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Midcingulate Cortical Activations Interrelate Chronic Craving and Physiological Responses to Negative Emotions in Cocaine Addiction

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Abstract

BACKGROUND: Negative emotions precipitate drug craving. Individuals vary in how they engage in negative emotions, as may be reflected in physiological arousal elicited by the emotions. It remains unclear whether physiological responses to negative emotions relate to cocaine craving and how regional brain activations support this relationship.

METHODS: We examined brain activation and skin conductance responses (SCRs) among 40 cocaine-dependent (CD) subjects and 37 healthy control subjects during exposure to negative-emotional and neutral images. Imaging and SCR data were processed with published routines, and the results were evaluated at a corrected threshold.

RESULTS: Relative to control subjects, CD subjects showed increased activation in the hippocampus, inferior parietal gyrus, and caudate in response to negative-emotional versus neutral images. CD subjects relative to control subjects showed diminished SCR to negative-

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emotional versus neutral images, and the difference (SCR_{NE-NU}) was positively correlated with chronic craving, as evaluated by the Cocaine Craving Questionnaire, and craving rating (negative-emotional – neutral), in CD subjects. Activations of the midcingulate cortex (MCC) were positively correlated with both chronic cocaine craving and SCR_{NE-NU} and completely mediated the correlation between chronic cocaine craving and SCR_{NE-NU}. Further, path analyses suggested a directional influence of SCR_{NE-NU} on craving rating (negative-emotional – neutral): chronic craving → MCC activation → SCR_{NE-NU} → craving rating.

CONCLUSIONS: CD subjects demonstrate hypoactive SCRs to negative emotions. Less diminution of SCR is associated with higher cocaine craving and MCC response to negative emotions. A hub of the limbic motor circuit, the MCC may translate chronic cocaine craving into physiological responses that precipitate cocaine seeking.

Emotional dysregulation is a hallmark feature of cocaine addiction (1). Cocaine-dependent (CD) individuals frequently experience negative emotions during abstinence (2). Individuals resort to drug use to override the negative emotional state, and the negative reinforcement perpetuates addiction. Decades of research has established that exposure to negative emotions aggravates cocaine craving and precipitates relapse (3-14). For example, recall of stressful experiences led to increases in cocaine use and shorter time to relapse in CD subjects (15-17).

Stress-induced cocaine craving has been studied with a number of behavioral paradigms (5,6,18,19). For instance, exposure to personal negative memory evoked higher activity in the caudate in CD subjects as compared with healthy control subjects, with caudate activation correlated with cocaine craving ratings (20). Exposure to general, negative-emotional images promoted re-experiencing of previous traumatic events, leading to stress and cocaine craving in CD subjects (21). On the other hand, studies have also shown impairment of CD subjects in recognizing and engaging in negative emotions (2,3,22). Thus, whereas stress elicits cocaine craving and seeking, the extent to which exposure to negative emotions elicits craving may vary among CD subjects, and those who are more engaged in negative emotions demonstrate higher craving. Here, we hypothesized that individual engagement as reflected in higher physiological arousal would be associated with higher craving in response to negative emotions.

Skin conductance response (SCR) represents a physiological index of arousal and may provide a quantitative measure of behavioral engagement (17,23-25). Indeed, individuals demonstrated higher SCR when viewing negative-emotional versus neutral pictures (26-31). Very few studies have directly investigated SCR to negative emotions in people with substance use disorders, and the findings appeared to vary according to the nature of stimuli. For instance, individuals with alcohol use disorder demonstrated reduction in SCR to negative-emotional (vs. neutral) images, and the difference in SCR to negative-emotional versus neutral images did not appear to be distinguishable from control participants (27). In another study, CD subjects demonstrated higher SCR when viewing disgusting (vs. neutral) images (29); however, the latter study did not contrast CD and control participants. Further, neither study examined the relationship between the SCR and alcohol or cocaine craving. A few studies of drug cue reactivity have reported elevated SCR during exposure to cocaine as compared with neutral cues (32,33) or to the baseline prior to cue exposure (34,35), whereas others showed a lack of differences in SCR to cocaine versus neutral cues (36-38) or versus baseline (39,40), in CD subjects. It is not entirely clear what may have accounted for the discrepancy in findings; noisy signals, sluggish time course, habituation to repeated stimuli, and individual differences are to be considered in the analyses of SCR.

Studies have investigated the neural correlates of negative emotion processing in cocaine addiction (3,22,41,42). For instance, the dorsomedial prefrontal cortex showed lower activation during exposure to negative-emotional versus neutral images in CD subjects as compared with healthy control subjects (42). In reappraisal of negative emotions, CD subjects as compared with control subjects showed higher activations in the dorsolateral prefrontal cortex, temporoparietal junction, and inferior frontal gyrus (3). However, no studies to our knowledge have combined brain imaging with concurrent recording of SCR or other physiological indices, and the neural processes interrelating negative emotions to arousal and craving remain to be clarified.

In current study, we examined the neural correlates of SCRs elicited by negative emotions and how regional activities and SCRs related to cocaine craving in 40 abstinent CD subjects as compared with 37 age- and sex-matched control subjects who were non–cocaine-using, social drinkers. CD subjects and healthy control subjects viewed a series of negative-emotional and neutral images and reported their cocaine and alcohol cravings, respectively. We hypothesized that CD subjects who demonstrated higher SCR to negative-emotional versus neutral images would report higher drug craving and that activation of the limbic motor circuit, including the cingulate cortex (17,23), would reflect differences in SCR to negative-emotional versus neutral images. Further, we conducted mediation and path analyses to examine the interrelationship between regional brain activities, SCR, and cocaine craving.

METHODS AND MATERIALS

Subjects, Informed Consent, and Assessments

Forty recently abstinent CD subjects (30 men) and 37 age- and sex-matched healthy control subjects (24 men) who were social drinkers participated in the study (Table 1). CD subjects met criteria for current cocaine dependence as diagnosed by the Structured Clinical Interview for DSM-IV (43). The Human Investigation Committee at Yale University School of Medicine approved the study procedures, and all participants signed an informed consent prior to the study. See the Supplemental Methods for details.

All participants were evaluated for drug and alcohol use, including history of use and current use. CD subjects were also interviewed with the 18-item Cocaine Selective Severity Assessment (CSSA) (44) to assess cocaine addiction severity. CSSA scores are highly correlated with recent cocaine use and with severity measures of the Addiction Severity Index, including the interviewer severity rating and composite score in the drug section (44). Chronic cocaine craving was assessed with the Cocaine Craving Questionnaire (CCQ)-Brief version for all CD subjects every 2 to 3 days (45). However, there was little day-to-day variation (mean ± SD of the coefficient of variation = 0.066 ± 0.044). Thus, the averaged

CCQ score was used as an index of chronic cocaine craving. The CCQ-Brief version is a 10-item questionnaire abbreviated from the CCQ-Now (46) and is highly congruent with the CCQ-Now and other cocaine craving measures (45). Each item was rated on a scale from 1 to 7, with a higher total score (ranging from 10 to 70) indicating greater craving.

Behavioral Task

Participants were exposed to negative-emotional and neutral stimuli in alternating blocks (Figure 1A). Briefly, a cross appeared on the screen to engage attention at the beginning of each block. After 2 seconds, six pictures displaying negative-emotional images (negative-emotional blocks) or neutral visual scenes (neutral blocks) were shown for 6 seconds each. Images were selected from the International Affective Picture System (47). Negative-emotional blocks included images depicting mutilations, murdered people, and human threats and neutral blocks included images of inanimate objects, natural scenes, and neutral social scenes. Negative-emotional relative to neutral images showed a higher rating in arousal (mean ± SD = 5.84 ± 0.48 vs. 3.35 ± 0.59; $p = 5.1 \times 10^{-30}$; 2-sample t test) but a lower rating in valence (i.e., more negative; 2.78 ± 0.40 vs. 5.53 ± 0.59; $p = 1.0 \times 10^{-34}$) (Figure 1B). At the end of each block, CD and control subjects reported how much they craved cocaine and alcohol, respectively, on a visual analog scale from 0 (no craving) to 10 (highest craving ever experienced). These ratings reflect craving elicited by negative emotions. Each block lasted about 45 seconds (including time for craving rating), and a total of six negative-emotional and neutral blocks took approximately 9 minutes to complete. Each participant completed two runs of the task during brain imaging, with the order of negative-emotional and neutral blocks counterbalanced across subjects.

SCR: Acquisition and Analysis

We followed published routines in SCR acquisition and analyses. See the Supplemental Methods for details (17,48-54). We discarded the SCR data from 3 CD subjects and 8 healthy control subjects owing to technical problems with the recording. Thus, skin conductance data were analyzed for 37 CD subjects and 29 healthy control subjects (Table 1). Because SCR was sluggish, typically taking 10 to 12 seconds to peak (49,50), and habituated to repeated exposure to similar stimuli (48,52,54), we focused specifically on the middle 12 to 24 seconds in data analyses.

Imaging Protocol, Data Preprocessing, and Modeling

Brain imaging data were collected with a 3T scanner and preprocessed with published routines. We distinguished the blood oxygen level–dependent signals of negative-emotional and neutral blocks in a general linear model and performed group analyses with age, sex, years of smoking, and years of drinking as covariates for all analyses (except for 1-sample t tests). To investigate the neural correlates of SCR in response to negative-emotional (vs. neutral) images, we performed a whole-brain linear regression against SCR during "negative-emotional – neutral" block with the same covariates. We used MarsBaR (http://marsbar.sourceforge.net/) in region-of-interest (ROI) analysis, with the ROIs identified from whole-brain analyses. See the Supplemental Methods for details.

Mediation and Path Analysis

We performed mediation and path analyses to examine the interrelationships of midcingulate cortex (MCC) activation, SCR, CCQ score, and craving rating during the task (see Results), as detailed previously (55-59) and in the Supplement.

RESULTS

Negative Emotion–Induced Craving

A repeated-measures analysis of variance with group and condition each as a between- and within-subjects factor showed significant condition ($p = .0056$) but neither a group main ($p = .63$) nor an interaction ($p = .29$) effect on craving rating. In post hoc analyses, CD subjects reported higher cocaine craving during negative-emotional (2.1 ± 2.3) as compared with neutral (1.4 ± 0.9) blocks ($t_{39} = 2.70$, $p = .01$; 2-tailed paired *t* test), whereas control subjects reported no difference in alcohol craving (2.1 ± 1.9 vs. 1.7 ± 1.3; $t_{36} = 1.31$, $p = .20$). Craving rating (negative-emotional – neutral) did not correlate with any of cocaine use characteristics (all *p*s > .47) in CD subjects (Table S1).

Negative Emotion–Induced Brain Activations and the Relationship With Clinical Characteristics

CD subjects showed higher activations to negative-emotional versus neutral images in the bilateral visual cortex, hippocampus, inferior frontal gyri, and precentral gyri (Figure S1A). No brain region showed higher activation to neutral versus negative-emotional images. Control subjects showed higher activations in the bilateral visual cortex and right precentral gyrus and lower activations in the calcarine cortex, precuneus, posterior cingulate cortex, and bilateral orbitofrontal gyri to negative-emotional versus neutral images (Figure S1B). Compared with control subjects, CD subjects showed higher activations in the caudate (Figure 2A), inferior parietal gyrus (IPG) (Figure 2B), and hippocampus (Figure 2C) in response to negative-emotional versus neutral images (Table 2). No brain regions showed higher activation in control subjects versus CD subjects.

We examined whether regional responses to negative-emotional versus neutral images were related to clinical characteristics with a linear regression of the beta contrast of each ROI, as identified from a group contrast of CD subjects versus control subjects, against years of cocaine use, days of cocaine use in the past month, amount of average monthly cocaine use (g) in the prior year, CCQ score, and CSSA score. We evaluated the results at a corrected $p = .05/(3 \times 5) = .0033$ and considered an arbitrary $p = .01$ as showing a trend toward significance. Caudate activation showed a positive correlation with CCQ ($r = .50$, $p = .0021$) and CSSA ($r = .57$, $p = .00028$) scores (Figure 2A), and IPG activation showed a positive correlation with days of cocaine use in the prior month ($r = .49$, $p = .0025$) and, at a trend level, with CCQ score ($r = .43$, $p = .0087$) (Figure 2B). Hippocampal activation did not show correlation with any measures (all *p*s > .11) (Figure 2C).

SCR and Its Relationship to Clinical Characteristics and Brain Activations

SCRs during negative-emotional and neutral blocks are shown in Figure 3A, B. As expected, we observed substantial temporal variation in SCR to stimulus exposure, with onset of stimuli eliciting a small peak in control subjects but not in CD subjects. In control subjects, the SCRs to both negative-emotional and neutral images habituated but less prominently for negative-emotional images, whereas in CD subjects the SCRs to both negative-emotional and neutral images habituated with time. We focused on the difference in SCR between the negative-emotional and neutral blocks (SCR_{NE-NU}) as an index of individual variation in physiological arousal in response to negative emotions. Relative to control subjects, CD subjects exhibited significant lower SCR_{NE-NU} (−0.0087 ± 0.091 vs. 0.091 ± 0.20; $t_{60} = -2.78$, $p = .0071$) (Figure 3C).

We examined whether SCR_{NE-NU} values were related to clinical characteristics with linear regressions. Evaluated at a corrected $p = .05/(1 \times 5) = .01$, the results showed a significant positive correlation of SCR_{NE-NU} with CCQ score at a trend level ($r = .36$, $p = .038$) (Figure 3D). Further, pertaining specifically to our hypothesis, SCR_{NE-NU} was correlated with visual craving rating (negative-emotional – neutral) positively in CD subjects ($r = .46$, $p = .0075$) but negatively in control subjects ($r = -.50$, $p = .012$), with a significant difference in the slope of regressions ($z = 4.02$, $p = .0001$) (Figure 3E).

Regional Activations to SCR

At voxel $p < .001$ uncorrected and cluster-level $p < .05$, familywise error corrected, the midcingulate cortex (MCC) (x = −9, y = −28, z = 37; peak voxel Z = 4.23; volume = 5157 mm^3) and the hippocampus (x = −24, y = −25, z = −20; peak voxel Z = 4.13; volume = 1620 mm^3) showed activation in positive correlation with SCR_{NE-NU} (Figure 4A, B). No brain regions showed negative correlation with SCR_{NE-NU} in CD subjects or any correlation in control subjects.

In ROI analysis, activation of the MCC was positively correlated with SCR_{NE-NU} in CD subjects ($r = .65$, $p = .000041$) but not in control subjects ($r = -.33$, $p = .11$), and the slope test showed a significant difference ($z = 4.29$, $p < .0001$) (Figure 4A). Further, the MCC activation showed positive correlation with CCQ ($r = .44$, $p = .0098$) and CSSA ($r = .45$, $p = .009$) scores. MCC activation was not correlated with craving rating during negative-emotional versus neutral blocks in CD subjects ($p = .18$). Hippocampal activity was positively correlated with the SCR_{NE-NU} in CD subjects ($r = .66$, $p = .000025$) but was negatively correlated in control subjects ($r = -.42$, $p = .038$), also with significant difference in the slope ($z = 4.76$, $p < .0001$; slope test) (Figure 4B). Hippocampal activation was not correlated with any of the clinical variables (all *p*s > .18) or with craving rating during negative-emotional versus neutral blocks ($p = .11$).

Mediation and Path Analyses

The MCC activation to negative-emotional versus neutral block was positively correlated with the SCRNE-NU as well as with the CCQ score, as shown earlier. The SCR_{NE-NU} was also positively correlated with the CCQ score ($r = .36$, $p = .038$). Thus, we conducted mediation analysis to examine the relationship between the CCQ score, MCC activation, and SCR_{NE-NU}. The results showed that MCC activation to negative-emotional (vs. neutral) cues significantly mediated the correlation between the CCQ score and SCR_{NE-NU} (Figure 4C). Without the mediation of MCC activation, the CCQ score was not correlated with

SCR_{NE-NU} ($p = .55$). None of the other five models showed significant mediation (Table S2). Thus, MCC activation to negative-emotional (vs. neutral) cue exposure completely mediated the correlation between the CCQ score and SCR_{NE-NU}.

Because SCR_{NE-NU} was correlated with subjective craving rating (negative-emotional – neutral), we followed up with path analyses to distinguish two models: whether 1) SCR_{NE-NU}, which was elevated by CD subjects' chronic cocaine craving (CCQ score) through MCC activation, led to the higher subjective craving rating (model 1) or 2) subjective craving rating led to SCR_{NE-NU} (model 2) (Figure 4D). The results showed a good fit for model 1 (fit indices: root mean square error of approximation = 0.00 [90% confidence interval, 0.00–0.15], $\chi^2/df = 0.29$, standardized root mean square residual = 0.03, and comparative fit index = 1.00) but not for model 2 (fit indices: root mean square error of approximation = 0.02 [90% confidence interval, 0.00–0.32], $\chi^2/df = 0.18$, standardized root mean square residual = 0.075, and comparative fit index = 0.99) (Figure 4D). Specifically, through MCC activation, CD subjects' chronic cocaine craving elevated SCR, which then increased subjective craving rating during negative-emotional versus neutral blocks.

DISCUSSION

This is the first study to examine both neural and physiological correlates of cocaine craving elicited by negative emotions. SCR_{NE-NU} was positively correlated with craving rating (negative-emotional – neutral) in CD subjects, confirming the hypothesis that individuals' differences in how they engage in negative-emotional processing, as reflected by physiological arousal, may relate to cocaine craving. Activations of the MCC completely mediated the correlation between chronic cocaine craving and SCR_{NE-NU}. Path analysis further suggested a directional influence of SCR_{NE-NU} on craving rating (negative-emotional – neutral): chronic craving → MCC activation → SCR_{NE-NU} → craving rating. Together, the findings suggest a distinct role of the MCC in interrelating negative emotion exposure, physiological arousal, and cocaine craving.

Neural Responses to Negative-Emotional Exposures: CD Subjects Versus Control Subjects

CD subjects versus control subjects showed higher activations in the caudate, IPG, and hippocampus during exposure to negative-emotional versus neutral images. Hippocampal activation was positively correlated with SCR_{NE-NU}, and the caudate showed activities in positive correlation with chronic cocaine craving (CCQ score) and cocaine addiction severity (CSSA score) in CD subjects.

Although typically considered as a subcortical hub of executive functions, the caudate partakes in emotion processing, as shown in a meta-analysis of imaging studies (60). The caudate showed higher responses to fearful versus neutral faces (61), and caudate lesions led to inability to recognize emotional facial expressions (62). The caudate has also been implicated in drug cue–induced craving. Specific binding of $[^{11}C]$raclopride in dorsal caudate and putamen was reduced, suggesting increased dopamine release, when subjects were shown a video of cocaine smoking, and the magnitude of this reduction was correlated with self-reported craving (63). Further, the caudate, anterior cingulate, and IPG showed greater activation in cocaine users viewing a cocaine smoking video than a sex film (64). With stress cue–induced craving tasks, studies have also shown higher caudate activation among CD subjects and alcohol drinkers as compared with control subjects, and the caudate activation was associated with higher craving (20,65). Thus, these findings, along with the current finding of caudate response to negative emotions in correlation with chronic cocaine craving and cocaine addiction severity, suggest a potentially unique role of the caudate in supporting drug craving during negative-emotional states.

The hippocampus is central to the acquisition and expression of contextual emotional memory (66) and negative-emotional processing (67). The hippocampus also responded to autobiographical script–guided imagery of cocaine use (18). During cocaine cue exposure, CD subjects exhibited feed-forward effective connectivities involving the amygdala, hippocampus, dorsal striatum, insula, and prefrontal cortex that were not observed in control subjects viewing the same images (68). Thus, consistent with a large literature, the current findings suggest that CD subjects involve the hippocampus to a greater extent than control subjects in processing negative emotions, potentially reflecting contextual memory of cocaine use. Notably, we reported in a recent study “deactivation” of the parahippocampal gyrus during drug versus neutral cue exposure, with less deactivation positively correlated with CCQ scores in CD subjects (69). More studies are needed to distinguish hippocampal and parahippocampal responses to stress versus drug cues.

Higher activation was also observed in the IPG, broadly consistent with parietal dysfunction in chronic cocaine users (64,70-73). We reported in earlier studies higher IPG activation during cocaine versus neutral cue exposures (74) and during cocaine (vs. neutral) as compared with food (vs. neutral) cue exposures in CD subjects (75). The current finding may suggest a heightened attention to the negative-emotional cues in CD subjects.

SCRs to Negative Emotions

CD subjects versus control subjects exhibited a hypoactive SCR to negative-emotional versus neutral images or diminished $SCR_{NE\text{-}NU}$, suggesting less engagement in negative emotion processing, whether via passive distancing from or active regulation and suppression of negative emotions (76). Although the underlying mechanism remains to be examined, one possibility is that, as we recently showed, the neurotoxic effects of cocaine may have compromised the midbrain noradrenergic circuits in supporting physiological arousal in CD subjects (77). Importantly, $SCR_{NE\text{-}NU}$ was positively correlated with both CCQ scores and craving rating (negative-emotional – neutral) in CD subjects, suggesting that the extent of engagement in negative emotions was related to both chronic and emotion-elicited craving (34). The findings of a significant correlation between SCRNE-NU and cocaine craving suggest an intact, albeit maladaptive, link between physiological arousal and subjective craving, and support skin conductance as a useful physiological index of an internal state central to cocaine seeking and consumption.

We demonstrated that hippocampal responses to negative-emotional versus neutral images were positively correlated with $SCR_{NE\text{-}NU}$ in CD subjects. In contrast, control subjects’ hippocampal responses showed a marginal but significant negative correlation with SCRNE-NU. Previous structural and functional imaging studies have linked the hippocampus to SCR during processing of emotional faces and fear conditioning (78-80). As measured by SCR to conditioning stimuli, individuals with larger hippocampal volumes learned to discriminate between two contexts during fear conditioning, whereas those with small volumes did not (79). Individuals with stronger renewal of conditioned SCR in a novel context showed higher effective connectivity of hippocampal activation foci with the fear network (78). Together, the hippocampus showed higher activation during negative-emotional processing in association with SCR, suggesting contextual specificity of cocaine use, in CD subjects (81). One may speculate that the healthy control subjects, who engaged in drinking likely in social or other emotionally positive occasions, would in contrast downregulate hippocampal activities during exposure to negative-emotional images.

In the limbic motor network, the MCC represents a hub to translate cognitive and emotional experiences to somatic motor and autonomic actions (82) and support goal-directed behavior (83). The MCC responds to a variety of behavioral contingencies involving intense, arousing emotions (83-88). The MCC was identified in a meta-analysis of responses to the reappraisal of negative affect (89). Distancing from aversive images was also associated with increases in MCC activity (90). The MCC showed higher activation in cannabis users versus control subjects who reappraised or reduced their negative emotion by distancing themselves from negative emotional images (91). Here, the MCC showed lower activity to negative-emotional versus neutral images in both CD subjects and control subjects (Figure 4), suggesting that the participants were not engaged in processing negative emotions. Further, many imaging studies have reported higher MCC activities during exposures to drug cues (92-95). Thus, although the participants were on average less engaged in processing negative emotions, those who demonstrated relatively higher MCC activities were more engaged and prone to craving elicited by negative emotions. This may also explain the positive correlation of the MCC activation with SCR_{NE-NU}. Importantly, MCC activation mediated the correlation between CCQ score and SCR_{NE-NU} in CD subjects. That is, the CD subjects with more severe chronic cocaine cravings were more engaged in negative emotions and demonstrated higher physiological arousal in response to negative emotions via MCC activities. This is consistent with an earlier report of MCC responding to fear conditioning in positive correlation with SCR in CD subjects (96). On the other hand, although healthy control subjects too demonstrated less MCC activity during negative emotions, this alone did not explain the negative correlation between SCR and alcohol craving rating. We speculated that healthy control subjects (social drinkers) typically engaged in alcohol use because of positive alcohol expectancy. Thus, exposure to negative emotions, though arousing, counteracts the desire to drink. Overall, the results add to the literature by highlighting the specific role of MCC activity and cocaine craving in response to negative emotions in CD subjects.

Craving Rating Elicited by Negative-Emotional Versus Neutral Images

Subjective craving ratings during negative-emotional versus neutral blocks were not related to years of cocaine use, CCQ score, CSSA score, days of use in the prior month, or average monthly quantity of use in the prior year, suggesting at best distal influences of these variables on drug craving elicited by negative emotions (Table S1). Studies of drug or emotion cue reactivity have typically identified regional cue responses and correlated these regional activities to subjective reports of craving. However, in the current study as well as our earlier studies (75,97), we were not able to identify specific regional activities in relation to subjective craving rating, possibly because of the fast-paced nature of the rating during the magnetic resonance scan and the fact that subjective report is more remote from the underlying neural processes, as compared with a physiological index of arousal. Individual variation in SCR_{NE-NU} was significantly correlated with craving rating, as shown both here and in earlier work (53). Importantly, MCC activation mediated the correlation between CCQ score and SCR_{NE-NU}, suggesting MCC activation as a proximal link to emotion-elicited arousal and drug craving. Indeed, the MCC responded to drug cues (98,99) and to the conscious decision to allow oneself to crave, as compared with resisting craving, among smokers (98). Furthermore, the intensity of withdrawal-induced craving among smokers correlated with the strength of connectivity between the anterior cingulate cortex and limbic structures, including the MCC (100). Deep brain stimulation of the nucleus accumbens remediated electrophysiological signals in the MCC along with amelioration of craving and drinking behavior in a patient with severe alcohol addiction (101). Together, these findings suggest a critical role of MCC dysfunction in substance misuse.

Limitations and Conclusions

First, we did not include positive-emotional stimuli in the study and thus could not rule out the possibility that the observed effects were not specific to negative emotions. On the other hand, a previous work reported that trait negative but not positive urgency was related to neural activities to olfactory cues and alcohol craving (102). Cerebral cue responses related to subjective alcohol craving and problem alcohol use through trait negative but not positive urgency, consistent with an outsized role of negative emotions in eliciting craving. Second, because of the moderate and unbalanced sample size, we did not examine sex differences in the findings. Male and female drug and alcohol users are known to demonstrate important differences in clinical characteristics and neural markers (97,103-106). More work is needed to address this issue. Third, participants were instructed to mentalize how they might engage in the images and scenes, rather than to regulate the emotion and craving elicited by the images. As discussed earlier, this may have accounted for the differences in regional responses to negative-emotional versus neutral images and should be considered in interpreting the current findings. Fourth, despite the findings of mediation and path analyses, the causal link between MCC activity, SCR, and subjective craving can only be confirmed by explicit manipulation of these variables.

In conclusion, we demonstrated higher activation in the caudate in response to negative-emotional images, in association with cocaine use severity, in cocaine-addicted individuals. Although not showing significantly higher activities, the MCC responded to negative emotions in link with increases in physiological arousal. Further, MCC activities support the relationship between chronic cocaine craving and physiological arousal, which in turn reflects subjective craving elicited by negative emotions. These findings highlight the importance of physiological arousal in cocaine craving elicited by negative emotions and a potentially specific role of the MCC in associating severity of cocaine use, engagement in negative emotions, and cocaine craving.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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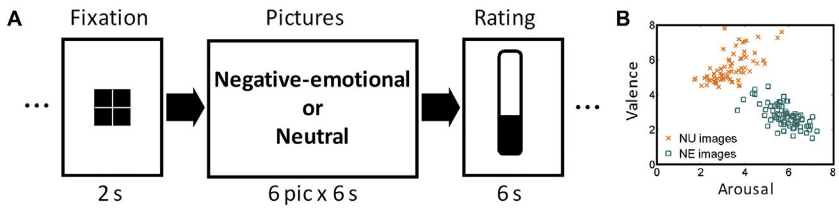

Figure 1.

(A) Example of a negative-emotional (NE)/neutral (NU) block with timeline: fixation (2 s) → pictures (36 s) → craving rating (6 s) or approximately 45 seconds total in a block.

(B) Scatterplot of all of the images as defined by valence and arousal rating according to the International Affective Picture System. NE relative to NU images were rated higher in arousal and lower in valence (i.e., less positive). Each data point represents one image.

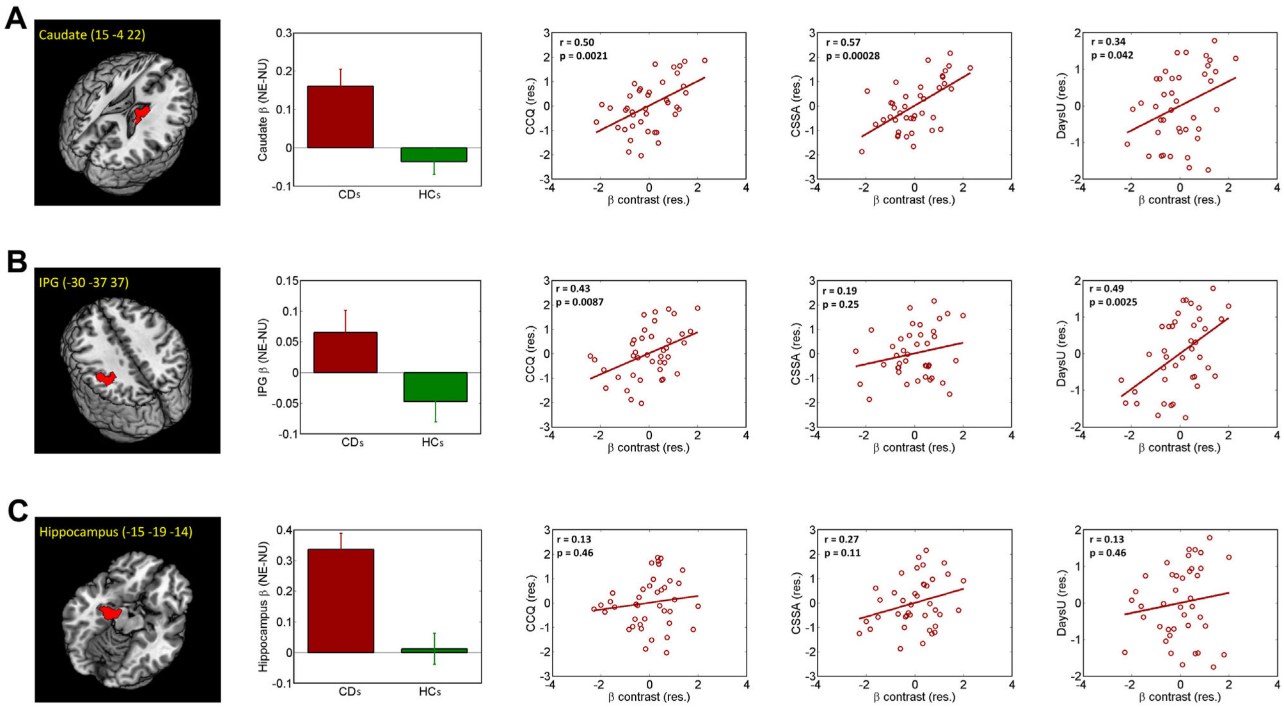

Figure 2.

The **(A)** caudate, **(B)** inferior parietal gyrus (IPG), and **(C)** hippocampus showed higher activation in response to negative-emotional (NE) vs. neutral (NU) stimuli in cocaine-dependent (CD) subjects as compared with healthy control (HC) subjects. Histograms (mean ± SE) represent the beta contrast (negative-emotional – neutral) of each region. The scatterplots show the linear correlation between brain activation (β contrast) and Cocaine Craving Questionnaire (CCQ) score, Cocaine Selective Severity Assessment (CSSA) score, and days of cocaine used in the prior month (DaysU). Each data point represents 1 subject. res., residual.

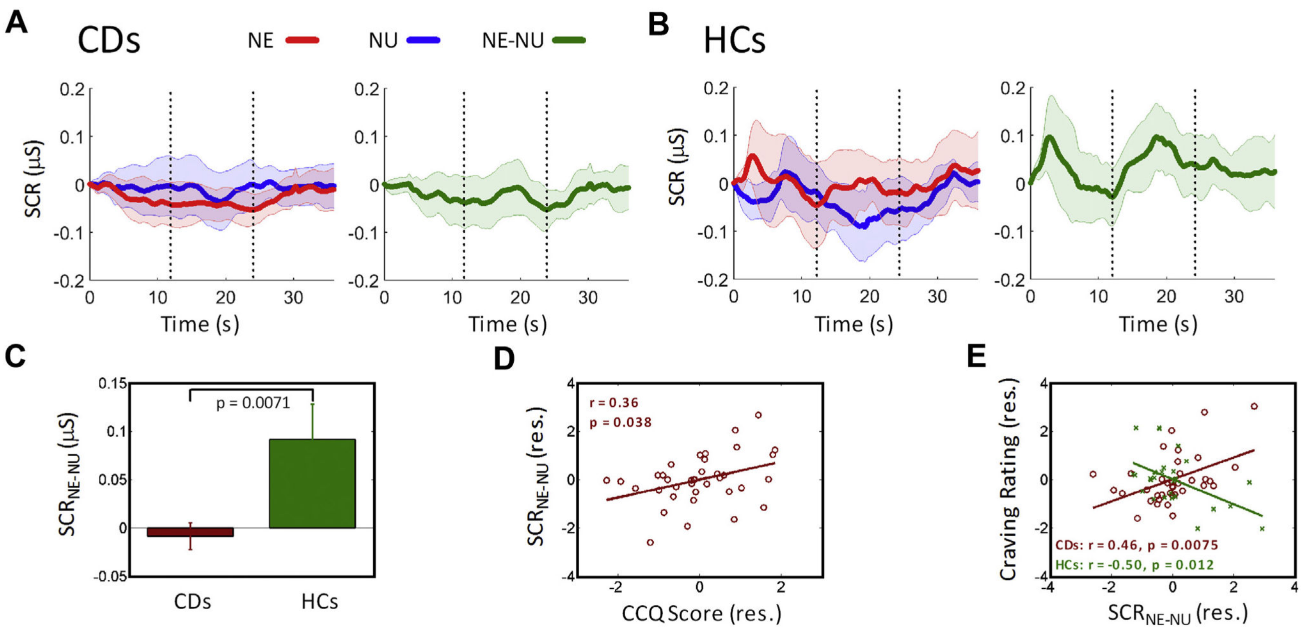

Figure 3.

Skin conductance responses (SCRs) to negative-emotional (NE) (red) and neutral (NU) (blue) images for **(A)** cocaine-dependent (CD) subjects and **(B)** healthy control (HC) subjects. (Right panel) Differences in SCR to NE vs. NU images (NE-NU) (green). **(C)** Histograms (mean ± SE) of the difference in SCR between the NE and NU blocks (SCR_{NE-NU}) during the middle 12-second window for CD subjects and HC subjects. **(D)** SCR_{NE-NU} was positively correlated with Cocaine Craving Questionnaire (CCQ) score in a linear regression with age, sex, years of drinking, and years of smoking as covariates, in CD subjects. **(E)** SCR_{NE-NU} was positively correlated with craving rating in CD subjects but was negatively correlated in HC subjects in a linear regression with age, sex, years of drinking, and years of smoking as covariates. Each data point represents 1 subject. res., residual.

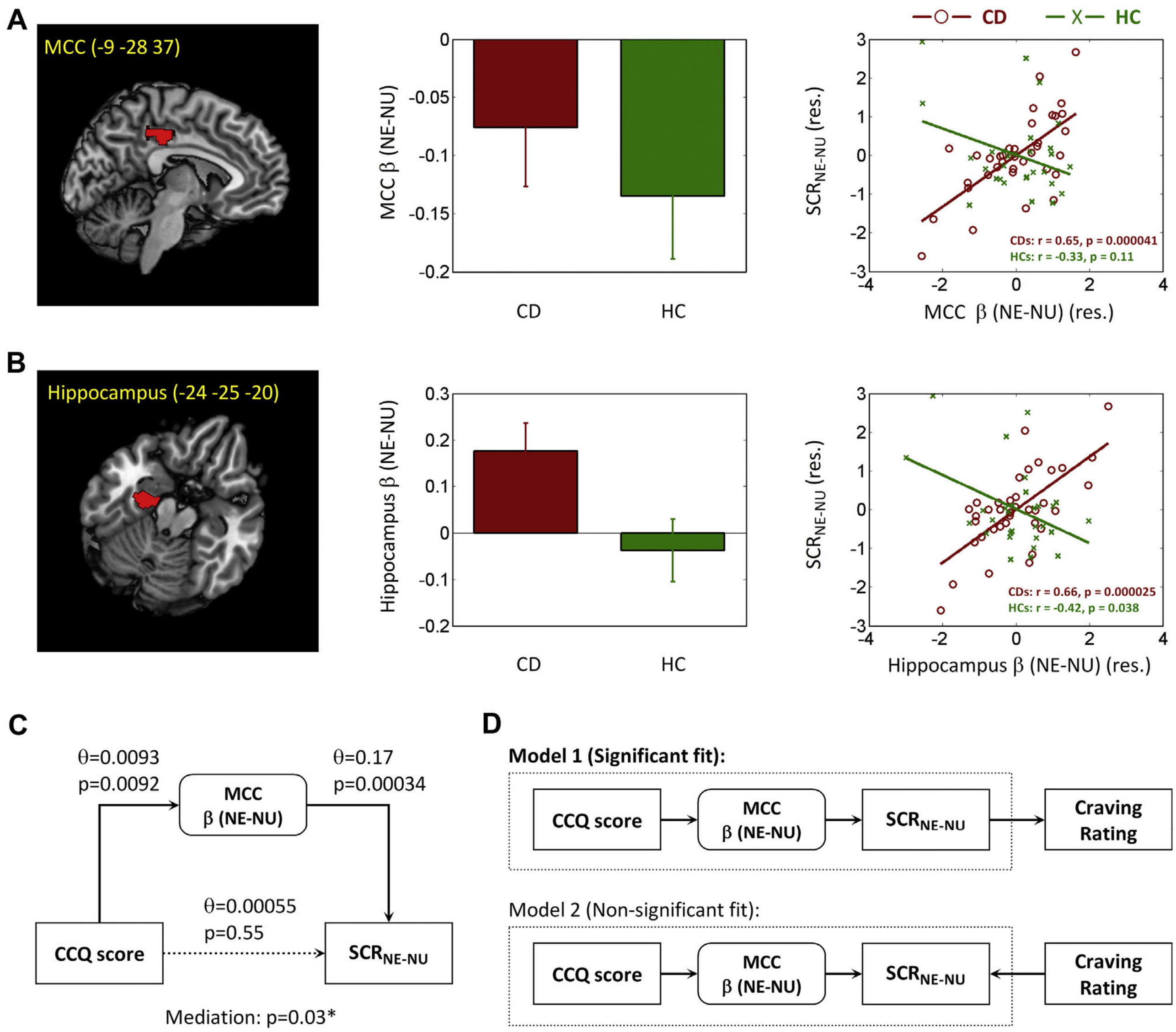

Figure 4.

(A) Midcingulate cortex (MCC) activation was positively correlated with the difference in skin conductance response (SCR) between the negative-emotional (NE) and neutral (NU) blocks (SCR_{NE-NU}) in cocaine-dependent (CD) subjects but not in healthy control (HC) subjects. **(B)** Hippocampus activation was positively correlated with SCR_{NE-NU} in CD subjects but was negatively correlated in HC subjects. Each data point represents 1 subject. **(C)** MCC activation completely mediated the correlation between Cocaine Craving Questionnaire (CCQ) score and SCR_{NE-NU}. **(D)** Path analysis suggested that model 1 (fit indices: root mean square error of approximation = 0.00 [90% confidence interval, 0.00–0.15], χ^2/df = 0.29, standardized root mean square residual = 0.03, and comparative fit index = 1.00) but not model 2 (fit indices: root mean square error of approximation = 0.02 [90% confidence interval, 0.00–0.32], χ^2/df = 0.18, standardized root mean square residual = 0.075, and comparative fit index = 0.99) showed a good fit. res., residual.

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Table 1.

Demographics and Clinical Measures of the Subjects

	All Subjects			SCR Subjects		
Characteristic	**CD Subjects (n = 40)**	**Healthy Control Subjects (n = 37)**	***p* Value**	**CD Subjects (n = 37)**	**Healthy Control Subjects (n = 29)**	***p* Value**
Age, Years	43.8 ± 7.6	41.8 ± 9.1	.31	44.0 ± 7.8	40.4 ± 9.0	.094
Sex, Male/Female	30/10	24/13	.33[a]	28/9	19/10	.37[a]
Duration of Drinking, Years	26.7 ± 10.4	24.1 ± 10.9	.29	27.0 ± 10.6	23.8 ± 10.5	.22
Duration of Smoking, Years	16.5 ± 12.9	2.0 ± 5.2	<.001[b]	15.9 ± 13.2	1.8 ± 4.7	<.001[b]
Duration of Cocaine Use, Years	15.3 ± 9.3	N/A	N/A	15.8 ± 9.3	N/A	N/A
CCQ Score	44.0 ± 14.5	N/A	N/A	45.1 ± 14.4	N/A	N/A
CSSA Score	32.8 ± 19.2	N/A	N/A	33.1 ± 19.3	N/A	N/A
Average Monthly Cocaine Use (Prior Year), g	30.2 ± 39.7	N/A	N/A	29.5 ± 38.9	N/A	N/A
Days of Cocaine Use (Prior Month)	20.0 ± 7.5	N/A	N/A	20.2 ± 7.3	N/A	N/A

Values are mean ± SD or *n*. The *p* values were based on 2-tailed, 2-sample *t* test, except for sex composition.

CCQ, Cocaine Craving Questionnaire; CD, cocaine-dependent; CSSA, Cocaine Selective Severity Assessment; N/A, not applicable; SCR, skin conductance response.

[a]Based on χ^2 test.

[b]$p < .05$.

Table 2.

Regions Showing Differences in Activations During Exposure to Negative-Emotional Versus Neutral Images Between CD Subjects and Healthy Control Subjects

		MNI Coordinate (mm)				
Volume (mm^3)	**Peak Voxel (Z)**	**x**	**y**	**z**	**Side**	**Identified Brain Region**
CD Subjects > Healthy Control Subjects						
4104	4.42	15	−4	22	R	Caudate
4185	4.40	−30	−37	37	L	Inferior parietal gyrus
1782	4.30	−15	−19	−14	L	Hippocampus
Healthy Control Subjects > CD Subjects – None						

Voxel $p < .001$ and cluster-level $p < .05$, whole-brain corrected for familywise error of multiple comparisons.

CD, cocaine-dependent; L, left; MNI, Montreal Neurological Institute; R, right.