

Neural Correlates of Reward-Based Spatial Learning in Persons with Cocaine Dependence

Gregory Z Tau^{*1,2}, Rachel Marsh^{1,2}, Zhishun Wang², Tania Torres-Sanchez^{1,2}, Barbara Graniello^{1,2}, Xuejun Hao², Dongrong Xu², Mark G Packard³, Yunsuo Duan², Alayar Kangarlu², Diana Martinez^{2,4} and Bradley S Peterson²

¹Division of Child and Adolescent Psychiatry, Columbia University and The New York State Psychiatric Institute, New York, NY, USA; ²Department of Psychiatry, Columbia University and The New York State Psychiatric Institute, New York, NY, USA; ³Department of Psychology, Texas A&M University, College Station, TX, USA; ⁴Division on Substance Abuse, Columbia University and The New York State Psychiatric Institute, New York, NY, USA

Dysfunctional learning systems are thought to be central to the pathogenesis of and impair recovery from addictions. The functioning of the brain circuits for episodic memory or learning that support goal-directed behavior has not been studied previously in persons with cocaine dependence (CD). Thirteen abstinent CD and 13 healthy participants underwent MRI scanning while performing a task that requires the use of spatial cues to navigate a virtual-reality environment and find monetary rewards, allowing the functional assessment of the brain systems for spatial learning, a form of episodic memory. Whereas both groups performed similarly on the reward-based spatial learning task, we identified disturbances in brain regions involved in learning and reward in CD participants. In particular, CD was associated with impaired functioning of medial temporal lobe (MTL), a brain region that is crucial for spatial learning (and episodic memory) with concomitant recruitment of striatum (which normally participates in stimulus-response, or habit, learning), and prefrontal cortex. CD was also associated with enhanced sensitivity of the ventral striatum to unexpected rewards but not to expected rewards earned during spatial learning. We provide evidence that spatial learning in CD is characterized by disturbances in functioning of an MTL-based system for episodic memory and a striatum-based system for stimulus-response learning and reward. We have found additional abnormalities in distributed cortical regions. Consistent with findings from animal studies, we provide the first evidence in humans describing the disruptive effects of cocaine on the coordinated functioning of multiple neural systems for learning and memory. *Neuropsychopharmacology* (2014) **39**, 545–555; doi:10.1038/npp.2013.189; published online 13 November 2013

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INTRODUCTION

The compulsive, habitual, and inflexible drug use that characterizes Cocaine Dependence (CD) is functionally disabling and difficult to treat. Preclinical studies have identified cocaine-associated adaptations in neural systems that support reward processing and habit learning, which in turn are associated with the compulsive use of cocaine (Everitt *et al*, 2008; Kalivas and O'Brien, 2008). These neural adaptations support cocaine's role as a powerful behavioral reinforcer and cocaine-related cues as triggers for compulsive drug seeking-behaviors that often lead to relapse (Kosten *et al*, 2005; Martinez *et al*, 2007). Accordingly, addiction is conceptualized as a disorder of learning wherein the transition from casual to habitual cocaine use

is associated with progressive adaptations in corticostriatal circuits that strengthen stimulus-response learning and erode the episodic memory processes that support flexible, goal-directed behaviors (Hyman *et al*, 2006; Kalivas and O'Brien, 2008). Performance deficits on behavioral tasks of episodic memory predict poor treatment outcomes in individuals who use cocaine (Aharonovich *et al*, 2006; Fals-Stewart and Schafer, 1992; Fox *et al*, 2009; Turner *et al*, 2009). Thus, intact episodic memory may be required to support the cognitive effort required in psychotherapies for CD. Whereas functional disturbances in habit learning systems are reported in substance use disorders (SUD) (Chiu *et al*, 2008; Ersche *et al*, 2011; Ghahremani *et al*, 2011; Park *et al*, 2010; Rose *et al*, 2012), the functioning of neural systems for episodic memory have not been assessed in CD. Additional disturbances in these systems would further support the learning model of human addiction, point to a putative mechanism of action for psychotherapies for CD, and offer additional targets for treatment development.

Episodic memory requires the functioning of brain structures in the Medial Temporal Lobe (MTL), including hippocampus, parahippocampal gyrus, and entorhinal

*Correspondence: Dr Gregory Tau, Psychiatry, Columbia University & New York State Psychiatric Institute, 1051 Riverside Dr, Unit 74, New York, NY 10032, USA, Tel: +212 543 6828, Fax: +212 954 5502, E-mail: gzt1@columbia.edu

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cortex (Burgess *et al*, 2002; Iaria *et al*, 2007; Marsh *et al*, 2010; Packard *et al*, 1989). Animal (Fole *et al*, 2011; Krasnova *et al*, 2008; Tanaka *et al*, 2011; Thompson *et al*, 2004; Tropea *et al*, 2008) and human postmortem studies (Mash *et al*, 2007; Meador-Woodruff *et al*, 1993; Zhou *et al*, 2011) have demonstrated that cocaine has wide-ranging molecular and cellular effects on MTL. Although neuroimaging studies have not identified cocaine-associated changes in hippocampus structure (Di Sclafani *et al*, 1998; Jacobsen *et al*, 2001; Makris *et al*, 2004), the impairments in episodic memory associated with cocaine use suggest that episodic memory systems (including MTL structures) are likely dysfunctional in CD.

Spatial learning is a form of episodic memory because it is goal-directed, flexible, and requires encoding of relational experiences (Eichenbaum and Cohen, 2001). Spatial learning in rodents is commonly assessed behaviorally using the 'win-shift' paradigm, which requires the use of spatial cues to navigate an 8-arm radial maze to find hidden food rewards. Like episodic memory, spatial learning in this paradigm depends upon the anatomical and functional integrity of MTL (Packard *et al*, 1989) and is sensitive to cocaine exposure (Fole *et al*, 2011; Muriach *et al*, 2010; Quirk *et al*, 2001). We adapted this spatial learning paradigm for use with functional Magnetic Resonance Imaging (fMRI) in humans (Marsh *et al*, 2010; Xu *et al*, 2012). Our previous use of this paradigm (Marsh *et al*, 2010) validated its ability to probe spatial learning, providing additional evidence for MTL activity during spatial learning in humans (Adcock *et al*, 2006; Ito *et al*, 2008).

We used this fMRI task for reward-based spatial learning to assess functioning of the neural system for episodic memory in CD. We hypothesized that participants with CD would fail to activate MTL and connected brain regions associated with spatial learning and would instead engage other regions in an effort to compensate for impaired MTL functioning. We further explored associations with cocaine use in participants with CD and group differences in the neural correlates of processing reward outcomes during spatial learning.

METHODS AND MATERIALS

Human Subjects

MRI scans were acquired from 13 males with CD (see Supplementary Materials) and 13 healthy males matched on socio-demographic characteristics. Clinical interviews and the Structured Clinical Interviews for DSM-IV-TR Axis I disorders (Biometrics Research, New York State Psychiatric Institute, New York) were conducted to ensure that participants were free of major psychiatric, medical, and neurological conditions (other than CD). For CD participants using other substances, cocaine was their primary drug of choice. CD participants were abstinent at the time of the scan. This study was approved by the Institutional Review Board of the New York State Psychiatric Institute, and informed consent was obtained from all participants.

Reward-Based Spatial Learning Paradigm

Our virtual reality (VR) assessment of reward-based spatial learning has been previously described (Marsh *et al*, 2010; Xu

et al, 2012). The VR environment consisted of an 8-arm radial maze that is surrounded by a naturalistic landscape that provided extra-maze cues (eg, mountains, trees and flowers) that could be used for spatial navigation (Supplementary Figure S1). Prior to scanning, participants practiced navigating a similar VR maze on a desktop computer.

Stimuli during scanning were presented through non-magnetic goggles. Participants used an MRI-compatible joystick (Current Designs Inc.) to navigate the maze. Before scanning, participants were informed that they will find themselves in the center of a virtual maze with eight identical arms extending outwards, and that hidden rewards (\$) would be available at the end of the arms. They were instructed to navigate the maze to collect the rewards and that they could keep any money they found, but that they would lose money if they revisited an arm. They were told that they would complete several sessions of the task, but not that the sessions would differ. They therefore believed that they would be performing the task multiple times.

The reward-based spatial learning paradigm consisted of an active condition and a control condition. In the active condition, all 8 arms were baited with rewards. As participants navigated the maze, they had to learn the spatial layout of the extra-maze cues to select novel arms and avoid revisiting arms. After each arm visit (trial), participants reappeared at the center of the maze with their viewing perspective randomly reoriented to prevent use of strategies such as chaining (systematically selecting neighboring arms). After collecting all 8 rewards, the active condition terminated.

Next, a screen indicated the beginning of new session. In this control condition (described in detail in Supplementary Materials), the identical extra-maze cues used in the active condition were randomized among locations after each trial to destroy any possibility of using the spatial layout of the cues (spatial learning). To control for the reward frequency, participants were rewarded at the same frequency as in the active condition but without regard to their actual performance. This control condition thus shared all salient features with the active condition, including lower-order stimulus features and higher-order task features. This condition terminated following the number of trials that a given participant needed to obtain all 8 rewards in the active condition. If a participant required 18 trials to find all 8 rewards in the active condition (ie, 8 correct and 10 error trials), they would be given 10 unbaited and 8 baited trials randomly in the control condition. Thus, contrasting neural activity in the active condition (during spatial learning) and the control condition (where spatial learning is impossible) reveals the neural correlates of reward-based spatial learning.

Participants underwent 2 runs of each condition (A-B-A-B sequence). The active condition always preceded the control condition to establish the number of trials and reward frequency for the control condition. Together, this reward-based spatial learning paradigm contained 32 rewarded navigation events (8 rewards \times 2 conditions \times 2 runs), but the number of unrewarded events varied for each participant. All participants earned the same amount of money for participating in the experiment regardless of performance.

Image Acquisition and Processing

Images were acquired on a GE Signa 3 Tesla LX scanner (Milwaukee, WI) with a standard quadrature GE head coil. Axial functional images were positioned parallel to the anterior commissure-posterior commissure line using a T1-weighted sagittal localizing scan. Functional images were obtained using a T2*-sensitive gradient-recalled, single-shot, echo-planar pulse sequence having a TR = 2800 msec, TE = 25 msec, 90° flip angle, single excitation per image, 24 × 24 cm FOV, a 64 × 64 matrix, 43 slices 3 mm thick, no gap, and covering the entire brain. The number of EPI volumes collected was determined by the performance of each participant in the active condition, with a maximum of 322 volumes/run.

As previously described (Marsh *et al*, 2010), image preprocessing was run in batch mode using MATLAB 7.9 (Mathworks, Natick, MA) and implemented with subroutines in SPM2 (Wellcome Department of Imaging Neuroscience, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) and FSL (FMRIB Software Library; www.fmrib.ox.ac.uk). Preprocessing consisted of slice-time correction using a windowed Fourier interpolation to minimize its dependence on the reference slice, motion-correction, and realignment to the middle image of the middle scanning run (Jazzard *et al*, 2002). Images with estimates for peak motion exceeding 3 mm displacement or 3° rotation were discarded (Friston *et al*, 1996). Motion-corrected functional images of each participant were then co-registered to the corresponding 3D spoiled gradient recall anatomical image, which was spatially normalized to MNI space (avg152T1) with a voxel size of 2 mm³. The normalization parameters were used to warp the functional images into the same MNI space as the SPGR image. The normalized images were then spatially smoothed using a Gaussian-kernel filter with a full width at half maximum (FWHM) of 8 mm. The spatially smoothed fMRI time series were then temporally high-pass filtered with a cutoff frequency of 1/128 Hz via a discrete cosine transform to remove low-frequency noise, such as scanner drift.

Image Analysis

Extraction of subject-level fMRI signal differences across the active and control conditions of the spatial learning task were conducted using general linear models in SPM8. Three regressors corresponding to specific events that occurred during each trial of each condition were defined (Supplementary Figure S1A). 'Searching' was defined from the start of a trial until a committed arm selection. The two types of outcome possible at an arm's terminus were defined either as 'reward,' when a monetary reward was earned, or 'no-reward,' when no monetary reward was allotted. These three regressors were generated by convolving with a canonical hemodynamic response function the boxcar functions derived from the timing of the onsets and duration of these events for each participant. For these regressors, a t-contrast vector was applied to the parameters (beta_j) that were estimated for each voxel j, producing 5 contrast images for each participant representing comparisons of the 3 regressors across the 2 conditions and the 2 outcomes within the active and control conditions as follows: (1) searching in active vs control condition; (2) reward in the active vs control condition; (3) no reward in

Table 1 Participant Characteristics

	HC	CD	Test statistic (p)
N	13	13	—
Age (SD)	35.5 (6.3)	39.7 (5.4)	1.80 ^a (0.07)
Range	26–43	30–47	
Race/ethnicity			
Black	5	6	0.11 ^b (1.00)
Hispanic	5	5	
Caucasian	3	2	
Years education (SD)	13.7 (1.9)	12.9 (2.1)	−1.25 ^a (0.21)
Range	11–17	10–17	
Employed	12	4	0.00^b (<0.01)
Subjective SES (SD)	6 (1.8)	4.7 (1.3)	−1.24 ^a (0.22)
Range	4–9	3–6	
Objective SES (SD)	41 (13.2)	25.2 (9.8)	−2.91^a (<0.01)
Range	18–66	12–45	
Parent SES (SD)	36 (10.8)	31.2 (12.4)	−1.08 ^a (0.28)
Range	19.5–54.5	13–60.5	
Annual income ^d (SD)	36 (21)	5 (10)	3.78^a (<0.01)
Range	0–90	0–40	
Family alcohol history ^c			
0	9	6	0.07 ^b (0.57)
1	3	4	
≥ 2	1	3	
Family drug history ^c			
0	12	7	0.03 ^b (0.07)
1	1	5	
≥ 2	0	1	
Tobacco smoking status			
Never	6	2	0.09 ^{b,e} (0.20)
Past	1	0	
Current	6	11	
PSS (SD)	11.2 (6)	18.7 (9.1)	1.88 ^a (0.06)
Range	0–18	5–36	
MSPSS (SD)	68.5 (11.7)	57 (7.6)	−2.09^a (0.04)
Range	51–83	42–66	

Abbreviations: CD, cocaine dependence; MSPSS, multidimensional scale of perceived social support; PSS, perceived stress scale; SD, standard deviation; SES, socioeconomic status.

^a'Years education' denotes number of years of school completed (eg, 12 = completed 12th grade of high school). Subjective SES refers to MacArthur Scale of Subjective Social Status (Adler *et al*, 2000). Objective SES refers to Hollingshead 4-factor index of socioeconomic status (Fox *et al*, 2006). Parent SES refers to mean of participants parents' Hollingshead score. Subjective SES, MSPSS (Zimet *et al*, 1988) and PSS (Cohen *et al*, 1983) data for 3 HC and 4 CD participants are missing. Boldface denotes statistically significant group differences.

^bWilcoxon-Mann-Whitney Test.

^cFisher's Exact Test.

^dtable values denote the number of participants with each 0, 1, or ≥ 2 first degree family members with problem alcohol or drug use.

^evalues denote annual income in \$1000s.

^fgroup differences in smoking status were tested by coding based on lifetime smoking status (note: coding the single past smoker in the cocaine group as current non-smoker yields the following a test statistic of 0.04 (p 0.10).

the active *vs* control condition; (4) reward *vs* no reward in the active condition; and (5) reward *vs* no reward in the control condition. The delineation of these events allowed the decomposition of spatial learning and the examination of group differences in two epochs: searching/navigating the maze and processing of monetary reward outcome information. Subject-level fMRI signal differences across the active or control conditions and an implicit baseline (consisting of the unmodeled components of the task) were also extracted in order to derive parameter estimates for individual participants at specific peaks of the statistical map for that contrast.

Group composite activation maps were generated using second-level Bayesian analyses (Friston and Penny, 2003; Neumann and Lohmann, 2003) covaried with age. Group differences in brain activations were also detected with Bayesian methods (Friston and Penny, 2003; Neumann and Lohmann, 2003; Thirion *et al*, 2007). Bayesian image analysis directly assesses the posterior probability of detecting group effect of neural activity given the data (Friston *et al*, 2002; Friston and Penny, 2003). The resultant posterior probability map (PPM) has no false positives and therefore requires no additional correction for multiple comparisons. In these PPMs we report voxels having a posterior probability of >98.75% and within a cluster of spatial extent of at least 20 contiguous voxels, to detect larger clusters of activation of interest.

Behavioral Analysis

Analogous to the BOLD contrast between neural activity in the active and control conditions, task behavior was compared across conditions within and between groups. Linear mixed models (using PROC MIXED) with repeated measures were implemented in SAS version 8.0 (SAS Institute, Cary, NC) with performance speed (time to complete the trials required to obtain the 8 possible rewards) entered as a dependent variable, condition entered as a within-subjects factor, and group entered as a between subjects factor. The model for total time (time taken to complete both runs) reflects the analytic approach to the neuroimaging data and was the primary behavioral assessment. Thus, group-by-condition interactions, and main effect of condition for total time assessed differences in behavior across conditions and between groups. In addition, separate models for run 1 and run 2 further assessed these differences in each run, and T tests separately assessed within group effects.

RESULTS

Demographic and Clinical Characteristics

The CD and HC participants did not differ significantly in age, race/ethnicity, educational attainment, subjective evaluation of socioeconomic status, socioeconomic status of their families of origin, cigarette smoking status, family alcohol history, or stress/anxiety (Table 1). Whereas twelve of the HC participants were employed, four CD participants worked at the time of the study, producing lower values of objective economic measures of CD participants. CD participants also reported poorer social supports. Although six CD participants and only one HC reported

Table 2 Substance Use and Psychiatric Assessments of CD Participants

Assessment		Finding
Cocaine route	Intranasal	2
	Smoked	4
	Both	7
Mean cocaine ingested (grams)	Past Year (SD)	445 (727)
	Range	10–3640
	Lifetime (SD)	6914 (11 901)
	Range	83–43 680
Abstinence prior to MRI scanning	31–50 days	2
	21–30 days	3
	11–20 days	7
	5–10 days	1
Alcohol use (SMAST)	Mean (SD)	3.5 (3.3)
	Range	0–11
	<2	4
	2	2
	>3	5
	ND	2
Lifetime alcohol diagnosis	Abuse	3
	Dependence	3
Lifetime cannabis diagnosis	Abuse	3
	Dependence	0
Lifetime opiate diagnosis	Abuse	1
	Dependence	0
Depression score (BDI-II)	Mean (SD)	8.7 (7.4)
	Range	0–21.5
	< 10	7
	10–20	4
	> 20	2

Abbreviations: BDI, beck depressions inventory; ND, no data collected. S-MAST, michigan alcohol screening test, short version.

a family drug history, this group difference was not statistically significant.

Assessment of CD participants also included substance use characteristics, and comorbid depression and anxiety symptoms (Table 2). Cocaine use and abstinence prior to scanning ranged widely. Comorbid substance use was prevalent; six met criteria for an Alcohol Use Disorder, three for Cannabis Abuse, and one for Opioid Abuse. Two carried a diagnosis of substance-induced mood disorder (with BDI scores greater than 20), and one had a diagnosis of Social Anxiety Disorder.

Behavioral Performance

Both groups completed the spatial learning task faster in the active relative to control condition (Table 3). Specifically, a main effect of condition was found for the combined time taken to complete each condition in runs 1 plus 2, in run 2 alone, but not in run 1 alone. Group differences in performance speed across conditions (group-by-condition

Table 3 Behavioral Performance Across the Active and Control Conditions

Comparison	HC	CD	Main effect ^a of condition F(p)
<i>Time to complete run 1 (SD)</i>			
Active	181 (82)	219 (103)	
Control	202 (73)	232 (101)	2.60 (0.12)
T stat condition active vs. control (p) ^b	-1.46 (0.17)	-0.84 (0.42)	
Main effect ^a of group F(p)		0.99 (0.33)	Group × Condition ^a 0.16 (0.70)
<i>Time to complete run 2 (SD)</i>			
Active	96 (36)	112 (53)	
Control	112 (37)	139 (56)	20.91 (<0.01)
T stat condition active vs. control (p) ^b	-3.24 (<0.01)	-3.38 (<0.01)	
Main effect ^a of group F(p)		1.46 (0.24)	Group × Condition ^a 1.40 (0.25)
<i>Total Time (SD)</i>			
Active	277 (97)	331 (101)	
Control	314 (80)	371 (107)	10.55 (<0.01)
T stat condition active vs. control (p) ^b	-2.39 (0.03)	-2.23 (0.05)	
Main effect ^a of group F(p)		2.32 (0.14)	Group × Condition ^a 0.01 (0.91)

Differences between in the active and control conditions in performance speed within and between the HC and cocaine dependence (CD) groups. Upper, middle, and lower panels show the times taken to complete each condition in run 1, run 2, and in both runs together (respectively).

Boldface denotes statistically significant findings.

^aAnalyses of between group performance were conducted using mixed models with repeated measures to generate statistics for main effects of group and condition, and Group × Condition (group-by-condition interactions).

^bAnalyses of within group (active vs. control condition) performance were conducted using paired T tests.

interactions or main effects of group) were not significant. The longer time taken to complete the same number of trials in the control relative to the active condition is consistent with the interpretation that spatial learning is guiding behavior in the active but not control condition in both groups. The Supplementary Materials also describe the ways in which both groups show similar patterns of faster speed, greater accuracy, and lower perseverative behavior in run 2 compared to run 1, but no group differences in any of these measures (Supplementary Table S1).

Neural Activity During Spatial Navigation

BOLD signal in the active relative to control condition during 'searching' was associated with significant group-by-condition interactions in prefrontal, temporal, and parietal cortices and striatum. In these regions, BOLD signal in the HC participants was greater in the active compared to the control condition, whereas BOLD signal in the CD participants was greater in the control than in the active condition (Figure 1).

A priori hypothesis testing. Significant group-by-condition interactions in MTL, particularly in left parahippocampal gyrus and hippocampus tail, derived from activations in amygdala and caudal and mid-parahippocampal gyrus, including entorhinal cortex and hippocampus tail in the HC participants, and deactivations in hippocampus tail in the CD participants (Figure 1a). Specifically, parahippocampal gyrus activity derived from increased BOLD signal in the active condition and

decreased BOLD signal in the control condition in the HC group but not in the CD group (Figure 1b, bottom panel). Group-by-condition interactions in right ventral and dorsal caudate and putamen (Figure 1a) derived from decreased BOLD signal in the active condition and increased BOLD signal in the control condition in the CD group but not in the HC group (Figure 1b, first and second panels). These findings suggest that, as hypothesized, spatial learning in CD is characterized by both impaired MTL functioning and abnormal neural activity in striatum.

Neural activity in other brain regions. Group-by-condition interactions were also detected throughout insula bilaterally, deriving from activations in the HC group (Figure 1a, Table 4). Interactions in large portions of prefrontal cortex (PFC), including dorsolateral and ventrolateral PFC, caudal anterior cingulate cortex, derived from deactivations in the CD group. Both HC and CD groups contributed to interactions in sensorimotor regions, superior temporal gyri, and frontal pole.

Correlations with cocaine use. Significant inverse associations with abstinence (time prior to scanning) were detected in left caudate nucleus as well as in bilateral sensorimotor and parietal cortices, suggesting that those who were abstinent the longest activated these regions the least when searching the maze (Supplementary Figure S4). No associations were found between amount of cocaine ingested and neural activity.

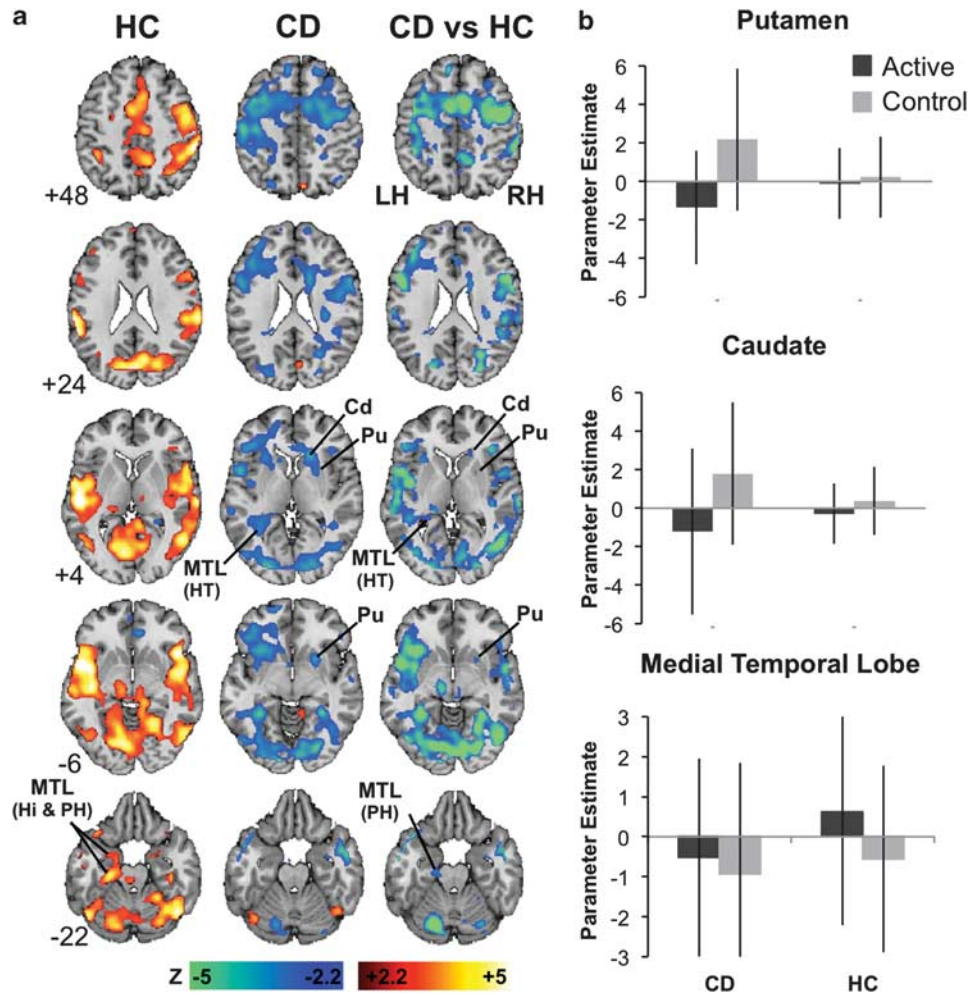


Figure 1 Neural Activity when Searching the Maze. PPMs of BOLD contrasts during the ‘searching’ event thresholded at posterior probability $>98.75\%$ ($z > 2.24$ and equivalent to $p > 0.0125$). (a) PPMs superimposed on axial and coronal slices of Colin27 Brain (Montreal Neurological Institute). (b) Parameter estimates at the statistical maxima of the clusters in the right putamen (24 10 -6), right caudate nucleus (18 24 8), and left parahippocampal gyrus (-23 -25 -19). HC and CD columns represent significant BOLD differences between Active and Control conditions in each group. HC and CD columns represent significant differences between the active and control conditions in HC and CD groups, respectively, with red color scheme representing Active > Control and blue color scheme representing Control > Active. CD vs HC column represents significant group-by-condition interactions, where red color scheme signifies either [CD Active > Control] > [HC Active > Control] or [HC Control > Active] > [CD Control > Active], and blue color scheme signifies either [CD Control > Active] > [HC Control > Active] or [HC Active > Control] > [CD Active > Control]. Cd, caudate nucleus; CD, cocaine dependence; Hi, hippocampus; HT, hippocampus tail; LH, left hemisphere; MTL, medial temporal lobe; PH, parahippocampal gyrus; Pu, putamen; RH, right hemisphere.

Neural Activity During Processing of Monetary Outcomes

We modeled neural activity separately during the two possible types of reward feedback, ‘reward’ and ‘no-reward.’ We contrasted successes with failures within each condition and also compared each event type separately across the active and control conditions.

Processing of unexpected rewards. To identify disturbances in reward processing unrelated to spatial learning in CD participants, we compared neural activity during ‘reward’ and ‘no-reward’ events in the control condition (Figure 2a and b). In both groups, neural activity during ‘reward’ events was greater than during ‘no-reward’ events. Although both groups activated ventral striatum in ‘reward’ trials, the CD group activated this region more robustly and drove this group-by-condition interaction. Group-by-con-

dition interactions were also detected in insula, somatosensory, supplementary motor, and posterior parietal cortices deriving from the HC group, and in visual and posterior cingulate cortices and middle temporal gyrus deriving from the CD group (Figure 2a, Table 5).

Processing of rewards in context of spatial learning. To define disturbances in reward processing during spatial learning in CD participants, we compared neural activity during ‘reward’ and ‘no-reward’ events in the active condition (Figure 2c and d). In this comparison, only CD participants contributed to significant group-by-condition interactions. Interactions in left MTL (amygdala) were driven by increased activity in the ‘reward’ and decreased activity in the ‘no-reward’ condition in CD group. Interactions were also detected in left inferior temporal gyrus, left

Table 4 Group Differences in Neural Activity when Searching the Maze

Brain region	Area	Side	Coordinates			Test statistic	Cluster size
Putamen	–	R	24	10	–6	2.75	49
Caudate nucleus	–	R	18	24	8	2.70	98
Frontal pole	10	R	28	46	2	2.70	25
Inferior frontal gyrus	44	L	–54	8	10	5.50	
Supramarginal gyrus	40	R	60	–32	46	5.53	
Middle & superior temporal gyri	21	L	–52	4	–20	5.24	
Precentral gyrus	6	L	–52	4	34	5.65	
Precentral gyrus	6	R	42	–6	50	5.35	47 897
Fusiform gyrus	19	L	–22	–78	–12	5.47	
Fusiform gyrus	19	R	26	–80	–8	5.21	
Cerebellum	–	L	–18	–74	–18	5.68	
Cerebellum	–	L	–10	–80	–42	3.17	
Cerebellum	–	R	8	–72	–36	2.65	140

Abbreviations: Area, Brodmann Area; Side, hemisphere; L, left; R, right.

Whole brain Bayesian analysis showing cluster sizes (voxels) and locations (MNI) of brain regions where group-by-condition interactions (between the active and control conditions in CD and HC participants) were statistically significant ($p < 0.05$). Test statistics represent significance at the cluster level.

motor cortex, and bilaterally in lingual gyrus (Figure 2c, Table 5).

DISCUSSION

Animal studies of cocaine administration and human postmortem studies indicate that cocaine disrupts molecular and cellular processes in the neural systems that support episodic memory (and spatial learning). This is the first study to characterize the functioning of these systems directly in cocaine-dependent humans. The VR spatial navigation paradigm allowed us to assess separately the distinct temporal components of spatial learning (searching and reward) and distinguish their neural correlates. In the absence of group differences in spatial learning behavior, cocaine dependent participants had altered neural functioning during these aspects of reward-based spatial learning.

Searching the Maze for Navigational Cues

When searching the maze, BOLD signal was generally greater in the active compared to the control condition in HC participants, whereas BOLD signal in CD participants was greater in the control relative to the active condition. Additionally, the groups engaged different neural systems. These findings suggest that individuals with CD differ profoundly from HC participants in their experience of spatial navigation regardless of whether learning was possible. For example, although participants from both groups experienced the control condition as especially challenging (because, unknown to them, the spatial cues were shuffled after each trial to render spatial learning impossible), the CD group activated frontal, striatal, and MTL regions more in the control condition than did the HC group. Perhaps the CD participants increased their cognitive effort during their attempts at spatial learning in the control condition in ways that the HC participants did not. Conversely, the CD participants did not engage any regions

during the active condition in any way similar to the HC group during spatial learning.

The learning model of addiction predicts disturbances both in episodic memory, which depends on MTL, and in habit learning, which depends on dorsal striatum (DS), such that habit learning processes increasingly predominate with worsening addiction (Kalivas and O'Brien, 2008). We therefore expected to find altered functioning of MTL and DS in CD participants during spatial learning (ie, when searching the maze). Consistent with these *a priori* hypotheses, MTL activations were reduced in CD compared to HC participants during spatial learning (ie, 'searching' in the active condition). Also consistent with these hypotheses, whereas HC participants did not engage DS, CD participants had decreased DS activity in the active and increased DS activity in the control condition. An inverse association of DS activations with abstinence suggests that the most abstinent CD participants engaged this region the least.

Group differences in MTL and DS activity between typical and clinical populations whose illness involves MTL or DS pathology can be interpreted in terms of the interactions (competitive or cooperative) between these regions, and thus between the learning strategies that they support. In one fMRI study of habit learning, for example, MTL activity was increased and striatal activity decreased in patients with Parkinson's Disease, an illness characterized by striatal degeneration (Moody *et al*, 2004). Conversely, in patients with CD, an illness in which habit learning is robust and episodic memory is impaired, we identified (1) abnormally reduced MTL activity and (2) abnormal striatal engagement characterized by amplified modulation of striatum across experimental conditions that differ in their potential for learning. Interpreting our findings based on the model of competition between these regions (Lee *et al*, 2008; Poldrack *et al*, 2001) suggests that in CD, increased potential to use striatum-based strategies for learning may inhibit activity within MTL, although an independent dysfunction of MTL cannot be excluded. Conversely, interpreting our findings based on a model of cooperation between these brain

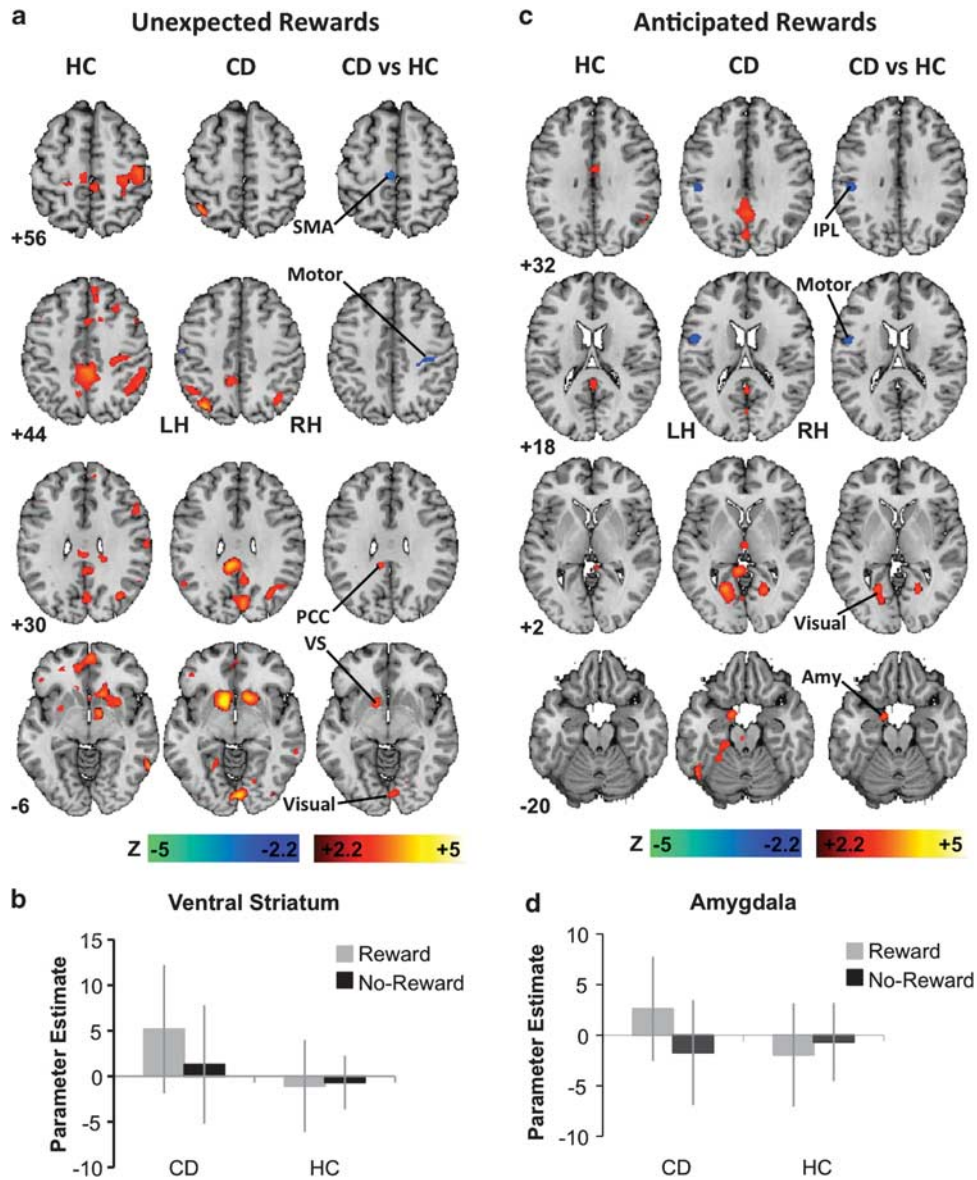


Figure 2 Neural Activity when Processing Monetary Reward. PPMs at posterior probability $>98.75\%$ ($z > 2.24$ equivalent to $p > 0.0125$) of BOLD contrasts of 'reward' vs 'no-reward' events that make up reward feedback in (a) the control condition, where monetary rewards are 'unexpected' because they are allotted pseudo randomly and without regards to performance, and (c) the active condition, where rewards are 'anticipated' because allotted based on performance on the spatial learning paradigm. Bar graphs represent parameter estimates at the statistical maxima of the clusters in (b) left ventral striatum ($-12\ 8\ -6$) in the control condition, and (d) left amygdala ($-14\ -2\ -20$). HC and CD columns represent significant differences between the feedback events in HC and CD groups, respectively, with red color scheme representing 'reward' $>$ 'no-reward' and blue color scheme representing 'no-reward' $>$ 'reward'. CD vs HC column shows significant group-by-conditions interactions, where red color scheme signifies either [CD 'reward' $>$ 'no-reward'] $>$ [HC 'reward' $>$ 'no-reward'] or [HC 'no-reward' $>$ 'reward'] $>$ [CD 'no-reward' $>$ 'reward'], and blue color scheme signifies either [CD 'no-reward' $>$ 'reward'] $>$ [HC 'no-reward' $>$ 'reward'] or [HC 'reward' $>$ 'no-reward'] $>$ [CD 'reward' $>$ 'no-reward']. Amy, amygdala; IPL, inferior parietal lobule; LH, left hemisphere; Motor, motor cortex; PCC, posterior cingulate cortex; RH, right hemisphere; SMA, supplementary motor area; VS, ventral striatum; Visual, visual cortex.

regions (Sadeh *et al*, 2011; Voermans *et al*, 2004) would suggest that in CD, inefficient representations of MTL-based strategies for learning may produce a compensatory modulation of striatal activity in the service of maintaining normal behavioral performance on the task, particularly when the task is difficult (as it was in our control condition).

Cortical activations also differed across groups. Searching-related activations in HC participants were most prominent within the cingulo-opercular network, a control

system that supports goal-directed behavior (Dosenbach *et al*, 2007), and in ventral and dorsal visual streams, supporting the visual processing of motion, object location and identity, and attention (Kravitz *et al*, 2011; Marsh *et al*, 2010). Activations in the CD group (in the control condition) included large portions of lateral PFC, as well as striatum, suggesting a failure to engage fronto-striatal circuits in the support of cognitive control functions during this more effortful of the two task conditions.

Table 5 Group Differences in Neural Activity when Processing Monetary Rewards

Brain region	Area	Side	Coordinates (x y z)			Test statistic	Cluster size
<i>'Reward' vs 'no-reward' outcomes in the control condition</i>							
Ventral striatum	–	L	– 12	8	– 6	3.01	142
Visual cortex	17,18	R	6	– 84	– 4	2.83	285
Insula	–	R	44	0	12	– 3.19	243
Primary somatosensory cortex	1,2	R	46	– 26	40	– 2.84	174
Supplementary motor area	4	L	– 6	– 24	56	– 3.37	138
Superior parietal lobule	7	L	– 36	– 40	50	– 2.63	62
Posterior cingulate cortex	–	L	– 10	– 38	30	2.81	40
Middle temporal gyrus	21	L	– 58	– 30	– 14	2.89	37
Cerebellum	–	R	34	– 70	– 22	2.93	52
<i>'Reward' vs 'no-reward' outcomes in the active condition</i>							
Hippocampus/amygdala	–	L	– 14	– 2	– 20	2.98	60
Parahippocampal gyrus	36	L	– 36	– 22	– 20	2.76	47
Inferior parietal lobule	40	L	– 48	– 28	30	3.08	171
Primary somatosensory cortex	1	L	– 46	– 24	46	2.48	46
Inferior temporal gyrus	20	L	– 40	2	– 32	2.59	68
Lingual gyrus	19	L	– 20	– 60	0	2.98	28
Lingual gyrus	19	R	22	– 62	2	2.86	31
Cerebellum	–	R	38	– 54	– 32	2.65	31
Cerebellum	–	–	0	– 44	– 38	2.81	31

Abbreviations: Area, Brodmann Area; Side, hemisphere; L, left; R, right.

Whole brain Bayesian analysis showing cluster sizes (voxels) and locations (MNI) of brain regions where group-by-condition interactions (between the active and control conditions in CD and HC participants) were statistically significant ($p < 0.05$). Test statistics represent significance at the cluster level.

Processing Monetary Reward Outcomes

Separately modeling each type of monetary outcome allowed a detailed examination of reward processing in CD. We detected increased sensitivity of VS to receipt of monetary reward compared to omission of reward in the CD group when the monetary outcome was unexpected (control condition), but no signal in VS in either group when the monetary outcome was anticipated and associated with spatial learning (active condition). These findings are consistent with studies showing cocaine-associated increases in BOLD response within VS to uncertain rewards (Jia *et al*, 2011). Conversely, during spatial learning we detected increased activity in the amygdala in CD (but not HC) participants when receiving monetary rewards, but no signal in either group when spatial learning was rendered impossible (control condition). Our findings suggest that in both groups, but especially in CD, activity in distinct emotional regions (ie amygdala and VS) distinguish reward-based learning from reward in the absence of learning.

We identified neural processing specific to each type of monetary reward (reward or no-reward) during spatial learning by comparing BOLD signal across the active and control conditions when experiencing each outcome. Neural activity when processing rewards during spatial learning was reduced in CD, but not HC participants, within fronto-parietal regions, motor cortex, and MTL, compared with activity when processing rewards in the control condition. These same regional group differences in activation were

accentuated substantially during the omission of rewards. These findings support our general conclusion that the neural systems that subservise reward-based spatial learning are profoundly altered in CD.

Limitations and Conclusions

Our findings are the first to demonstrate disturbances in the functioning of MTL- and striatum-based neural systems for learning and memory that are associated with cocaine dependence in humans, and consistent with animal models of cocaine use. A limitation of this study includes the possibility that the additional difficulty of the control condition (due to reward unpredictability) contributed to group differences in brain activations. This unpredictability, however, was necessary for isolation of the neural correlates of reward-based learning. Our study sample was modest and consisted of only males, thereby requiring replication of our findings in a larger sample of both genders. Sex differences are reported in many aspects of SUD (Brady and Randall, 1999) and in spatial learning (Astur *et al*, 1998; Moffat *et al*, 1998), suggesting that studying only males may have improved our ability to detect group differences. The groups differed in socio-demographic and clinical characteristics, but in ways consistent with the CD literature (Rounsaville, 2004). Together, our findings point to dramatically altered neural correlates of episodic memory that may profoundly influence many aspects of how persons with CD navigate their real, quotidian world.

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