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Temporal Difference Error Prediction Signal Dysregulation in Cocaine Dependence

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Cocaine dependence impacts drug-related, dopamine-dependent reward processing, yet its influence on non-drug reward processing is unclear. Here, we investigated cocaine-mediated effects on reward learning using a natural food reinforcer. Cocaine-dependent subjects ($N = 14$) and healthy controls ($N = 14$) learned to associate a visual cue with a juice reward. In subsequent functional imaging sessions they were exposed to trials where juice was received as learned, withheld (negative temporal difference error (NTDE)), or received unexpectedly (positive temporal difference error (PTDE)). Subjects were scanned twice in sessions that were identical, except that cocaine-dependent participants received cocaine or saline 10 min before task onset. In the insula, precentral and postcentral gyri NTDE signals were greater, and PTDE-related function was reduced in cocaine-dependent subjects. Compared with healthy controls, in the cocaine-dependent group PTDE signals were also reduced in medial frontal gyrus and reward-related function, irrespective of predictability, was reduced in the putamen. Group differences in error-related activity were predicted by the time as last self-administered cocaine use, but TDE function was not influenced by acute cocaine. Thus, cocaine dependence seems to engender increased responsiveness to unexpected negative outcomes and reduced sensitivity to positive events in dopaminergic reward regions. Although it remains to be established if these effects are a consequence of or antecedent to cocaine dependence, they likely have implications for the high-cocaine use recidivism rates by contributing to the drive to consume cocaine, perhaps via influence on dopamine-related reward computations. The fact that these effects do not acquiesce to acute cocaine administration might factor in binge-related escalated consumption.

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INTRODUCTION

Addiction to cocaine and other abused substances is characterized by a cycle involving the compulsion to consume the drug (craving), difficulty-limiting intake (intoxication, bingeing), and negative emotional states (withdrawal, anhedonia)(Goldstein and Volkow, 2011; Koob and LeMoal, 1997). Changes in motivational processing are an essential component of these addiction phenomena (Koob and Volkow, 2010). Indeed, drug dependence engenders functional alterations in dopamine (DA) pathway regions that constitute the brain's reward system (eg the substantia nigra (SN) and ventral tegmental area (VTA) in the midbrain and the basal ganglia structures (ie nucleus accumbens, putamen caudate), and the prefrontal regions (eg, medial prefrontal (mPFC) and orbitofrontal cortices) they principally project to (Diekhof *et al*, 2008; Haber and Knutson, 2010). Clinical and preclinical investigations confirm the role of these regions in diverse motivational processes, such as incentive salience (Knutson *et al*, 2000; Knutson *et al*, 2001; Knutson *et al*, 2003), the hedonic experience of reward (O'Doherty *et al*, 2001), and reward learning (Asaad and Eskandar, 2011; Berns *et al*, 2001; McClure *et al*, 2003; O'Doherty *et al*, 2003; Schultz, *et al*, 1997; Schultz, 1998; Schultz and Dickinson, 2000). Consequently, drug dependence is often considered to be a disease of abnormal reward processing (Volkow *et al*, 2010).

During reward learning, unpredictability arises from a variety of events, including temporal shifts in reward delivery and the unexpected occurrence of reward-predictive stimuli—so-called 'temporal difference errors' (TDEs).

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Transient decreases in dopaminergic function follow omission of temporally anticipated (ie, predicted) rewards, ie negative TDE (NTDE), while positive TDE (PTDE) processing following unanticipated rewards requires phasic increases in DA signaling (McClure *et al*, 2003; Montague *et al*, 1996; Montague *et al*, 2004; Schultz *et al*, 1997; Schultz, 2000; Schultz, 2002; Schultz, 2007; Wise, 2009). Although TDE signals are typically thought to arise in the midbrain, other brain regions may also be important for error signaling (Roesch *et al* 2012). For example, gain prediction error computations for monetary rewards can be mediated by mPFC function (Knutson and Wimmer, 2007), whereas orbitofrontal activity correlates with error signals for appetitive rewards (O'Doherty *et al*, 2003). Abused drugs produce transient increases in DA signaling (Koob *et al*, 1998; Koob and Volkow, 2010) that become conditioned (Bolieau *et al*, 2007), leading to positive error signals that increase drug value and reinforce drug-seeking behavior. Thus, drug dependency may be driven in part by changes in TDE reward learning (Redish, 2004).

Neuroimaging studies of cocaine-dependent (CD) adults suggest functional alterations in brain regions that support reward processing, including reward learning. For example, acute cocaine engages the same dopaminergic pathways in CD individuals that mediate acute drug response in preclinical addiction models (Breiter *et al*, 1997; Kufahl *et al*, 2005; Risinger *et al*, 2005). Moreover, large-scale brain networks (eg default mode, salience, and executive control networks; Sutherland *et al*, 2012) involving mesocorticolimbic DA areas, like the striatum, are dysfunctional in those who abuse cocaine (Gu *et al*, 2010; Tomasi *et al*, 2010). Similarly, DA release in the striatum following methlyphenidate or amphetamine challenge is blunted in CD individuals (Martinez *et al*, 2007; Volkow *et al*, 1997). Interestingly, this blunting is predictive of choosing cocaine *vs* alternative rewards (Volkow *et al*, 1997). Impaired non-drug reward valuation in cocaine dependence likely arises from dysfunction in prefrontal reward regions (Goldstein *et al*, 2007a; Goldstein *et al*, 2007b). Furthermore, incentive processing for monetary rewards in motivation-related corticolimbic regions is altered during reward anticipation and receipt in abstinent CD adults, with these differences predicting treatment outcome (Jia *et al*, 2011).

Dysfunction in reward processing regions in CD individuals may contribute to the incentive to consume cocaine, continued cocaine abuse, and high recidivism rates. Moreover, given the ubiquitous nature of processing for a range of reinforcing stimuli, CD abnormalities in reward processing likely extend beyond drug rewards to non-drug reinforcers. As the reinforcing nature of non-drug stimuli may be critical to maintaining long-term abstinence, understanding the impact of cocaine-mediated changes for non-drug reward is crucial for intervention strategies. However, despite evidence of compromise in reward pathways in CD individuals, the impact of acute cocaine on the mechanisms of non-drug reward processing, including reward learning, is not well delineated in either preclinical or clinical models.

The allostasis hypothesis of drug abuse (eg, Koob and LeMoal, 2007) postulates that chronic exposure to stimulants, like cocaine, engenders a gradual decline in dopaminergic function, which is associated with a preference for the abused substance over other reinforcing stimuli. This hypothesis is complimentary to the computational account of addiction noted above (ie Redish, 2004), whereby acute drug exposure is believed to overstimulate compromised DA reward systems; resulting in aberrant learning signals that also bias toward the drug. As TDE processing has been shown to rely on the integrity of DA systems, TDE learning paradigms have the potential to act as excellent probes of the response of dopaminergic reward pathways to both chronic and acute cocaine exposure.

This study considered the impact of cocaine dependence on reward learning for a non-drug, primary reward. We investigated the neurobiology of TDE processing in CD individuals using a classical conditioning paradigm and considered the relative impact of the trait of cocaine dependence and an acute cocaine administration state on these processes. It was hypothesized that: (1) during cocaine abstinence and compared with controls, CD individuals would show reduced TDE/reward-related activity, due to impaired function in DA pathway regions, and (2) acute cocaine administration would 'normalize' cocaine-dependent alterations in TDE-related signaling.

MATERIALS AND METHODS

Participants

Healthy controls (HC; $N=26$) and non-treatment seeking CD ($N=22$) individuals were recruited from the general population. Participants were right-handed, aged 18–45 years and had no scientific, medical, or ethical contraindications for magnetic resonance imaging (MRI). Participants had no current or past DSM-IV-TR Axis I or II diagnoses, except nicotine dependence in all participants ($N=14$ HC and 22 CD current/past smokers) and current cocaine dependence in CD participants only. Throughout the study, CD subjects were offered access to treatment services as an alternative to participation. Those expressing a preference for treatment were automatically excluded.

Eight CD subjects were disqualified due to excessive head motion (ie, more than 3 mm/° in any direction between consecutive TRs), resulting in an analysis cohort of $N=14$. A subsample ($N=14$) was selected from HC that passed data quality control ($N=21$) to best match the included CD group (see Table 1 for demographics and Supplementary Table S1 for summary of cocaine use). The subsequent description of methods and results refers only to those included in imaging analyses.

Procedure

The NIDA-IRP IRB approved this study and subjects provided written, informed consent prior to participation. Participation consisted of task training in a mock scanner and two MRI sessions. CD subjects also completed a 'drug toleration' session prior to scanning, which included monitoring of blood plasma concentrations of cocaine and metabolites (see Supplementary Methods for details). MRI sessions were identical for HC and CD subjects, except for drug administration. Using a within-subjects, single-blind, randomly counter-balanced design, CD subjects received intravenous cocaine or saline during scanning ($N=7$

Table 1 Participant Demographics

	CD ($N=14$)	HC ($N=14$)
Age at time of testing[a] (years; mean (SD))	42.93 (2.13)	41.57 (2.14)
Years of education[a] (mean (SD))	13.14 (1.79)	13.71 (2.49)
WAIS full-scale IQ[a] (mean (SD)	98.86 (8.93)	105.71 (11.74)
WTAR estimated IQ[a] (mean (SD)	96.50 (13.33)	100.92 (13.14)
Gender[a] (male: female)	11: 3	12: 2
Ethnicity ratio[a] (AA: C)	12: 2	11: 3
Smoker past or present (Yes: No)	14: 0	8: 6
Age at first cocaine use (years; mean (SD) and [range])	22 (5.80) [14–36]	n/a
Years of regular cocaine use (mean (SD) and [range])	16.36 (4.99) [8–25]	n/a
Number of days used cocaine in week pre-study (mean (SD) and [range])	1.79 (1.67) [0–6]	n/a
Time since last cocaine use (days; mean (SD) and [range])	3.00 (2.28) [0–7]	n/a

Abbreviations: CD, cocaine dependent; HC, healthy control.
[a]Non-significant ($p>0.05$) between-group comparisons (independent sample t or χ^2).

cocaine first). HC were scanned twice to control for the potential timing effects arising from repetition of the experimental paradigms. CD participants were tested on consecutive days and stayed overnight between sessions (Supplementary Figure S1). HC completed experimental sessions on separate days, scheduled as closely as possible.

TDE/Juice Paradigm

The TDE paradigm is described elsewhere (Rose *et al*, 2012). In brief, before scanning, participants learned to associate a visual cue and the subsequent receipt of a primary reward (ie, 0.6 ml juice/6 s delay). During scanning the paradigm consisted of trials mimicking learning trials interspersed with trials in which juice was not received as predicted but instead received 4–7 s later, ie 'catch' trials (Figure 1a(i)). It was intended that omission of the predicted reward would engender NTDE signals, whereas its unanticipated receipt after a pseudo-randomly selected delay would result in a PTDE signal (Hollerman and Schultz, 1998). Normal ($N=58$) and catch ($N=20$) trials were divided across three 9-min task 'blocks'. At the end of each block, participants rated how much they liked the juice on a visual analog scale (range 0–800). CD subjects also rated how high and satisfied they felt, and how much they were craving cocaine (Supplementary Tables S3 and S4). As the TDE measure was passive, requiring no response, participant vigilance was confirmed verbally at the start of each block and visually by inspection of data time series captured in real-time during scanning.

Timing Paradigm

Accurate temporal difference prediction is critical for the generation of NTDE and PTDE signals. To determine whether general timing processes were potentially compromised in CD individuals, participants completed a test of timing function after their final session. This task is described elsewhere (Rose *et al*, 2012).

Functional Imaging

Whole-brain echo planar images were acquired on a 3T Siemens Allegra scanner (Erlangen, Germany). Thirty-nine 4-mm slices were acquired in an oblique axial plane (30° to AC–PC) with the following imaging parameters: TR = 2000 ms, TE = 27 ms, FOV = 220 × 220 mm at 64 × 64, and flip angle = 78°. T1-weighted MPRAGE structural imaging series were also acquired (voxel = 1 mm^3).

Using a within-subjects design, participants completed two identical scans. They performed two reward measures per session (Figure 1a(ii)). The TDE task was performed second, ~70 min after beginning the session, and is the only measure reported here. CD subjects received two 3 min/10 ml bolus injections of 30 mg cocaine hydrochloride/70 kg bodyweight or saline, about 1 h apart. Each bolus was administered ~10 min prior to each tasks. Drug administration procedures and physiological monitoring for scanning were as described for the toleration session. For the purposes of matching experimental conditions, physiological measures were also obtained for HC.

Characterization

Characterization measures completed upon study entry included indices of psychiatric history, personality, exposure to stressful life events, and cognitive function (see Supplementary Methods). CD subjects provided a detailed history of cocaine use and completed measures of craving and withdrawal.

Data Analysis

Functional imaging data were analyzed using AFNI (Cox, 1996). Data preprocessing and quality control procedures were as previously described (Rose *et al*, 2012). Data time series were analyzed using voxel-wise, multiple regression in which regressors were expressed as a series of delta functions time-locked to event onset and convolved with a hemodynamic response function and its temporal derivative.

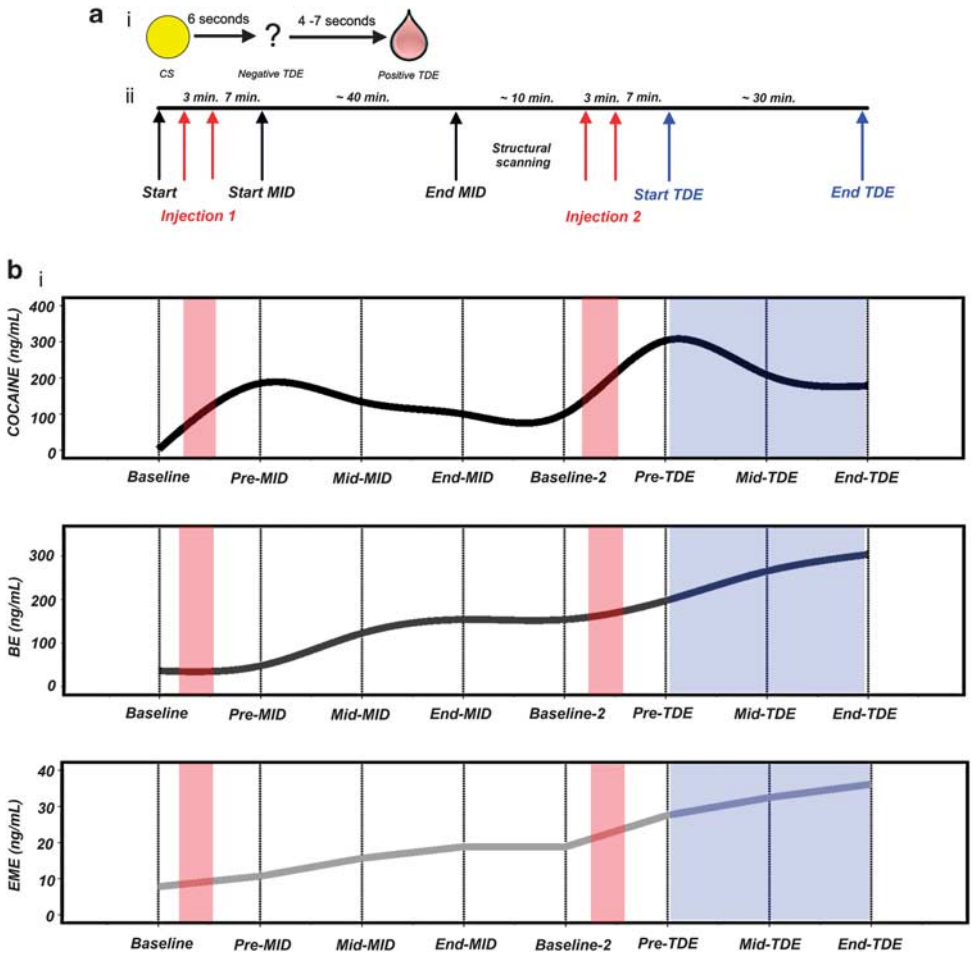

Figure 1 Experimental timeline and relative plasma concentration of cocaine and metabolites. (a) (i) TDE 'catch' event (ii) Scanning timeline including timing of cocaine injections relative to imaging tasks. (b) Estimated mean plasma concentrations (ng/ml) of (i) cocaine, (ii) Benzolecgonine (BE), and (iii) Ecgonine methyl ester (EME) across the scanning session. Notes; 1 Metabolite estimates were derived from blood samples obtained during the drug toleration session, which mimicked the scanning session with regards to relative timing of injections and functional measures; Supplementary Table S6 includes a summary of these data. Spline interpolation was used for these graphs. 3: Red shading corresponds to timing of bolus injections of cocaine; blue shading corresponds to TDE task duration. 4: 'Baseline-2' refers to those samples obtained prior to the commencement of the second cocaine injection.

Regressors of interest were: visual cue/conditioned stimulus (CS), normal events/unconditioned stimulus (UCS; juice expected/juice delivered), NTDE (juice expected/juice not delivered), and PTDE (juice not expected/juice delivered). In addition, six motion parameters were included as regressors of no interest. Voxel-wise average response amplitude in units of percentage signal change from baseline was calculated for each event type, participant, and session. Resultant activation maps for each of the individual regressors were registered to a higher resolution (1 μl) standard space (Talairach and Tournoux, 1988) and spatially blurred using a 4.2 mm FWHM Gaussian isotropic kernel.

Random effects analyses considered experimental *GROUP* (HC *vs* CD), drug *CONDITION* (cocaine *vs* saline), and *EVENT TYPE* (CS, UCS, PTDE & NTDE). *SESSION* (1 *vs* 2) was also considered for HC only. Comparisons between HC and CD subjects included regressors averaged across sessions. To account for TDE signals in traditional reward pathways and other brain areas, *a priori* small volume correction (SVC) analyses in hypothesized DA pathway regions and whole-brain (WB) analyses were carried out. SVC analyses considered bilateral volumes in the SN, striatum (nucleus accumbens, caudate, and putamen), and medial prefrontal cortex (BA10 and BA32) and a midline volume encompassing the VTA, which were defined using a Talairach template. Using the AlphaSim program in AFNI, voxel-wise thresholds corrected for multiple comparisons were calculated using Monte Carlo simulations. Thresholds were calculated separately for WB and SVC analyses and determined as meeting or exceeding minimum cluster extent (KE) criteria at $P_{corrected} \leqslant 0.05$ (ie WB KE = 290 voxels; SVC KE = 26 voxels). For SVC analyses, this correction accounted for the total volume. The directionality and nature of significant main effects and interactions were confirmed with contrasts that were defined *a priori* in analysis of variance models and corrected for multiple comparisons. This included contrasts between HC and CD and between individual event types.

Exploratory *post-hoc* linear regressions were utilized to examine the relationship between cocaine use factors (chronic and acute) and CD changes in reward-related brain activity. As TDE processes are impacted by chronic

nicotine exposure (Rose *et al*, 2012), the relationship between nicotine use and TDE-related function across groups was also explored. Finally, *post-hoc* regressions were conducted to determine the impact of characteristics that differed between groups on TDE-related brain activity. These latter analyses revealed no significant impact of nicotine or characterization measures on group-related differences in TDE function (see Supplementary Results).

RESULTS

Behavioral Measures

For behavioral measures with multiple indices correction for multiple comparisons (ie, Bonferroni) was considered within each measure (Note: uncorrected values are noted in Supplementary Table S2).

Personality

Compared with HC, CD individuals had higher novelty seeking scores ($t_{(22)} = 3.34$, $p < 0.007$; Cloninger *et al*, 1994). There were no other group differences in personality.

Affect

CD subjects did not differ from HC on any measure of affect ($p > 0.05$) (Bagby *et al*, 1994; Beck, 1993; Beck, 1996; Chapman *et al*, 1976; Kessler *et al*, 2002; Mroczek and Kolarz, 1998).

Stress

There were no between-group differences in exposure to stressful life events (Brugha *et al*, 1997), history of childhood abuse, or emotional neglect (Bernstein *et al*, 1994) ($p > 0.008$).

Cognition

There were no between-group differences on any measure of cognition (Randolph *et al*, 1998; Wechsler, 2001; Wechsler, 2007), including the timing task ($p > 0.05$), and acute cocaine did not alter timing performance in CD participants ($p > 0.05$).

fMRI

Full details of significant imaging results can be found in Supplementary Table S7.

Acute Cocaine

Acute cocaine did not impact TDE-associated brain activity in WB or SVC analysis ($p_{corrected} > 0.05$). As HC-only analyses were indicative of no session (1 *vs* 2) effects, between-group analysis (HC *vs* CD) focused on the contrast of TDE-related activity averaged across sessions.

Main Effect of Event Type

In general, TDE activation patterns were consistent with previous implementations of this task (McClure *et al*, 2003). In SVC analyses, there was an effect of *EVENT TYPE* in the bilateral putamen (Supplementary Figure S3A). Planned contrasts indicated that in the putamen CS and NTDE-related function were equivalent, and that activity for both was lower compared with UCS and PTDE events. WB analysis confirmed *EVENT TYPE*-related activation in the putamen and further suggested a main effect of the *EVENT TYPE* in bilateral postcentral gyri and declive, and in the right posterior cingulate (PCC), left BA19, and left cuneus (Supplementary Figure S3B). Activity in the postcentral gyri, PCC, putamen, and left declive was lowest for the CS condition, whereas activity for UCS either exceeded that for all other stimuli or was equivalent only to the unexpected reward/PTDE. In contrast, in the right declive, left cuneus, and left BA19 CS-related function exceeded activity for all other events.

Main Effect of Group

SVC (Figure 2a and b) and WB (Figure 2c and d) analyses revealed *GROUP* effects in the bilateral putamen and the left middle frontal gyrus (MFG), where the CD group exhibited less neuronal activity than the HC across event types. CD reductions in TDE-related function were also seen in the right caudate in the SVC analysis.

Group × Event Type Interactions

GROUP-by-*EVENT TYPE* interactions were observed in the bilateral putamen and left BA32 in SVC analyses. Activity in the putamen was lower in CD *vs* HC subjects for UCS and PTDE events (Figure 3a and b) and did not vary as a function of event type in CD individuals. In left BA32, PTDE-related activity was also lower in CD individuals.

WB analyses suggested *GROUP*-by-*EVENT TYPE* interactions in the bilateral insula, right precentral gyrus, left postcentral gyrus, left medial frontal gyrus/BA32, and left putamen (Figure 3c and d). In these clusters, PTDE-related activity was lower in CD *vs* HC subjects. UCS-related activity in the left putamen was also lower in the CD *vs* HC group. In contrast, NTDE-related activity in CD subjects was greater than in HC in the right precentral gyrus, left postcentral gyrus, and left insula.

Cocaine Use History

In those regions where *GROUP*-dependent functional differences (main effects and interactions) were noted, we considered the impact of cocaine-use history on brain activity via linear regression analyses. We included chronic (ie, *AGE* at first use and *YEARS* of use) and acute (ie, how many *DAYS* the subject had used cocaine, the number of *ROCKS* of cocaine used, total *SPENT* on cocaine in the week preceding the study, and *TIME* (days) between last cocaine binge and study entry) factors.

Although chronic-use factors did not predict *GROUP*-dependent variability in TDE function, *TIME* and *DAYS* were associated with *GROUP*-by-event type interactions. Time was positively correlated with PTDE-dependent activity in bilateral putamen and left BA32 (Figure 4a), CS-related function in the left insula, and activity for UCS in the left putamen (Figure 4b). Conversely, *TIME* negatively correlated with NTDE events in the right putamen. *DAYS*

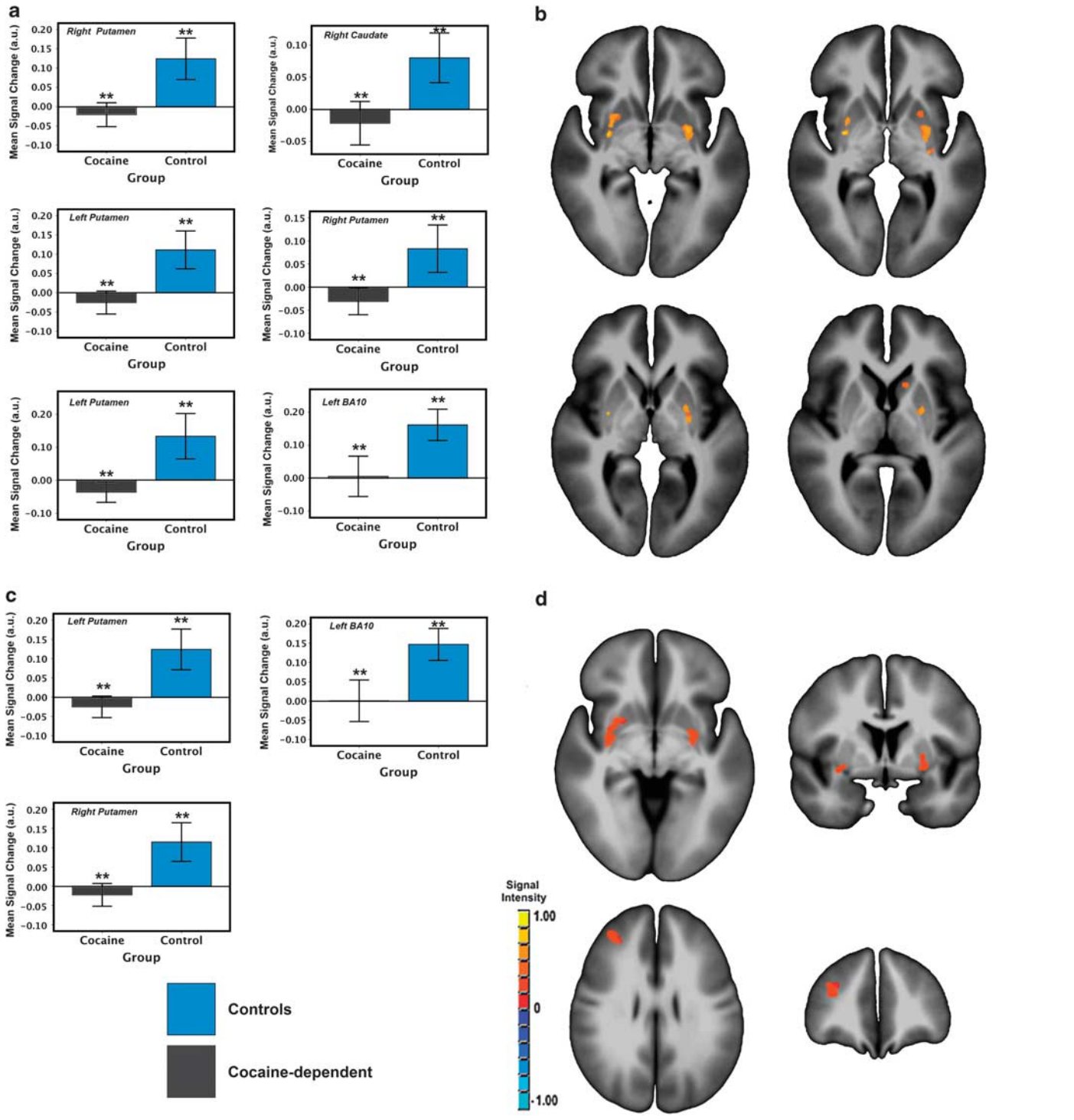

Figure 2 The main effect of group (HC *vs* CD) on TDE-related activity in SVC (a and b) and WB (c and d) analyses. Notes: Error bars show ± 2: SE; brain images are rendered on the ICBM452 T1 template from AFNI; left = left. $^{**}p < 0.001$.

was negatively associated with UCS-dependent activity in the right putamen (Figure 4a).

DISCUSSION

Functional representations of TDE signals were considered in CD individuals in the presence and absence of acute cocaine. Compared with matched HC, reward processing in CD subjects was characterized by greater activity for unpredicted negative outcomes (ie, omission of expected rewards) and less activity for predicted and unpredicted natural rewards in a distributed network of brain regions including major components of the mesocorticolimbic reward system. Moreover, CD individuals exhibited a relative reduction in activity in dopaminergic pathway

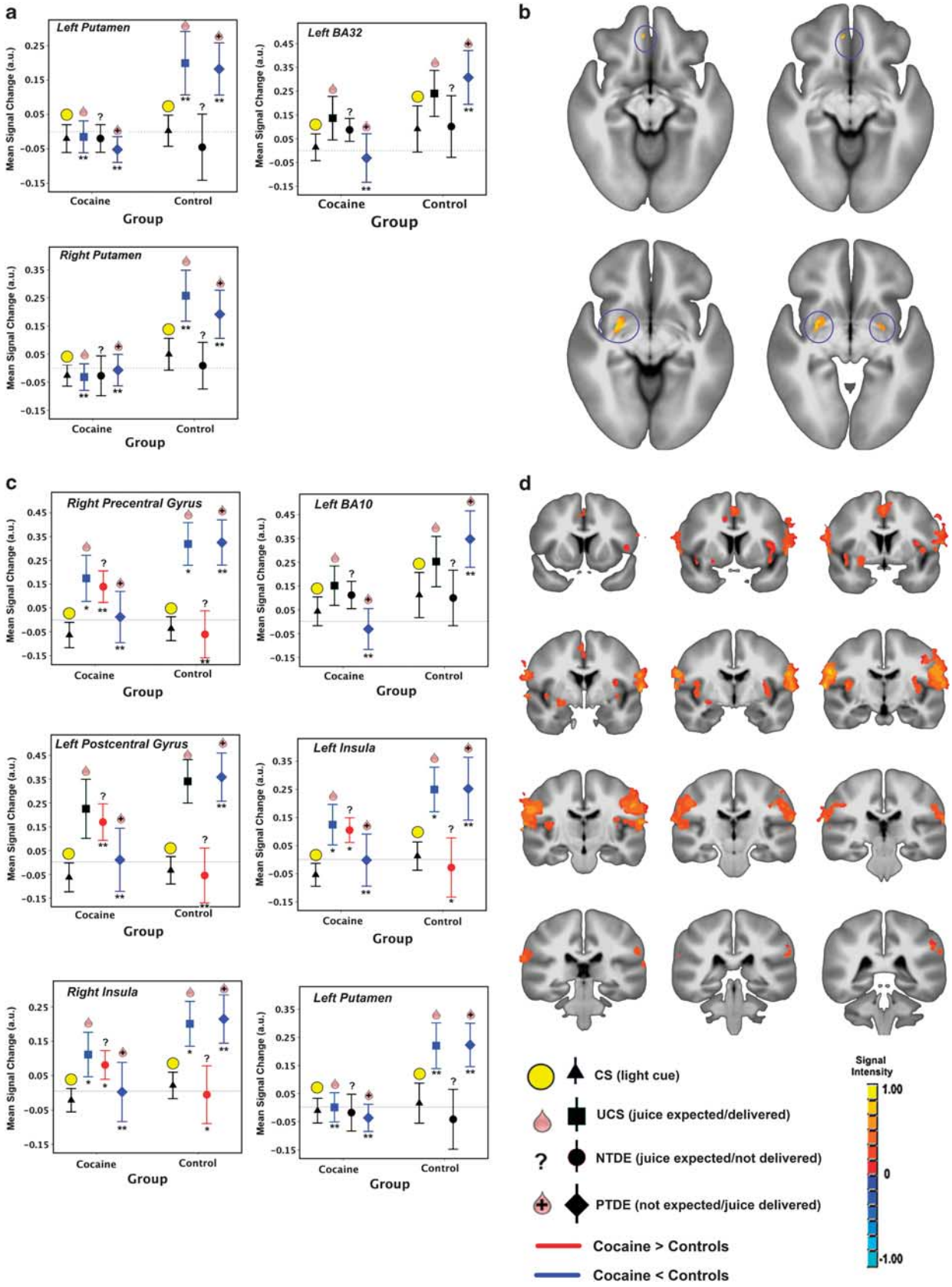

Figure 3 Group (HC *vs* CD) by event-type interactions on TDE-related activity in SVC (a and b) and WB (c and d) analyses. Notes: Error bars show SEM; brain images are rendered on the ICBM452 T1 template from AFNI; left = left. $^{**}p < 0.001$, $^{*}p < 0.05$.

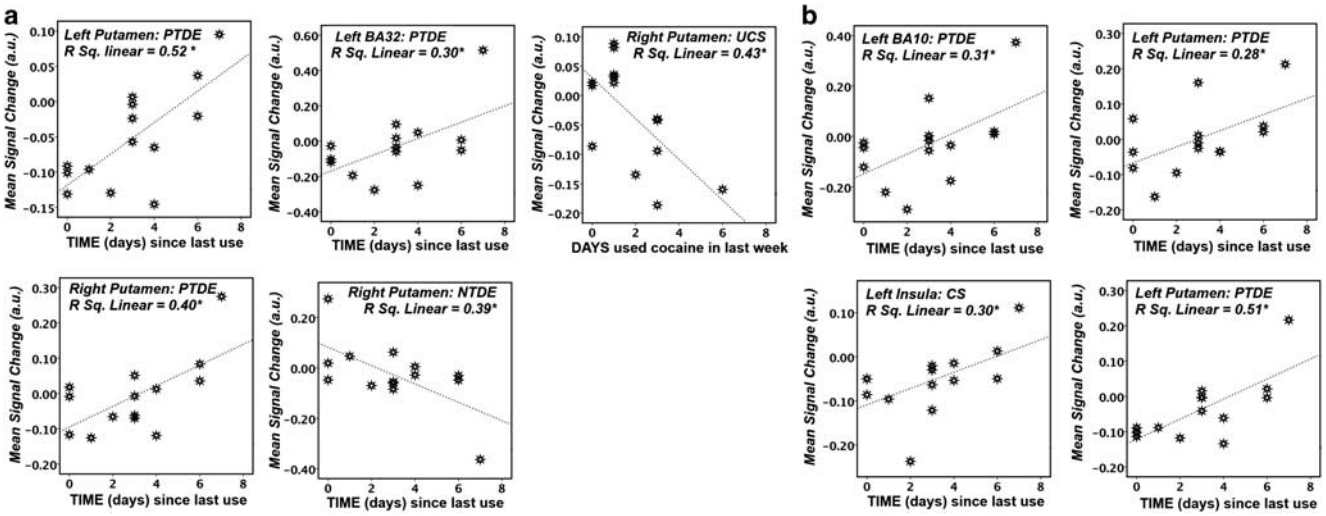

Figure 4 Significant associations between cocaine-use history and group-dependent differences in TDE-related activity in (a) SVC and (b) WB analysis. $^{*}p < 0.05$.

regions in the basal ganglia and prefrontal cortex, independent of reward outcome event type. Functional alterations in the CD group were predicted by the time since last cocaine use/binge, but not by acute cocaine.

Cocaine Dependence and TDE

Cocaine dependence predicted a general blunting of reward-related function in mesocorticolimbic DA terminal areas (eg putamen, BA10). For CD individuals, activity in the putamen did not vary as a function of event type, suggesting a failure to differentiate between events or simply a failure to respond to reinforcing stimuli. In line with a lack of striatal response to acute drug challenge (Martinez *et al*, 2007; Volkow *et al*, 1997) and reduced $D_{2/3}$ receptor availability in cocaine dependence (Martinez *et al*, 2004), trait-related decreases in activity in DA pathway regions may be a consequence of reduced presynaptic DA function. Furthermore, this general lowering in activity lends support to the notion that response sensitization in DA-mediated processing is not readily apparent in human cocaine users, even when individuals are not substantially abstinent (Note: even during saline scanning sessions, the maximum duration since last cocaine use would have been approximately 1 day due to drug toleration or cocaine scanning session the previous day). Although this contrasts with observed, persistent decreases in [C^{11}]raclopride binding following repeated stimulant challenge in healthy individuals (Boileau *et al*, 2006), our participants were drug-dependent and had far greater accumulative exposure to stimulants. Thus, sensitization mechanisms may be critically and differentially impacted by chronic and sustained cocaine consumption.

Reduced activity in reward network regions for non-drug rewards in cocaine dependence may impact incentive salience processing and likely has critical implications for CD individuals. Indeed, decisions to abstain from cocaine and maintain abstinence may rely on satisfaction derived from alternative/non-drug stimuli (eg, food, money, social interactions). As with prior habit formation, failure to respond optimally to non-drug reinforcers likely contributes to continued cocaine consumption (Balleine and O'Doherty, 2010). Intriguingly, here computational activity in reward pathways was not influenced by acute cocaine-administered immediately preceding task performance, thus one potentially 'desirable' (and hypothesized) effect of drug intake (ie enhanced response to reinforcing stimuli) was not achieved by cocaine administration. This may be a critical factor in escalated cocaine use and the persistent cycle of addiction.

It is interesting that CD deficits in reward learning were noted in the dorsal striatum (DS). Such CD decreases in function are in contrast to preclinical and clinical evidence suggesting increased DS activity accompanying cocaine craving (Everitt and Robbins, 2013; Volkow *et al* 2006). We saw general reductions in DS activity for non-drug reinforcers, which implies that increased function in DS in CD individuals may be cocaine-specific, occurring only during drug craving and perhaps at the cost of processing for normally reinforcing non-drug stimuli. From a processing perspective, it is postulated that the ventral striatum (VS) mediates error prediction learning on passive measures, whereas active learning requires VS and DS (O'Doherty *et al*, 2004). Thus, CD deficits in learning-related signals in the putamen may reflect a failure of chronic cocaine users to engage in active learning following errors in reward prediction.

More specific CD changes included lower reward-related activity coupled with increased activity for unpredicted negative outcomes. In the insula, mPFC and pre- and post-central gyri the CD group exhibited a blunting of the response to positive outcomes, irrespective of predictability, and enhanced activity following unpredicted negative events. The lack of *GROUP*-related discrepancies in the perceived pleasantness of the juice suggests that these data do not likely reflect hedonic differences but rather functional distinctions in the salience of reinforcing outcomes. For example, CD individuals may attribute greater salience to unpredicted negative events than their non-CD counterparts, while simultaneously placing less value on positive/rewarding outcomes. Misattributed salience for negative outcomes may compound the lack of risk-averse behavior in cocaine

dependence and increase negative emotional sequelae of addiction, thus driving continued cocaine use.

Intriguingly, regions where saliency-related changes were observed, ie mPFC and insula, are those that have an established role in drug craving and seeking behaviors (Naqvi and Bechara, 2010; Van den Oever *et al*, 2010). The mPFC and insula form part of a network that mediates interoceptive signals and their affective appraisal, and which communicates this information with the striatum and extended amygdala during reward processing. Aberrant processing in this system is suggested to be a critical factor in drug addiction (Verdejo-Garcia *et al*, 2012). With regards to the current observations, it is probable that CD functional alterations in these regions disrupt reward and decision-making computations in a manner consistent with poor behavioral regulation and misattribution of salience for positive and negative reinforcers in the environment, perhaps due to misinterpretation of interoceptive signals computed in the insula or their emotional evaluation in mPFC.

Although lower reward-related activity in CD individuals appears contradictory to previous evidence of heightened sensitivity to rewards in cocaine dependence (Jia *et al*, 2011), in contrast to prior investigations, our participants were not undergoing treatment nor were they seeking treatment. It is probable that the motivational value of cocaine varies between those who do and do not wish to stop using, which in turn may reflect dissociation in the state of brain networks mediating reward processes. Furthermore, while we used a primary reward, Jia *et al* (2011) found CD increases in reward-related function using money as a reward. Money may have very specific value to CD individuals due to its intrinsic association with the ability to obtain cocaine. Thus, the value of money as a reinforcer in CD populations cannot be wholly extricated from the subjective worth of cocaine itself. As a primary reward, juice lacks this inherent connection to cocaine use. The distinction between cocaine dependence's impact on processing for primary and non-primary rewards is supported by work demonstrating blunted activation in CD individuals while viewing erotic material compared with salient drug cues (Garavan *et al*, 2000).

It is particularly notable that as time since last pre-study use increased, there was a relative increase in reward-related activity and a decrease in activity related to the NTDE event; ie the more reward processes were effectively 'normalized'. These differences were not simply due to the absolute time since last cocaine administration (ie $\sim$24 h/time since last session (toleration or scanning)), and thus do not appear related to the bioavailability of cocaine or its metabolites. Alternatively, this effect may be attributed to long-term plastic changes at the level of receptor and/or neurotransmitter function that occurs in the days following an extended cocaine binge. However, this is speculative and requires exploration in both human and preclinical models of cocaine dependence.

Limitations

Despite the novelty and strengths of this study, limitations exist. The number of participants was relatively small for an imaging study, thus replication in larger samples would be advantageous, particularly in determining how periods of use and/or abstinence impact upon group differences. Furthermore, despite having reasonably well-matched groups, we are unable to determine whether or not pre-existing differences (eg, genetics, environmental factors) contributed to functional alterations. Also, the dose and timing of cocaine administered did not replicate that seen naturalistically, thus central and peripheral responses (eg, heart rate/blood pressure) that may act as internal cues (Wise *et al*, 2008; Wise and Kiyatkin, 2011) were likely quite different in the research setting.

Another limitation is the absence of reward learning effects in regions where group differences were observed, which leaves us unable to determine conclusively whether CD and HC subjects differ in reward learning specifically or in other aspects of reward processing eg outcome/receipt. It should also be noted that PTDE events always occurred after the omitted expected reward (ie, $>$6 s post-cue), which may have impacted the 'expectedness' of the juice reward on catch trials, and thus the reliability of the brain response to this reward as a true TDE signal. Although it may be possible to avoid this confounding effect by including catch trials in which the unexpected juice reward is given before the completion of the 6-s interval, this may have an adverse effect on the strength of the learning signal and thus the ability to generate NTDE signals. Alternative modeling of the data (eg, TDE equation modeling) may contribute to a more complete pattern of results.

As the TDE paradigm was always performed $\sim$70 min after the start of scanning and after performing another reward measure, it is possible that participants may have been fatigued, which could have impacted the results. To combat potential fatigue the reward paradigms were interspersed with rest periods (eg, structural scans, resting state fluctuations). Nonetheless, in recognition of the fact that participants may have still experienced some fatigue at the time of the TDE paradigm, the timing of the task relative to the start of testing was consistent across participants in order to somewhat standardize such effects.

CONCLUSION

Our data provide evidence of altered TDE signaling in cocaine dependence in DA pathway regions known to mediate reward processing. Specifically, cocaine dependence was associated with increased sensitivity for unpredicted negative outcomes, coupled with decreased sensitivity for predicted and unpredicted rewarding outcomes. These group-related differences were not influenced by acute cocaine administration. Abnormalities in reward processing in cocaine dependence may be driven by differences in incentive salience processing for positive and negative reinforcers. These acquired effects of cocaine addiction likely contribute to continued and escalating cocaine consumption and high recidivism rates; effects that may be exacerbated by a failure of acute cocaine administration to ameliorate dependence-related deficits.

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