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Overlapping patterns of brain activation to food and cocaine cues in cocaine abusers: association to striatal D2/D3 receptors

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Abstract

Cocaine, through its activation of dopamine (DA) signaling, usurps pathways that process natural rewards. However, the extent to which there is overlap between the networks that process natural and drug rewards and whether DA signaling associated with cocaine abuse influences these networks have not been investigated in humans. We measured brain activation responses to food and cocaine cues with fMRI, and D2/D3 receptors in the striatum with [¹¹C]raclopride and PET in 20 active cocaine abusers. Compared to neutral cues, food and cocaine cues increasingly engaged cerebellum, orbitofrontal, inferior frontal and premotor cortices and insula and disengaged cuneus and default mode network (DMN). These fMRI signals were proportional to striatal D2/D3 receptors. Surprisingly cocaine and food cues also deactivated ventral striatum and hypothalamus. Compared to food cues, cocaine cues produced lower activation in insula and postcentral gyrus, and less deactivation in hypothalamus and DMN regions. Activation in cortical regions and cerebellum increased in proportion to the valence of the cues, and activation to food cues in somatosensory and orbitofrontal cortices also increased in proportion to body mass. Longer exposure to cocaine was associated with lower activation to both cues in occipital cortex and cerebellum, which could reflect the decreases in D2/D3 receptors associated with chronicity. These findings show that cocaine cues activate similar, though not identical, pathways to those activated by food cues and that striatal D2/D3 receptors modulate these responses, suggesting that chronic cocaine exposure might influence brain sensitivity not just to drugs but also to food cues.

Keywords

reward; addiction; obesity; fMRI; PET

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INTRODUCTION

The mesolimbic DA pathway reinforces behaviors necessary for survival in part by activating brain circuits involved with reward and conditioning. Drugs of abuse such as cocaine stimulate these DA pathways (Bernier, et al. 2011; Mameli, et al. 2009) triggering neuroadaptations with repeated use (Thomas, et al. 2008). Specifically, preclinical studies show that chronic cocaine decreases tonic DA cell firing and enhances phasic DA cell firing in response to drug cues (Grace 2000; Wanat, et al. 2009) and reduces DA signaling during cocaine intoxication (Park, et al. 2013), and imaging studies in humans reported reductions in striatal D2/D3 receptor availability (Volkow, et al. 1990) and reduced DA signaling during intoxication in cocaine abusers (Volkow, et al. 1997b; Volkow, et al. 2012a). PET and fMRI studies have also shown that drug addiction impairs the limbic system and regions involved in salience attribution, conditioning, motivation, executive function, and interoception, which mediate responses to natural rewards (Volkow, et al. 2011b). However, little is known about the role of striatal D2/D3 receptors in modulating responses to drug or natural cues, and there is also limited knowledge on the overlap between the brain networks that process them in the human brain (Tomasi and Volkow 2013).

Foods and drugs increase DA release in the nucleus accumbens (NAc) (Norgren, et al. 2006; Volkow, et al. 2011a; Wise 2009), which is associated with their rewarding effects (Koob 1992). With repeated exposures to food or drugs these DA responses shift to the cues that predict them (Schultz, et al. 1997). Indeed when neutral stimuli are paired with a rewarding drug they will, with repeated associations, acquire the ability to increase DA in NAc and dorsal striatum (becoming conditioned cues) and these neurochemical responses are associated with drug-seeking behavior in laboratory animals (Di Ciano and Everitt 2004; Phillips, et al. 2003; Weiss, et al. 2000) and with craving in humans (Volkow, et al. 2006; Wong, et al. 2006). In humans, drug conditioned cues trigger craving (desire to take the drug), playing a critical role in the cycle of relapse in addiction (O'Brien, et al. 1998). The mechanisms underlying conditioning responses to natural and drug cues involve striatal regions (dorsal and ventral) modulated by DA (reviewed Tomasi and Volkow 2013).

Prior studies using ¹⁸Fluorodeoxyglucose-PET documented that cocaine cues (pictures of cocaine and related objects) activate visual cortex, ventral striatum and orbitofrontal cortex (OFC) (Grant, et al. 1996). However, using a similar paradigm we showed lower glucose metabolism in OFC and ventral striatum when cocaine subjects watched a cocaine-cue video than when they watched a neutral-cue video (Volkow, et al. 2010b) though, paradoxically, we had previously shown that when stimulant drugs induced craving in cocaine abusers this was associated with increased activation of the orbitofrontal cortex (Volkow, et al. 1999a). These opposite findings might reflect differences in cue reactivity paradigms (objects vs. videos). Lesions studies (Naqvi, et al. 2007) and studies on cue-induced craving (Bonson, et al. 2002; Garavan, et al. 2000; Kilts, et al. 2004; Kilts, et al. 2001; Potenza, et al. 2012; Wang, et al. 1999) have also implicated the insula in drug addiction. On the other hand fMRI studies on food stimulation that contrasted brain responses to sucrose taste and tasteless water, associated hunger with fMRI activation in insula as well as cortical and subcortical brain regions (Haase, et al. 2009).

Thus, drug and food cues likely activate similar but not identical pathways. However, to our knowledge no study reported a direct comparison of the effects of drug and food cues on brain activation in humans. Here we compared the responses to cocaine and food cues in cocaine abusers in whom we hypothesized that drug (cocaine) and natural (food) cues would activate brain networks with significant, but not complete, spatial overlap. Particularly since eating behaviors are modulated by both the homeostatic (responding to energetic and nutritional needs) and the reward pathways (Volkow, et al. 2013), and thus food cues are likely to engage circuits other than those activated by cocaine cues. On the other hand, drugs might cause greater disruption of DA pathways than those triggered by excessive food consumption since they directly activate these pathways through their pharmacological actions (Tomasi and Volkow 2013).

The aim of the present study was to assess the modulation effect of D2/D3 receptors on brain activation, independently for food and for drug cues and in the same participants. Thus we tested 20 chronic active cocaine abusers with PET and [^{11}C]raclopride to measure DA D2/D3 receptor availability in the striatum, and with a novel cue video fMRI paradigm to assess the overlapping and differential patterns of brain activation to cocaine cues, food cues and neutral cues. Videos are optimal for engaging human emotions because they capture motion, making life scenes more vivid and appealing. Cue video paradigms were previously proposed for neuroimaging on addiction (Crockford, et al. 2005; Volkow, et al. 2006) also because the saliency of a given cue may take several seconds to increase brain activity in a given region. Previous fMRI studies have shown that exposure to a cocaine-cue video induced craving and consequent fMRI responses in cocaine subjects (Garavan, et al. 2000), and that relapse to cocaine abuse is associated with increased activation in the sensory association, motor and posterior cingulate cortices (Kosten, et al. 2006). Others and we have shown that compared to neutral cues, exposure to a cocaine-cue video decreased glucose metabolism in limbic brain regions in cocaine addicts (Volkow, et al. 2010b) and increased DA release in the dorsal striatum (Volkow, et al. 2006; Wong, et al. 2006).

The fMRI measures were repeated in identical conditions on a different day in order to assess their test-retest reproducibility. We hypothesized that compared to neutral cues, cocaine and food cues would produce stronger activation in regions processing reward, motivation and conditioning and that striatal DA D2/D3 receptors would modulate these responses. We further hypothesized that compared to cocaine cues, food cues would produce stronger fMRI signals in the insula and in somatosensory regions involved with palatability (Wang, et al. 2002).

MATERIALS AND METHODS

Subjects

The study participants were 20 active cocaine-abusing males (46.4 ± 3.3 years old; 12.8 ± 1.4 years of education; body mass index (BMI) of $26 \pm 4 \text{ kg/m}^2$; mean $\pm$ SD). Participants were recruited from advertisements on public bulletin boards, in local newspapers and by word-of-mouth. All subjects provided written informed consent as approved by the local Institutional Review Board (Stony Brook University's Committee on Research Involving Human Subjects, CORIHS), and were screened for absence of medical, psychiatric or

neurological diseases. A clinical psychologist conducted a semi-structured diagnostic interview which included the Structured Clinical Interview for DSM-IV Axis I Disorders [research version (First, et al. 1996; Ventura, et al. 1998)] and the Addiction Severity Index (McLellan, et al. 1992).

Standard laboratory tests (e.g., electrocardiogram, blood lab and urine drug screen) were performed during the screening visit to ensure the inclusion/exclusion criteria of the study. Male subjects were included if they were 1) able to understand and give informed consent; had 2) DSM IV diagnosis for active cocaine dependence; 3) at least a 2 year history of cocaine abuse using at least 3 grams of cocaine/week; 4) predominant use of cocaine by smoked or iv route, and 5) not seeking cocaine treatment. Subjects were excluded if they had 6) present or past history of neurological disease of central origin or psychiatric disease including abuse or dependence to alcohol or to drugs other than cocaine and nicotine, 7) high levels of anxiety, panic attacks, psychosis, apart from those associated with cocaine abuse; 8) current medical illness that may affect brain function; 9) current or past history of cardiovascular disease including heart disease and high blood pressure or endocrinological disease; 10) head trauma with loss of consciousness > 30 minutes; 11) history of vascular headaches; 12) metal implants or other contraindications for MRI.

Thirteen of the subjects were cigarette smokers (17 ± 7 years of smoking; 8 ± 7 cigarettes per day). All subjects had a positive urine toxicology screen for cocaine on both study days, indicating that they have used cocaine during the prior 72 hours.

Cocaine-cue and food-cue video paradigms

Two novel cue video paradigms were used in the present fMRI study. The 6 minute long cocaine-cue video stimulation task (Fig 1A and 1B) was composed by six cocaine, six neutral and 6 control (black screen with a fixation center cross) epochs, each lasting 20 seconds and occurring in pseudo random order. The cocaine epochs featured non-repeating video segments portraying scenes that simulated purchase, preparation, and smoking of cocaine that were previously published (Volkow, et al. 2006; Volkow, et al. 2010b). The neutral epochs featured routine administrative/technical work as control items.

Similarly, the 6 minute long food-cue video stimulation task was composed by six 'food', six 'neutral' (routine administrative/technical work) and 6 'control' (black screen with a fixation cross) epochs, each lasting 20 seconds and occurring in pseudo random order. The food epochs featured non-repeating video segments that were recently published (Wang, et al. 2013), which portray scenes of serving and consumption of prepared ready to eat foods (i.e., meatballs, pasta, omelets, burger, pancakes).

The subjects were instructed to watch the screen continuously and press a response button with their right thumb whenever they liked features of the scenes. The cue video fragments were recorded indoors and saved in Audio Video Interleave format by professional video personnel at Brookhaven National Laboratory. These cue videos were presented to the subjects on MRI-compatible goggles (Resonance Technology Inc., Northridge, CA) connected to a personal computer. The display software was written in Visual Basic and C

languages in the Visual Studio package (Microsoft Corp., Redmond, WA) and was synchronized precisely with the MRI acquisition using a trigger pulse.

Food and cocaine valences

The more the subjects pressed the response button during the food, cocaine and/or neutral epochs the more they liked the features displayed in the respective scenes. The number of button presses was used to compute relative valences in a scale from 0 to 10. Specifically, the number of button presses during food (f), neutral (n) and control baseline (b) epochs in the food-cue video were used to compute $food = f / (f + n + b)$ and the $neutral = n / (n + f + b)$ valences corresponding to the food-cue video. Similarly, the number of button presses during the cocaine (c) epochs were used to compute the $cocaine = c / (c + n + b)$ as well as the $neutral = n / (n + c + b)$ valences during the cocaine-cue video. Note that food and cocaine valences are normalized measures that have negative correlation with the corresponding neutral valence, and that b (number of button presses during the fixation baseline epochs) models the noise level and reduces the negative correlation between these valences from the perfect negative correlation.

MRI data acquisition

The subjects checked-in the day before the study in an effort to avoid use of drugs the night before the study. They were brought to the Guest Housing Facility at Brookhaven National Laboratory at 5:00PM, where they had dinner and stayed overnight. The next morning, between 8:00AM and 8:30AM, the subjects had a light breakfast consisting of water and a bagel, roll or cereal depending on their preferences. Brain activation to cocaine cues, food cues and neutral cues was assessed between 9:00AM and 10:00AM twice on 2 different study days, 2 weeks apart. The presentation order of the food- and cocaine-cue videos was randomized across subjects. A 4-Tesla whole-body Varian (Palo Alto, CA)/Siemens (Erlangen, Germany) MRI scanner with a T2*-weighted single-shot gradient-echo planar imaging (EPI) pulse sequence (TE/TR = 20/1600 ms, 4-mm slice thickness, 1-mm gap, 35 coronal slices, 64×64 matrix size, 3.125×3.125 mm² in-plane resolution, 90°-flip angle, 226 time points, 200.00 kHz bandwidth) with ramp-sampling and whole brain coverage was used to collect functional images with blood-oxygenation-level-dependent (BOLD) contrast. Padding was used to minimize motion. Subject's motion was monitored immediately after each fMRI run using a k-space motion detection algorithm (Caparelli, et al. 2003) written in Interactive Data Language (IDL; ITT Visual Information Solutions, Boulder, CO). Earplugs (−28 dB sound pressure level attenuation; Aearo Ear TaperFit 2; Aearo Co., Indianapolis, IN), headphones (−30 dB sound pressure level attenuation; Commander XG MRI Audio System, Resonance Technology inc., Northridge, CA) and a “quiet” acquisition approach were used to minimize the interference effect of scanner noise during fMRI (Tomasi, et al. 2005). Anatomical images were collected using a T1-weighted three-dimensional modified driven equilibrium Fourier transform pulse sequence (TE/TR = 7/15 ms, $0.94 \times 0.94 \times 1.00$ mm³ spatial resolution, axial orientation, 256 readout and 192×96 phase-encoding steps, 16 minutes scan time) and a modified T2-weighted hyperecho sequence (TE/TR = 0.042/10 seconds, echo train length = 16, 256×256 matrix size, 30 coronal slices, 0.86×0.86 mm² in-plane resolution, 5 mm thickness, no gap, 2 min scan time) to rule out gross morphological abnormalities of the brain.

Data Processing

An iterative phase correction method that minimizes signal-loss artifacts in EPI was used for image reconstruction (Caparelli and Tomasi 2008). The first four imaging time points were discarded to avoid non-equilibrium effects in the fMRI signal. The statistical parametric mapping package SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK) was used for subsequent analyses. Image realignment was performed with a 4th degree B-spline function without weighting and without warping; head motion was less than 2-mm translations and 2°-rotations for all scans. Spatial normalization to the stereotactic space of the Montreal Neurological Institute (MNI) was performed using a 12-parameter affine transformation with medium regularization, 16-nonlinear iterations and voxel size of 3×3×3 mm³ and the standard SPM8 EPI template. Spatial smoothing was carried out using an 8-mm full-width-half-maximum (FWHM) Gaussian kernel. The fMRI responses during the video stimulation paradigms were estimated using a general linear model (Friston, et al. 1995) and a design matrix with 2 regressors, modeling the onsets of the 20sec long cocaine/food epochs and the 20sec long neutral epochs (Figure 1B), convolved with low-pass (HRF) and high-pass (cut-off frequency: 1/800 Hz) filters. Thus, 2 contrast maps reflecting the % BOLD-fMRI signal change from baseline (black screen with a fixation cross) caused by the cocaine/food cues and neutral cues were obtained from each fMRI run for each subject.

Test-retest reliability

The reliability of the brain activation responses to the cues was evaluated for each imaging voxel using two-way mixed single measures intraclass correlation (Shrout and Fleiss 1979).

$$ICC(3,1) = \frac{BMS - EMS}{BMS + (k - 1) EMS}$$

Specifically, ICC(3,1) was mapped in the brain in terms of between-subjects (BMS) and residuals (EMS) mean square values computed for each voxel using the IPN test-retest reliability matlab toolbox (<http://www.mathworks.com/matlabcentral/fileexchange/22122-ipn-tools-for-test-retest-reliability-analysis>) and the fMRI contrast maps corresponding to cocaine/food cues from all subjects and sessions ($k = 2$). Note that ICC(3, 1) coefficients range from 0 (no reliability) to 1 (perfect reliability).

PET scanning

Thirty minutes after MRI scanning (approximately 60 minutes after the end of the fMRI session) the subjects underwent a PET scan to map the availability of DA D2/D3 receptors in the brain. We used an HR+ tomograph (resolution 4.5×4.5×4.5 mm³ full width half-maximum, 63 slices) with [¹¹C]raclopride, a radiotracer that binds to DA D2/D3 receptors, and methods previously described (Volkow, et al. 1993a). Briefly, emission scans were started immediately after injection of 4-8 mCi (specific activity 0.5-1.5 Ci/μM). Twenty dynamic emission scans were obtained from time of injection up to 54 minutes. Arterial sampling was used to quantify total carbon-11 and unchanged [¹¹C]raclopride in plasma. The distribution volume (DV), which corresponds to the equilibrium measurement of the ratio of the radiotracer's tissue concentration to that of its plasma concentration, was

estimated for each voxel using a graphical analysis technique for reversible systems that does not require blood sampling (Logan J 1990). These images were then spatially normalized to the MNI stereotactic space using SPM8 and resliced using 2-mm isotropic voxels. A custom MNI template, which was previously developed using DV images from 34 healthy subjects that were acquired with [^{11}C]raclopride and the same PET scanning methodology (Wang, et al. 2011), was used for this purpose. DV ratios, which correspond to the non-displaceable binding potential (BP_{ND}) in each voxel, were obtained by normalizing the intensity of the DV images to that in the cerebellum (left and right regions-of-interest). The Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer, et al. 2002) was used to locate the MNI coordinates of the centers of mass for putamen and caudate; the center coordinates of the boundary between caudate and putamen was selected for the ventral striatum. Thus, isotropic (cubic) masks with a volume 1 ml (125 imaging voxels) were centered at the putamen [$xyz = (\pm 26, 8, 2)$ mm], caudate [$xyz = (\pm 12, 12, 8)$ mm] and ventral striatum [$xyz = (\pm 20, 10, -12)$ mm] to compute the average availability of D2/D3 receptors for each individual in these striatal regions (Fig 2A).

Statistical analyses

A one-way within-subjects analysis of variance model in SPM8 with age, BMI and years of cocaine use covariates (ANCOVA) was used to test the significance of common and differential brain activation signals to neutral, food and cocaine cues. Voxelwise SPM8 regression analyses were additionally used to test the linear association of brain activation signals with the availability of D2/D3 receptor (BP_{ND}) in caudate, putamen and ventral striatum, as well as with years of cocaine use, cue valence and BMI across subjects. Statistical significance was set as $P_{\text{FWE}} < 0.05$, corrected for multiple comparisons with the random field theory and a family-wise error correction at the cluster level. A cluster-forming threshold $P < 0.005$ and a minimum cluster size of 200 voxels were used for this purpose. The conservative Bonferroni method for multiple comparisons was additionally used to control for the number of independent SPM regression analyses. A stringent cluster-level corrected threshold $P_c < 0.05$ that simultaneously accounted for Bonferroni corrections and whole-brain FWE-corrections was used for this purpose.

Functional ROI-analyses

Brain activation and deactivation clusters were further evaluated with region-of-interest (ROI) analyses to identify outliers that might influence strongly correlation analyses, and to report average values in a volume comparable to the image smoothness (e.g. resolution elements, or “resels” (Worsley, et al. 1992)) rather than single-voxel peak values. The volume of the resels was estimated using the random field calculation in SPM8 as a near cubic volume with Cartesian FWHM = 12.7 mm, 12.3 mm, 13.1 mm. Thus, 9-mm isotropic masks containing 27 voxels (0.73 ml) were defined at the centers of relevant activation/deactivation/correlation clusters to extract the average % BOLD signal from individual contrast maps. These masks were created and centered at the precise coordinates listed in Tables 1-4.

RESULTS

Behavior

The valences were lower for neutral cues than for food or cocaine cues ($P < 10^{-6}$, $t > 7.4$, $df = 19$, paired t-test; Fig 3A) but did not differ for food and cocaine cues. There was a negative correlation across subjects between the valence of the neutral cues and that of the cocaine/food cues, such that the more the subjects liked the cocaine/food cues the less they liked the neutral cues ($R < -0.8$, $P < 0.0001$, $df = 18$, Pearson correlation; Fig 3B).

Striatal DA D2/D3 receptors

The average availability of DA D2/D3 receptors in the striatal ROIs was higher for putamen than for caudate, and for caudate than for ventral striatum ($P < 10^{-9}$, left and right hemispheres values averaged). The availability of D2/D3 receptors in the striatum did not show significant correlation with age, BMI, chronicity or with the valence of the cues.

Brain activation

Compared to the fixation baseline, *neutral cues* produced bilateral activation in middle occipital, fusiform and superior frontal gyri (BAs 19 and 6), cerebellum (posterior lobe), inferior parietal cortex (BA 40), inferior frontal operculum (BA 44) and the hippocampus, and bilateral deactivation in posterior default mode network (DMN) regions (cuneus, precuneus and angular gyrus) ($P_{FWE} < 0.0005$; Fig 4).

Compared to the fixation baseline, *cocaine cues* produced bilateral activation in calcarine and inferior parietal cortices (BAs 18 and 40), fusiform (BA 19), precentral (BA 6) and middle frontal gyri (BA 44), and the hippocampus, and bilateral deactivation in posterior DMN regions (cuneus, precuneus, posterior cingulum and angular gyrus) ($P_{FWE} < 0.0005$; Fig 4).

Compared to the fixation baseline, *food cues* produced bilateral activation in calcarine cortex (BA 18), fusiform gyrus (BA 19), temporal pole (BA 38), inferior parietal cortex (BA 40), inferior frontal operculum (BA 45), OFC (BA 11) and the hippocampus, and bilateral deactivation in rostral/ventral ACC (rvACC, BAs 10, 11 and 32), cuneus (BAs 18 and 19), precuneus (BA 7) and the angular gyrus (BA 39) ($P_{FWE} < 0.0005$; Fig 4).

Test-retest reliability

The ICC analysis of the test-retest fMRI data demonstrated moderate to high reliability for the BOLD-fMRI responses to the cues. Specifically, the fMRI signals in rvACC, occipital cortex, ventral striatum, cerebellum, inferior frontal operculum, postcentral, precentral and inferior frontal gyri, cuneus, precuneus and the angular gyrus had $ICC(3,1) > 0.5$ (Fig 5).

Common activation patterns for food and cocaine cues

Cocaine and food cues produced higher activation than neutral cues in cerebellum, inferior frontal and precentral gyri, OFC and the insula, and lower activation than neutral cues in ventral striatum, rvACC and the calcarine cortex ($P_{FWE} < 0.0005$; ANCOVA; Fig 6 and Table 1).

Specific activation patterns for food and cocaine cues

Cocaine cues produced higher activation than neutral cues in inferior frontal and occipital, parahippocampal and postcentral gyri and the cerebellum, and lower activation than neutral cues in visual areas, auditory cortex, OFC, rvACC, posterior insula, paracentral lobule and precentral gyrus, caudate, putamen and ventral striatum (location of NAc) ($P_{FWE} < 0.05$, ANCOVA; Supplementary Table S1, Figs 6 and 7). Similarly, food cues produced higher activation than neutral cues in postcentral gyrus, temporal pole inferior and superior frontal cortex, insula and the cerebellum, and lower activation than neutral cues in primary visual cortex, precuneus, cuneus, middle occipital gyrus, ventral striatum, hypothalamus and the midbrain [location of ventral tegmental area (VTA) and substantia nigra (SN); $P_{FWE} < 0.01$; Table S1 and Fig 7].

Compared to food cues, cocaine cues produced lower activation in insula and postcentral gyrus, lower deactivation in hypothalamus, precuneus and posterior cingulum and higher activation in middle temporal gyrus and the inferior parietal cortex (Table 2; $P_{FWE} < 0.005$; Fig 7). In contrast compared to cocaine cues, food cues produced greater deactivation in hypothalamus/midbrain and in posterior cingulum and they deactivated the posterior cingulum whereas cocaine cues activated it.

Striatal D2/D3 receptor availability and brain activation

We assessed the linear association between brain activation and D2/D3 receptors independently for dorsal caudate and putamen and ventral striatum because different regions of the striatum have demonstrated different cortical projections, and have different modulatory effects on brain regions involved with control of behavior (Grahn, et al. 2008), salience attribution and reward processing (Volkow, et al. 2011b). There were significant correlations between the availability of DA D2/D3 receptors in the striatum and the average co-activation responses elicited by food and cocaine cues ($P_{FWE} < 0.05$; Table 3; Fig 2B and 2C). Specifically, increased BP_{ND} in caudate was associated with stronger activation in hippocampus and parahippocampus, rvACC and OFC, and weaker activation in cuneus, superior frontal gyrus and caudal dorsal ACC (cdACC). Increased BP_{ND} in putamen was associated with stronger activation in OFC, midbrain, cerebellum and superior frontal and parahippocampal gyri and with weaker activation in cdACC and middle frontal gyrus, cuneus and superior occipital and lingual gyri. The linear associations with BP_{ND} in caudate and putamen survived additional Bonferroni corrections for the number of BP regressions ($P_c < 0.05$, cluster level corrected in whole-brain with the FWE correction and for the three BP regressions with the Bonferroni method). Increased BP_{ND} in ventral striatum was associated with stronger activation in inferior and superior parietal cortices, paracentral lobule, postcentral gyrus and precentral gyrus and weaker activation in the cerebellum. However, the linear associations with BP_{ND} in ventral striatum did not survive additional Bonferroni corrections for the number of BP regressions. These correlations were not significantly different for cocaine and food cues (Fig 2C). The correlation patterns for caudate and putamen had significant overlap in occipital cortex, cdACC and rvACC (Fig 2B). The correlation patterns for ventral striatum did not show significant overlap with those for caudate and putamen.

Associations with chronicity, behavioral responses and BMI

Linear regression analyses revealed associations between the average co-activation elicited by food and cocaine cues, the number of years of cocaine use and valences of food and cocaine cues ($P_{FWE} < 0.05$; Table 4; Fig 8). Specifically, longer cocaine exposure was associated with lower activation in a cluster region that contained the right calcarine cortex and the right and left cerebellum to both food and cocaine cues (Table 4, Figure 8). Increased valence for food and cocaine cues was associated with increased activation in inferior and superior parietal and middle and inferior temporal cortices, cerebellum and the postcentral gyrus, and with lower activation in cuneus for both cocaine and food cues. In addition higher BMI was associated with increased activation to food cues in OFC (BA 11) and the postcentral gyrus ($P_{FWE} < 0.05$; Table 4; Fig 8). These linear associations with years of cocaine use, cue valence and BMI survived additional Bonferroni corrections for the number of regressions ($P_c < 0.05$).

DISCUSSION

The current study demonstrates for the first time common and distinct functional circuits involved in drug (cocaine cues) and natural (food cues) reward for men that actively abuse cocaine, and shows significant correlation between striatal D2/D3 receptors and brain activation to cocaine and food cues.

D2/D3 receptors and brain activation

The availability of DA D2/D3 receptors in striatum was associated with brain activation to cocaine and food cues. Interestingly, while the correlation patterns were similar for cocaine and food cues, the linear associations between striatal D2/D3 receptor availability and BOLD responses had significant overlap for caudate and putamen (dorsal striatum) but ventral striatum showed a distinct pattern. These findings are consistent with the modulatory role of DA and of D2/D3 receptors in reactivity to food and drug cues (Salamone and Correa 2012) and with the distinct role that dorsal and ventral striatal region have in modulating cue responses (Di Ciano, et al. 2008).

The pattern of correlations between striatal D2/D3 receptors and BOLD activation included cortical areas (parietal cortex) and cerebellum, which are brain regions that have relatively low levels of D2/D3 receptors (Mukherjee, et al. 2002). This widespread pattern of correlations is likely to reflect the modulatory role that D2/D3 receptors containing neurons in the striatum have in cortical activity through their thalamo-cortical projections (Haber and Calzavara 2009). Thus, the strength of the correlation between D2/D3 receptors and BOLD activation in a given region would reflect the modulatory role of striatal D2 and D3 receptors expressing projections into the relevant cortical and subcortical networks activated by the cues.

The role of D2/D3 receptors in reactivity to food and drug cues is consistent with prior clinical findings. Specifically, using PET and [^{11}C]raclopride we and others have shown that exposure to drug cues increases dopamine following exposure to cocaine (Volkow, et al. 2006; Wong, et al. 2006), amphetamine (Boileau, et al. 2007) and heroin (Zijlstra, et al.

2008) cues. Pharmacological studies with haloperidol and amisulpiride have also shown that D2/D3 receptor blockade reduces attentional bias to heroin cues in heroin addicts (Franken, et al. 2004), and normalizes hypo activation to smoking cues in ACC and PFC in smokers (Luijten, et al. 2012) and to alcohol cues in ACC and OFC in alcoholics (Hermann, et al. 2006). Thus, our findings along with those of others (Saunders and Robinson 2013) indicate that DA, in part through D2 receptors but presumably also D3 receptors, has a key role in the processing of drug and food cues. Different from our prior studies (Wang, et al. 2001), striatal BP_{ND} was not associated with BMI in the present study, which might reflect differences between samples. Specifically, whereas the present study includes only a small fraction of obese individuals (3/20 subjects with BMI > 30 kg/m²; BMI range: 20-35 kg/m²) and all of them were cocaine abusers, our previous study included 10 severely non-drug abusing obese individuals with a BMI greater than 40 kg/m² (range: 42-60 kg/m²) and 10 healthy non-drug abusing controls (range: 21-28 kg/m²).

The common network

Identification of overlapping brain circuits which are activated by food and drug cues could help identify treatment strategies that may benefit both drug addicts and obese individuals. Natural rewards release dopamine in the ventral striatum, which is believed to underlie their rewarding effects. However with repeated exposure to the reward the dopamine increases are transferred from the reward to the cues that predict them (Schultz, et al. 1997), thus triggering the motivational drive required to ensure behaviors necessary for reward consumption (Pasquereau and Turner 2013). Repeated exposure to drugs of abuse also results in conditioning. In this way, conditioned responses for food and drugs shift the incentive motivation to the conditioned cue stimuli that predict the reward (Berridge and Robinson 2003).

Interestingly we show that dopaminergic regions were deactivated by exposure to the reward cues, including ventral striatum (to both food and drug cues) and hypothalamus and midbrain (to food cues) when compared to neutral cues (Table 2 and Fig 4), which is consistent with the inhibitory properties of DA in non-human primates (West and Grace 2002) and in humans (Volkow, et al. 2010b) and with the increases in DA in the striatum following drug cues in cocaine abusers (Volkow, et al. 2006) and food cues in controls (Volkow, et al. 2002). All addictive drugs increase DA in the ventral striatum (NAc) (Koob 1992), and their rewarding effects are associated with these **increases in DA release** (Drevets, et al. 2001; Volkow, et al. 1999b; Wise 2009). Foods can also increase DA in ventral striatum (de Araujo, et al. 2008; Norgren, et al. 2006) and are potently rewarding (Lenoir, et al. 2007). The cerebellum and the insula, on the other hand, showed stronger activation to cocaine and food cues than to neutral cues (Table 2 and Fig 4). These findings are consistent with the activation of the cerebellum and the insula during taste perception in hunger conditions (Haase, et al. 2009) and with cerebellar (Grant, et al. 1996) and insular activation in cocaine abusers exposed to cocaine cues (Wang, et al. 1999). Moreover, when exposed to cocaine cues, cocaine abusers instructed to inhibit their craving deactivate the insula (Volkow, et al. 2010a), and damage to the insula can disrupt addiction to cigarette smoking (Naqvi, et al. 2007). Indeed the insula is increasingly recognized as being a critical neural substrate for addiction in part by mediating interoceptive awareness of drug craving

(Naqvi and Bechara 2010). Our results differ from those obtained in rats trained to associate odor cues with the availability of a reinforcer (intravenous cocaine/oral sucrose), which show different brain activity in NAc for cocaine than for sucrose (Liu, et al. 2013). This discrepancy might reflect differences between species (addicted humans versus rats exposed to cocaine), the use of odors versus visual cues and confounds from the effects of anesthesia used for the rodent studies.

Cerebellar activation was stronger for cocaine and food cues than for neutral cues, which is consistent with prior studies documenting a role of the cerebellum in reward-based learning (Thoma, et al. 2008), cocaine-induced memory (Carbo-Gas, et al. 2013) and in the regulation of visceral functions and feeding control (Haines, et al. 1984). Cerebellar activation to food and cocaine cues decreased with years of cocaine use (Table 4). This finding is consistent with the cocaine subjects' weaker brain responses compared to controls (Bolla, et al. 2004; Goldstein, et al. 2009; Hester and Garavan 2004; Li, et al. 2008; Moeller, et al. 2010; Volkow, et al. 2010b), and with our prior findings showing that the increases in cerebellar metabolism observed after a challenge with an intravenous stimulant drug (methylphenidate) were correlated with striatal D2/D3 receptor availability (Volkow, et al. 1997a), which tend to be decreased in cocaine abusers (Martinez, et al. 2004; Volkow, et al. 1993b; Volkow, et al. 1990).

Compared to neutral cues, cocaine/food cues also elicited increased activation in lateral OFC, inferior frontal and premotor cortices and stronger deactivation in rvACC, precuneus and visual areas (Table 1). Previous studies have shown that compared to neutral cues, food cues elicit significant **activation** responses in the insula, somatosensory cortex, parietal and visual cortices (Cornier, et al. 2013), and children at risk for obesity show stronger activation to food cues in the somatosensory cortex (Stice, et al. 2011). Furthermore, the anterior insula, and inferior frontal and OFC are interconnected to the striatum by cortico-striatal projections modulated by DA (Haber 2003) and play important roles in inhibitory control, decision making, emotional regulation, motivation and salience attribution (Goldstein and Volkow 2002; Phan, et al. 2002; Volkow, et al. 1996). Moreover, OFC gray matter volume demonstrated negative correlations with BMI in cocaine addicts and controls as well as with years of cocaine use in cocaine addicts (Smith, et al. 2013), which could also reflect the effects of cocaine in regions underlying natural rewards responses such as OFC.

Differential networks

Cocaine cues produced stronger fMRI activation in cerebellum, occipital and prefrontal cortices and greater deactivation in rvACC and ventral striatum than neutral cues. These findings are consistent with the craving-related metabolic increases in PFC, medial temporal lobe and cerebellum (Grant, et al. 1996) and with the metabolic decreases in ventral striatum (Volkow, et al. 2010b) and the cerebral blood flow decreases in basal ganglia (Childress, et al. 1999) in cocaine addicts during cocaine-cue stimulation paradigms.

Food cues produced stronger fMRI activation than neutral cues in the insula, gustatory and visual association cortices, and greater deactivation in rvACC, hypothalamus, midbrain and primary visual cortex, precuneus and angular gyrus. Whereas cocaine cues did not activate BA 43 (gustatory cortex; Table 2) significantly across subjects, the fMRI responses to food

cues in BA 43 were significant (Table 2) and positively correlated with the availability of DA D2/D3 receptors in ventral striatum (Fig 2C), which would suggest dopaminergic modulation of this brain region. Supporting this were the significant correlations between fMRI activation responses in the gustatory cortex and food cue valence (Table 4), since DA modulates the value of food rewards (Volkow, et al. 2012b).

Deactivation in posterior DMN regions was higher for food than for cocaine cues. Activation of the DMN has been associated with the generation of spontaneous thoughts during mind-wandering (Mason, et al. 2007) and its deactivation occurs during the performance of attention-demanding cognitive tasks (Fox, et al. 2005). Importantly, the degree of DMN deactivation during attention demanding cognitive tasks varies across tasks (Tomasi, et al. 2006), likely reflecting the degree of suppression of spontaneous thoughts. Thus, weaker DMN deactivation for cocaine cues than for food cues could reflect higher degree of generation of spontaneous thoughts during cocaine cues than during food cues. This could reflect in part differences in dopamine release between food cues and cocaine cues because DA increases are associated with DMN deactivation (Thanos, et al. 2013; Tomasi, et al. 2009). The negative correlation observed between D2/D3 receptors in dorsal striatum and fMRI responses in cuneus, such that the higher the receptor levels the greater the deactivation of the cuneus, is consistent with the inhibiting role of DA in the DMN (Thanos, et al. 2013; Tomasi, et al. 2009).

The BOLD-fMRI signals in this study were not significantly different across study days, suggesting lower variability within- than between-subjects. Furthermore the test-retest reliability of the activation and deactivation patterns elicited by the cues was similar to that of standard working memory fMRI tasks that use blocked designs (Bennett and Miller 2013). Specifically, the reliability of the fMRI signals ranged from 0.4 (moderate reliability) to 0.8 (high reliability), also suggesting lower variability of brain activation to food and cocaine cues for within-subject than between-subjects measures.

In interpreting our results we considered the possibility that cocaine abusers might be particularly sensitive to reward-cues (natural and drug reward), which in turn might contribute to their vulnerability for addiction (Saunders and Robinson 2013). Moreover, in our results the valence of the cocaine cues correlated with the valence of the food cues, consistent with a common sensitivity to general cue reactivity (Saunders and Robinson 2013). Thus we cannot exclude the possibility that the differences we observe in the cocaine abusers might have preceded their drug use and might have made them more vulnerable to cocaine abuse. In this respect, it would have been desirable to include a control group to assess the specificity of the effects to food and cocaine cues in addicted versus non-addicted individuals and to determine if their sensitivity to food cues also differed between the groups. We postulate that differences in behavioral responses and brain activation elicited by food cues versus cocaine cues would be significantly larger for controls than for cocaine abusers. Furthermore, we used [^{11}C]raclopride, which maps D2/D3 receptor availability, and it would have been desirable to use radiotracers that would help us to distinguish between the contribution of D2 receptors and that of D3 receptors. Also, [^{11}C]raclopride is sensitive to competition to endogenous DA (Volkow, et al. 1994), so we cannot determine if the association with brain activation reflects differences in D2/D3 receptors levels or

competition of dopamine with the radiotracer for binding to D2/D3 receptors. However since we and others have consistently shown that cocaine abusers show decreased DA release (Volkow, et al. 2011b) it is very likely that differences in brain activation reflect different levels of D2/D3 receptors in striatum. In addition, the fMRI session preceded PET scanning by 60 minutes and could have increased endogenous DA release, systematically reducing the BP_{ND} measures. However, increases in DA release triggered by cues are fast and short-lasting (2-3 minutes) (Erhardt, et al. 2002) and thus it is expected that DA release would have returned to baseline by the time of the PET scan procedure. Nonetheless, because we cannot corroborate its absence, DA release during fMRI is a confounding factor in our study.

Our results show that food and cocaine cues engaged a common network modulated by DA D2/D3 receptors that includes cerebellum, insula, inferior frontal, OFC, ACC, somatosensory and occipital cortices, ventral striatum and DMN. Food cues produced stronger **activation** responses than cocaine cues in the posterior insula and the postcentral gyrus, higher deactivation in DMN and hypothalamic regions and lower activation in temporal and parietal cortices. Brain activation responses to food and cocaine cues in prefrontal and temporal cortical regions involved with reward processes increased with the valence of the cues and was correlated with D2/D3 receptors; consistent with a common neuronal substrate for the value of natural and drug cues that is modulated via D2/D3 receptor mediated signaling in addiction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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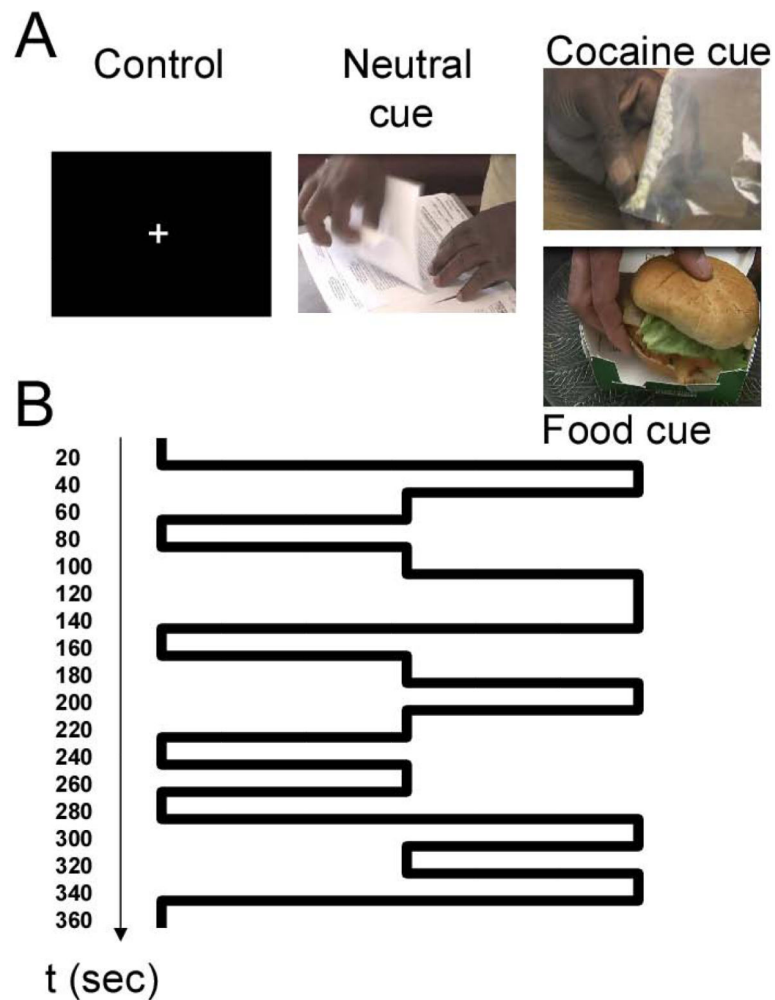
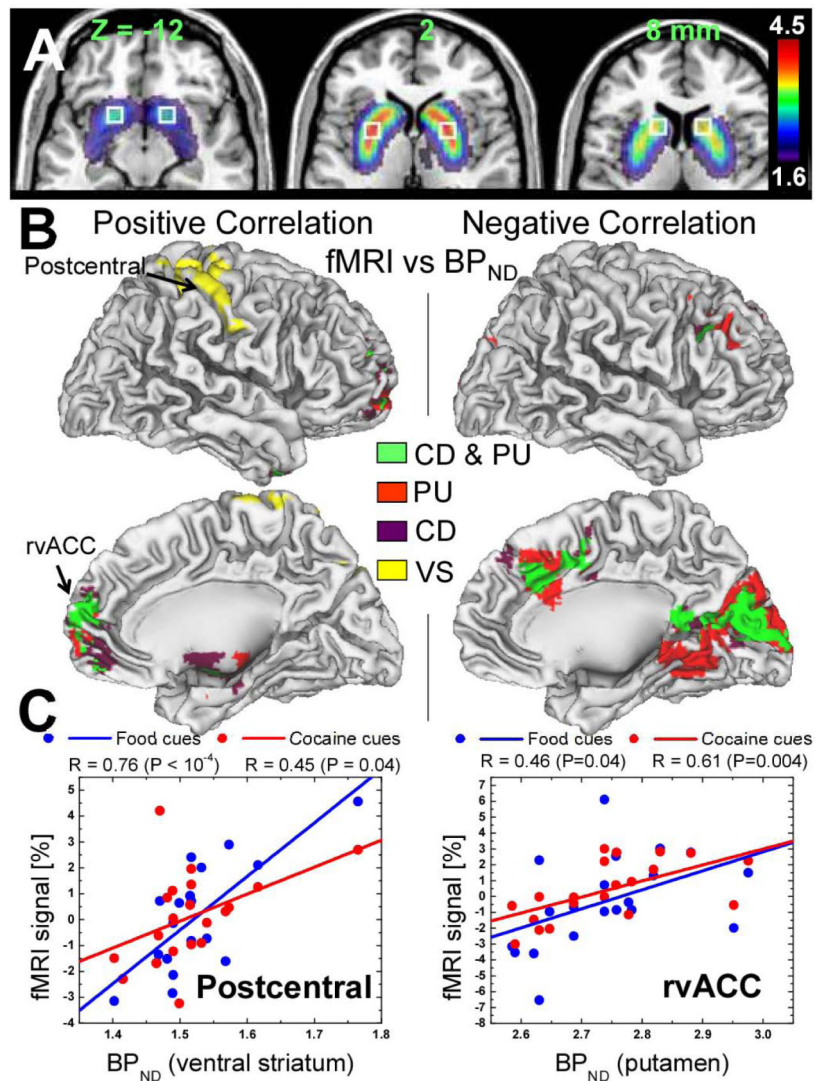
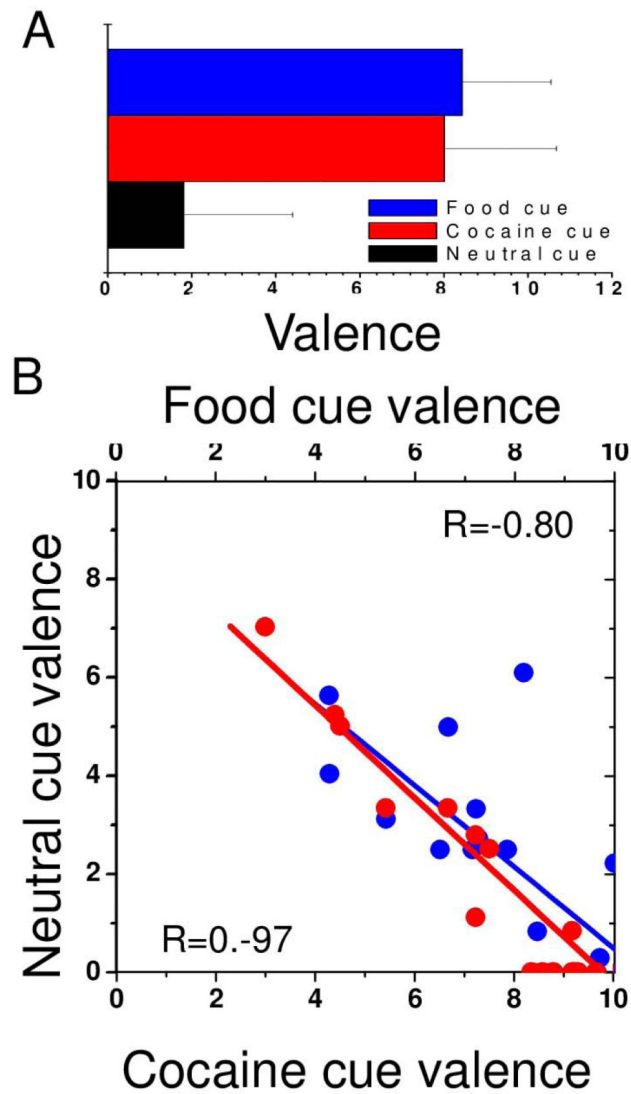


Fig 1.

A: The cue video stimulation tasks features control (black screen with and a fixation center cross), neutral and either cocaine or food video epochs (20 seconds long) portraying scenes that simulated purchase, preparation, and smoking of cocaine (cocaine cue video), or serving and consumption of the restaurant foods (food cue video). **1B:** Time course of the 6-minutes long stimulation paradigm showing that each video epoch lasted 20 seconds and occurred in pseudo random order.

**Fig 2.**

A: Binding potential superimposed on axial MRI views of the human brain showing the availability of DA D2/D3 receptors in the striatum. PET with [^{11}C]raclopride was used to compute distribution volumes relative to values in the cerebellum, which correspond to the non-displaceable binding potential in each voxel (BP_{ND}). White squares highlight the regions-of-interest in ventral striatum ($Z = -12$ mm), putamen ($Z = +2$ mm) and caudate ($Z = +8$ mm). **2B:** Brain regions showing significant positive (left panel) and negative (right panel) correlations between brain activation and the availability of DA D2/D3 receptors in ventral striatum (VS), putamen (PU) and caudate (CD) and their overlapping correlation patterns (CD & PU). **2C:** Scatter plots showing the association between the availability of DA D2/D3 receptors in the striatum and fMRI responses in postcentral gyrus and rostral ventral PFC across subjects.

**Fig 3.**

Behavioral responses during cue video stimulation. **A:** The subjects were instructed to press a response button whenever they liked features of the scene. The number of button presses was used to determine how much the subjects liked the cocaine, food and neutral scenes in the videos in a scale from 0 to 10. **B:** Scatter plots showing the strong negative correlation between cocaine liking scores and neutral liking scores (red) and the weak negative correlation between food liking scores and neutral liking scores (blue) across subjects.

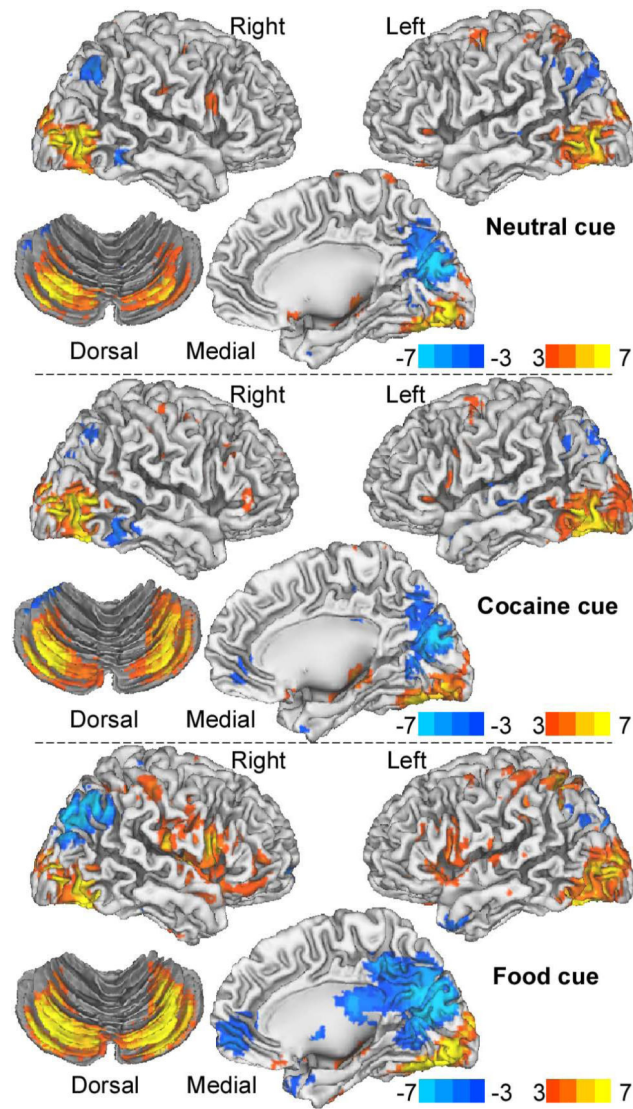


Fig 4.

Statistical significance of brain activation (red-yellow)/deactivation (blue-cyan) responses to the cue videos relative to the fixation baseline epochs, rendered on lateral and ventral views of the cerebrum and a dorsal view of the cerebellum.

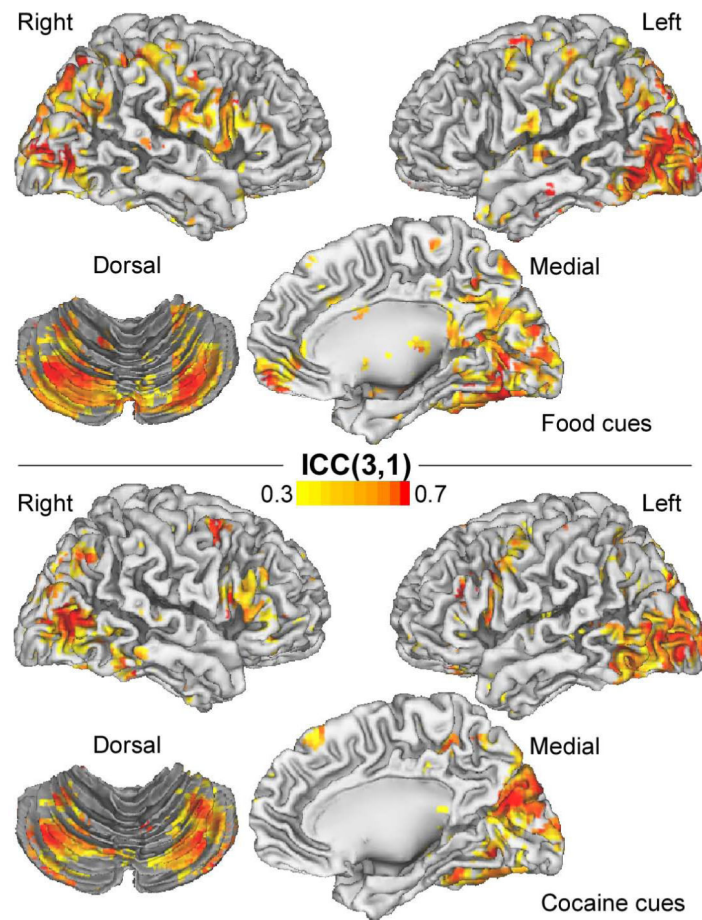


Fig 5. Intraclass correlation (ICC) maps, rendered on lateral and ventral views of the cerebrum and a dorsal view of the cerebellum, depicting the reliability of the fMRI signals. The ICC(3,1) voxel values were computed from BOLD-fMRI responses to food and cocaine cues recorded on two study days under identical conditions using the same MRI acquisition parameters.

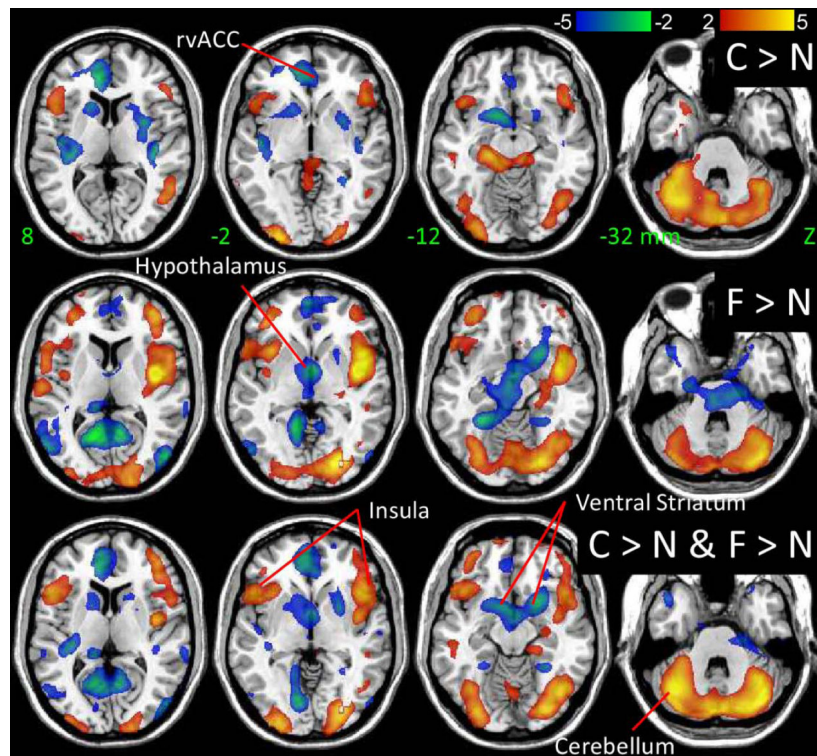


Fig 6. Statistical significance of brain co-activation responses to the cocaine and food cues relative to that of the neutral cues rendered on axial views of the human brain. SPM8 model: ANCOVA. Color bars are t-scores.

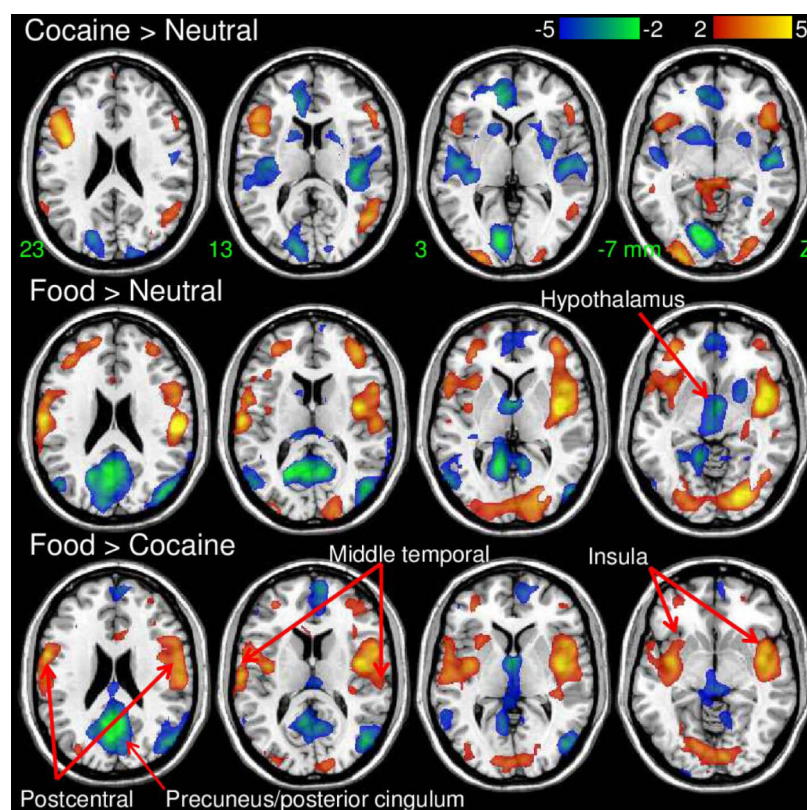
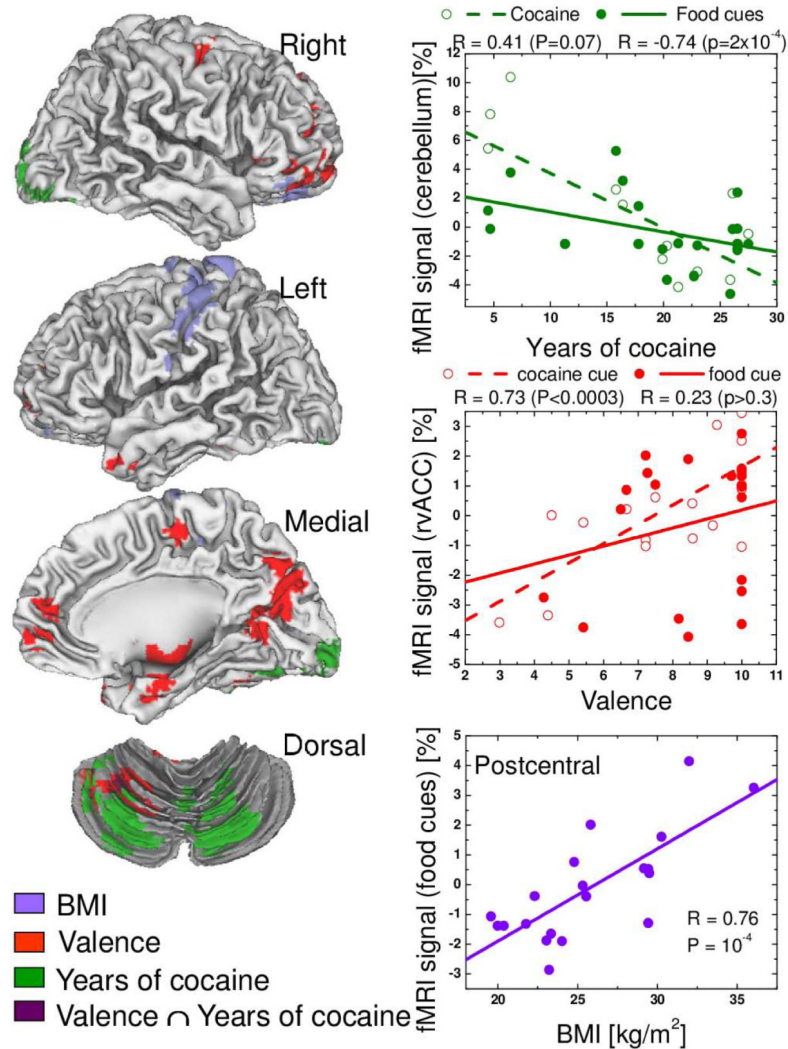


Fig 7. Statistical significance of differential activation responses to the cues rendered on axial views of the human brain. SPM8 model: ANCOVA. Color bars are t-scores.

**Fig 8.**

Correlation patterns between the average activation to cocaine and food cues and BMI, cue valence and years of cocaine use and their overlap (Valence $\cap$ Years of cocaine use), superimposed on lateral and ventral views of the cerebrum and a dorsal view of the cerebellum (left), as well as the corresponding linear regression plots showing the significant correlation of these variables (right).

Table 1

Statistical significance for brain activation clusters that were commonly activated by cocaine (C) and food (F) cues compared to neutral (N) cues.

Region	BA	MNI coordinates [mm]			Cluster [voxels]	t-score		
		x	y	z		C > N	F > N	C > N & F > N
Cerebellum		-42	-70	-29	2242	3.5	4.4	5.3
Cerebellum		36	-64	-26		4.2	3.8	5.3
Cerebellum		39	-76	-29		3.1	3.1	4.1
Inferior Frontal	44	45	8	28	452	4.8	1.9	4.4
Insula	47	42	20	-8		2.5	2.6	3.4
Inferior Frontal	45	51	20	10		3.1	2.0	3.4
Supramarginal	42	-57	-19	22		NS	5.5	3.8
OFC	47	-45	20	-5	185	2.2	3.7	4.0
Inferior Frontal	44	-54	14	19	106	1.6	3.2	3.1
Precentral	6	-42	-4	52		2.6	1.6	2.7
Ventral striatum		-21	11	-14		-2.1	-3.2	-4.3
Hypothalamus		-3	-1	-5		NS	-3.5	-3.7
rvACC	32	9	44	4	163	-3.8	-1.8	-3.7
rvACC	11	-3	41	-5		-2.5	-1.8	-2.8
Calcarine	18	9	-67	19	517	NS	-4.3	-3.6
Calcarine	17	-9	-61	13		NS	-4.2	-3.5
Calcarine	18	21	-64	13		NS	-4.3	-3.4

Average statistical values computed within functional ROIs (9-mm isotropic) with 27 voxels. Statistical significance for C>N & F>N conjunction analyses: cluster level $P_{FWE} < 0.05$.

Table 2

Statistical significance for brain activation clusters that were differentially activated by cocaine, food and neutral cues.

Region	MNI coordinates [mm]				Cluster [voxels]	T-score		
	BA	x	y	z		C > N	F > N	F > C
Middle Temporal	21	-51	-58	19	480	3.7	n.s.	-2.6
Middle Temporal	22	-57	-49	13		3.4	n.s.	-2.1
Inferior Parietal	40	-54	-52	37		2.4	n.s.	-3.6
Hypothalamus/VTA		-3	-10	-8		n.s.	-3.6	-2.0
Insula	13	-45	2	-5	1101	n.s.	4.7	3.1
Insula	13	-39	-4	10		n.s.	4.1	2.7
Insula	13	-45	14	1		n.s.	3.8	2.9
Postcentral	43	63	-13	19	707	n.s.	4.2	2.0
Postcentral	43	60	-1	16		n.s.	3.3	2.4
Posterior cingulum	26/29	0	-55	28	994	n.s.	-2.6	-4.3
Precuneus	23	-9	-49	43		n.s.	n.s.	-3.4
Cingulum	23	6	-52	37		2.0	-2.6	-3.6

Average statistical values computed within functional ROIs (9-mm isotropic) with 27 voxels. Statistical significance for F > C: cluster level PFWE < 0.05.

Table 3

Statistical significance for the correlation between average fMRI responses to food (**F**) and cocaine (**C**) cues and the availability of DA D2 receptors (**D2R**) in caudate, putamen and ventral striatum.

Region	BA	MNI coordinates [mm]			Cluster-level		D2R-corr [t]	
		x	y	z	P _{FWE}	voxels	F & C	(F / C)
D2R in caudate								
Parahippocampal	28	-18	5	-23	0.016	599	4.2	3.0/2.8
Hippocampus	34	18	-7	-11			3.9	2.8/2.7
OFC	10	-6	47	-8	0.016	534	3.9	4.0/NS
rvACC	32	9	53	25			3.9	2.7/2.7
Cuneus	18	-9	-88	19	0.002	775	-6.0	-4.6/-3.9
Superior frontal	9	12	47	43	0.012	515	-4.0	-2.8/-2.9
cdACC	32	6	26	37			-3.7	-3.1/-2.2
D2R in putamen								
OFC	10	-12	47	1	0.004	637	4.0	2.5/3.3
Superior Frontal	10	18	50	13			3.7	1.9/3.4
Parahippocampal	28	-18	5	-23	0.003	745	3.7	2.0/3.3
Midbrain		-3	-25	-11			3.5	2.1/3.1
Cerebellum		-21	-46	-44			3.5	2.5/2.5
Lingual	37	24	-52	-5	<0.001	1576	-5.5	-4.0/-3.7
Superior Occipital	19	-3	-85	43			-5.4	-4.0/-3.6
Cuneus	18	-9	-85	16			-5.2	-4.2/-3.1
cdACC	32	6	26	37	0.005	612	-4.6	-3.0/-3.7
Middle frontal	8	27	14	49			-3.6	-2.4/-2.8
D2R in ventral striatum								
Precentral	4	-33	-31	64	0.029	450	5.0	4.7/-3.1
Inferior parietal	2	-30	-46	55			4.4	4.5/NS
Postcentral	3	-51	-22	52			3.2	2.8/NS
Superior parietal	7	21	-67	55	0.024	536	4.9	3.1/NS
Paracentral lobule	4	6	-37	79			3.5	4.2/NS
Cerebellum		42	-76	-50	0.051	441	-6.5	-4.2/NS

P_{FWE}: P-value corrected for multiple comparisons at the cluster level.

Table 4

Statistical significance for the correlations between average fMRI responses to food (F) and cocaine (C) cues and years of cocaine, liking scores and body mass index (BMI).

Region	BA	MNI coordinates [mm]			Cluster-level		Correlation [T]	
		x	y	z	P _{FWE}	k	F & C	F / C
Years of cocaine								
Calcarine	17	3	-103	1	< 0.001	1366	-5.9	-6.3/-2.6
Cerebellum		-30	-73	-23			-4.7	-3.9/-1.7
Cerebellum		36	-82	-26			-4.7	-4.9/NS
Valence								
Inferior parietal	2	-30	-46	55	0.008	1296	4.5	2.6/3.6
Postcentral	3	39	-28	49			3.7	2.9/NS
Superior parietal	40	39	-55	61			3.6	2.7/2.7
Cerebellum		33	-49	-47	0.003	1693	3.7	NS/NS
Inferior temporal	20	51	-43	-17			3.7	2.5/1.9
Middle temporal	22	63	-46	7			3.6	3.3/2.4
Cuneus	18	12	-76	28	0.002	1779	-4.3	-2.7/-3.6
Lingual	18	12	-61	4			-3.8	NS/-2.9
BMI								
Postcentral	43	63	-22	43	0.004	508	4.4	4.3/NS
Postcentral	4	33	-31	73			NS	3.8/NS
Postcentral	1	18	-43	73			2.6	3.7/NS
OFC	11	-24	44	-11	0	784	NS	4.0/NS

T: t-score.

P_{FWE}: P-value corrected for multiple comparisons at the cluster level.

k: number of voxels in the cluster.