, C.L., Zhuo, F.Z., Hu, S.Y., Tian, J.Z., 2011. Amplitude low-frequency oscillation abnormalities in the heroin users: a resting state fMRI study. Neuroimage 57, 149–154.

Kilts, C., Schweitzer, J.B., Quinn, C.K., Gross, R.E., Faber, T.L., Muhammad, F., Ely, T.D., Hoffmann, J.M., Drexler, K.P.G., 2001. Neural activity related to drug craving in cocaine addiction. Arch. Gen. Psychiatry 58, 334–341.

Knutson, B., Westdorp, A., Kaiser, E., Hommer, D., 2000. FMRI visualization of brain activity during a monetary incentive delay task. Neuroimage 12, 20–27.

Kolar, A.F., Brown, B.S., Weddington, W.W., Ball, J.C., 1990. A treatment crisis: cocaine use by clients in methadone maintenance programs. J. Subst. Abuse Treat. 7, 101–107.

Konova, A.B., Moeller, S.J., Goldstein, R.Z., 2013. Common and distinct neural targets of treatment: changing brain function in substance addiction. Neurosci. Biobehav. Rev. 37, 2806–2817.

Konova, A.B., Moeller, S.J., Tomasi, D., Goldstein, R.Z., 2015. Effects of chronic and acute stimulants on brain functional connectivity hubs. Brain Res. 1628, 147–156.

Koob, G., 1992. Drugs of abuse: anatomy, pharmacology and functions of reward pathways. Trends Pharmacol. Sci. 13, 177–184.

Kosten, T., Oliveto, A., Feingold, A., Poling, J., Sevarino, K., McCance-Katz, E., Stine, S., Gonzalez, G., Gonsai, K., 2003. Desipramine and contingency management for cocaine and opiate dependence in buprenorphine maintained patients. Drug Alcohol Depend. 70, 315–325.

Langleben, D.D., Ruparel, K., Elman, I., Busch-Winokur, S., Pratiwadi, R., Loughead, J., O'Brien, C.P., Childress, A.R., 2008. Acute effect of methadone maintenance dose on brain FMRI response to heroin-related cues. Am. J. Psychiatry 165, 390–394.

Lyoo, I.K., Streeter, C.C., Ahn, K.H., Lee, H.K., Pollack, M.H., Silveri, M.M., Nassar, L., Levin, J.M., Sarid-Segal, O., Ciraulo, D.A., Renshaw, P.F., Kaufman, M.J., 2004. White matter hyperintensities in subjects with cocaine and opiate dependence and healthy comparison subjects. Psychiatry Res. 131, 135–145.

Marhe, R., Luijten, M., van de Wetering, B.J., Smits, M., Franken, I.H., 2013. Individual differences in anterior cingulate activation associated with attentional bias predict cocaine use after treatment. Neuropsychopharmacol 38, 1085–1093.

Martinez, D., Carpenter, K., Liu, F., Slifstein, M., Broft, A., Friedman, A., Kumar, D., Van Heertum, R., Kleber, H., Nunes, E., 2011. Imaging dopamine transmission in cocaine dependence: link between neurochemistry and response to treatment. Am. J. Psychiatry 168, 634–641.

McHugh, M.J., Demers, C.H., Braud, J., Briggs, R., Adinoff, B., Stein, E.A., 2013. Striatal-insula circuits in cocaine addiction: implications for impulsivity and relapse risk. Am. J. Drug Alcohol Abuse 39, 424–432.

Merali, Z., Ghosh, P.K., Hrdina, P.D., Singhal, R.L., Ling, G.M., 1974. Alterations in striatal acetylcholine, acetylcholine esterase and dopamine after methadone replacement in morphine-dependent rats. Eur. J. Pharmacol. 26, 375–378.

Owen, A.M., McMillan, K.M., Laird, A.R., Bullmore, E., 2005. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum. Brain Mapp. 25, 46–59.

Patel, K.T., Stevens, M.C., Meda, S.A., Muska, C., Thomas, A.D., Potenza, M.N., Pearlson, G.D., 2013. Robust changes in reward circuitry during reward loss in current and former cocaine users during performance of a monetary incentive delay task. Biol. Psychiatry 74, 529–537.

Paulus, M.P., Stewart, J.L., 2014. Interoception and drug addiction. Neuropharmacology 76, 342–350.

Potenza, M.N., Hong, K., Lacadie, C.M., Fulbright, R.K., Tuit, K.L., Sinha, R., 2012. Neural correlates of stress-induced and cue-induced drug craving: influences of sex and cocaine dependence. Am. J. Psychiatry 169, 406–414.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proc. Natl. Acad. Sci. U. S. A. 98, 676–682.

Robinson, O.J., Frank, M.J., Sahakian, B.J., Cools, R., 2010. Dissociable responses to punishment in distinct striatal regions during reversal learning. Neuroimage 51, 1459–1467.

Schottenfeld, R.S., Chawarski, M.C., Pakes, J.R., Pantalon, M.V., Carroll, K.M., Kosten, T.R., 2005. Methadone versus buprenorphine with contingency management or performance feedback for cocaine and opioid dependence. Am. J. Psychiatry 162, 340–349.

Sharp, D.J., Bonnelle, V., De Boissezon, X., Beckmann, C.F., James, S.G., Patel, M.C., Mehta, M.A., 2010. Distinct frontal systems for response inhibition, attentional capture, and error processing. Proc. Natl. Acad. Sci. U. S. A. 107, 6106–6111.

Sofuoglu, M., DeVito, E.E., Waters, A.J., Carroll, K.M., 2013. Cognitive enhancement as a treatment for drug addictions. Neuropharmacology 64, 452–463.

Stewart, J.L., Connolly, C.G., May, A.C., Tapert, S.F., Wittmann, M., Paulus, M.P., 2014. Striatum and insula dysfunction during reinforcement learning differentiates abstinent and relapsed methamphetamine-dependent individuals. Addiction 109, 460–471.

Swick, D., Ashley, V., Turken, A.U., 2008. Left inferior frontal gyrus is critical for response inhibition. BMC Neurosci. 9, 102.

Tross, S., Hanner, J., Hu, M.C., Pavlicova, M., Campbell, A., Nunes, E.V., 2009. Substance use and high risk sexual behaviors among women in psychosocial outpatient and methadone maintenance treatment programs. Am. J. Drug Alcohol Abuse 35, 368–374.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15, 273–289.

Upadhyay, J., Maleki, N., Potter, J., Elman, I., Rudrauf, D., Knudsen, J., Wallin, D., Pendse, G., McDonald, L., Griffin, M., Anderson, J., Nutile, L., Renshaw, P., Weiss, R., Becerra, L., Borsook, D., 2010. Alterations in brain structure and functional connectivity in prescription opioid-dependent patients. Brain 133, 2098–2114.

Wilcox, C.E., Teshiba, T.M., Merideth, F., Ling, J., Mayer, A.R., 2011. Enhanced cue reactivity and fronto-striatal functional connectivity in cocaine use disorders. Drug Alcohol Depend. 115, 137–144.

Williamson, A., Darke, S., Ross, J., Teesson, M., 2006. The effect of persistence of cocaine use on 12-month outcomes for the treatment of heroin dependence. Drug Alcohol Depend. 81, 293–300.

Xu, J., Kober, H., Wang, X., DeVito, E.E., Carroll, K.M., Potenza, M.N., 2014. Hippocampal volume mediates the relationship between measures of pre-treatment cocaine use and within-treatment cocaine abstinence. Drug Alcohol Depend. 143, 74–80.

Yip, S., Devito, E., Kober, H., Worhunsky, P., Carroll, K., Potenza, M., 2014. Pretreatment measures of brain structure and reward-processing brain function in cannabis dependence: an exploratory study of relationships with abstinence during behavioral treatment. Drug Alcohol Depend. 140, 33–41.

Yip, S., Worhunsky, P.D., Rogers, R.D., Goodwin, G.M., 2015. Hypoactivation of the Ventral and dorsal striatum during reward and loss anticipation in antipsychotic and mood stabilizer-naive bipolar disorder. Neuropsychopharmacology 40, 658–666.