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Hypothalamic response to cocaine cues and cocaine addiction severity

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Abstract

The dopaminergic motive system is compromised in cocaine addiction. Abundant research has examined the roles of the dopaminergic midbrain and ventral striatum (VS) in cue-induced craving and habitual drug consumption. Interconnected with the dopaminergic circuits, the hypothalamus is widely implicated in motivated behavior, including food and drug seeking. However, very few studies have investigated how the hypothalamus responds to drug cues and whether hypothalamic responses are related to clinical features such as craving and addiction severity. Here, in 23 cocaine-dependent individuals (CD) exposed to cocaine vs neutral cues during functional magnetic resonance imaging (fMRI), we examined regional responses using established routines. At a corrected threshold, CD demonstrated increased activation to cocaine vs neutral cues in bilateral visual cortex, inferior parietal and middle frontal gyri, and the hypothalamus. The extent of hypothalamus but not other regional response was correlated with craving and cocaine addiction severity, each as assessed by the Cocaine Craving Questionnaire (CCQ) and Cocaine Selective Severity Assessment (CSSA). In contrast, subjective “acute” craving as elicited by cocaine cues during fMRI involved deactivation of bilateral orbitofrontal cortex (OFC) and angular gyri (AG), and the OFC and AG responses were not related to CCQ or CSSA score. These findings distinguished tonic craving as a critical factor in capturing cocaine addiction severity and substantiated a role of the hypothalamus in motivational dysfunction in cocaine addiction.

Keywords

cocaine addiction; fMRI; hypothalamus

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DISCLOSURE/CONFLICT OF INTEREST

We declare no financial interests in the current work.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

1 | INTRODUCTION

Individuals with drug addiction are characterized by motivation deficits and underresponsiveness to natural reinforcers.¹ The dopaminergic (DA) pathways process reinforcing stimuli and play a critical role in motivated behavior.² Dopamine establishes the motivational value of extrinsic stimuli and links incentives to action through conditioning and instrumental learning.² Repeated administration of psychostimulants alters DA signaling and motivational behaviors.³ Substantial research has focused on the role of the DA motive system in conditioned responses to drug cues.^{4,5} In humans, drug-conditioned cues trigger craving and, along with altered saliency attribution and impulse control, precipitate relapse to drug use.^{6–10}

The hypothalamus also receives extensive projections from the DA midbrain and is implicated in functions from those essential to survival to cognitive and affective processes in support of goal-directed behavior.^{11,12} Previous animal studies have implicated the hypothalamus in drug addiction. For instance, reinstatement of cocaine seeking was associated with increased c-Fos expression in the hypothalamus.¹³ Compulsive cocaine use altered an array of dopamine gene expression, leading to functional reorganization of the hypothalamus.¹⁴ On the other hand, whereas many human imaging studies have elucidated ventral striatal (VS) responses to drug cues and craving, it remains unclear how the hypothalamus partakes in these processes.

Drug cues precipitate craving and drug seeking. Craving is a subjective experience of wanting to use a drug.¹⁵ Numerous studies have examined cerebral responses to cue-induced craving.^{16,17} However, craving measure may reflect tonic or phasic shifts in desire for drug,¹⁸ and extant research has not distinguished these processes. In the current study, we examined the neural correlates of cue-induced cocaine craving in cocaine-dependent individuals (CD). We posited that motivation dysfunction would manifest as higher hypothalamus activation to drug cues in CD and that cue-evoked hypothalamic activation would be associated with tonic craving, as evaluated by the Cocaine Craving Questionnaire (CCQ) over a period of 2 to 3 weeks of inpatient stay. In contrast, craving rating during cue exposures would reflect acute desire for the drug and engage neural processes not necessarily related to tonic craving or addiction severity.

2 | MATERIALS AND METHODS

2.1 | Subjects, informed consent, and assessment

Twenty-three recently abstinent, treatment-seeking individuals (17 men) with cocaine dependence (CD) participated in this study (Table 1). CD met criteria for current cocaine dependence, as diagnosed by the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition.¹⁹ Recent cocaine use was confirmed by urine toxicology screens. They were drug free while staying in the Clinical Neuroscience Research Unit (CNRU) of the Connecticut Mental Health Center prior to the current functional magnetic resonance imaging (fMRI) study. The CNRU was a locked inpatient unit where alcohol or drug (except coffee) use was strictly prohibited and (for smokers) all smoking breaks were supervised. Daily activities in the CNRU were highly regimented with

85% of day time occupied. All subjects were physically healthy with no major medical illnesses or current use of prescription medications. None reported having a history of head injury or neurological illness. Other exclusion criteria included dependence on another psychoactive substance (except nicotine) and current or past history of Axis I disorders. Individuals with current depressive or anxiety symptoms requiring treatment or currently being treated for these symptoms were excluded as well. The Human Investigation Committee at Yale University School of Medicine approved all study procedures, and all subjects signed an informed consent prior to study participation.

CD participants were interviewed with the 18-item Cocaine Selective Severity Assessment (CSSA) Scale²⁰ to evaluate cocaine withdrawal signs and symptoms. CSSA scores were highly correlated with recent cocaine use and with severity measures from the Addiction Severity Index (ASI) including the interviewer severity rating and composite score in the drug section. A previous study suggested that initial CSSA scores were higher for those who failed to achieve abstinence or who subsequently dropped out of treatment.²⁰ Cocaine craving was assessed with the CCQ, Brief version (CCQ-Brief), for all CDs every 2 to 3 days.²¹ The CCQ-Brief is a 10-item questionnaire, abbreviated from the CCQ-Now²² and highly congruent with the CCQ-Now and other cocaine craving measures.²¹ Each item was rated on a scale from 1 to 7, with a higher total score (ranging from 10 to 70) indicating greater craving. We used CCQ score averaged across all assessments during the 2- to 3-week inpatient stay to index tonic level of craving. All participants were assessed with the Cloninger's Tridimensional Personality Questionnaire—Short Form (TPQ-Short)²³ for personality traits that may be related to substance misuse. Derived from the 100-item long form of the TPQ,²⁴ the TPQ-Short demonstrated reliability and validity.²³ It consists of 44 yes/no questions covering novelty seeking (NS; 13 items), harm avoidance (HA; 22 items), and reward dependence (RD; 9 items). Each personality subscale score was calculated by summing the item scores, with reverse scoring where necessary. A higher subscore each represents a higher level of NS, HA, and RD. All these assessments were obtained on the admission day of the inpatient stay.

2.2 | Behavioral tasks

We employed a cue-induced cocaine craving task (CCT). In a block design, participants were exposed to different cocaine/neutral pictures and reported cocaine craving on a visual analog scale. Briefly, a fixation cross appeared on the screen to engage attention at the beginning of each block. The task started with a 10-second instruction ("Look at the pictures and think about how you may relate to the scenes"). Each block contained a fixation period of 2 s, six pictures (with cocaine or neutral cues, in alternating blocks, Figure S1) each presented for 6 seconds, a 6-second window for craving rating. There were a total of 12 blocks. Thus, the total duration of a "run" was $10s + (2s + 6 \times 6s + 6s) \times 12 = 538s$ or approximately 9 minutes. Each subject participated in two runs, with the order of cocaine and neutral blocks counterbalanced across subjects. Participants were asked to look at the pictures and think about how they may relate to the scenes. At the end of each block, participants were asked to report how much they craved for cocaine on a visual analog scale from 0 (no craving) to 10 (highest craving ever) by pressing a button on the handheld box in the scanner within a 6-second window. Cocaine and neutral pictures were obtained from the

Internet. Cocaine pictures included those displaying people preparing and snorting/smoking cocaine whereas neutral pictures comprising scenes of people performing various acts with similar color and complexity as inspected visually.

2.3 | Imaging protocol

Brain images were collected using multiband imaging with a 3-Tesla Siemens Trio TIM system equipped with a 32-channel head coil. Conventional T1-weighted spin-echo sagittal anatomical images were acquired for slice localization. Anatomical 3D MP RAGE image was next obtained with spin-echo imaging in the axial plane parallel to the AC-PC line with TR = 1900 milliseconds, TE = 2.52 milliseconds, inversion time = 900 milliseconds, bandwidth = 170 Hz/pixel, field of view = 250×250 mm, matrix = 256×256 , and 176 slices with slice thickness = 1 mm and no gap. Functional, blood oxygenation level-dependent (BOLD) signals were then acquired with a single-shot gradient-echo echo-planar imaging (EPI) sequence. Fifty-one axial slices parallel to the AC-PC line covering the whole brain were acquired with TR = 1000 milliseconds, TE = 30 milliseconds, band-width = 2290 Hz/pixel, flip angle = 62° , field of view = 210×210 mm, matrix = 84×84 , 51 slices with slice thickness = 2.5 mm and no gap, and acceleration factor = 3. Images from the first 10 TRs at the beginning of each trial were discarded to enable the signal to achieve steady-state equilibrium between radio frequency (RF) pulsing and relaxation.

2.4 | Imaging data preprocessing

Data were analyzed with Statistical Parametric Mapping (SPM8). Standard image preprocessing was performed. Images of each individual subject were first realigned (motion corrected) and corrected for slice timing. A mean functional image volume was constructed for each subject per run from the realigned image volumes. These mean images were coregistered with the high-resolution structural image and then segmented for normalization with affine registration followed by non-linear transformation. The normalization parameters determined for the structure volume were then applied to the corresponding functional image volumes for each subject. The images were normalized to Montreal Neurological Institute (MNI) space with voxel size of $3 \times 3 \times 3$ mm³. Finally, the images were smoothed with a Gaussian kernel of 8 mm at full width at half maximum.

2.5 | Imaging data modeling

Data blocks were first distinguished of “cocaine picture” and “neutral picture.” A statistical analytical block design was constructed for each individual subject using general linear model (GLM). Because each block was associated with a craving rating, we included a column of block onset parametrically modulated by its corresponding craving score as a regressor in the model. Realignment parameters in all six dimensions were also entered in the model. Serial autocorrelation caused by aliased cardiovascular and respiratory effects was corrected by a first-degree autoregressive or AR(1) model. The GLM estimated the component of variance that could be explained by each of the regressors.

In the first-level analysis, we constructed for each individual subject statistical contrasts of “cocaine picture” versus “neutral picture.” These contrasts allowed us to evaluate brain regions that responded differently to viewing of cocaine pictures, as compared with viewing

of neutral pictures, in CD. The contrast images of the first-level analysis were then used for the second-level group statistics. Following current reporting standards, all imaging results were evaluated with at voxel $P < 0.05$ corrected for familywise error (FWE) of multiple comparisons or at voxel $P < 0.001$, uncorrected, in combination with cluster $P < 0.05$, FWE corrected, on the basis of Gaussian random field theory as implemented in SPM.

In region of interest (ROI) analysis, we used MarsBaR (<http://marsbar.sourceforge.net/>) to derive for each individual subject the effect size of activity difference for the ROIs.

Functional ROIs were defined based on clusters as obtained from whole brain analysis. All voxel activations were presented in MNI coordinates.

3 | RESULTS

3.1 | Cue-induced craving

CD reported higher craving when viewing cocaine pictures as compared with viewing neutral pictures ($P = 0.0006$, $t = 3.85$, two-tailed paired sample t test; cocaine picture: mean $\pm$ SD = 4.2 ± 3.1 , neutral picture: 1.6 ± 1.2). The differences (cocaine-neutral) in visual analog rating of craving did not correlate with either CCQ score ($P = 0.82$, $r = -0.05$, averaged across days; $P = 0.59$, $r = -0.12$, current CCQ) or CSSA score ($P = 0.54$, $r = 0.13$). The CSSA score was positively correlated with days of cocaine use in the prior month ($P = 0.004$, $r = 0.58$) and amount of average monthly cocaine use in the prior year ($P = 0.01$, $r = 0.51$).

3.2 | Cue-induced brain activations

CD showed increased activations during viewing of cocaine vs neutral pictures in bilateral visual cortex, bilateral inferior parietal cortex (IPC), bilateral middle frontal gyri (MFG), and hypothalamus at voxel $P < 0.05$ corrected for FWE of multiple comparisons (Figure 1 and Table 2). No brain regions showed higher activation during viewing of neutral vs cocaine pictures.

3.3 | Brain activations to acute cue craving rating

We performed whole brain linear regression analysis on contrast images of cocaine greater than neutral against differences (cocaine-neutral) in visual analog rating of craving. Bilateral lateral orbital frontal gyri and angular gyrus (AG) showed negative correlation with the differences in craving in CD at voxel $P < 0.001$ uncorrected and cluster-level $P < 0.05$, FWE corrected (Figure 2 and Table 3).

There are more men than women in CD. Thus, in an additional analysis, we examined brain activations with gender as a covariate. The results were nearly identical (Figure S2). Further, because the duration between last cocaine use and fMRI scan varied across CDs, we examined brain activations with days of abstinence as a covariate. The results again showed that the brain activations were nearly identical with or without days of abstinence as a covariate (Figure S3).

3.4 | Relationship to clinical characteristics

We examined whether regional responses to cocaine vs neutral cues were related to clinical characteristics with a linear regression of the effect size of each ROI against years of cocaine use, tonic craving (averaged CCQ score), current craving (CCQ score on the scan day), addiction severity (CSSA score), and TPQ NS, RD, and HA subscores. With the four ROIs and seven clinical measures, we evaluated the results at a corrected $P = 0.05/(4 \times 7) = 0.0018$ and considered an arbitrary $P = 0.01$ as showing a trend toward significance.

Across CD, the hypothalamus activation was correlated positively with averaged ($P = 0.0009$, $r = 0.64$) and current ($P = 0.0012$, $r = 0.63$) CCQ score and with CSSA score ($P = 0.0017$, $r = 0.62$) (Figure 3). The hypothalamus activation was not correlated with years of cocaine use ($P = 0.36$, $r = -0.2$), NS ($P = 0.76$, $r = 0.07$), HA ($P = 0.13$, $r = -0.33$), or RD ($P = 0.15$, $r = -0.31$) subscore. Visual cortical activation was negatively correlated with the NS subscore ($P = 0.006$, $r = -0.55$) at a trend level, but not with other clinical measures (all P s > 0.41). Inferior parietal and middle frontal cortical activation was not correlated with any clinical measures (all P s > 0.02 and > 0.17 , respectively).

We also explored potential relations between acute craving rating-related activations to cue exposure and the same set of clinical variables. Across CD, activations of bilateral lateral orbital frontal cortex were negatively correlated with RD subscore at a trend level

4 | DISCUSSION

The current findings showed increased activation of the hypothalamus in recently abstinent cocaine-dependent individuals (CD) viewing cocaine versus neutral pictures at a stringent, corrected threshold. Importantly, the effect size of hypothalamic activation was significantly correlated with CCQ and CSSA scores, with greater hypothalamic activation reflecting stronger daily cocaine craving and addiction severity. These findings provided new evidence of DA circuit dysfunction in cocaine addiction. Higher hypothalamic response to cocaine cue is related to tonic level of craving and addiction severity.

The hypothalamus regulates arousal, food intake, sexual drive, reward, and affective responses.^{26,27} Numerous animal studies have implicated the hypothalamus in drug addiction, and the cellular and molecular mechanisms of feeding and drug addiction are interlinked in the hypothalamus.²⁶ Cocaine administration induced activation of the hypothalamic-pituitary-adrenal axis²⁸ and altered the levels of neurohypophyseal hormones oxytocin and vasopressin in the hypothalamus.²⁹ In rodents, the transition from controlled to compulsive cocaine self-administration was associated with substantial remodeling of hypothalamic circuitry.¹⁴ Despite preclinical evidence implicating the hypothalamus in drug addiction, few human imaging studies have examined the role of the hypothalamus in the etiological processes of addiction. In an earlier work, increased hypothalamic activation was observed after intravenous injections of nicotine in current cigarette smokers.³⁰ Another study reported decreased activation in a cluster encompassing the hypothalamus in CD as compared with healthy controls (HC) during viewing erotic vs neutral pictures.³¹ Hypothalamic response to monetary reward vs nonreward was increased in CD as compared with HC³² and was associated with the duration of abstinence in CD.³³ The current findings

add to this literature by specifying hypothalamic activation to cocaine cues and the relationship of hypothalamic cue response with tonic cocaine craving and addiction severity.

Increased activations were also observed in bilateral visual cortex, MFG, and IPC during viewing of cocaine vs neutral pictures. Although not typically a focus of the addiction literature, the visual cortex was often reported to be activated during exposure to drug cues.^{34–36} A recent meta-analysis showed that 86% of published functional imaging studies reported significant drug cue-induced activity in the visual cortex.³⁵ Notably, treatment-seeking participants as well as participants with strong motivation to quit demonstrated decreased cocaine cue-induced visual cortical activation, as compared with non-treatment-seeking and less-motivated participants.³⁷ The current finding of increased activation in bilateral visual cortex is consistent with these earlier studies. The MFG and IPC are part of the saliency circuit and cocaine-induced craving correlated positively with MFG activity during cocaine self-administration in non-treatment-seeking CD.³⁸ On the other hand, visual, frontal, and parietal cortical response to cocaine cues did not correlate with tonic craving or addiction severity. Together, these findings distinguished a specific role of the hypothalamus in registering tonic cocaine craving and cocaine addiction severity and add to the literature in characterizing clinically relevant craving and addiction severity measures in cocaine dependence.^{39,40}

Bilateral orbitofrontal cortex (OFC) and AG responded negatively to higher craving rating during exposure to cocaine than to neutral cues. Interconnected with mesolimbic brain regions, the OFC integrates reward values and sensory and interoceptive signals to guide motivated behavior.^{41,42} In particular, the lateral OFC is involved in inhibition of actions.⁴³ Activation of the lateral OFC is associated with resisting highly tasty food in weight-concerned women.^{44,45} In rats, inactivation of the lateral OFC impaired behavioral reversals in a probabilistic learning task.⁴⁶ Together, this body of work supports a role of the lateral OFC in goal-directed impulse control. Decreased lateral OFC activity in response to cue-elicited craving may reflect diminished control of the desire to use drugs. The AG is part of the default mode network, which deactivates in response to cognitive and affective challenges. AG response to drug cues may reflect disruption of internal mental states as a result of directed attention to environmental influences. Notably, lateral OFC and AG responses to cue exposures were not correlated with CCQ or CSSA score, suggesting that these regional activities were effects of acute craving and may not be related to addiction severity.

Examining brain activations to food and cocaine cues in 20 cocaine-dependent individuals (CD) using both fMRI and positron emission tomography (PET) imaging, a recent work reported that cocaine and food cues elicited similar circuit responses and that striatal dopamine D2/D3 receptor binding potentials modulated these responses.³⁶ Specifically, the authors observed “deactivations” of the VS and hypothalamus to food and cocaine as compared with neutral cues, with less deactivation in the hypothalamus to cocaine as compared with food cues. The study highlighted hypothalamic responses to cue exposure; on the other hand, as acknowledged by the authors, the findings of decreased hypothalamus and VS activations were surprising and in contrast to a literature of enhanced DA circuit activation to drug cues.^{3,47} The authors suggested that the findings might reflect the use of

videos rather than pictures in their cue reactivity paradigms. More research is needed to determine how video and picture cues may engage regional brain activations differently in cue craving studies.

In summary, we observed robust activation of the hypothalamus to cocaine cues in cocaine addicted individuals in spite of a relatively small sample size in the current study. Hypothalamic response to drug cues was correlated with daily cocaine craving, as assessed by the CCQ and cocaine addiction severity, as evaluated by the CSSA. These findings together substantiate a role of the hypothalamus in cue-induced tonic craving and addiction severity in cocaine dependence, and add to the literature of biomarkers of this chronic illness.^{48–50}

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Brain regions showing activations during cocaine vs neutral cue exposure in CD at voxel $P < 0.05$, corrected for familywise error of multiple comparisons. Hot color represents clusters showing higher responses to cocaine vs neutral pictures. VC, visual cortex; IFG, inferior frontal gyrus; IPC, inferior parietal cortex

FIGURE 2.

Bilateral orbital frontal cortex (OFC) and angular gyri (AG) showed negative correlation with the differences in visual analog ratings of craving during viewing of cocaine versus neutral pictures in CD; $P < 0.001$ uncorrected and cluster-level $P < 0.05$, FWE corrected

FIGURE 3.

A, Hypothalamus (HT) cluster shown in a 3D structural image. The inset shows the cluster along with the center coordinates of medial (blue +) and lateral (green +) hypothalamus as characterized in a previous study.²⁵ HT activation was positively correlated with B, Cocaine Craving Questionnaire (CCQ) score and with C, Cocaine Selective Severity Assessment (CSSA) score across CD subjects ($P = 0.009$, $r = -0.53$). None of the other correlations were significant (all P s > 0.03).

TABLE 1

Demographics and clinical measures of the subjects

Subject Characteristic	CD (n = 23)
Age (y)	42.2 ± 7.6
Gender (M/F)	17/6
Race (EA/AA/others)	7/15/1
Years of drinking	20.3 ± 13.7
Years of smoking	14.2 ± 12.7
TPQ HA score	9.3 ± 6.5
TPQ RD score	4.9 ± 2.2
TPQ NS score	5.7 ± 2.9
Averaged CCQ score	41.0 ± 12.6
CCQ score on the day of the MR scan	41.2 ± 12.4
CSSA score	32.9 ± 15.8
Amount of average monthly cocaine use (gm) in the prior year	17.5 ± 15.5
Amount per use in grams	1.1 ± 0.7
Days of cocaine use in the prior month	15.4 ± 8.7
Years of cocaine use	16.0 ± 9.7
Days between last cocaine use and fMRI	12.1 ± 5.8

Abbreviations: AA, African American; CCQ, Cocaine Craving Questionnaire; CSSA, Cocaine Selective Severity Assessment; EA, European American; fMRI, functional magnetic resonance imaging; HA, harm avoidance; NS, novelty seeking; RD, reward dependence; TPQ, Tridimensional Personality Questionnaire. Values are mean ± SD.

Cocaine vs neutral cue-induced brain activations; voxel $P < 0.05$ corrected for FWE of multiple comparisons

TABLE 2

Volume, mm ³	Peak Voxel (z)	MNI Coordinates, mm			Side	Identified Brain Region
		x	y	z		
Cocaine > neutral						
19 737	6.96	-39	-58	-14	L	Visual cortex
18 036	6.80	42	-82	-8	R	Visual cortex
7452	6.32	-30	-61	55	L	Inferior parietal cortex
4914	6.26	33	-46	49	R	Inferior parietal cortex
729	5.39	-54	2	28	L	Middle frontal gyrus
540	5.14	51	8	25	R	Middle frontal gyrus
675	5.14	3	-4	-14	L/R	Hypothalamus
Neutral > cocaine						
None						

Abbreviations: FWE, familywise error; MNI, Montreal Neurological Institute. R, right; L, left.

Brain activations to cocaine vs neutral cues in correlation with acute craving rating; $P < 0.001$ uncorrected and cluster-level $P < 0.05$ corrected for FWE of multiple comparisons

TABLE 3

Volume, mm ³	Peak Voxel (z)	MNI Coordinates, mm			Side	Identified Brain Region
		x	y	z		
Positive correlation						
None						
Negative correlation						
3753	4.67	-48	26	-8	L	Lateral orbital frontal gyrus
2646	4.18	48	35	-14	R	Lateral orbital frontal gyrus
2754	4.22	-45	-58	46	L	Angular gyrus

Abbreviations: FWE, familywise error; MNI, Montreal Neurological Institute. R, right; L, left.