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Temporal Difference Error Prediction Signal Dysregulation in Cocaine Dependence

Emma Jane Rose*[,1,5], Betty Jo Salmeron[1], Thomas J Ross[1], James Waltz[2], Julie B Schweitzer[3], Samuel M McClure[4] and Elliot A Stein[1]

[1]Neuroimaging Research Branch, National Institute on Drug Abuse, Intramural Research Program, NIH, Baltimore, MD, USA; [2]Maryland Psychiatric Research Center, University of Maryland, School of Medicine, Baltimore, MD, USA; [3]Department of Psychiatry and Behavioral Sciences, M.I.N.D. Institute, University of California-Davis School of Medicine, Sacramento, CA, USA; [4]Department of Psychology, Stanford University, Stanford, CA, USA

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).

*Correspondence: Dr EJ Rose, Center for Translational Research on Adversity, Neurodevelopment and Substance Abuse, Department of Psychiatry, University of Maryland School of Medicine, 4th Floor, 110 S.Paca Street, Baltimore, MD 21201, USA, Tel: +410 328 6803, Fax: +410 328 3693, E-mail: ejrose@rti.org
[5]Current address: Center for Translational Research on Adversity, Neurodevelopment and Substance Abuse, Department of Psychiatry, University of Maryland School of Medicine, 4th Floor, 110 S.Paca Street, Baltimore, MD 21201, USA.
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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/$^\circ$ 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.

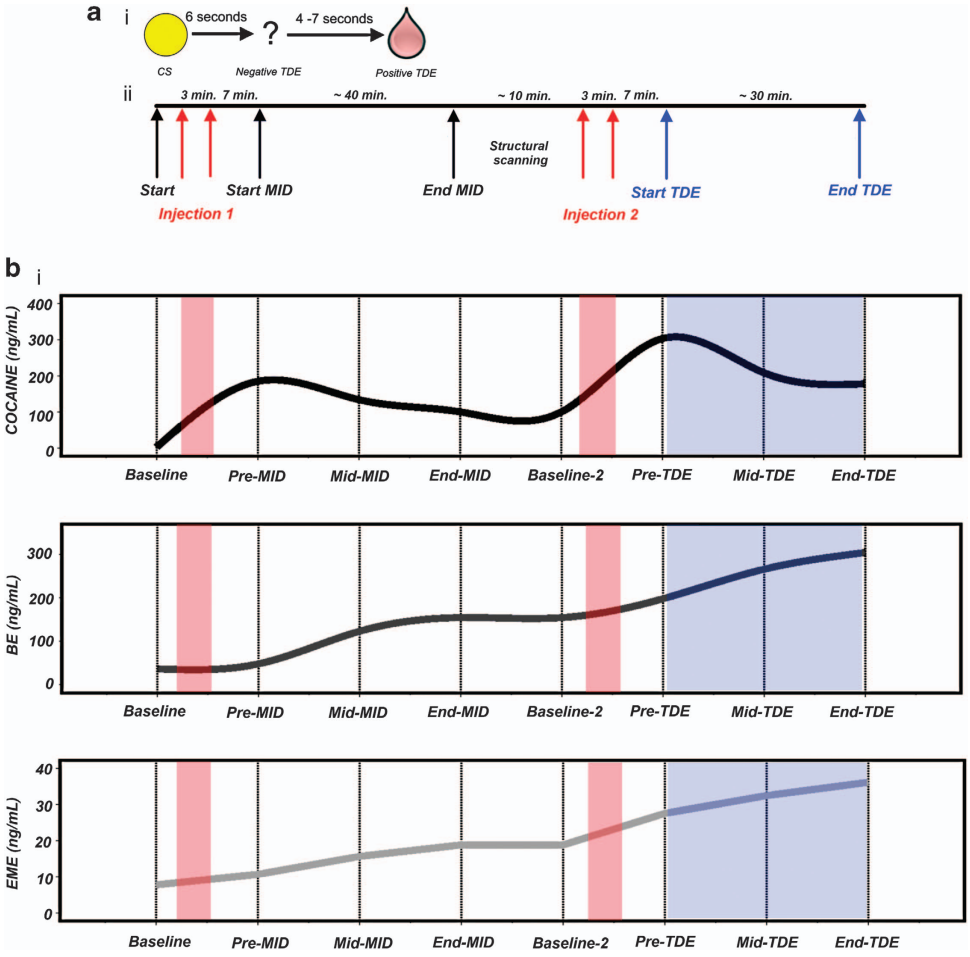

Figure 1 Experimental timeline and relative plasma concentration of cocaine and metabolites. (a) (i) TDE 'catch' event (ii) Scanning timeline including timing of cocaine injections relative to imaging tasks. (b) Estimated mean plasma concentrations (ng/ml) of (i) cocaine, (ii) Benzolecgonine (BE), and (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*

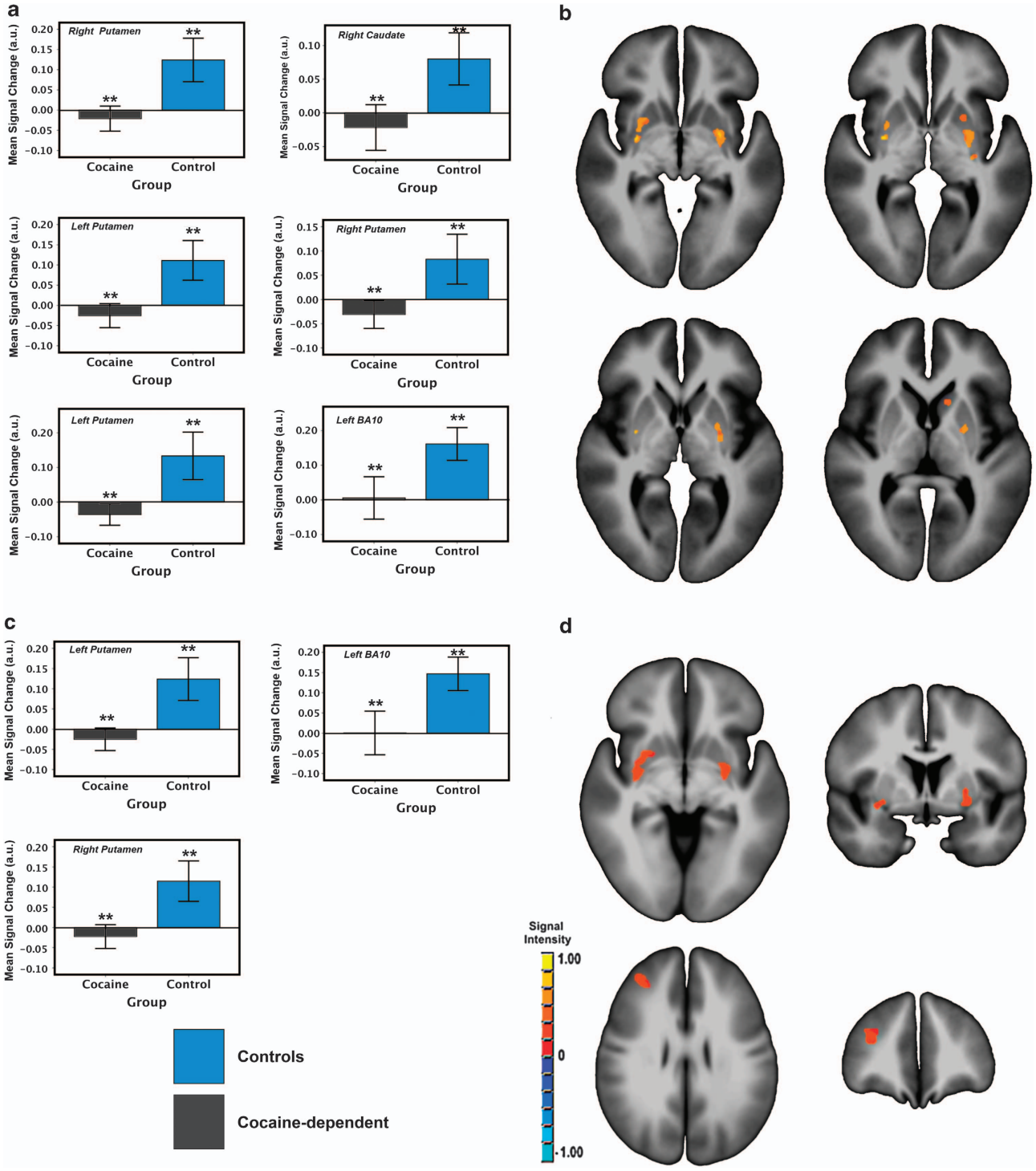

Figure 2 The main effect of group (HC *vs* CD) on TDE-related activity in SVC (a and b) and WB (c and d) analyses. Notes: Error bars show ± 2: SE; brain images are rendered on the ICBM452 T1 template from AFNI; left = left. $^{**}p < 0.001$.

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

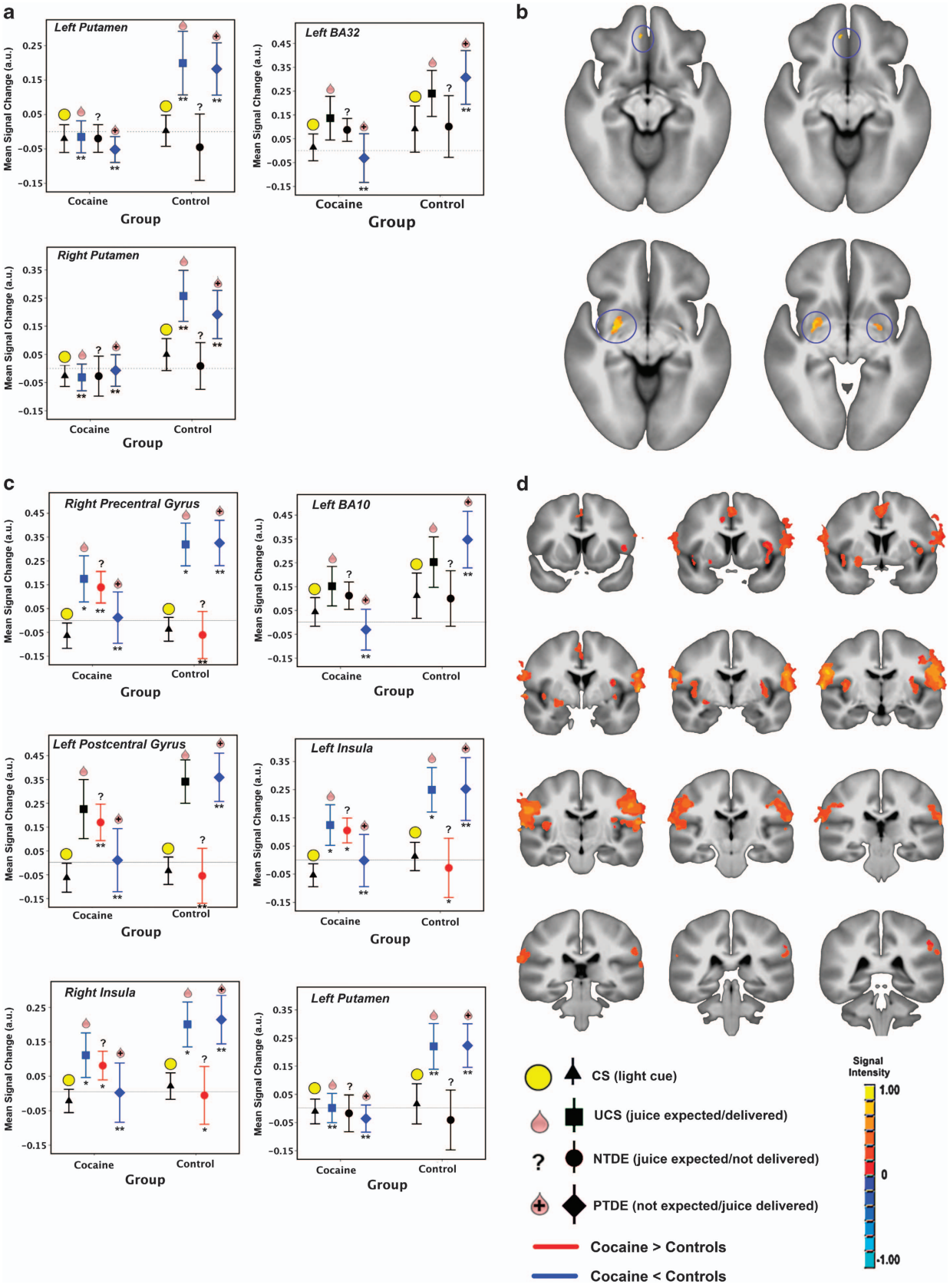

Figure 3 Group (HC *vs* CD) by event-type interactions on TDE-related activity in SVC (a and b) and WB (c and d) analyses. Notes: Error bars show SEM; brain images are rendered on the ICBM452 T1 template from AFNI; left = left. $^{**}p < 0.001$, $^{*}p < 0.05$.

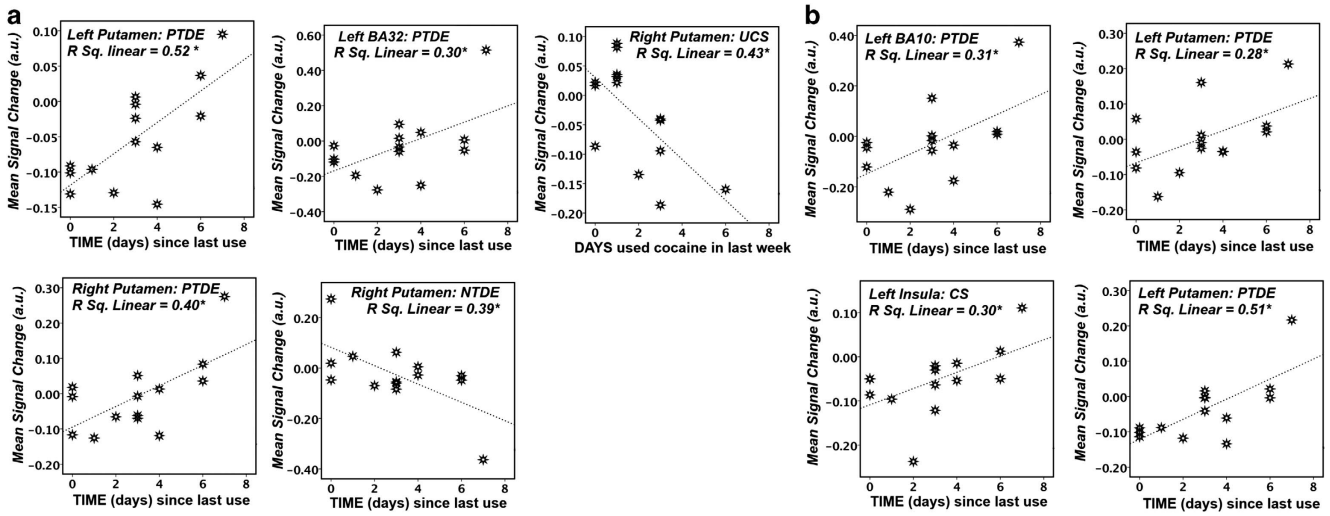

Figure 4 Significant associations between cocaine-use history and group-dependent differences in TDE-related activity in (a) SVC and (b) WB analysis. $^{*}p < 0.05$.

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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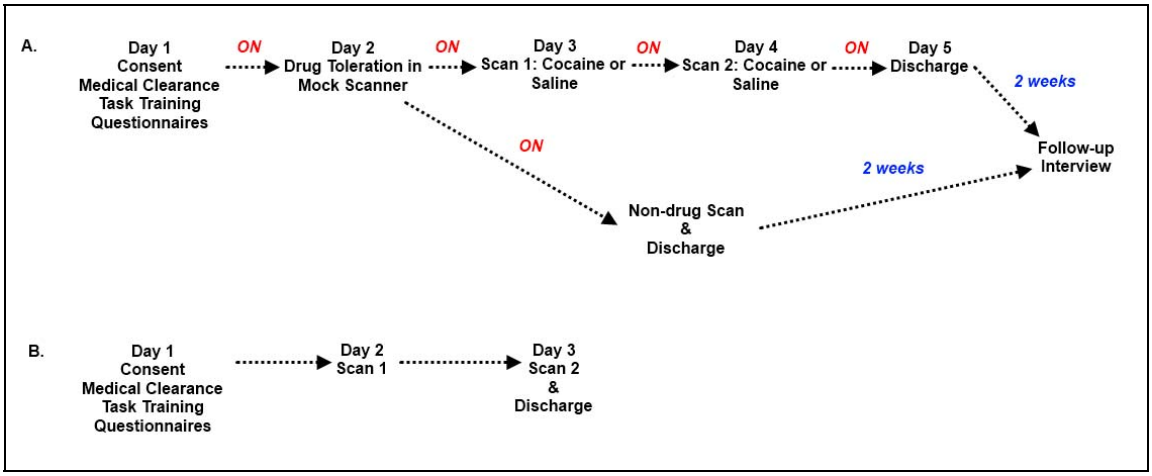
Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)

SUPPLEMENTARY MATERIALS

CONTENTS

SUPPLEMENTARY METHODS

FIGURE S1: EXPERIMENTAL TIMELINE FOR A. COCAINE-DEPENDENT (CD) ADULTS AND B. HEALTHY CONTROL (HC) PARTICIPANTS. NOTE: ON=OVERNIGHT STAY.



INCLUSION/EXCLUSION CRITERIA

While current and past abuse of alcohol and marijuana and past dependence on other substances was tolerated in CD individuals, all other current or past DSM-IV-TR diagnoses were exclusionary. CD subjects were also excluded if they had a history of adverse reaction to cocaine, such as cardiac arrhythmia or chest pain.

PRE-SESSION ASSESSMENTS

Participants were not permitted to consume alcohol or over-the-counter medications for 24h prior to each session and were limited to ½ cup of caffeinated beverage before each scan. Prior to each session, participants were tested for recent drug use (TRIAGE® urine drug test), alcohol use (Alco-Sensor IV, Intoximeters Inc., USA), pregnancy, and expired carbon monoxide (Vitalograph Breath CO monitor, USA).

COCAINE ADMINISTRATION

Participants received a bolus injection of 30mg cocaine hydrochloride per 70kg bodyweight, over a 3min period about 10mins prior to each of two reward tasks (i.e. about 1h apart). Cocaine hydrochloride (Mallinckrodt, Hazelwood, MO) was prepared for use in sterile vials using sterile saline, on the day of testing by a research pharmacist. Skilled medical professionals placed an intravenous catheter in an arm vein and the lines were monitored throughout the session to ensure accordance with NIDA-IRP standard procedures. Injections were administered via this catheter using a Harvard 2000 series pump (Harvard, MA), set to infuse 10cc over 3 minutes, followed by a saline flush.

DRUG TOLERATION SESSION.

Prior to scanning, CD subjects completed a session in a mock scanner mimicking the scanning procedure including cocaine administration. This session was designed to: (a) familiarize participants with the cocaine administration procedure; (b) obtain baseline physiological and behavioral reactions in a controlled situation; (c) deliver drug in a setting where any untoward responses could be dealt with expeditiously; and (d) expose participants to simultaneous MR data collection procedures and the experience of intravenous cocaine.

PHYSIOLOGICAL MONITORING DURING DRUG ADMINISTRATION SESSIONS

During the toleration session participants were continuously monitored for blood pressure, ECG changes, and pulse rate. Blood pressure was monitored via auto-inflatable cuff every 2 minutes during the 10 minute period following drug administration during scanning and throughout the entire drug toleration session, reporting systolic, diastolic and mean arterial pressure and pulse, with a display in both the control room and the

scanner room. ECG monitoring during toleration studies and fMRI sessions (to the extent possible) took place on line, however potential interference from the scanner decreases the value of ECG during MRI sessions. A 12-lead ECG was obtained at baseline prior to each study, between cocaine injections during the toleration phase and after completion of each study session. Pulse was monitored from three sources, the blood pressure monitor, the ECG leads, and a pulse oximeter. Based on the judgment of the medically responsible physician (MRP) or physician designate, participants who experienced a significant drop in blood pressure and heart rate (20% drop in MAP from one reading to the next or 20% drop in heart rate over 2 minutes), or any drop accompanied by clinically significant symptoms, were not allowed to continue in the protocol. If heart rate exceeded 0.85 x (220-age of participant), no further cocaine was delivered and the participant was withdrawn from the full study. The second cocaine injection was not given unless heart rate had been <130, SBP had been less than 160 and DBP had been less than 100 for the preceding 5 minutes. The experiment was ceased and the participant no longer allowed to participate if a single BP spike exceeding 180 systolic or 130 diastolic was noted during the acute administration of cocaine. These criteria are consistent with the NIDA-IRP cocaine administration policy. Participants were monitored for arrhythmia, and any clinically significant arrhythmia, including but not limited to atrial fibrillation, PVC's, or PAC's greater than five per minute, ventricular couplets, atrial triplets (SVT), lead to the experiment being terminated. In addition, the toleration study was terminated if the mid-study ECG showed 1mm ST depression measured at .08 seconds after the J point if the baseline ECG was fully normal or if the baseline ECG showed some non-specific ST depression 2mm of additional ST depression .08 seconds after the J point. In the event that a patient developed ST depression during the toleration phase, the ECGs were sent to reviewed by a cardiologist and a dobutamine echocardiogram was performed. If similar ECG changes were found without evidence of ischemia by echocardiogram, the participant was allowed continue in the protocol. If ECG changes were not duplicated or if ischemia was seen, the participant was discharged from the protocol. During toleration sessions in the mock scanner, the primary monitoring was via ECG and BP. Due to interference with the ECG during MRI scanning sessions, the MRP or designate monitored QRS complexes from the ECG and pulse oximeter output for beat to beat variability and rate in order to assess arrhythmia. Sinus tachycardia or sinus bradycardia exceeding the limits described above led to study terminations. The lockouts for arrhythmia in the NIDA-IRP cocaine administration policy referred to above are based upon clinical evidence of cocaine induced premature atrial contractions and premature ventricular contractions. Since it is impossible to predict all possibilities, the discretion of the clinician was used determine the presence of clinically significant arrhythmia.

A licensed ACLS certified physician was present at all sessions that required IV cocaine administration and a crash cart was always readily available when administering drugs. The medical and experimental staff performed regular safety drills in both the mock and real MRI scanners to prepare for any untoward events.

During toleration, venous blood samples (8 x 5mL) were acquired for the purposes of monitoring cocaine blood serum levels. Samples were obtained before each cocaine injection, immediately before each task, and at the midpoint and end of each task. It was presumed that serum levels during toleration would approximate those during scanning.

At the end of the session, participants had a 12-lead ECG and their vital signs data were reviewed. Only those CD participants who successfully completed toleration with no untoward effects entered into the scanning phase. Those who didn't were given the option to complete a single non-drug scanning session, involving neither saline nor cocaine administration.

BLOOD PLASMA ANALYSIS AND COCAINE METABOLISM

Plasma samples obtained during drug toleration were analyzed for cocaine and metabolites using liquid chromatography-tandem mass spectrometry with conditions for cocaine, benzoylecgonine (BE), ecgonine methyl ester (EME) and norcocaine (Lin et al, 2001; Lin et al, 2003). Cocaine levels peaked following cocaine injection and then declined across the interval corresponding to each reward task (Figure 1B(i)). Compared to baseline, cocaine, BE and EME levels were greater before the second injection ($t_{(21)}$=14.49, $t_{(21)}$=15.13 & $t_{(21)}$=11.87 $p<0.001$), suggesting an accumulative effect across injections. There was a linear increase in metabolite levels across the session ($p<0.001$; Figure 1B(ii) & (iii)). Norcocaine was below reliable detection levels.

STUDY FOLLOW-UP

CD participants were contacted via telephone approximately 2wks following study discharge to complete an interview-based assessment of their drug use since study completion.

Of the CD subjects who completed both drug sessions or a single non-drug scan (N=31), we were able to re-contact and assess current cocaine use since participation in 24. Within this sub-sample, there were no

differences in the number of days subjects had used cocaine in the preceding week, nor how many rocks they had used or how much they had spent on cocaine. However, the average number of days they reported using cocaine was comparatively less following participation ($t(23)=2.60$, $p<0.05$), as was the duration of their last cocaine binge ($t(23)=2.25$, $p<0.05$) and the amount of money spent during their last binge ($t(23)=2.15$, $p<0.05$).

CHARACTERIZATION MEASURES

PSYCHIATRIC HISTORY

Structured Clinical Interview for DSM Disorders (SCID): The SCID is a diagnostic exam used to determine presence of DSM-IV disorders.

Structured Interview for DSM-IV Personality Disorders (SIDP-IV; Pfohl et al., 1997): This interview is used to determine the presence/absence of DSM-IV Axis II personality disorders.

PERSONALITY

Temperament and character inventory (TCI; Cloninger et al., 1994): **The TCI is a widely used** measure which yields dimensions of personality, including Harm Avoidance, Novelty Seeking, Reward Dependence, and Persistence, which are purported to be dependent on monoaminergic function.

AFFECT

Beck Depression Inventory – II (BDI-II; Beck, 1996): A brief inventory that assesses symptoms of depression currently and in the preceding 14 days, which was used as an exclusion criterion in the study.

Beck Anxiety Inventory (Beck, 1993): A brief inventory, similar to the BDI-II, which assesses symptoms of anxiety across the preceding week prior.

Toronto Alexithymia Scale (TAS; Bagby et al., 1994). This 20-item scale is designed to measure difficulty with awareness of feelings.

Chapman Scales for Physical and Social Anhedonia (Chapman et al., 1976)**:** The Chapman uses 100 true/false items to quantify the ability of study participants to experience pleasure both physically and in social contexts.

Positive and Negative Affect Scale (PANAS; Mroczek and Kolarz, 1998): This self-rated questionnaire was designed to measure the extent of emotions such as sadness, hopelessness, anxiety, and restlessness in community studies. It is in turn based on a number of well known instruments measuring affect and anxiety.

K10 Screening Scale of Psychological Distress: This is a 10 item interviewer-rated questionnaire scale that discriminates cases from non-cases in general purpose health surveys (Kessler et al, 2002). In the current context, where subjects are all non-cases this scale was useful in separating those with and without perceived distress.

EXPOSURE TO STRESSFUL EVENTS

Childhood Trauma Questionnaire: A 70 item self-rated questionnaire that assesses 5 kinds of childhood trauma (emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect) (Bernstein et al, 1994, 2003). It has established reliability and validity, and has been widely used in both clinical and community samples (Bernstein et al, 1994; 2003).

A Life Events questionnaire: This measure is based on earlier work (Brown and Harris, 1978; Brugha et al, 1997), and was modified to assess a series of past and recent (6 month) life events, as well as their impact.

COGNITIVE FUNCTION

Wechsler Adult Intelligence Scale – Abbreviated (Wechsler, 1981; The Psychological Corporation, 1999): This is an abbreviated version of the Wechsler Adult Intelligence Scale (3rd Edition), which provides IQ measures of appropriate reliability for matching participants.

Wechsler Test of Adult Reading (WTAR): The WTAR uses the ability of participants to read aloud 50 words that do not conform to normal grapheme/phoneme pronunciation (e.g. psalm) to estimate premorbid level of intellectual competence. (The Psychological Corporation, 2001).

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998): The RBANS includes multiple measures of cognitive function, e.g. immediate memory, delayed memory, language function, visuospatial skills.

COCAINE USE

Cocaine use, pattern, and withdrawal questionnaire: This is an interview-guided questionnaire that asks cocaine using individuals to provide quantitative and qualitative information regarding their cocaine use history (e.g. age at first use, how long used, last use, average amount used, describe factors that induce cocaine use or techniques used to control cravings etc.) and quantitative information about current symptoms of craving and withdrawal. It was designed by Dr BJ Salmeron (a co-author on this manuscript) and has been successfully employed by our group in a number of previous studies.

Cocaine craving questionnaire (CCQ; Tiffany et al., 1993): This measure includes 45 items that measure current craving for cocaine.

Cocaine craving scale (CCS; Weiss et al., 1997): Five questions on intensity and frequency of craving, both currently and in the preceding 24 hours that have been shown to possess short-term predictive validity of cocaine use.

SUPPLEMENTARY RESULTS

TABLE S1: SUMMARY OF COCAINE USE PARAMETERS OBTAINED UPON STUDY ENTRY (DAY 1) IN CD ADULTS

	Min.	***Max.***	***Mean***	***Std. Deviation***
Age at first cocaine use	14.00	36.00	22.00	5.80
Years regular cocaine use	8.00	25.00	16.35	4.98
Average number of days/week using cocaine	1.00	7.00	2.39	1.64
Number of days used cocaine in last week	.00	6.00	1.78 1	1.67
Number of rocks of cocaine used in last 7 days	.00	40.00	10.38	12.80
Amount ($) spent on cocaine in last 7 days	.00	1000.00	186.42	263.92
Duration of average cocaine binge (days)	.15	7.00	1.97	2.27
Duration of last cocaine binge (days)	.08	14.00	2.16	3.47
Amount ($) spent on cocaine during last binge	50.00	1200.00	260.35	362.28
Longest period of abstinence since first use (days)	10.00	1825.00	408.92	508.75
Number of quit attempts in last 5 years	.00	6.00	2.07	2.16
Number of treatments for cocaine use in last 5 years	.00	30.00	2.57	7.91
Number of treatments completed	.00	2.00	0.28	0.61
Number of treatments that were voluntary	.00	30.00	2.50	7.92
Time (days) since last cocaine use	.00	7.00	3.00	2.28
Currently feeling high	1.00	1.00	1.00	0.00
Currently craving	1.00	6.00	1.85	1.61

TABLE S2: SUMMARY OF NON-SCANNING CHARACTERIZATION MEASURES.

Measure	CD (mean (s.d.))	HC (mean (s.d.))	Comparison
TCI – Cooperativeness	32.71 (7.02)	34.82 (4.05)	NS
TCI – Harm Avoidance	10.14 (6.41)	9.17 (6.19)	NS
TCI – Novelty Seeking	22.62 (4.57)	15.83 (5.57)	$t_{(21)} = 3.34$ $p = 0.003$
TCI – Reward Dependence	13.64 (3.99)	14.82 (4.05)	NS
TCI – Self-directedness	31.29 (6.92)	36.50 (5.65)	$t_{(22)} = -2.08$, $p = 0.048$
TCI – Self-transcendence	15.64 (4.43)	16.08 (8.13)	NS
TCI – Persistence	5.86 (1.03)	5.92 (1.51)	NS
TAS – Difficulty Identifying Feelings	12.93 (7.18)	9.23 (2.68)	NS
TAS – Difficulty Describing Feelings	10.21 (5.18)	9.23 (3.63)	NS
TAS – Externally Oriented Thinking	19.21 (3.81)	18.38 (4.45)	NS
TAS – Total	42.36 (14.35)	36.85 (7.40)	NS
Chapman – Inf	0.36 (0.49)	0.86 (0.86)	NS
Chapman – Physical Anhedonia	13.21 (4.90)	13.00 (8.28)	NS
Chapman - Social Anhedonia	12.57 (8.10)	10.71 (6.13)	NS
RBANS – Immediate Memory	98.57 (16.51)	101.92 (13.11)	NS
RBANS – Visuospatial	105.79 (15.11)	107.54 (17.24)	NS
RBANS – Language	94.36 (5.79)	97.08 (7.89)	NS
RBANS – Attention	101.07 (11.74)	95.92 (14.73)	NS
RBANS – Delayed Memory	95.57 (10.68)	105.00 (11.98)	NS
RBANS – Total Scale	98.93 (12.46)	101.46 (10.27)	NS
WTAR – Raw Score	31.14 (8.33)	34.31 (8.61)	NS
WTAR – Scaled Score	96.50 (13.33)	100.92 (13.14)	NS
CTQ – Emotional Abuse	10.21 (5.63)	7.46 (2.60)	NS
CTQ – Physical Abuse	9.50 (4.96)	8.31 (3.25)	NS
CTQ – Sexual Abuse	6.07 (4.01)	6.85 (4.85)	NS
CTQ – Emotional Neglect	12.93 (5.82)	9.38 (2.87)	NS
CTQ – Physical Neglect	8.86 (4.31)	5.92 (1.55)	$t_{(23)} = 2.32$ $p = 0.029$

Measure	CD (mean (s.d.))	HC (mean (s.d.))	Comparison
CTQ – Minimizatio/Denial	0.36 (0.84)	0.31 (0.63)	NS
K10	3.64 (4.09)	3.23 (3.56)	NS
PANAS – Negative	2.57 (4.29)	1.85 (2.11)	NS
PANAS – Positive	16.14 (3.72)	17.31 (2.93)	NS
Life Events < 6 months	3.86 (3.46)	1.85 (3.34)	NS
Life Events > 6 months	5.93 (5.33)	4.75 (4.03)	NS
BDI	4.07 (3.69)	3.54 (3.18)	NS
BAI	2.36 (2.13)	1.23 (2.01)	NS
WAIS – Full	98.92 (9.29)	106.00 (12.17)	NS
WAIS – Verbal	95.54 (11.26)	106.38 (12.22)	$t_{(22)} = -2.35$, $p = 0.027$
WAIS – Performance	101.69 (8.22)	105.69 (13.78)	NS
Timing Task	Average: 8.85 (1.95) Cocaine: 8.08(1.88) Saline: 8.72(2.68)	8.85 (2.88)	HC vs. CD: NS Cocaine vs. Saline NS

Note: TCI – Cloninger Temperament & Character Inventory; TAS – Toronto Alexithymia Scale; Chapman – Chapman Scales for Physical and Social Anhedonia; RBANS – Repeatable Battery for Assessment of Neuropsychological Status; WTAR – Wechsler Test of Adult Reading; CTQ – Childhood Trauma Questionnaire; K10 – K10 Screening Scale for Psychological Distress; PANAS – Positive and Negative Affect Scale; Life Events – Lifetime Events Questionnaire; BDI – Beck Depression Inventory; BAI – Beck Anxiety Inventory ; WAIS – Wechsler Adult Intelligence Scale.

RATING SCALES

JUICE PALATABILITY

Juice ratings (range 0-800) across sessions were positive for CD and HC (mean (s.d): CD = 515.67 (43.24); HC = 455.48 (43.24)), but did not differ between groups, sessions or TDE task blocks ($p>0.05$).

COCAINE-RELATED RATINGS

Pre-session ratings (range 0-800) of high and satisfied did not differ between conditions ($p>0.05$). However, pre-session levels of craving were lower in cocaine vs. saline sessions ($t_{(13)}=-2.18$, $p<0.05$). Furthermore, while ratings did not vary across the session ($p>0.05$), how high subjects felt was greater ($t_{(13)}=1.84$, $p<0.05$) and the extent of craving was lower ($t_{(13)}= -1.78$, $p<0.05$) in cocaine vs. saline sessions.

TABLE S3: SUMMARY OF COCAINE RATINGS DURING SCANNING

RATING	TIME							
	Pre-scanning		***Start Juice***		***Mid Juice***		***End Juice***	
	Cocaine	*Saline*	*Cocaine*	*Saline*	*Cocaine*	*Saline*	*Cocaine*	*Saline*
High	294.29 (182.05)	201.71 (237.19)	284.57 (183.86)	110.00 (187.68)	228.29 (199.21)	141.43 (176.41)	228.00 (173.76)	218.57 (251.48)
Craving	436.57 (290.33)	604.86 (235.56)	506.57 (220.31)	633.14 (217.99)	473.71 (246.79)	623.71 (222.68)	547.14 (212.58)	601.43 (258.91)
Satisfied	422.57 (234.09)	486.00 (262.39)	434.00 (210.95)	493.14 (258.69)	489.14 (190.92)	511.43 (212.36)	495.43 (202.82)	463.14 (237.16)

TABLE S4: SUMMARY OF JUICE PALATABILITY RATINGS DURING SCANNING

RATING	TIME					
	Start Juice		***Mid Juice***		***End Juice***	
	CD	*HC*	*CD*	*HC*	*CD*	*HC*
Session 1	503.71 (198.64)	388.86 (269.22)	508.86 (200.99)	472.57 (197.64)	498.00 (196.77)	493.71 (163.81)
Session 2	547.14 (197.87)	491.43 (185.41)	560.29 (215.55)	420.57 (259.78)	476.00 (195.09)	465.71 (229.65)

TABLE S5: COMPARISON OF COCAINE USE CHARACTERISTICS BEFORE AND AFTER STUDY PARTICIPATION.
Note: post-study assessment was carried out approximately 2 weeks after study completion. 'All subjects' data included all CD individuals who received cocaine as part of the study, regardless of whether or not they completed all scanning phases (i.e. N=31; completed follow up assessment N=26). 'Juice subjects' are those subjects who completed both scanning sessions and passed data quality control (i.e. N=14; completed follow up assessment = 12). NS=non-significant.

	Pre-study (mean (s.d.))	***Post-study (mean (s.d.))***	***Comparison (paired samples t-test; 2-tailed)***
All subjects			
Average number of days using cocaine per week	3.47 (2.16)	2.54 (1.96)	$t_{(23)}=2.60$, $p<0.05$
Number of days have used cocaine in the week preceding assessment	2.62 (2.37)	2.12 (1.99)	NS
Number of rocks of cocaine used in the week preceding assessment	10.90 (12.90)	8.15 (11.40)	NS
Amount ($) spent on cocaine in the week preceding assessment	$131.04 ($119.95)	$133.54 ($145.26)	NS
Duration of last cocaine binge (days)	1.79 (2.77)	0.74 (0.91)	$t_{(23)}=2.25$, $p<0.05$
Amount ($) spent on cocaine during last binge	$206.88 ($256.83)	$100.42 ($113.73)	$t_{(23)}=2.15$, $p<0.05$
Juice subjects			
Average number of days using cocaine per week	2.45 (1.78)	2.17 (1.69)	NS
Number of days have used cocaine in the week preceding assessment	1.75 (1.76)	1.08 (0.51)	NS
Number of rocks of cocaine used in the week preceding assessment	9.00 (12.42)	5.55 (5.07)	NS
Amount ($) spent on cocaine in the week preceding assessment	$125.83 ($132.15)	$88.33 ($83.21)	NS
Duration of last cocaine binge (days)	2.19 (3.77)	0.65 (0.88)	NS
Amount ($) spent on cocaine during last binge	$215.00 (315.69)	$100.00 ($97.14)	NS

TABLE S6: SUMMARY OF BLOOD PLASMA CONCENTRATIONS (NG/ML) OF COCAINE AND METABOLITES (BENZOLYECGONINE (BE) AND ECGONINE METHYL ESTER (EME)) DURING THE MOCK SCANNING SESSION.

	Baseline	**Pre-MID**	**Mid-MID**	**End-MID**	**Baseline-2**	**Pre-TDE**	**Mid-TDE**	**End-TDE**
Cocaine (mean (s.d.)) [range]	2.82 (0.79) [2.50-6.00]	188.38 (64.89) [38.20-326.70]	134.06 (48.71) [50.80-281.30]	103.69 (32.47) [63.40-176.70]	103.69 (32.47) [63.40-176.70]	313.75 (119.02) [95.50-632.90]	209.13 (65.52) [108.20-408.50]	183.69 (56.09) [107.60-304.70]
BE (mean (s.d.)) [range]	34.55 (78.74) [2.50-320.30]	46.04 (68.96) [4.10-282.20]	122.84 (86.54) [20.80-380.60]	150.54 (85.49) [63.60-410.40]	150.54 (85.49) [63.60-410.40]	194.98 (90.21) [85.40-407.80	265.75 (104.71) [104.50-504.10]	300.33 (106.39) [156.00-538.60]
EME (mean (s.d.)) [range]	7.55 (15.54) [2.50-64.00]	10.40 (14.87) [2.50-60.50]	15.67 (15.27) [4.00-65.60]	18.55 (14.97) [8.10-65.20]	18.55 (14.97) [8.10-65.20]	27.71 (16.03) [11.20-73.10]	32.48 (18.05) [13.50-83.10]	36.15 (17.52) [19.50-86.60]

TABLE S7: SUMMARY OF SIGNIFICANT DIFFERENCES IN REGIONAL ACTIVITY IN WB AND SVC ANALYSES OF CD VS. HC ACROSS SESSIONS.

	Region	Talairach coordinates x	y	z	K_E/ mm^3	*A priori* contrast ($p_{CORRECTED}$<0.05)
WB						
GROUP	L. putamen	-28	0	-3	641	HC > CD
	R. putamen	27	-4	0	612	HC > CD
	L. middle frontal gyrus/BA10	-32	40	27	499	HC > CD
EVENT TYPE	L. postcentral gyrus	-57	-13	23	22111	CS < UCS, NTDE & PTDE; NTDE & PTDE < UCS
	R. postcentral gyrus	54	-10	22	21813	CS < UCS, NTDE & PTDE; NTDE & PTDE < UCS
	R. declive	21	-58	-13	7138	CS > UCS, NTDE, PTDE; UCS > NTDE
	L. cuneus	0	-87	10	6272	CS > UCS, NTDE, PTDE
	L. BA19	-17	-52	-3	2342	CS > UCS, NTDE & PTDE
	R. posterior cingulate	20	-43	17	1579	CS < UCS, NTDE & PTDE; UCS > PTDE
	L. putamen	-28	-6	-3	1062	CS & NTDE< UCS & PTDE
	L. putamen	-24	-46	16	925	CS < UCS, NTDE, & PTDE; UCS > PTDE
	L. declive	-17	-60	-21	878	CS & NTDE < UCS & PTDE
	R. putamen	27	-8	-2	455	CS & NTDE < UCS & PTDE
GROUP x EVENT TYPE	R. precentral gyrus	57	-11	26	13600	CD > HC: NTDE; CD < HC: PTDE
	L. postcentral gyrus	-58	-13	24	10020	CD > HC: NTDE; CD < HC: PTDE
	R. insula	38	-2	10	1969	CD < HC: PTDE
	L. medial frontal gyrus/BA32	-1	3	49	1627	CD < HC: PTDE
	L. insula	-39	-8	7	1374	CD > HC: NTDE; CD < HC: PTDE
	L. putamen	-25	-1	-6	741	CD < HC: CS; CD < HC: PTDE
SVC						
GROUP	R. putamen	26	-4	0	477	HC > CD
	L. putamen	-24	5	-3	196	HC > CD
	L. putamen	-28	-4	-1	87	HC > CD
	R. caudate	13	15	6	38	HC > CD
	R. putamen	23	9	0	33	HC > CD
	L. middle frontal gyrus/BA10	-32	42	23	25	HC > CD
EVENT TYPE	L. putamen	-27	-5	0	519	CS & NTDE< UCS & PTDE
	R. putamen	27	-8	-2	304	CS & NTDE< UCS & PTDE
	R. putamen	22	5	-4	155	CS & NTDE< UCS & PTDE; NTDE < CS
GROUP x EVENT TYPE	L. putamen	-25	0	-4	269	CD < HC: UCS & PTDE
	R. putamen	25	0	0	180	CD < HC: UCS & PTDE
	L. medial frontal gyrus/BA32	-5	8	43	88	CD < HC: PTDE

CD: Cocaine Dependent; HC: Healthy Control.

CS: Conditional Stimuli; UCS: Unconditional Stimuli; NTDE: Negative Temporal Difference Prediction Error; PTDE: Positive Temporal Difference Prediction Error

POST HOC ANALYSES

NICOTINE/SMOKING

The number of smokers, current and past was greater in the CD group vs. HC (i.e. current: 12 vs. 2; χ^2=14.86, p<0.001; past: 14 vs. 8; χ^2=7.64, p=0.006). *DURATION*, *CPD* (cigarettes per day) and nicotine dependence[53] were only measured in current smokers, and there were insufficient active HC smokers to meaningfully compare across groups. However, age at first cigarette was noted for all those with a history of smoking, and did not differ across groups (CD: 20.36±7.89; HC: 18.88±5.25).

The relationship between smoking-related characteristics and TDE-dependent activity in regions that difference as a function of *GROUP* or showed a *GROUP* x *EVENT TYPE* interactions was considered in current smokers, across groups. In those regions showing a *GROUP* effect there was no impact of these smoking-related factors (p>0.05). Similarly, age at first cigarette and *DURATION* were not associated with activity in regions exhibiting *GROUP* by *EVENT TYPE* interactions (p>0.05). However, *CPD* influenced activity in regions showing an interaction effect (p<0.05; Figure 5). *CPD* was positively associated with UCS- and PTDE-related activity in the l.putamen, and negatively correlated with NTDE-related activity in the r.putamen.

In light of the impact of *CPD* on TDE-related function, *post hoc* repeated measures ANOVA were carried out in order to ascertain whether including this factor in the model would alter the nature of *GROUP* by *EVENT TYPE* interactions. In both whole brain and SVC analysis all interactions remained significant despite the inclusion of *CPD* as a covariate.

CHARACTERIZATION MEASURES

CD and HC participants differed significantly on measures of novelty seeking, physical neglect and self-directedness (see Table S2). These differences may reflect underlying trait differences between cohorts that is predictive of the risk of drug abuse/dependence and, therefore, may be related to differences seen here in TDE-related activity. In order to ascertain whether this was the case, we conducted *post hoc* linear regression analyses that considered whether or not characteristic differences between CD and HC contributed to variability in TDE-related function. Since inclusion of these variables that have been shown to differ significantly between groups in models that include group may simply replicate the dichotomous group variable, linear regressions were carried out independently for CD and HC. In all of these regression analyses there was no significant association between characterization measures (i.e. novelty seeking, self-directedness or physical neglect) and brain activity in regions demonstrating either a main effect of *GROUP* or an interaction between *GROUP x EVENT TYPE* (p>0.05). Therefore, we conclude that differences seen between CD and HC in TDE-related brain activity were not simply a product of underlying differences in factors that might potentially increase the risk for drug abuse/dependence.

To confirm that these factors were *not* predictive of brain activity in regions where we observed functional differences between HC and CD, supplementary analysis were also carried out using the 3dRegAna program in AFNI. In these analyses all participants were included as a single group, in whole brain analysis of brain activity related to *EVENT TYPE*. Following correction for multiple comparisons (i.e. Monte Carlo simulation in AlphaSim) there were no regions in which TDE-related activity was predicted by variability in novelty seeking, self-directedness or a history of physical neglect.

REWARD EXPECTEDNESS

In order to determine any effects of the expectedness of the rewarding stimulus, a one-group (i.e. HC plus CD) t-test of the contrast of the UCS and PTDE events was carried out using 3dttest in AFNI. Following correction for multiple-comparisons, there was an effect of the expectedness of the reward in a single cluster in the right precentral gyrus/BA6 (cluster extent/mm^3 = 264 voxels/ mm^3), in which activity was greater for the expected reward (i.e. UCS) vs. the unexpected one (i.e. PTDE).

FIGURE S2: REGIONS SHOWING A SIGNIFICANT FUNCTIONAL ASSOCIATION (P<0.05) WITH NICOTINE USE .

*Shown here are correlations between nicotine use and activity in A. SVC analysis. B. whole brain analysis, *=p<0.05.*

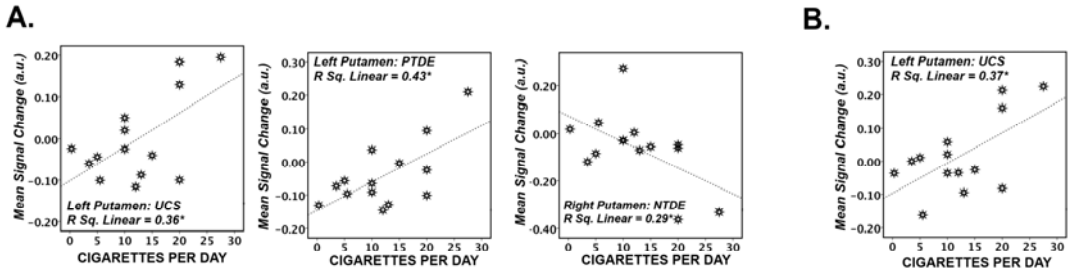
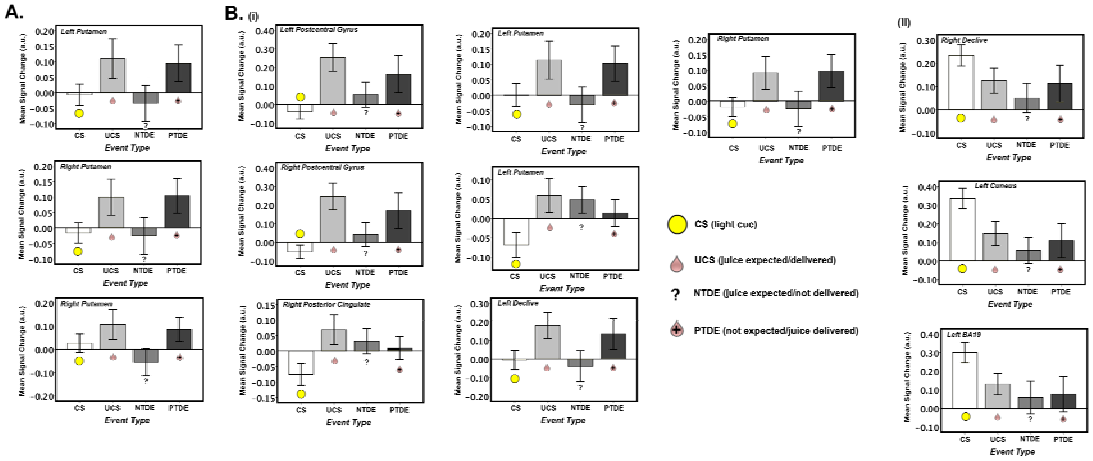


FIGURE S3: MAIN EFFECT OF EVENT TYPE ON TDE-RELATED ACTIVITY in A. SVC analysis and B. Whole-brain analysis (see Table S7 for summary of post-hoc comparisons). (i) Regions showing a primary effect of reward outcome (i.e. UCS &/or PTDE > CS & NTDE) (ii) Regions where CS > UCS, PTDE and NTDE. Error bars show +/- 2 s.e.



SUPPLEMENTAL DISCUSSION

EVENT TYPE

TDE models predict specific shifts in phasic dopamine signaling following reward learning (Niv & Schoenbaum, 2008). Here, increased PTDE-related and decreased NTDE-dependent activity in dopamine pathway nodes supports the notion of TDE-related function in these regions. However, there were no regions where activity for predicted rewards was less than for unpredicted ones, as expected by the model. The model also predicts greater activity for the CS vs. UCS after conditioning. This effect was seen bilaterally in BA10 and was also noted in the occipital cortex and cerebellum. The cerebellar effect may reflect its role in reinforcement learning (Swain et al, 2011), while occipital variations might reflect salience-dependent alterations in visual attention (Treue, 2003). The presence of these TDE-signals in 'atypical' areas while not expected, is in line with recent studies demonstrating the ubiquity of reward learning signals across the brain (Vickery et al, 2011).

EVENT TYPE influenced activity in a distributed network of brain regions. In keeping with the 'incentive salience' model of mesencephalic dopamine function (Berridge, 2007; Berridge & Robinson, 1998; Berridge & Robinson, 2003), the similarity in negative activity for CS and NTDE events and positive responding to UCS and PTDE in this network suggests effects that were salience-driven. While this seems contradictory to the TDE account, from a computational standpoint these models are highly similar and it is probable that they share neural underpinnings (Wise, 2009; Wise & Kiyatkin, 2011).

CHARACTERIZATION MEASURES

Compared to HC, CD individuals scored higher on measures of novelty-seeking and lower for self-directedness (Cloninger et al, 1994), suggesting reduced ability to regulate and adapt behavior coupled with impulsive decision-making. While these differences did not drive group differences in TDE-related activity (Supplemental Results), they may be related to an atypical pattern of salience attribution.

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