HHS Public Access

Author manuscript

Biol Psychiatry Cogn Neurosci Neuroimaging. Author manuscript; available in PMC 2019 May 01.

Published in final edited form as:

Biol Psychiatry Cogn Neurosci Neuroimaging. 2018 May ; 3(5): 485–494. doi:10.1016/j.bpsc.2017.11.001.

Neural correlates of drug-biased choice in currently-using and abstinent individuals with cocaine use disorder

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Abstract

Background—The choice for drugs over alternative reinforcers is a translational hallmark feature of drug addiction. The neural basis of such drug-biased choice is not well-understood, particularly in individuals with protracted drug abstinence who cannot ethically participate in studies that offer drug-using opportunities.

Methods—We developed an fMRI drug-choice task to examine the choice for viewing drug-related images, rather than for actually consuming a drug. Actively-using (N=18) and abstaining (N=19) individuals with a history of cocaine use disorder (CUD: dependence or abuse), and matched healthy controls (N=26), participated.

Results—The individuals with CUD, especially those actively using cocaine outside the laboratory, made more choices than controls to view images depicting cocaine [especially when directly compared against images depicting an alternative appetitive reinforcer (food)]. The fMRI data revealed that, in individuals with CUD, the act of making drug-related choices engaged brain regions implicated in choice difficulty or ambivalence (i.e., dorsal anterior cingulate cortex, which was higher in all CUD individuals than controls). Drug-related choices in CUD also engaged brain regions implicated in reward (e.g., midbrain/ventral tegmental area, which was most activated in active users, although this region was not hypothesized *a priori*).

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Disclosure/Conflict of Interest

The authors report no biomedical financial interests or potential conflicts of interest.

Conclusions—These results help clarify the neural mechanisms underlying drug-biased choice in human addiction, which, beyond those involved in value assignment or reward, may critically involve those that contribute to resolving difficult decisions. Future studies can validate these behavioral and neural abnormalities as markers of drug-seeking and relapse in treatment contexts.

Keywords

Drug addiction; abstinence; fMRI; value; choice behavior; decision-making

INTRODUCTION

Decision-making biases are central to neuropsychiatric disorders such as addiction (1), which is marked by the pursuit of drug reinforcement at the expense of alternative reinforcement (2). This phenomenon is well-captured by the drug-choice procedure (3), where an individual selects between a drug reinforcer and a non-drug reinforcer (e.g., money or chocolate) (4–6). The primary outcomes of this procedure, including the number or percentage of drug choices relative to the alternative, are important markers of addiction severity in both humans and non-human animals (6, 7), and have been linked to drug-mediated changes in dopaminergic functioning (8, 9).

However, ethical considerations typically prohibit administering drugs to human drug users who are abstaining or seeking treatment (10); instead, tasks that assess choice antecedents, such as drug cue-reactivity or attention bias (11–14), are used. Such tasks do not capture the crucial *choice* aspects of drug administration studies. Compared with cue-reactivity, drug-choice could be driven by distinct neural substrates (e.g., those involved in computing and comparing values of the options under consideration) (15, 16). Moreover, active and abstaining users may differ in drug-related choice and underlying circuitry, stemming from treatment motivation (17), recent drug use that may prime further use (5), the expectation of imminent drug use (18), or abstinence (19–21).

To measure the neural mechanisms of drug-choice in currently-using and abstaining individuals with cocaine use disorder (CUD), we developed an fMRI task that investigates value-based decision-making for drug *images*, rather than actual drugs. Neural responses during real and hypothetical choices share many common features (22), suggesting that choices for images will engage comparable circuitry to choices for actual drugs. The current fMRI task design was inspired by neuroeconomics (23), which aims to uncover the neurobiological mechanisms of decision-making in health (24) and neuropsychiatric diseases including addiction (25–27).

The following hypotheses guided our research. Individuals with CUD (A) will make more cocaine-image choices than healthy controls, and in doing so (B) will show greater engagement in brain regions involved with value computation [i.e., orbitofrontal cortex (OFC)/ventromedial prefrontal cortex (vmPFC) (Brodmann Area, BA, 10, 11)] (15, 28, 29) and cognitive control during decision-making [i.e., dorsal anterior cingulate cortex (dACC) (BA 32) and dorsolateral PFC (DLPFC) (BA 9, 46)] (16, 30); previously, healthy controls showed value-modulated activations in these same regions during a similar task (23). For both (A) and (B), a primary interest was in directly comparing choices and activations for

cocaine images versus food images, another appetitive reinforcer. In our prior work, a similar cocaine>pleasant 'preference difference' was correlated with shorter current abstinence (31), more frequent drug use (32), and lower dopamine D2-type receptor availability in the OFC (33). We further hypothesized that (C) these behavioral and neural effects will be accentuated in active CUD participants, reflecting context dependency in valuation (34). In testing these hypotheses, we inspected for group differences in the overall value of the images (i.e., are there group differences in mean choice or brain activation?), and (independently) in the process of computing such value (i.e., are there group differences with respect to which behavioral variables or brain activations correlate with choice trial-by-trial?).

METHODS

Participants

Thirty-seven non-treatment-seeking individuals with CUD and 26 matched healthy controls participated (Table 1). All participants provided written informed consent in accordance with the local Institutional Review Board. History of CUD was determined by a comprehensive diagnostic interview based on DSM-IV criteria (see Supplement), which was also used to partition CUD into active users (i.e., use of cocaine within the past month; median 3 days abstinent; N=18) and abstainers (i.e., no use of cocaine within the past month; median 365 days abstinent; N=19).

Exclusion criteria were: (A) history of head trauma or loss of consciousness (> 30 min) or other neurological disease of central origin (including seizures); (B) abnormal vital signs at time of screening; (C) history of major medical conditions, encompassing cardiovascular (including high blood pressure), endocrinological (including metabolic), oncological, or autoimmune diseases; (D) history of major psychiatric disorder [for CUD, exceptions to this criterion included other substance use disorders and/or highly prevalent comorbidities, such as post-traumatic stress disorder (though not eating disorders); and for controls, the only exception was nicotine dependence]; (E) psychotropic or cardiovascular medication use within six months; (F) pregnancy (urine test); (G) contraindications to MRI; (H) except for cocaine in CUD participants, positive urine screens for psychoactive drugs or their metabolites (i.e., cocaine, amphetamine or methamphetamine, phencyclidine, benzodiazepines, cannabis, opiates, barbiturates, and inhalants); and (I) current evidence of intoxication from alcohol determined by breathalyzer, or any illicit drug determined by trained research staff.

fMRI Drug-Choice Task

Task Design—The fMRI drug-choice task closely paralleled, in concept and structure, a design used in previous neuroeconomic research (23). The task included images from the International Affective Picture System (IAPS) (35), supplemented with freely-available online images. These images depicted palatable food images (e.g., hamburger), threat images (e.g., pointed gun), and cocaine images (25 images per category, each repeated 3x), with all categories matched on size and ratio of human to non-human content. The cocaine images depicted cocaine and individuals using cocaine (half relevant to powder cocaine, the

other half relevant to crack cocaine). The food images provided an appetitive, high-value comparison category, such that cocaine-choice was not assessed in isolation of other rewarding stimuli (2, 3, 7). The threat images provided a salient, low-value control image category.

At the beginning of the task, participants were shown a neutral IAPS image (an unadorned brown wicker basket). Then, during each trial, participants were asked to choose whether they would prefer to view this reference image or the food, threat, or cocaine image presented on the current trial (Figure 1); all choices therefore were made relative to this neutral reference (wicker basket) image. Choice was indicated using a four-point scale: *Strong No*, *No*, *Yes*, and *Strong Yes*, enabling the measurement of choice and the *strength* of the choice/preference simultaneously (36). Participants were instructed that both *Strong No* and *No* meant they chose the reference image, whereas *Yes* and *Strong Yes* meant they chose the current trial image, which they potentially would have the opportunity to view at the conclusion of the experiment. That is, following standard procedures from behavioral economics, to ensure that each decision was perceived as independent and important, and to instill a choice consequence applicable to viewing images so that the current measure reflects more than a simple self-report of preference, participants were told that one of their chosen images (i.e., one responded to with *Yes* or *Strong Yes*) would be randomly selected to take home with them as an 8.5×11 picture keepsake (and indeed such a picture was given to all participants) (for additional discussion on task design, see the Supplement).

On each trial, participants had a maximum of 3s to respond; trials of non-response, which did not differ among the groups across all task conditions (one-way ANOVA: p=0.20), were excluded. Once a decision was made, the picture was replaced by a fixation cross of variable duration (i.e., distributed uniformly between 4s and 9s, plus whatever time remained from the 3s decision phase) to reset the blood-oxygenation-level dependent (BOLD) signal. The task contained 5 runs of 45 pseudorandomly-presented trials (with the constraint that the same image could not appear more than once per run). The task spanned approximately 45 minutes, and it was completed during a two-hour scanning session (which incorporated additional MRI procedures that will be reported elsewhere). Participants arrived at the laboratory typically at 9:00 AM, and they did not eat before scanning (typically around 11:00 AM).

MRI Data Acquisition—Scanning was conducted on a Siemens 3T MAGNETOM Skyra (Siemens, Erlangen, Germany), using a 32-channel head coil. The BOLD-fMRI responses were measured as a function of time using a T2*-weighted single shot multi-band accelerated gradient-echo EPI sequence [TE/TR=35/1000ms, 2.1mm isotropic resolution, no gap, 70 axial slices for whole brain (14.7cm) coverage, FOV 206×181mm, matrix size 96×84, 60°-flip angle (approximately Ernst angle), multi-band factor of 7, blipped CAIPIRINHA phase-encoding shift=FOV/3, ~2 kHz/Pixel bandwidth with ramp sampling, echo spacing 0.68ms, and echo train length 57.1ms]. T1- weighted anatomical images were acquired using a 3D MPRAGE sequence [FOV 256×256×179mm^3, 0.8mm isotropic resolution, TR/TE/TI=2400/2.07/1000ms, flip angle 8° with binomial (1, −1) fat saturation, bandwidth 240 Hz/pixel, echo spacing 7.6ms, and in-plane acceleration (GRAPPA) factor of 2, with a total acquisition time of ~7min].

MRI Data Processing—The fMRI images were reconstructed (including multi-band, simultaneous multi-slice, image unaliasing) in the Siemens image calculation environment, incorporating navigator-based phase correction, which produces minimal ghost artifacts. Motion correction, spatial normalization (voxel size: $2\times2\times2mm^3$) to the standard stereotactic space of MNI, and smoothing (FWHM=8mm Gaussian kernel) were conducted using Statistical Parametric Mapping (SPM8) (Wellcome Trust Centre for Neuroimaging, London, UK).

Statistical Analyses

Behavior

Trial-by-Trial Choice Preference: Model 1: To determine the behavioral correlates of value processing as a function of group, we conducted trial-by-trial analyses (with trials nested within participants) on choice preference (i.e., *Strong No* to *Strong Yes*, a continuous measure that was linearly coded 1–4). This type of measure is an established index of value in neuroeconomics research (23). Our first model (Model 1) was a full factorial linear mixed model, with these predictors: Diagnosis (active CUD, abstinent CUD, control; two dummy-coded variables at the subject level), Image (food, threat, cocaine; two dummy-coded variables at the individual trial level), and trial-by-trial reaction time [RT (continuous), which can serve as a measure of choice indecision (37)].

Trial-by-Trial Choice Preference: Model 2: Our second model (Model 2) tested whether craving might also modulate choice preference in CUD, potentially biasing choice toward cocaine images. Thus, here we replaced RT with baseline craving at the subject level (‘Crave’), and we excluded healthy controls (who did not have Crave data). Model 2 was also a full factorial linear mixed model, with these predictors: Diagnosis (active CUD, abstinent CUD; one dummy-coded variable at the subject level), Image (food, threat, cocaine; two dummy-coded variables at the individual trial level), and Crave.

Both Models also covaried for depression and cigarette smoking history, which differed among the groups (Table 1). Note that task-induced craving, operationalized as the difference in craving before and after the task, did not differ between active and abstinent CUD (Table 1). This null effect reduces the possibility that group differences in behavior and neural function are attributable to simple cue-reactivity, with the results instead presumably reflecting abnormal valuation/choice in CUD. In the Supplement, we present the results of two additional models (Models 3 and 4), which used the same analytical approach as Models 1 and 2, but with choice certainty as the dependent variable (i.e., the parabolic ordering of the choice preference data); choice certainty is another construct that potentially may drive brain activations during choice (independently of value).

Subject-Level Cocaine>Food Choice Preference Difference: To test the ‘preference difference’ between cocaine and food images among the groups (i.e., whether the groups differ in the overall value ascribed to cocaine versus food images), we conducted a one-way ANCOVA on the averaged responses across all trials for cocaine minus the averaged responses across all trials for food (i.e., cocaine>food contrast); this ANCOVA controlled for depression and cigarette smoking history.

BOLD-fMRI Analyses—For all fMRI analyses, we modeled the fMRI BOLD response trial-by-trial from the beginning of image onset until a choice was registered (max 3s) (i.e., a hemodynamic response function was convolved with a boxcar function for the "decision" phase of the trial; see Figure 1). For statistical inference, we specified a height threshold (voxel-wise significance) of $p<0.001$ uncorrected (38), which corresponded to T>3.23. Given our imaging parameters and this height threshold, 56 contiguous voxels were needed to achieve a conservative $p<0.01$ cluster-corrected threshold (AlphaSim), which was our criterion for significance. All models controlled for depression and cigarette smoking. Post-hoc tests were used to clarify omnibus effects.

Average Activation Group Differences: Full Model: To test for group differences in mean preference brain activation when making a choice, we computed a first GLM (GLM 1) containing the following regressors of interest, for each participant: (A) an indicator for a food-image trial, (B) an indicator for a threat-image trial, (C) an indicator for a cocaine-image trial, and (D) an indicator for a non-response trial. Additionally, six motion parameters (3° rotation, 3mm translation) were included as nuisance regressors. For the betas of the first-level regressors, we estimated a second-level 3 (Diagnosis: active CUD, abstinent CUD, control) × 3 (Image: food, threat, cocaine) flexible factorial model in SPM8. In this second-level analysis, all three behavioral choice preference ratings were included as covariates, both to minimize motor effects but also to examine correlations of the fMRI signal with value-based choice.

Average Activation Group Differences: Cocaine>Food: Using this same GLM 1, we also formally tested for group differences on activations to cocaine relative to food images, which is consistent with the direct comparison between drugs and alternative reinforcers that guided our study. We subtracted the food betas from the cocaine betas, creating the first-level cocaine>food contrast, and then used ANOVA in SPM8 to compare the groups on this contrast; cocaine>food preference ratings were also included in the model. Although one could anticipate that effects for this cocaine>food contrast should be detectable using the full model above, differences between these analyses indeed can occur (see Supplement).

Trial-by-Trial Parametric Modulation by Choice Preference: A second GLM (GLM 2) examined the computation of value, reflected by the *correlation* between brain activation and choice preference (value). We created a first-level parametric modulator contrast correlating the trial-by- trial fMRI response at the decision phase with the trial-by-trial choice rating (responses: 1–4). Comparisons between groups in the linear betas ask if the computation of value differs in a particular brain region (i.e., whether one group has a higher correlation between brain activation and behavior than another). Note that we could not conduct parametric modulators separately for each image type because there was low choice variability within image categories, especially for threat images (all participants) and cocaine images (in controls and abstinent CUD), leading to problems of model fit. At the second level, this parametric modulator contrast was analyzed using ANOVA, examining trial-by-trial brain-behavior correlations across all participants and between groups. The same six motion parameters were controlled as nuissance regressors.

Taken together, in GLM 1, we parsed trials based on picture category and measured activation differences between the groups, particularly on trials in which decisions were made about cocaine stimuli versus trials in which decisions were made about food stimuli, irrespective of the participant's choice on those trials. In GLM 2, we modeled the data instead according to choice, but irrespective of picture type, and examined the linear relationship between this choice and BOLD activity as a representation of the neural computation of value.

RESULTS

Behavior

Trial-by-Trial Choice Preference: Model 1 (controls included)—There were main effects of Diagnosis (both CUD groups > controls), Image (food and cocaine > threat), and RT (longer RT associated with greater overall choice preferences in all participants, perhaps reflecting an attention bias) (Table 2). All 2-way interactions were significant. The Diagnosis × Image interaction most directly pertains to Hypothesis A. It was explained by higher choice preference ratings, specifically for cocaine images, in active CUD [$\chi^2(1)=38.32$, $p<0.001$] but not abstinent CUD ($p>0.15$), as compared with controls (reference group) (Figure 2A). The three-way interaction was not significant.

Trial-by-Trial Choice Preference: Model 2 (controls excluded)—When we replaced RT with Crave and removed controls, the Diagnosis × Image interaction was still significant (Table 2). There was also a significant Image × Crave interaction: across all CUD, craving was positively associated with choice preference only during cocaine trials ($\beta=0.34$, $z=4.33$, $p<0.001$; for all other image conditions, $p>0.26$) (Figure 2B).

Subject-Level Cocaine>Food Choice Preference Difference—Choice preference for cocaine versus food images differed among the three groups [$F(2,58)=11.06$, $p<0.001$] (Figure 2C), with active CUD showing greater preferences than the other two groups (pairwise comparisons: $p<0.003$).

BOLD-fMRI Analyses

Average Activation Group Differences: Full Model—Analysis of the full Diagnosis × Image model revealed no main effects of Image, no Image × Diagnosis interactions, and no correlations with choice preference at the corrected threshold. However, there were multiple Diagnosis main effects (Supplement).

Average Activation Group Differences: Cocaine>Food—Analysis of the first-level cocaine>food contrast showed that both CUD groups had higher whole-brain activations when making decisions about cocaine (versus food) images than controls in the dACC (BA 24, 32) extending to the supplementary motor area (SMA) (BA 8, 6) (Figure 3A–B), and in the midbrain [ventral tegmental area (VTA)] (Table 3). Further analyses showed that the dACC and SMA activations reflected a Diagnosis effects (i.e., driven by all CUD differing from controls), whereas the midbrain activation reflected an active CUD effect (i.e., driven

by active CUD differing from the other two groups) (Figure 3A–C). Abstinent CUD did not show unique activations.

As part of the same SPM model, there was a whole-brain negative correlation across all participants between cocaine>food activations in the OFC and subject-level cocaine>food choice preference ratings (which were included in the SPM model as a covariate of interest). That is, the greater the choice preference for cocaine relative to food images, the lower were the OFC activations during cocaine relative to food trials (Figure 3D) (Table 3). A similar negative correlation emerged in the right postcentral gyrus/motor cortex (Peak T=4.08, 260 voxels), likely attributable to button-pressing demands (and thus not discussed further).

Trial-by-Trial Parametric Modulation by Choice Preference: Linear Contrast— Across all participants and image types, trial-by-trial choice preference ratings were negatively correlated with BOLD-fMRI activity in the midcingulate cortex (BA 23) (Figure 4A) and temporal cortex (Figure 4B). These trial-by-trial (negative) correlations between midcingulate activity and choice could have been marking aversion (low value) associated with the respective image (39). Additional effects in the left (positive correlation) and right (negative correlation) motor cortex (Peak T>12.19, voxels>1028) were likely attributable to button-pressing demands (and therefore not discussed further). There were no group differences.

DISCUSSION

Relative to abstinent CUD and controls, active CUD appeared to have the greatest decision difficulty during cocaine-related choice: their cocaine choice preference ratings neared neutral (while other groups showed aversion), and their certainty ratings (Supplement) indicated ambivalence (while the other groups showed conviction). Despite this ambivalence, active CUD had the highest ‘preference difference’ between cocaine images and food images, consistent with Hypotheses A and C. This heightened cocaine>food choice is consistent with prior work linking drug-related choice to actual drug use (4, 6, 26, 31, 32). Although it may appear surprising that food-choice ratings eclipsed cocaine-choice ratings even in CUD, this finding is largely consistent with previous research (31, 32, 40), and it confirms that these food images provided a palatable contrast to those of cocaine.

Consistent with Hypothesis B, individuals with CUD had higher activation to cocaine relative to food images in the dACC, a region hypothesized *a priori* as contributing to cognitive control during decision-making. In a neuroeconomic context, studies have reported dACC engagement as reflecting choice difficulty (41), salience (36), the comparison of value between options (42), or the selection of the best long-term option versus the most immediately valuable option (43). These interpretations are bolstered by a region of interest (ROI) negative correlation in the current study between dACC activations and behavioral choice certainty (computed as the parabolic ordering of the choice options) (see Supplement): the more the dACC activations, the less participants responded with *Strong Yes*/*Strong No* when making decisions about cocaine relative to food images. Therefore, the act of deciding whether to view drug-related images may have elicited ambivalence in CUD. Current dACC activations are also consistent with research reporting dACC/dorsomedial

PFC activations during decisions to pay for real alcohol (44) or cannabis (45). Similar effects in the SMA (a cluster adjacent to the dACC) should be interpreted more cautiously because this region, although reaching corrected significance, was not hypothesized *a priori*.

Results also revealed a whole-brain correlation between cocaine>food OFC activations and lower respective choice preference. The OFC plays a central role in computing and mediating the hedonic experience associated with choosing or receiving rewards (29), perhaps encoding the moment-to-moment value of task-relevant stimuli, choices, or actions based on internal states (46). In chronic drug users, the OFC is engaged by (12), and has been linked to choosing (33), drug-associated stimuli. Because the negative correlation with choice in our study was observed in a somewhat more lateral OFC subregion, such an activation could be marking an aversive response (47): the more the aversion marked by OFC, the lower the choice.

If the OFC was a potential mechanism of lower drug-related choice, then the midbrain/VTA could have been a potential mechanism for enhanced drug-related choice. Such activation, which was highest in active CUD, positively correlated with cocaine choice preference in an ROI analysis (Supplement); although a correlation with cocaine>food choice preference would have provided more definitive evidence of association, a correlation with underived cocaine choice is informative nonetheless. The midbrain plays a key role in mediating the behavioral reactivity to motivationally salient stimuli through phasic and tonic dopamine release (48). A recent study reported that change in midbrain activation was associated with change in preference for a novel drink in healthy individuals (49). In CUD, midbrain activations during reward tasks have correlated with behavioral drug-related choice (19) and prospective cocaine abstinence (21). Again, however, the midbrain, despite reaching corrected significance, was not hypothesized *a priori* and should be interpreted with some caution.

This study has several limitations. First, choice was executed for abstract reinforcers, which could have resulted in lower drug-related choice or blunted brain activations in CUD (50). Nevertheless, significant effects were still observed. Second, this task did not explicitly disambiguate decision-making from cue-reactivity. Instead, our goal was to examine a more specific decision process (value computation), which integrates many lower-level processes, such as attention and memory; therefore, such constituent processes were not explicitly manipulated during the experiment. Future research could consider contrasting an active choice condition (i.e., where the choice reflects one's strength of preference, as done here) with a "passive" choice condition (e.g., where participants have to execute a choice preference predetermined by the computer). Even so, these processes are highly interrelated and not easily disentangled: neuroeconomics research has shown that attention, which is highly relevant to cue-reactivity, temporally precedes choice (51); and some of the same regions engaged during choice are also engaged during cue-reactivity (e.g., ACC) (12, 52). Third, cocaine has appetite suppressing effects that could have modulated the value of food. However, CUD were not intoxicated during scanning, and they reported high choice preferences for food images overall. Moreover, the study groups did not differ in ratings of hunger prior to scanning (Table 1) or in weight/body mass index (in whom these data were available; Supplement). Fourth, the low drug-related choice in abstinent CUD may have

partially reflected demand characteristics. However, experimenters emphasized that there were no right/wrong answers, and that responses would remain confidential. Finally, approximately half of the active CUD had positive cocaine urine screens. However, the means of cocaine>food choice preference and dACC activation were largely similar in active CUD testing positive (preference: −0.4±1.0; dACC: 1.2±1.9) versus negative (preference: −0.7±1.0; dACC: 1.3±2.5) for cocaine in urine.

In conclusion, individuals with CUD differed from controls in mean choice and brain activation when making decisions about whether to view cocaine (relative to food) images. These decisions, however, were non-trivial; beyond eliciting activations in classical dopaminergic reward regions anticipated from non-human animal work (53), cognitive control regions were prominently involved. In contrast, individuals with CUD did not differ from controls in the mechanisms underlying the computation of value (i.e., in the trial-by-trial correlations between choice and fMRI-BOLD activations). Taken together, the process of valuation in CUD appears to be largely intact, but the content of this valuation (i.e., what is valued) appears to be biased toward drug-related stimuli. Insofar as choice behavior approximates DSM-IV and DSM-5 diagnostic criteria that largely emphasize drug-seeking behavior (e.g., using more drug than intended, inability to curb use, etc.), this fMRI-choice framework examining value provides a potentially useful complement to traditional paradigms of cue exposure (11–14).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by grants from the National Institute on Drug Abuse (K01DA037452 and R21DA40046 to SJM; F32DA039648 to ABK; F32DA033088 to MAP; T32DA007135-31 to RPC and KB; and 1R01DA041528, R01DA023579, and R21DA034954 to RZG) and the National Institute of Mental Health (R01MH090134 to NAK). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Additional support came from Rubicon 446-14-015 (NW0, The Netherlands) (to AZ) and from the Icahn School of Medicine at Mount Sinai (seed funds to NAK and RZG; a joint pilot grant from the Departments of Preventive Medicine and Social Work Services to KB). We thank Antonio Rangel for early consultation on task design. We also thank Federico d'Oleire Uquillas, Kristin E. Schneider, Thomas Maloney, Pias Malaker, and Nia Williams for help with data collection.

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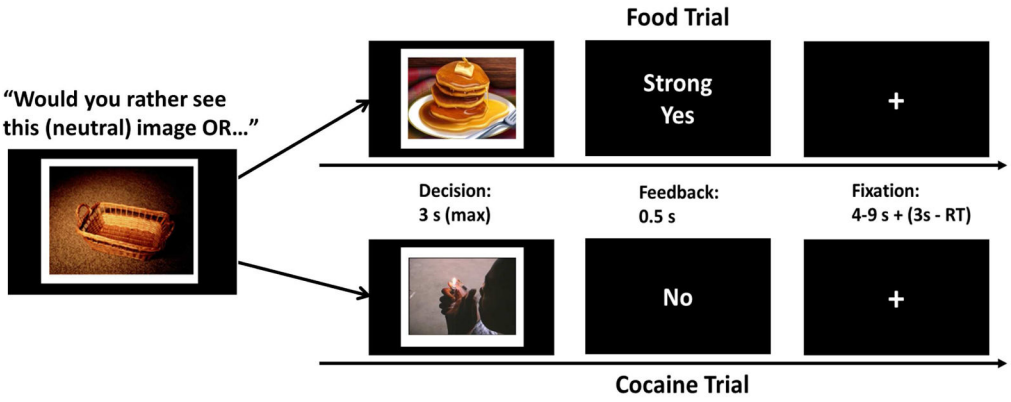

Figure 1.

Task schematic and individual data on cocaine versus food choices. (A) On each trial, participants viewed an image belonging to one of three global categories: food, threat, or cocaine (food and cocaine are depicted here) and made a choice (with strength of preference associated with that choice: *Strong No*, *No*, *Yes*, *Strong Yes*, coded 1–4) about whether they prefer to view the current image over a neutral image (wicker basket). Participants chose while only viewing the food, cocaine, or threat image – that is, the basket did not appear on the screen in each trial; a constant neutral stimulus could have artificially inflated the appeal of the alternative image, where the resulting behavior may not have provided an accurate depiction of an individual's absolute preference.

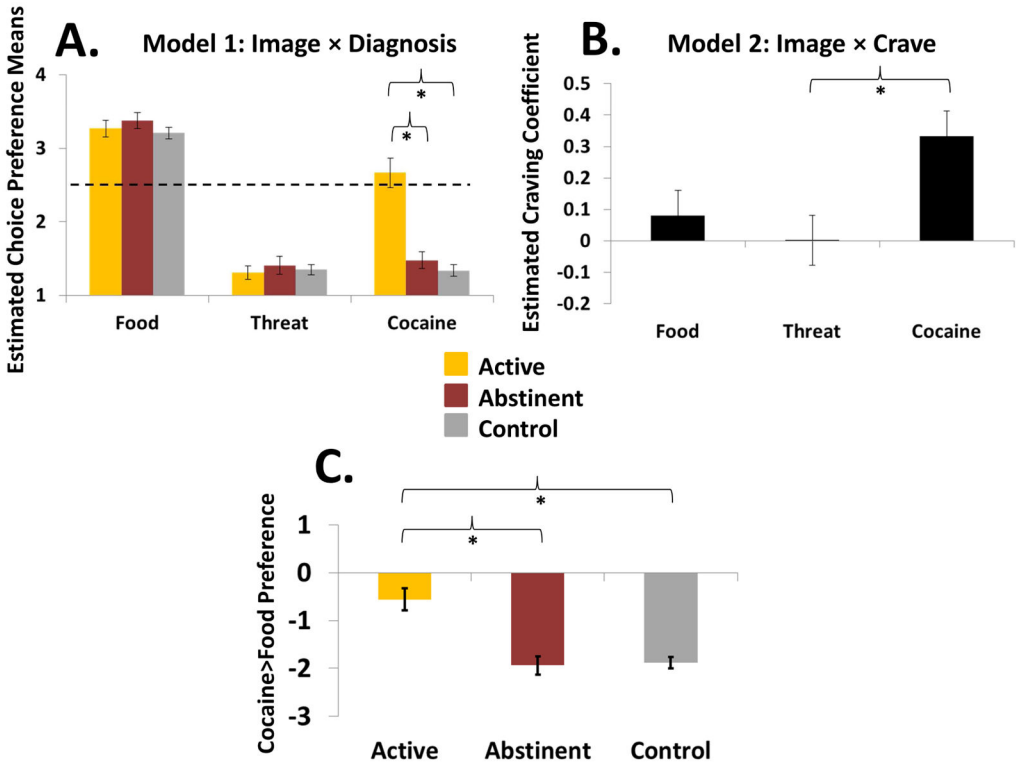

Figure 2.

Behavioral data. (A–B) Trial-by-trial analyses, spotlighting the hypothesized interaction between Image and Diagnosis, and the interaction between Image and baseline craving ('Crave'), respectively (see Table 2 for complete information). (A) Individuals with active cocaine use disorder (CUD) had greater choice preference than the other groups specifically for cocaine images. The y-axis has values 1 (*Strong No*), 2 (*No*), 3, (*Yes*), and 4 (*Strong Yes*). The dashed line in (A) reflects decision indifference between the respective picture category and the neutral wicker basket, with values above signifying preference for the trial image and values below signifying preference for the neutral reference image. (B) Across all CUD, craving was more positively associated with choice preference during cocaine trials than during other trials. (C) Subject-level data, showing that across the entire task individuals with active CUD had greater (less negative) choice preference ratings for cocaine relative to food, and thus appeared to have the greatest ambivalence about their cocaine-related choices (with corroborating evidence when examining cocaine>food choice certainty scores; see Supplement). Asterisks mark significant group differences at $p<0.05$.

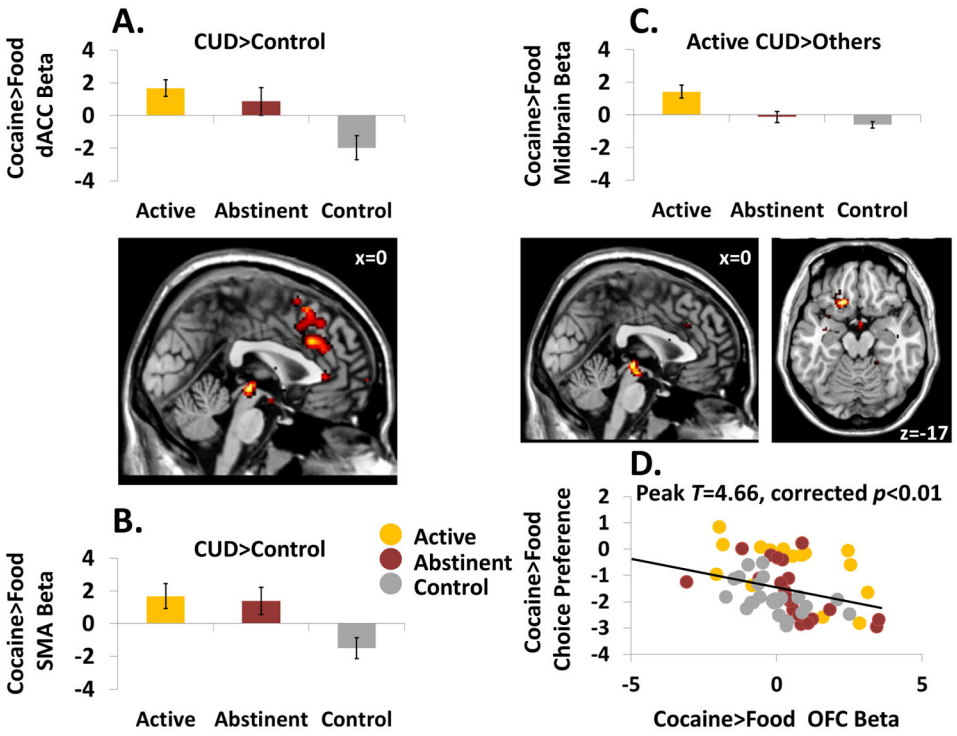

Figure 3.

Whole-brain group differences during cocaine relative to food (cocaine>food) decisions. Individuals with cocaine use disorder (CUD) displayed higher cocaine>food activation than controls in the (A) dorsal anterior cingulate cortex (dACC) extending to the (B) supplementary motor area (SMA). Individuals with active CUD, relative to abstinent CUD and controls, displayed greater cocaine>food activation in the (C) midbrain/ventral tegmental area. In the same model, across all participants, (D) greater cocaine>food activation in the orbitofrontal cortex (OFC) negatively correlated with behavioral cocaine>food choice preference. For display purposes, activations are thresholded at $2.75 \leq T \leq 4.5$.

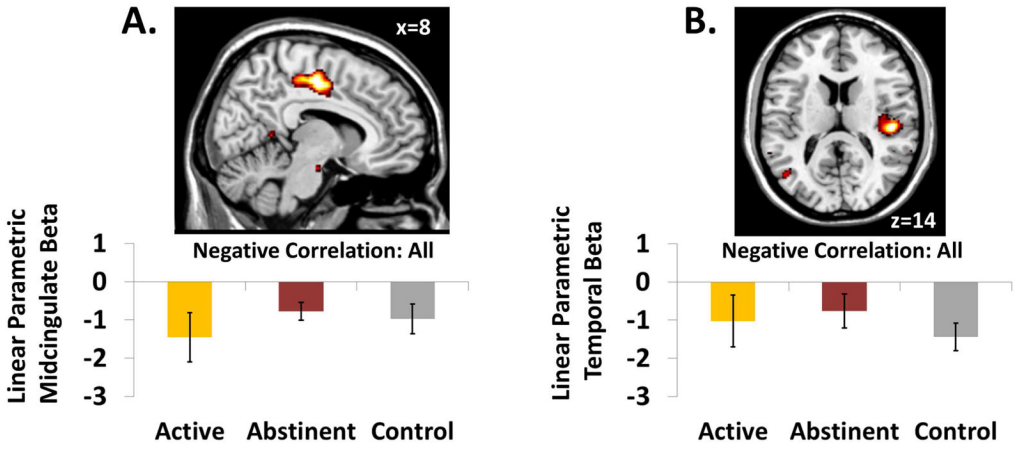

Figure 4.

Trial-by-trial parametric modulation by choice preference (linear ordering of preferences). There was a negative trial-by-trial correlation with choice preference across all task conditions in the (A) midcingulate and (B) temporal cortex, effects that did not differ by group but rather emerged in all participants. For display purposes, activations are thresholded at $2.75 \leq T \leq 4.5$.

Biol Psychiatry Cogn Neurosci Neuroimaging. Author manuscript; available in PMC 2019 May 01.

Table 1

Demographics and cocaine use of all study participants.

	Active Cocaine (N=18)	Abstinent Cocaine (N=19)	Healthy Controls (N=26)	Between-Group Test[D]
Gender: Male/Female	11/7	17/2	18/8	χ^2=4.10
Race: African-American/Caucasian/Other[E]	15/1/2	12/3/4	19/3/3	χ^2=2.21
Age (years)	46.9 ± 8.7	45.2 ± 7.9	43.1 ± 7.2	*F*=1.28
Education (years)	13.2 ± 2.0	13.1 ± 1.5	14.3 ± 2.1	*F*=2.87
IQ: WASI – Matrix Reasoning Scale (54)	9.6 ± 3.4	10.4 ± 2.2	10.8 ± 2.3	*F*=1.19
Depression: Beck Depression Inventory II (55)	6.7 ± 7.1[C]	9.0 ± 8.9[C]	2.5 ± 3.1[A,B]	*F*=5.92*
Smoking status (smoker/nonsmoker)[F]	16/2[C]	12/7[C]	4/22[A,B]	χ^2=24.66*
Pre-MRI hunger ratings (1–7)	3.6 ± 2.3	3.4 ± 2.1	3.2 ± 1.9	*F*=0.17
Change in cocaine craving (post-MRI minus pre-MRI: 1–7)	0.4 ± 2.1	−0.1 ± 0.8	--	*t*=0.95
History of substance- or psychiatric comorbidity (no/yes)	8/10	4/15	--	χ^2=2.31
Cocaine urine status: positive/negative	10/8	0/19	--	χ^2=14.47*
Cocaine age of onset (years)	22.9 ± 6.7	24.3 ± 6.2	--	*z*=−0.76
Cocaine duration of use (years)	21.4 ± 9.5	16.4 ± 8.2	--	*z*=−1.76
Cocaine past month use: days/week	4.0 ± 1.9	0.0 ± 0.0	--	*z*=−5.59*
Cocaine past month use: $/use[D]	101.7 ± 98.0	0.0 ± 0.0	--	*z*=−4.42*
Cocaine current abstinence: days (min – max, median)[D]	1–14, 3	90–5840, 365	--	*z*=−5.07*
Cocaine heaviest use: days/week	6.2 ± 1.2	5.8 ± 1.7	--	*z*=−0.55
Cocaine heaviest use: $/use[D]	187.2 ± 164.4	127.0 ± 68.6	--	*z*=−0.58
Cocaine longest abstinence: days (min – max, median)[D]	60–7300, 730	120–5840, 1275	--	*z*=−0.55
Withdrawal symptoms: CSSA (0–126)	18.4 ± 10.5	12.7 ± 15.2	--	*t*=1.33
Severity of Dependence Scale (0–15)	4.2 ± 3.6	6.4 ± 6.3	--	*t*=1.31
Cocaine Craving Questionnaire (0–45)	21.6 ± 10.1	6.9 ± 9.5	--	*t*=4.56*

Note. Values are frequencies or means ± standard deviation;

*$p<0.05$; for 3-group tests,

[A]mean value differs from that of active cocaine participants,

[B] mean value differs from that of abstinent cocaine participants,

[C] mean value differs from that of controls;

[D] the collection of differences between active and abstinent CUD on drug use variables confirms that these groups can be defined by current addiction severity, rather than overall addiction severity;

[E] missing data in one or more participants, but never more than 20% missing;

[F] cigarette smoking on study day was not restricted to avoid possible confounding effects of cigarette withdrawal on the fMRI results.

Table 2

Trial-by-trial behavioral results for choice preference.

Regressor	χ^2	df	P-value	Source of Effect
Model 1: Choice Preference/Controls Included (4-Point Continuous Scale)				
Diagnosis	20.57	2	<0.0001*	Both CUD groups > controls (ref)
Image	402.16	2	<0.0001*	Food and cocaine > threat (ref)
Reaction time (RT)	8.39	1	0.0038*	Longer RT, greater choice preference
Diagnosis × Image	33.77	4	<0.0001*	Active CUD (but not abstinent CUD) > controls (ref) during cocaine trials
Diagnosis × RT	10.13	2	0.0063*	Longer RT, greater choice preference except in active CUD
Image × RT	10.57	2	0.0051*	Longer RT, greater choice preference except during food trials
Diagnosis × Image × RT	1.34	4	0.8540	NA
Model 2: Choice Preference/Controls Excluded (4-Point Continuous Scale)				
Diagnosis	0.49	1	0.4855	NA
Image	167.66	2	<0.0001*	Food and cocaine > threat (ref)
Crave	0.31	1	0.5771	NA
Diagnosis × Image	8.58	2	0.0137*	Active CUD > abstinent CUD (ref) during cocaine trials
Diagnosis × Crave	2.93	1	0.0870	NA
Image × Crave	13.09	2	0.0014*	Higher craving, greater choice preference only during cocaine trials
Diagnosis × Image × Crave	0.01	2	0.9932	NA

Note. Models 1 and 2 are linear mixed models (with trials nested within participants); depression and cigarette smoking were controlled in all analyses; continuous variables were standardized prior to analysis; model intercepts were: −0.734 (Model 1) and −0.639 (Model 2); asterisks denote a significant interaction at $p<0.05$. NA = not applicable, ref = reference group or image in the analysis, Crave = baseline craving at the subject level.

Table 3

Whole-brain results on the cocaine>food contrast from the fMRI simulated drug-choice task.

Region	Contrast	BA	Side	Voxels	Peak T	x	y	z
Effects of Diagnosis								
ACC	All CUD>Control	24,32	L	146	4.14	−2	26	31
						−2	37	25
SMA	All CUD>Control	8,6	L	58	3.83	0	22	54
						−6	16	44
						0	16	63
Midbrain/VTA	All CUD>Control	--	M	69	4.48	2	−22	−5
Midbrain/VTA	Active CUD>Others	--	M	65	4.39	0	−22	−5
Correlation with Preference: All Participants								
OFC	Neg Corr	11	L	58	4.66	−15	24	−17

Note. All results were significant at $p<0.01$ cluster-corrected (56 contiguous voxels), with a search threshold (voxel-wise significance) of $p<0.001$ uncorrected (T>3.23). Effect of diagnosis refers to group differences between individuals with cocaine use disorder (CUD) who are active users, individuals with CUD who are abstinent, and healthy controls; correlation with preference refers to cocaine>food behavioral choice preference. Neg corr = negative correlation, BA = Brodmann Area, ACC = anterior cingulate cortex, SMA = supplementary motor area, VTA = ventral tegmental area, OFC = orbitofrontal cortex.