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Structural and behavioral correlates of abnormal encoding of money value in the sensorimotor striatum in cocaine addiction

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Abstract

Abnormalities in frontostriatal systems are thought to be central to the pathophysiology of addiction, and may underlie maladaptive processing of the highly generalizable reinforcer, money. Although abnormal frontostriatal structure and function have been observed in individuals addicted to cocaine, it is less clear how individual variability in brain structure is associated with brain function to influence behavior. Our objective was to examine frontostriatal structure and neural processing of money value in chronic cocaine users and closely matched healthy controls. A reward task that manipulated different levels of money was used to isolate neural activity associated with money value. Gray matter volume measures were used to assess frontostriatal structure. Our results indicated that cocaine users had an abnormal money value signal in the sensorimotor striatum (right putamen/globus pallidus) which was negatively associated with accuracy adjustments to money and was more pronounced in individuals with more severe use. In parallel, group differences were also observed in both function and gray matter volume of the ventromedial prefrontal cortex; in the cocaine users, the former was directly associated with response to money in the striatum. These results provide strong evidence for abnormalities in the neural mechanisms of valuation in addiction and link these functional abnormalities with deficits in brain structure. In addition, as value signals represent acquired associations, their abnormal processing in the sensorimotor striatum, a region centrally implicated in habit formation, could signal disadvantageous associative learning in cocaine addiction.

Keywords

sensorimotor striatum; ventromedial prefrontal cortex; reward; addiction; fMRI; VBM

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None declared.

Cocaine addiction is characterized by persistent seeking of cocaine at the expense of other rewarding outcomes and even in the face of negative consequences. Preclinical work suggests that an underlying neurobiological mechanism of addiction may involve adaptations in frontostriatal brain circuits (Kalivas & Volkow, 2005).

The prefrontal cortex, and specifically its ventromedial aspect (VMPFC), participates in evaluating the motivational value of rewards (Grabenhorst & Rolls, 2011), particularly when faced with different reward options (McClure *et al.*, 2004; Kable & Glimcher, 2007; Hare *et al.*, 2009; Smith *et al.*, 2010). In this context of reward processing, the VMPFC has been linked to goal-directed behavior (Hare *et al.*, 2008) and its adaptive adjustment (Hikosaka & Watanabe, 2000). While studies have also supported a role in goal-directed behavior for the ventral striatum and caudate nucleus (O'Doherty *et al.*, 2004; Tricomi *et al.*, 2004; Valentin *et al.*, 2007; Wrase *et al.*, 2007a), the sensorimotor striatum (post-commissural putamen) appears to have a unique, potentially implicit, role in reward processing, as it is engaged as stimulus-response-reward contingencies are learned (Graybiel, 2005; Tricomi *et al.*, 2009). In the context of cocaine addiction, the functions of the VMPFC have been linked to self-control (Baler & Volkow, 2006) and craving (Volkow *et al.*, 2010), the ventral striatum to impulsivity (Bjork *et al.*, 2008) and treatment course (Jia *et al.*, 2011), and the sensorimotor striatum to the habitual aspects of drug-seeking (Everitt & Robbins, 2005; Volkow *et al.*, 2006; Pierce & Vanderschuren, 2010).

Preclinical work suggests that cocaine affects the morphology of dopamine neurons and their target projection structures (like the VMPFC and striatum) to directly contribute to addiction [e.g., (Gerdeman *et al.*, 2003; Robinson & Kolb, 2004; Kauer & Malenka, 2007)]. Studies in humans with poly-substance or cocaine dependence also report changes in gray matter volume, as most notably observed in the VMPFC (Franklin *et al.*, 2002; Matochik *et al.*, 2003; Tanabe *et al.*, 2009; Alia-Klein *et al.*, 2011) and striatum (Chang *et al.*, 2007; Berman *et al.*, 2008), and link these frontostriatal gray matter changes to more compulsive patterns of cocaine use (Ersche *et al.*, 2011).

In the present study, we sought to extend this previous work by directly examining both functioning and gray matter volume of the VMPFC and striatum, and their relevance to behavior, in individuals with chronic cocaine use disorders (CUD) and closely matched healthy controls. We used money, a highly generalizable reinforcer, to target these regions and evaluate their putative dysfunction in addiction. Previous studies examining response to money in cocaine (Jia *et al.*, 2011) or alcohol dependence with comorbid cocaine use (Bjork *et al.*, 2008) found relatively increased activation in the ventral striatum and putamen during the anticipation and receipt of monetary gain, which in the former case predicted poorer treatment outcome. Abnormalities in the VMPFC during notification of success versus failure to win money have also been observed (Bjork *et al.*, 2008). We therefore hypothesized that CUD would show abnormal frontostriatal gray matter and response to money, and that these variables would be differentially associated with behavior.

Materials and Methods

Subjects

Forty-two right-handed native English speakers were recruited using advertisements in local newspapers and by word-of mouth. Exclusion criteria were: (1) history of head trauma or loss of consciousness (> 30 min) or other neurological disease of central origin; (2) abnormal vital signs at time of screening and history of major medical conditions; (3) history of major psychiatric disorder (other than substance abuse or dependence in CUD); note also that subjects in either study group were not excluded for alcohol or nicotine use disorders (except if subjects were intoxicated at the time of the study as determined by

clinical observation and study personnel); (4) except for cocaine, positive urine screens for other psychoactive drugs or their metabolites; (5) pregnancy as tested with a urine test in all females; (6) contraindications to the MRI environment; and (7) less than 12 years of education and/or a verbal intelligence score < 70 (as measured with the Wide Range Achievement Test III – Reading Scale). Of a total of 71 subjects who were screened, further exclusions from this study were based on: (1) probable pathological gambling [South Oaks Gambling Screen score > 5] (n=5); (2) psychiatric comorbidity (n=6); (3) failure to successfully complete a structural MR scan (n=16); and (4) age in healthy controls for group matching purposes (n=2). After exclusions, there were 21 CUD and 21 healthy controls included in the analyses, matched on all demographic variables except for cigarette smoking history (see Table 1). Twenty-three (11 CUD and 12 controls) of these 42 subjects were included in our previous report (Goldstein *et al.*, 2009a), which focused on group effects in the functional subdivisions of the anterior cingulate cortex during the most (50¢ drug words) and least (0¢ neutral words) salient conditions of the task; this prior study did not assess neural encoding of money value and did not include gray matter volume measures. All subjects provided written informed consent for their involvement in all study procedures as approved by the local Institutional Review Board at Stony Brook University.

Nineteen of the 21 CUD used crack/cocaine (mostly smoked route) in the past 14 days and all CUD met DSM-IV criteria for current cocaine dependence (n = 15) or abuse (n = 6; five of these subjects met criteria for cocaine dependence in remission); 15 CUD tested positive for cocaine in urine. Current comorbid disorders met by the CUD group were for alcohol and ecstasy abuse and alcohol and marijuana dependence (total of n = 3 CUD). The impact on results of drug urine status and drug use comorbidity was examined as described in Results.

Task Design

Subjects performed a monetary reward paradigm [also described in (Goldstein *et al.*, 2007; Goldstein *et al.*, 2009a; Goldstein *et al.*, 2010)]. This task required successful (fast and accurate) button pressing for the color of drug and neutral words to earn money. There were 4 counterbalanced money conditions (0¢, 1¢, 25¢, or 50¢), presented twice for a total of 8 runs. Each run contained 40 trials (split into two blocks of 20 trials interleaved with three 20 sec fixation periods). Each block began with a 3000 ms window informing subjects of the amount of money they could earn for every trial in that block. In total, there were four blocks (80 trials) for each money condition. The trial structure consisted of fixation (500 ms), the presentation of a word cue (2000 ms), response (500 ms), and a feedback slide indicating the amount gained for a correct response (500 ms); in the case of an error, an “X” rather than money was displayed. During the response window, subjects were instructed to provide fast and accurate responses by pressing 1 of 4 buttons (blue, yellow, green, and red) matching the color of the word they had just read. The total amount of money earned on the task (up to $75) was entirely contingent on performance (mean $65.69 ± 7.21, with no difference between the groups in this amount, $p>0.46$). We did not observe any significant word × group or money × word × group interaction effects on behavior ($p>0.15$) or neural activity in the current sample. This was not unexpected as detection of any of these more subtle word effects may have necessitated the use of a more lenient statistical threshold than currently used [e.g., see (Goldstein *et al.*, 2009b)]. Therefore, the analyses described below focused on the effects of money value collapsed across word type. To monitor task engagement, subjects were asked to provide money wanting ratings (“how much do you want money right now” from 0 to 10) at 4 time points during the experiment (before training, before the task, in the middle of the task, and immediately following the task). To assure that the four monetary amounts included in the task did not differ in their subjective value between the groups, subjects also provided subjective value ratings (“how valuable”

an amount is to them from 0 to 10) immediately before and after the task but before receiving remuneration.

Image Acquisition

Scanning was performed on a 4T whole-body Varian/Siemens MRI scanner. Blood-oxygen-level-dependent (BOLD) responses were measured as a function of time using a T2*-weighted single-shot gradient-echo EPI sequence (TE/TR = 20/1600 ms, 4 mm slice thickness, 1 mm gap, 33 coronal slices, 20 cm field of view, 64 × 64 matrix size, 90°-flip angle, 200 kHz bandwidth with ramp sampling, 128 time points, and 4 dummy scans, discarded to avoid non-equilibrium effects in the fMRI signal). Anatomical images were collected using a T1-weighted 3D-MDEFT sequence (Lee *et al.*, 1995) (TE/TR = 7/15ms, 0.94 × 0.94 × 0.94 mm spatial resolution, 144 axial slices, 256 readout and 192 × 96 phase-encoding steps, 16 min scan time). A modified T2-weigthed Hyperecho image (TE/TR = 42/10000 ms, echo train length = 16, 256 × 256 matrix size, 30 coronal slices, 0.86 × 0.86 mm in-plane resolution, 5 mm slice thickness, no gap, 2 min scan time) was also acquired and reviewed by a neurologist to rule out gross structural brain abnormalities.

Image Processing and Analysis

Functional Data—Subsequent analyses were performed with the statistical parametric mapping package (SPM8; Wellcome Department of Cognitive Neurology, London UK) running on Matlab version 7.7 (Mathworks Inc., Natick, MA). A six-parameter rigid body transformation (3 rotations, 3 translations) was used for image realignment and to correct for head motion; 2 mm displacement and 2° rotation in any of the axes in any of the task runs were used as criteria for acceptable motion. Spatial normalization to a standard EPI template [Montreal Neurological Institute] was performed using a 12-parameter affine transformation, resulting in a final voxel size of 3 × 3 × 3 mm. An 8 mm^3 full-width at half maximum Gaussian kernel was used to smooth the data.

A general linear model and a box-car design convolved with a canonical hemodynamic response function and high-pass filter (cut-off frequency: 1/520 sec) were used to calculate individual BOLD-fMRI maps. Contrast maps reflecting % signal change from the fixation baseline were calculated for the 0¢, 1¢, 25¢, and 50¢ money conditions for each subject. These functional contrast maps were then entered into a 4 (Money: 0¢, 1¢, 25¢, 50¢) × 2 (Group: CUD, control) mixed analysis of variance in SPM8.

Structural Data—Voxel-based morphometry (VBM) analysis was conducted with the VBM toolbox (VBM 8) (Gaser, C, University of Jena, Department of Psychiatry, Germany; http://dbm.neuro.uni-jena.de/vbm/), which combines spatial normalization, tissue segmentation, and bias correction into a unified model. The MDEFT scans were first spatially normalized to standard proportional stereotaxic space and segmented into gray matter, white matter, and cerebrospinal fluid tissue classes according to *a priori* tissue probability maps (Ashburner & Friston, 2000; 2005). The MDEFT sequence is particularly effective for such tissue differentiation, producing the most precise characterization of gray matter tissue compared with other sequences (Tardif *et al.*, 2009). A hidden Markov random field (Cuadra *et al.*, 2005) was applied to maximize the accuracy of the segmentation. Jacobian modulation was used to compensate for the effect of spatial normalization and to restore the original absolute gray matter volume in the gray matter segments. Total brain volume was computed as the sum of the extracted total gray and white matter volumes for each subject. A one-way between-subjects analysis of variance was performed after smoothing the normalized and modulated segments with a 10 mm^3 full-width at half maximum Gaussian kernel. Consistent with the VBM literature in addiction (Franklin *et al.*,

2002; Matochik *et al.*, 2003; Makris *et al.*, 2008; Tanabe *et al.*, 2009; Alia-Klein *et al.*, 2011), age and total brain volume were used as covariates of no interest.

Statistical Analyses

Voxels were considered significant if they exceeded a voxel-level threshold of $p<0.005$ uncorrected and $p<0.05$ family-wise error (FWE) corrected (within our two *a priori* regions of interest) and a minimum cluster size of 5 contiguous voxels. The striatum was isolated as an anatomical region of interest, created separately for the left and right side to correspond to the putamen, caudate, and pallidum in PickAtlas (Maldjian *et al.*, 2003). The VMPFC was isolated with an 18-mm radius sphere centered on coordinates reported in Ersche *et al.* [x= −2, y=32, z=−18; (Ersche *et al.*, 2011)], where individuals with CUD who had more compulsive patterns of cocaine use also had more gray matter loss compared with controls. Regions meeting a cluster-level $p<0.05$ FWE corrected threshold outside of our *a priori* regions of interest are also reported but are not the focus of the present study. For follow-up analyses with task behavior across the entire sample and cocaine use variables in CUD, in SPSS 11.5 (SPSS Inc., Chicago, IL), the average percent signal change and gray matter volume in significant coordinates were extracted using the entire cluster around the peak with the EasyROI toolbox (http://www.sbirc.ed.ac.uk/cyril/cp_download.html). Bonferroni correction was used to correct for multiple comparisons in the region of interest analyses with cocaine use variables, which included lifetime years of use, current abstinence, frequency of cocaine use in the past 12 months, withdrawal symptoms, and cocaine craving ($0.05/5 = p<0.01$; Table 1). Cook's distance test was used to assess the effect of potential outliers in all regression analyses (cutoff value < 1). The Fisher's Z-transformation was used to determine differences in correlation coefficients between the groups.

Results

Subjective Ratings and Task Behavior

Motivation to obtain money remained high throughout the task and did not significantly differ between the groups ($F<2.03$, $p>0.14$). Similarly, both groups provided higher subjective value ratings for the higher money amounts than the lower ones [main effect of money: 50¢ (mean ± standard error of the mean, 3.89 ± 0.49) > 25¢ (3.18 ± 0.48) > 1¢ (1.92 ± 0.45) > 0¢ (0.87 ± 0.30), $F_{(3,120)}=65.78$, linear effect, $p<0.001$] and across subjects and money amounts, these ratings increased following the task (main effect of time: after (2.72 ± 0.45) > before (2.21 ± 0.39), $F_{(1,40)}=4.02$, $p=0.05$; all other effects: $F<2.35$, $p>0.09$).

These self-reported ratings were reflected in subjects' behavior on the task. Task accuracy improved with increasing potential gain such that accuracy was higher for the high than the low money conditions [main effect of money: 50¢ = 25¢ > 1¢ = 0¢, $F_{(3,120)}=3.82$, $p=0.01$, linear effect, $p=0.003$; Figure 1]. There were no significant group or money × group interaction effects on accuracy ($F<2.43$, $p>0.069$). Possibly because stimulus presentation and response were separated and the former preceded the latter, leaving subjects ample time to prepare a response before the onset of the response window, reaction times for correct (or all) trials did not differ as a function of money amount or group ($F<1.11$, $p>0.35$).

Group Differences in Neural Activity Associated with Money Value

Following the observed linear progression in self-reported subjective value ratings and behavior, we performed region of interest analyses to determine (1) if the VMPFC and striatum similarly tracked money value and (2) if their pattern or magnitude of activation differed between the groups. The 4 (Money: 0¢, 1¢, 25¢, 50¢) × 2 (Group: CUD, control) mixed analysis of variance revealed a significant money main linear effect (50¢ > 25¢ > 1¢ > 0¢) in the left dorsal caudate and left pre/subgenual anterior cingulate and a significant

group main effect (Controls > CUD) in the subgenual anterior cingulate extending to the medial orbitofrontal cortex (Figure 3*A*, Table 2). That is, across the entire sample, the caudate and VMPFC tracked money value. Irrespective of the money amount, CUD additionally deactivated the VMPFC to a greater extent than controls. In addition to these main effects, we also observed a significant money (linear effect) × group interaction in the right putamen extending to the external segment of the globus pallidus (Figure 2, Table 2), which was explained by increased activations in this region to money in CUD but not controls. Follow-up *t*-contrasts indicated that this interaction was driven by the maximal differential, 50¢>0¢ (CUD>controls); in addition, significant effects in the right putamen were observed within CUD for 50¢>0¢, 25¢>0¢, and any money > 0¢ (all $p<0.05$ FWE-corrected). Similar pattern of effects was observed within CUD for the left putamen but did not reach significance. Together these differences between the groups in response to money in the putamen parallel previous findings of relatively increased activation in the ventral striatum and putamen during the anticipation and receipt of monetary gain in cocaine (Jia *et al.*, 2011) or alcohol dependence with comorbid cocaine use (Bjork *et al.*, 2008).

Whole-brain significant regional activations are summarized in Table 3. Across subjects, the linear contrast for money revealed increased activation in several brain regions that have been reported in previous reward studies (Liu *et al.*, 2011), including the right cerebellum and left inferior frontal gyrus (a cluster encompassing the left anterior insula). In addition, parametric deactivations with increasing money value were observed in the left pre/subgenual anterior cingulate cortex and bilateral middle/posterior cingulate, consistent with these regions' roles within the default mode network (Gusnard *et al.*, 2001; Buckner *et al.*, 2008). There were no other significant group or interaction effects that survived whole-brain cluster-level correction for multiple comparisons.

Group Differences in Gray Matter Volume

We performed an analysis of variance, statistically controlling for the effects of age and total brain volume, to identify any differences between the groups in gray matter volume within our regions of interest. Compared with controls, CUD had reduced gray matter volume of the medial orbitofrontal cortex extending to the gyrus rectus (Figure 3*B*, Table 4). No group differences were observed for the striatum. Outside of our regions of interest, gray matter reductions in CUD did not survive whole-brain cluster-level correction for multiple comparisons. Similarly, there were no significant regions of increased gray matter volume in CUD compared with controls.

Region of Interest Correlations with Neural Activity and Gray Matter Volume

In follow-up analyses in SPSS we examined the relationship between activity in the VMPFC and putamen using the mean extracted signal in these regions (coordinates from the group effect and the money × group interaction, respectively; Table 2). VMPFC BOLD (50¢>0¢) and putamen BOLD (50¢>0¢) were not significantly correlated across the entire sample ($r=-0.21$, $p=0.18$). To address the question of differences in correlations between the groups, we performed the same analysis separately in each group. In CUD, higher activation in the putamen (50¢>0¢) was associated with more VMPFC deactivation (0¢>50¢) ($r=-0.47$, $p=0.03$) whereas in controls this effect was not significant (after removing one outlier, Cook's $d > 1$; $r=-0.11$, $p=0.64$; Figure 4). A comparison of the correlation coefficients using the Fisher's Z transformation did not indicate that this relationship was significantly stronger in CUD ($Z=-1.18$, $p=0.11$).

Because CUD had reduced gray matter volume and greater overall task-related deactivations in the VMPFC, we inspected the relationship between these two measures. However, the relationship between gray matter and overall activity in the VMPFC (average of the four

money values) did not reach significance across the entire sample or within each group separately (r<0.28, p>0.068, controlling for age and total brain volume). Similarly, gray matter volume in the VMPFC and response to money in the putamen (BOLD 50¢>0¢) were not significantly correlated across the entire sample or within both subject groups separately (all r<−0.20, p>0.19).

Region of Interest Correlations with Behavior

To establish the specific relationship of money-related brain activations to behavior, we performed correlations with task accuracy and drug use. Behavioral sensitivity to money (differential task-related accuracy, 50¢>0¢) was negatively correlated with activation in the putamen to money (50¢>0¢) when considering the entire sample (r=−0.33, p=0.03), but this effect appeared to be driven by the CUD. We therefore tested this correlation separately in each group. Two outliers (one control, one CUD) were removed (Cook's d>1 when considering the groups separately). In CUD, accuracy was negatively correlated with putamen BOLD (50¢>0¢) such that higher activity was associated with lower differential accuracy 50¢>0¢ (r=−0.50, p=0.024; Figure 5*A*). In controls, this relationship was not significant (r=−0.019, p=0.94). This difference in correlations between the groups did not reach nominal significance (Z=−1.55, p=0.060). Because CUD also had greater VMPFC deactivations, which were not specific to a particular money condition, we assessed the relationship between average VMPFC activation (cluster from the group effect, averaged across the four money values) and average accuracy on the task. These two measures were not significantly correlated across the entire sample or within each group separately (r< −0.42, p>0.063).

Cocaine use days/week in the past year correlated positively with activation in the putamen 50¢>0¢ (after removing one outlier, Cook's d>1; r=0.62, p=0.006; Figure 5*B*). There were no other significant correlations with drug use (cocaine use variables in Table 1, p>0.11). For the VMPFC (cluster from the group effect), there was a negative correlation with cocaine craving (p=0.01; all other effects did not survive correction for multiple comparisons, p>0.03), such that subjects who reported more craving deactivated this region to a greater extent overall.

VMPFC gray matter volume was not associated with task accuracy in either group (p>0.58) or with drug use in CUD (p>0.20).

Effects of Subject Exclusions

The potential confounding effects of diagnostic comorbidity were assessed by removing CUD from the main analyses who met DSM-IV criteria for abuse or dependence on any drug other than cocaine or nicotine (n=3 subjects; see Subjects section of Methods). In addition to the main effect of money on accuracy, a money × group interaction was observed in this reduced sample (n=39) which was explained by reduced accuracy for the 1¢ condition in CUD [$F_{(3,111)}$=2.72, p=0.048]. All other reported main or interaction effects on task activation and gray matter volume, and correlations between task activation with behavior were unchanged (p<0.03). The effect of negative pre-scan drug urine tests (found in n=6 CUD; 3 of whom reported being cocaine abstinent for <7 days, 1 for <14 days, and 2 for >6 months) was similarly inspected. Even after excluding these 6 subjects, all results still mirrored those of the entire sample (p<0.05, except for the correlation between activity in the putamen and task accuracy within CUD which became non-significant, p=0.18). Because of the minimal influence of these factors on our results, CUD with comorbid diagnoses and cocaine urine negative scans were not excluded from the current report to increase generalizability. Because of the almost parallel distribution between cigarette

smokers versus non-smokers and group membership, we could not reliably use smoking status as a covariate in our statistical analyses (Miller & Chapman, 2001).

Discussion

In the present study, we evaluated the hypothesis that functioning of the VMPFC and striatum under varying reward contingencies would be altered in cocaine addiction. We further hypothesized that such altered VMPFC-striatum neural activity would be related to alterations in the gray matter volume of these regions and would have negative consequences for behavior in individuals with CUD. Consistent with our first hypothesis, CUD showed abnormal response to money value in the right putamen, a region extending to the external segment of the globus pallidus, and greater overall deactivations in the VMPFC across the money conditions. Consistent with our second hypothesis, CUD also had reduced gray matter volume in the VMPFC. Abnormal responses to money in the putamen and VMPFC, but not gray matter in the VMPFC, were related to task behavior and cocaine use, such that individuals with more severe use and craving, and less behavioral adjustment to money, had the highest activations in the putamen and deactivations in the VMPFC. Thus, our findings, which are consistent with preclinical models of addiction [e.g., (Gerdeman *et al.*, 2003; Robinson & Kolb, 2004; Kauer & Malenka, 2007)] and extend prior work that has separately examined VMPFC and striatum function (Bjork *et al.*, 2008; Jia *et al.*, 2011) or gray matter volume (Franklin *et al.*, 2002; Matochik *et al.*, 2003; Chang *et al.*, 2007; Berman *et al.*, 2008; Tanabe *et al.*, 2009; Alia-Klein *et al.*, 2011; Ersche *et al.*, 2011) in human cocaine addiction, provide strong evidence for frontostriatal abnormalities in the neural mechanisms of valuation in addiction and link these functional abnormalities with deficits in brain structure.

Group Differences in Neural Activity Associated with Money Value

Both CUD and healthy controls reported high levels of motivation to obtain money and did not differ in the subjective value assigned to the different money amounts used in the task. These self-reported ratings were reflected in subjects' behavior on the task, where subjects were more accurate for the high than the low money amounts. Consistent with previous studies (Liu *et al.*, 2011), across the entire sample, the VMPFC, associative striatum (dorsal caudate), cerebellum, posterior cingulate, and inferior frontal gyrus responded to money, but in CUD there was also an ectopic response in the sensorimotor striatum (right putamen/globus pallidus). The post-commissural putamen (or dorsolateral striatum in rodents) is centrally implicated in habits (Tricomi *et al.*, 2009), stimulus-response associations that render behavior insensitive to outcomes (Yin & Knowlton, 2006; Yin *et al.*, 2006; Balleine & O'Doherty, 2010). With the progression of cocaine addiction (Porrino *et al.*, 2007), this striatal subregion is suggested to underlie the habitual aspects of drug use like cue-induced drug-seeking and craving in both rodents (Vanderschuren *et al.*, 2005; Pierce & Vanderschuren, 2010) and humans (Volkow *et al.*, 2006). The cluster of activation also included the external segment of the globus pallidus, which is a target projection for the indirect D2 dopamine pathway (Hikida *et al.*, 2010) and more recent studies also implicate upregulated dopamine D3 receptor expression (Boileau *et al.*, 2012) and disrupted activity of this pathway (Lobo *et al.*, 2010) in addiction. This increased sensitivity to money in the putamen is in line with previous studies that have revealed hypersensitivity to money in individuals addicted to cocaine (Jia *et al.*, 2011) and marijuana (Nestor *et al.*, 2010). While studies have also reported increased (Bjork *et al.*, 2008) or decreased (Wrase *et al.*, 2007b; Beck *et al.*, 2009) response to money in the ventral striatum in alcohol dependence, likely due to the low level of uncertainty associated with our task, we did not observe activity in this region in either group. Importantly, increased activity in the putamen was associated with reduced adjustments in task accuracy with higher money value and with more frequent

cocaine use in CUD. Thus, these differential associations with behavior on the task and drug use outside the lab point to altered neural valuation mechanisms in CUD that may render these individuals less sensitive to potentially positive (e.g., earning more money on the task) or potentially negative (e.g., the physical and emotional impact of their use) behavioral outcomes.

In contrast to differential responses in the striatum, parametric deactivations in the VMPFC were observed with increasing money value in both CUD and controls, in line with this region's role in processing the motivational value of rewards during goal-directed behavior, including money and drugs of abuse (Grabenhorst & Rolls, 2011). Although the pattern of activation in the VMPFC is consistent with that observed in default mode network regions, where deactivations vary as a function of task engagement or task features (Gusnard *et al.*, 2001; Buckner *et al.*, 2008), the directionality of these results is at odds with previous studies showing positive activations in the VMPFC to reward value. This apparent inconsistency may reflect differences in the tasks used to elicit responses (e.g., blocked designs like ours capture sustained activation while event-related designs capture transient activation). Indeed, because blocked designs may produce initial positive responses in the hemodynamic signal that are followed by sustained negative responses, as has been observed in regions of the default model and particularly the medial prefrontal cortex (Meltzer *et al.*, 2008), the estimate for the block can be negative when the model assumes homogeneity in the signal.

Group Differences in Function and Gray Matter Volume of the VMPFC

Although there was no significant difference between the groups as a function of money value, echoing our prior findings in a partly overlapping sample of CUD and controls (Goldstein *et al.*, 2009a), across the four money conditions, cocaine addicted individuals, and especially those with higher self-reported craving, deactivated the VMPFC to a greater extent than controls. In addition, the VMPFC and putamen were strongly correlated in CUD such that the magnitude of VMPFC deactivation was proportional to the magnitude of striatal activation to money. Thus, enhanced VMPFC deactivation in the cocaine users might represent a compensatory mechanism necessary to maintain comparable levels of task performance, particularly in those individuals with higher activations in the putamen and more severe craving.

Confirming findings from previous studies (Franklin *et al.*, 2002; Matochik *et al.*, 2003; Tanabe *et al.*, 2009; Alia-Klein *et al.*, 2011; Ersche *et al.*, 2011), we further found reduced gray matter volume of the VMPFC in CUD. Although our data cannot answer questions related to causality, functional abnormalities in the VMPFC (and striatum) in CUD could also signal inefficiency of cortical processing due to gray matter volume loss in this region. Interestingly, repeated psychostimulant exposure (Robinson & Kolb, 2004; Everitt & Robbins, 2005; Nelson & Killcross, 2006; Wickens *et al.*, 2007; Briand *et al.*, 2008; Zapata *et al.*, 2010) or lesions of the VMPFC (Corbit & Balleine, 2003; Yin *et al.*, 2005) in experimental animals have been shown to shift control of behavior in response to reinforcers and drug-seeking to the putamen, suggesting that these two regions compete for control of behavior (Balleine & O'Doherty, 2010). Thus, irrespective of the underlying mechanism, frontostriatal abnormalities (i.e., via greater engagement of the putamen, craving, or gray matter loss) may reduce addicted individuals' ability to inhibit stimulus-driven responses and contribute to disadvantageous behavior (Goldstein & Volkow, 2002; 2011).

Limitations, Future Directions, and Conclusions

Potential limitations of this study include the use of a blocked design, differences in smoking histories between the groups, and the relatively small sample size for investigating

possible differences between subgroups of cocaine users (e.g., based on recent cocaine use) or differences in correlations between cocaine users and controls. Because we were interested in identifying *which* regions represented money value, we used a blocked design. Blocked designs are more sensitive compared with event-related designs in detecting such regional activations because they offer maximal variance in terms of BOLD amplitude changes between conditions (i.e., value in this case) (Huettel, 2008). The cost is in the ability to separate anticipatory from outcome related activity. However, frontostriatal abnormalities in addicted individuals during both anticipation of monetary gain (Wrase *et al.*, 2007b; Beck *et al.*, 2009; Nestor *et al.*, 2010) and at gain outcome (Bjork *et al.*, 2008; Nestor *et al.*, 2010; Jia *et al.*, 2011) suggest that such a separation is not likely to substantially modify our interpretations. Indeed, a recent meta-analysis found vastly overlapping neuroanatomical correlates (including VMPFC and striatum) of anticipation of reward and reward outcome (Liu *et al.*, 2011). This is particularly relevant in the case of money where reward delivery is always delayed and therefore somewhat anticipatory even in event-related studies [e.g., note “real” vs. hypothetical money has similar neural and behavioral correlates (Bickel *et al.*, 2009)]. Because only a few (23%) controls and most (76%) CUD reported a history of cigarette smoking, we were unable to control for differences in smoking status between the groups (Miller & Chapman, 2001). As nicotine use rates in our sample of CUD are comparable to those reported in previous studies (Grant *et al.*, 2004; Kalman *et al.*, 2005; Weinberger & Sofuoglu, 2009; Jia *et al.*, 2011), this may be an inherent feature of this population and future studies would need to recruit more cigarette smoking controls to better address this potential confound. Because most CUD were urine positive for cocaine, our findings may be specific to early abstinence and studies using larger and more heterogeneous samples of CUD are needed to examine the effects of recent use on frontostriatal structure and function. Similarly, although the relationship between response to money in the putamen and task accuracy or between responses in the putamen and VMPFC tended to be stronger in CUD, larger samples may be needed to detect such correlation differences statistically.

In summary, we report that CUD had abnormal value signals in the sensorimotor striatum (right putamen extending to the external globus pallidus), potentially explained by reduced gray matter volume and function of the VMPFC. As value signals represent acquired associations, our results could indicate disadvantageous associative learning in CUD. Indeed, activity in this region was differentially associated with maladaptive task- and drug use-related behaviors. Future studies should directly inspect learning mechanisms in CUD as well as their resistance to extinction procedures to more fully establish the role of habit systems in addiction in humans. In addition, reward processing is only one function of the VMPFC and striatum that may be altered by addiction; future studies could explore the link between gray matter in these regions and the neural correlates of self-control or impulsive choice to determine the functional specificity of these abnormalities. Elucidating the relationship between brain structure and function may not only facilitate better comparison with findings reported in the animal literature, but may also help move beyond reporting of gray matter differences in addiction in humans and attempt to understand the relationship of these differences to behavior and to the underlying function of connected networks of brain regions.

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Abbreviations

BOLD	blood oxygen-level-dependent
CUD	cocaine use disorders
fMRI	functional magnetic resonance imaging
FWE	family-wise error
SPM	statistical parametric mapping
VBM	voxel-based morphometry
VMPFC	ventromedial prefrontal cortex

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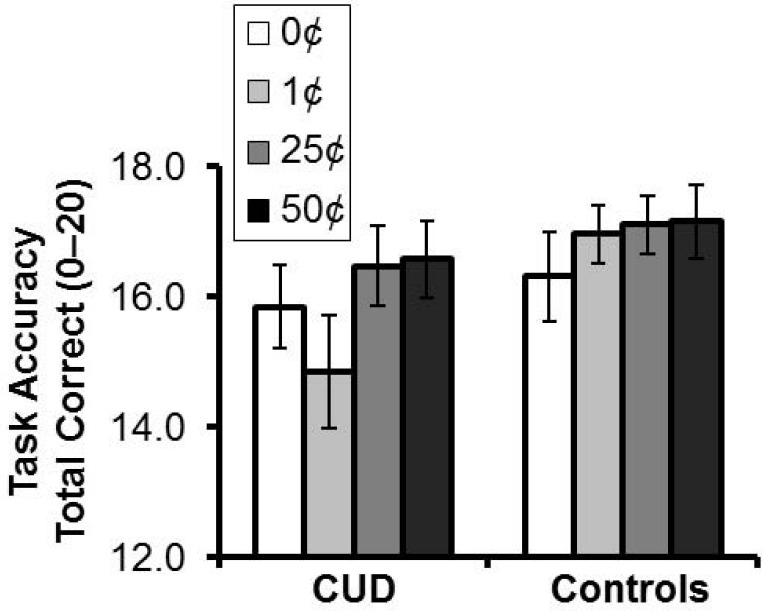

Figure 1. Task behavior

Mean task accuracy for the four monetary reward conditions (linear effect: 50¢>25¢>1¢>0¢, p=0.003). There were no significant group or money × group interaction effects on accuracy (F<2.43, p>0.069). Error bars represent standard error of the mean.

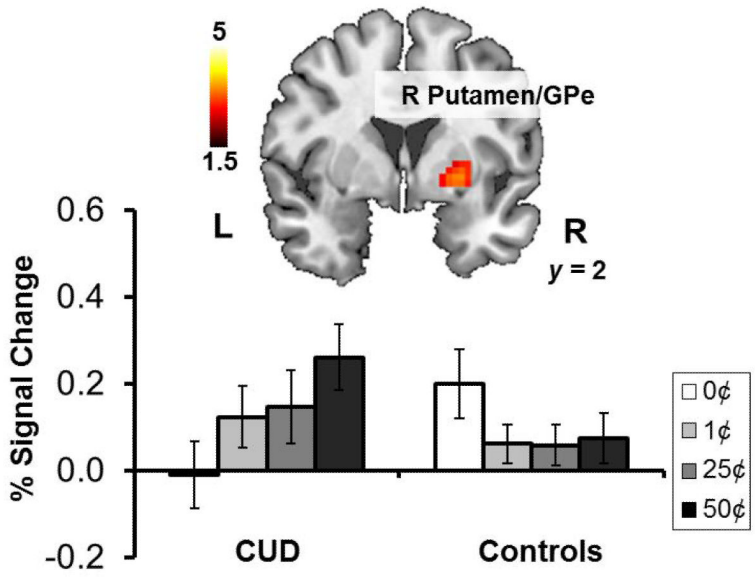

Figure 2. Money × group interaction on sensorimotor striatum response to money value

A money (linear contrast) × group interaction was observed in the right putamen, a region extending to the external segment of the globus pallidus, such that only individuals with cocaine use disorders (CUD) but not healthy comparison controls exhibited increased activation in this region to money. See Table 2. Statistical maps are thresholded at $p<0.005$ voxel-level uncorrected and 5 contiguous voxels for display. Error bars represent standard error of the mean. GPe: globus pallidus externus; R: right; L: left.

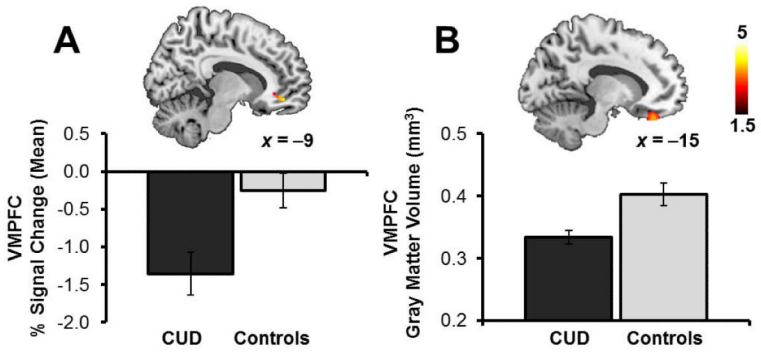

Figure 3. Group differences in activation and gray matter volume of the ventromedial prefrontal cortex

A, Individuals with cocaine use disorders (CUD) had greater deactivations and ***B***, reduced gray matter volume of the ventromedial prefrontal cortex (VMPFC) as compared with healthy controls. See Tables 2 & 4. Statistical maps are thresholded at $p<0.005$ voxel-level uncorrected and 5 contiguous voxels for display. Error bars represent standard error of the mean.

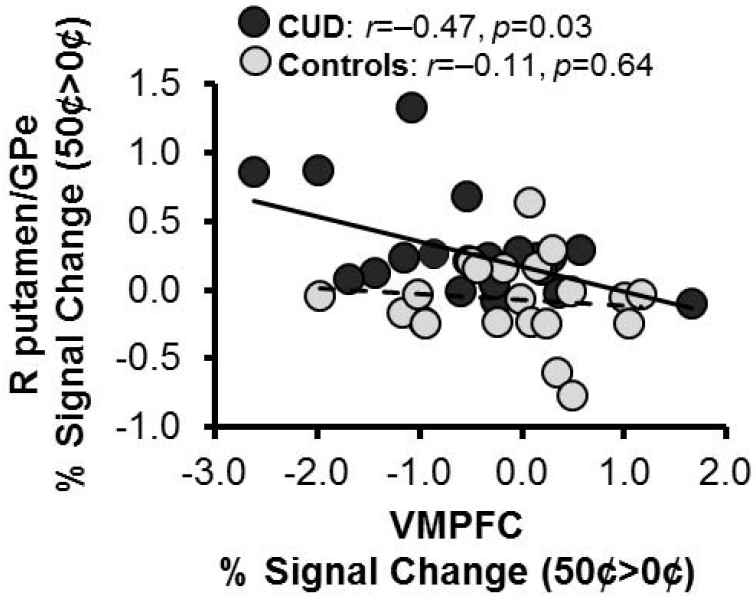

Figure 4. Correlation between sensorimotor striatum activations and ventromedial prefrontal cortex deactivations

Ventromedial prefrontal cortex (VMPFC) deactivation was associated with increased activation in the sensorimotor striatum to money in individuals with cocaine use disorders (CUD). In controls this relationship was not significant (one outlier was removed, Cook's *d* > 1). GPe: globus pallidus externus; R: right.

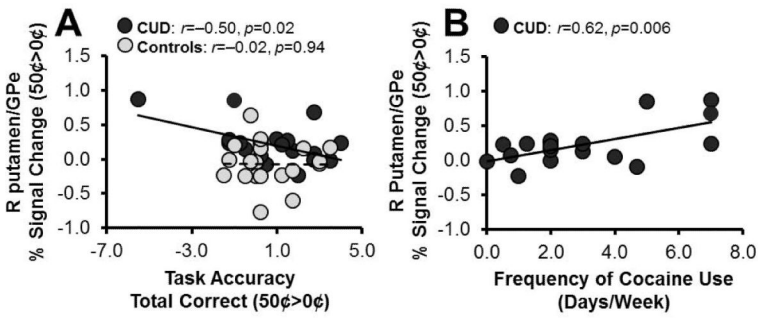

Figure 5. Correlations between sensorimotor striatum activation and behavior

A, Higher activations in the right putamen to money were associated with reduced behavioral adjustment to money (differential task-related accuracy, 50¢>0¢) and with ***B***, more frequent cocaine use in the past 12 months in individuals with cocaine use disorders (CUD). One CUD and one control were removed from the analyses with accuracy and one CUD was removed from the analysis with cocaine use (for all excluded subjects, Cook's $d > 1$).

Table 1

Demographic and drug use characteristics.

	Test	Control (*n*=21)	CUD (*n*=21)
Demographics			
Age (years)	$t_{40} = 2.0$	38.9 ± 1.3	43.1 ± 1.6
Gender (male/female)	$\chi^2 = 0.2$	18/3	17/4
Race (African-American/Caucasian/Hispanic/Asian)	$\chi^2 = 2.9$	12/6/2/1	16/4/0/1
Education (years)	$t_{40} = 0.9$	14.1 ± 0.4	13.6 ± 0.4
Verbal IQ: Wide Range Achievement Test III - Reading Scale	$t_{40} = 1.8$	101.5 ± 2.5	94.9 ± 2.8
Nonverbal IQ: Wechsler Abbreviated Scale of Intelligence – Matrix Reasoning Scale	$t_{40} = 0.7$	10.8 ± 0.6	10.2 ± 0.8
State Depression: Beck Depression Inventory II	$Z = 1.9$	2.7 ± 0.8	5.0 ± 1.0
Socioeconomic Status: Hollingshead Index	$t_{40} = 0.1$	34.6 ± 2.6	35.0 ± 2.9
Drug Use			
Cigarette smokers (current or past/nonsmokers)	$\chi^2 = 11.5$ †	5/16	16/5
Daily cigarettes (current smokers: *N*=4/13)	$Z = 1.0$	8.3 ± 2.3	12.3 ± 1.8
Time since last cigarette (within 4 hrs./>4 hrs./overnight or more)	$\chi^2 = 3.8$	1/3/0	7/3/3
Alcohol use lifetime (years) (*N*=9/20)	$t_{27} = 1.0$	10.6 ± 3.5	15.1 ± 2.8
Cocaine use lifetime (years) [b]	--	--	17.8 ± 1.5
Duration of current abstinence/time since last cocaine use (days)	--	--	100.6 ± 86.8 [a] (median=3)
Days/week of cocaine use during the past 12 months [c]	--	--	3.1 ± 0.5
Withdrawal symptoms: 18-item CSSA (0–126)	--	--	12.7 ± 1.9
Cocaine craving: 5-item Questionnaire (0–45)	--	--	15.2 ± 2.3

CSSA: Cocaine Selective Severity Assessment Scale;

Values are frequencies or means ± standard error of the mean (SEM).

† $p<0.005$;

[a] When two outliers (days abstinent = 1825 and 210 days, respectively) are excluded, group mean = 4.1 ± 1.0;

[b] Data missing for one subject;

[c] Data missing for two subjects;

Table 2

VMPFC and striatum region of interest analyses on task activations.

	BA	Side	Voxels	peak *Z*	*p*-corrected	*x* (mm)	*y* (mm)	*z* (mm)
Money (Linear Contrast: 50¢ > 25¢ > 1¢ > 0¢): All Subjects								
Striatum: Caudate		L	22	+3.9	0.010	−18	−10	22
VMPFC: Pre/Subgenual ACC	25,11	L	43	−3.7	0.016	−6 0	32 26	−2 −2
Controls > CUD								
VMPFC: Subgenual ACC/Medial OFC	25,10,11	L	18	3.9	0.005	**−9**	**44**	**−11**
CUD > Controls								
None								
Money (Linear Contrast: 50¢ > 25¢ > 1¢ > 0¢): × Group Interaction								
Striatum: Putamen/Globus Pallidus		R	68	3.4	0.044	**27**	**2**	**−2**
Money (Linear Contrast: 50¢ > 25¢ > 1¢ > 0¢): CUD								
Striatum: Putamen/Globus Pallidus		R	85	+3.8	0.015	24	5	−2
Striatum: Putamen/Globus Pallidus		L	25	+3.2	0.083	−33	2	1
Money (Linear Contrast: 50¢ > 25¢ > 1¢ > 0¢): Controls								
None								

Statistical threshold: $p<0.005$ uncorrected and $p<0.05$ family-wise error (FWE) corrected at voxel-level, $k>5$ voxels;

Striatum was defined anatomically with PickAtlas to correspond to the caudate, putamen, and pallidum;

Ventromedial prefrontal cortex (VMPFC) was defined as an 18-mm radius sphere centered on x=−2, y=32, z=−18 (from Ersche *et al.*, 2011);

ACC: anterior cingulate cortex; OFC: orbitofrontal cortex; R: right; L: left;

+/− *Z* values indicate direction of significant contrast;

Coordinates in bold font are depicted in the figures.

Table 3

Whole-brain results from the Money × Group analysis of variance on task activations.

	BA	Side	Voxels	peak *Z*	*p*-corrected	*x* (mm)	*y* (mm)	*z* (mm)
Money (Linear Contrast: 50¢ > 25¢ > 1¢ > 0¢): All Subjects								
Cerebellum: Vermis		R	220	+3.9	0.046	6 21 12	−64 −46 −46	−17 −50 −17
Inf. Frontal G./Insula	44,45,6	L	204	+3.7	0.060	−45 −33 −30	5 11 17	13 22 28
VMPFC: Pre/Subgenual ACC	24,25,11	L	459	−4.3	0.001	−3 −18	29 35	10 −5
Mid./Posterior Cingulate G.	23	R L	211	−3.6	0.053	9 −3 −15	−25 −16 −19	37 31 52
Controls > CUD								
None								
CUD > Controls								
None								
Money (Linear Contrast: 50¢ > 25¢ > 1¢ > 0¢): × Group Interaction								
None								

Statistical threshold: $p<0.005$ uncorrected and $p<0.05$ family-wise error (FWE) corrected at cluster-level, $k>5$ voxels;

Inf.: inferior; Mid.: middle; VMPFC: ventromedial prefrontal cortex; ACC: anterior cingulate cortex; R: right; L: left;

+/− *Z* values indicate direction of significant contrast.

Table 4

VMPFC and striatum region of interest analyses on gray matter volume.

	BA	Side	Voxels	peak *Z*	*p*-corrected	*x* (mm)	*y* (mm)	*z* (mm)
Controls > CUD								
VMPFC: Medial OFC	11	L	347	3.5	0.029	−15 −3	36 39	−25 −28
CUD > Controls								
None								

Statistical threshold: $p<0.005$ uncorrected and $p<0.05$ family-wise error (FWE) corrected at voxel-level, $k>5$ voxels;

Striatum was defined anatomically with PickAtlas to correspond to the caudate, putamen, and pallidum;

Ventromedial prefrontal cortex (VMPFC) was defined as an 18-mm radius sphere centered on x=−2, y=32, z=−18 (from Ersche et al., 2011);

OFC: orbitofrontal cortex; L: left;

Coordinates in bold font are depicted in the figures.