Hyperresponsiveness of the Neural Fear Network During Fear Conditioning and Extinction Learning in Male Cocaine Users

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Objective: The authors investigated whether cocaine use disorder is associated with abnormalities in the neural underpinnings of aversive conditioning and extinction learning, as these processes may play an important role in the development and persistence of drug abuse.

Method: Forty male regular cocaine users and 51 male control subjects underwent a fear conditioning and extinction protocol during functional MRI. Skin conductance response was measured throughout the experiment as an index of conditioned responses.

Results: Cocaine users showed hyperresponsiveness of the amygdala and insula during fear conditioning, as well as hyporesponsiveness of the dorsomedial prefrontal cortex during extinction learning. In cocaine users, but not in control subjects, skin conductance responses were positively correlated with responsiveness of the insula, amygdala, and dorsomedial prefrontal cortex during fear conditioning but negatively correlated with responsiveness of the ventromedial prefrontal cortex during extinction learning.

Conclusions: Increased sensitivity to aversive conditioned cues in cocaine users might be a risk factor for stress-relief craving in cocaine use disorder. These results support the postulated role of altered aversive conditioning in cocaine use disorder and may be an important step in understanding the role of aversive learning in the pathology of cocaine use disorder.

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Cocaine is the second most commonly used illicit drug in Europe, particularly among young adult males, and it is often used in combination with alcohol and cannabis (1). There are no registered pharmacological treatments for cocaine addiction (2), although cognitive-behavioral therapy and contingency management have been shown to be fairly successful (3). Learning processes, including Pavlovian and instrumental conditioning, play an essential role in the development and persistence of substance use disorder (4). While these learning processes may form a potential treatment target (5), psychotherapies targeting conditioning have not yet been shown to be effective (6). A possible reason is that previous research has focused primarily on the learning mechanisms underlying appetitive conditioning (cue exposure treatment), while aversive conditioning may be equally important in the etiology and treatment of cocaine use disorder.

Through the process of appetitive conditioning, drug responses become associated with drug-related cues. When these drug-related cues are subsequently encountered in an abstinent state, they can trigger the retrieval of memories of previous drug experiences and thereby induce cue reactivity, craving, and drug-seeking and drug-taking behavior (7, 8). However, there is increasing evidence that aversive conditioning plays an equally important role in substance use disorder (9). First, stress-induced relief craving is a frequently observed phenomenon in addiction (10, 11), and addicted individuals are thought to take drugs to avoid aversive states such as stress (12, 13). Through the process of aversive conditioning, external stimuli can become associated with internal stress states, thereby (indirectly) motivating drug-seeking and drug-taking behavior itself (5, 14). Second, there is a high comorbidity between anxiety disorders and substance use disorder (15). Since abnormalities in aversive conditioning and extinction learning have been reported in anxiety disorders (16), similar abnormalities are expected to be found in substance use disorder. And third, the neural underpinnings of aversive and appetitive conditioning are thought to largely overlap, since the mesolimbic dopamine system is a key player in both types of conditioning and extinction learning (9). As a consequence, neuroadaptive

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changes within the mesolimbic dopamine system due to stress or drug use may also modulate the processing of appetitive conditioning or aversive conditioning, respectively (17–19). Knowledge about the role of aversive conditioning in substance use disorder could thus have important implications for understanding its pathophysiology and the development of prevention and treatment strategies. However, so far no studies have been reported on the neural and physiological underpinnings of aversive conditioning in substance use disorder.

From studies in healthy individuals, we know that aversively conditioned stimuli evoke an increase in skin conductance response (20) and activation of the neural fear network, including the amygdala, dorsomedial prefrontal cortex, and insula, and deactivation of the ventromedial prefrontal cortex (21, 22). Within this network, the amygdala, dorsomedial prefrontal cortex, and insula are involved in the expression of aversive conditioned responses, while the ventromedial prefrontal cortex is involved in the inhibition of conditioned behavior (21, 23, 24). Anxiety disorders are characterized by hyperresponsiveness of the amygdala, dorsomedial prefrontal cortex, and insula during fear learning and hyporesponsiveness of the ventromedial prefrontal cortex during extinction learning, reflecting the presence of enhanced fear learning and impaired fear extinction capabilities (25). Counterintuitively, these differences in neural plasticity are typically not associated with enhanced differential skin conductance responses (16, 26, 27).

In this study, we investigated the physiological (skin conductance responses) and neural (regional brain activation) correlates of fear conditioning and extinction in cocaine abusers and non-drug-using control subjects. While the neural and physiological underpinnings of aversive conditioning and extinction learning have not yet been investigated in substance use disorder, previous studies have demonstrated that substance use disorder is associated with hyperresponsiveness of the dorsomedial prefrontal cortex, insula, and amygdala to conditioned drug cues, a response that is slowly extinguished (6). We therefore hypothesized that cocaine abuse is associated with enhanced fear conditioning and impaired extinction learning, as reflected by hyperactivation of the amygdala, insula, and dorsomedial prefrontal cortex during fear conditioning and hypoactivation of the ventromedial prefrontal cortex during extinction learning as compared with control subjects.

METHOD

Participants

Seventy male regular cocaine users and 73 male control subjects were included in this study. Complete skin conductance response and MRI data sets were collected from 53 cocaine users and 58 control subjects. An additional three cocaine users and four control subjects were excluded because of MRI artifacts, resulting in the inclusion of 48 cocaine users and 54 control subjects. Participants were 18–50 years of age, and were recruited through local advertisements in the greater Amsterdam area. Cocaine users had to be actively using cocaine (at least once per week for a minimum of 6 months) and currently non–treatment seeking. Participants were screened using the Mini International Neuropsychiatric Interview (28). Exclusion criteria for all participants were major medical or neurological disease, a lifetime history of psychotic or bipolar disorders, current use of antidepressants or antipsychotics, and any contraindication for MRI scanning. Control subjects were excluded if they met DSM-IV criteria for lifetime substance abuse or dependence or currently took any psychotropic medications other than antidepressants or antipsychotics. Alcohol, cocaine, and cannabis use in the previous 6 months was quantified using the timeline followback procedure (29). Smoking severity was measured using the Fagerström Test for Nicotine Dependence, state anxiety was measured with the State-Trait Anxiety Inventory (30), and premorbid verbal intelligence was estimated using the Dutch version of the National Adult Reading Test (31). The study was approved by the Ethical Review Board of the Academic Medical Center of the University of Amsterdam. All participants gave written informed consent.

Experimental Paradigm

Briefly, the classical fear conditioning paradigm, which was conducted in the MRI scanner, consisted of habituation, conditioning, and extinction phases. The conditioned stimuli (CS) were yellow and blue squares, of which one (CS+) was followed by the unconditioned stimulus (US) in 33% of the conditioning trials. The CS− was never followed by the US. The US was an aversive electrical shock to the wrist. The shock intensity was set individually to be highly annoying but not painful. Skin conductance responses were measured simultaneously with functional MRI (fMRI) acquisition. Additional details are provided in the data supplement that accompanies the online edition of this article.

Imaging Data Acquisition and Analysis

Images were acquired on a 3-T Philips Achieva scanner and analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), including standard preprocessing and first-level modeling (see the data supplement). In accordance with previous studies, first-level contrasts were computed for the CS+ (unpaired to the US) and the CS− during the early and late conditioning phases and early and late extinction phases in order to assess temporal gradation of signal intensity (22). Early and late phases included the first and the last half of the CS+ and CS− trials, respectively. These contrast images were entered into a second-level full factorial design to investigate task and group effects.

A whole-brain correlation analysis was performed to investigate whether individual differences in conditioned responses measured by skin conductance and neural responses by fMRI were associated and whether these correlations during fear conditioning and extinction learning differed between groups. An additional whole-brain correlation analysis was performed to test for the possible confounding effects of

state anxiety, amount and type of substance use, and days since last use (see the online data supplement).

All analyses were family-wise-error-rate-corrected for multiple comparisons (cluster $p<0.05$, height threshold $p<0.01$). A small-volume correction was applied for the amygdala ($p<0.05$) because of its a priori role in aversive conditioning. With regard to the correlation analyses, interactions that assessed group differences in correlations were tested and followed by within-group correlation analyses when significant.

Statistical Analysis

Group differences in clinical characteristics were assessed using independent-samples t tests or nonparametric tests when appropriate. Stimulus-induced skin conductance responses were defined as the difference between maximum and minimum responses within 8 seconds after CS onset. Responses were divided by the largest response for that individual to account for individual differences and square-root-transformed (+1) to normalize the data. Subjects were said to show conditioned responses when differential skin conductance responses were positive in the first or second half of the conditioning phase. A repeated-measures analysis of variance was used, including CS type (CS+, CS−), phase (conditioning, extinction), and time (early, late) as within-subject factors, and group (controls, cocaine users) as a between-subject factor.

RESULTS

Clinical Characteristics

To enable the assessment of extinction learning, successful acquisition of fear conditioning is required. Of all subjects, 40 cocaine users (83%) and 51 control subjects (94%) showed a positive differential skin conductance response during early or late conditioning, which was not a statistically significant difference. In line with previous studies, the nonconditioners were excluded based on these physiological data (22), and all further analyses were conducted on the remaining subsamples (cocaine users, N=40; control subjects, N=51). The two groups were of similar age and IQ, but cocaine users scored significantly higher on state anxiety and weekly alcohol intake and had more comorbid DSM-IV diagnoses of depression and anxiety disorders (Table 1). On average, cocaine users used 7.6 g on 8.7 separate days on a monthly basis and had an onset age of 19.4 years, an average of 8.8 years of cocaine use, and 3 days since last use. All cocaine users met DSM-IV criteria for cocaine dependence or abuse. In addition, 86% of the cocaine users also smoked tobacco, and 45% used cannabis at least once a week.

Physiology

The median shock intensity did not differ significantly between groups (cocaine users, 2.8 mA; control subjects, 2.4 mA). The skin conductance response during conditioning and extinction revealed a significant CS type-by-phase interaction ($F=10.78$, $df=3, 87$, $p<0.001$). As expected, because of the exclusion of participants who did not show successful fear conditioning, paired-sample t tests revealed that both groups showed a significant CS+/CS− difference on skin conductance responses during early conditioning ($t=4.62$, $df=90$, $p<0.001$) and late conditioning ($t=7.39$, $df=90$, $p<0.001$), but also during early extinction ($t=3.24$, $df=90$, $p=0.002$). No significant CS+>CS− differences in skin conductance response were observed during late extinction, indicating successful extinction learning. Similar to previous findings in anxiety disorders, there was no significant group-by-CS type-by-phase interaction, indicating equal levels of fear conditioning and extinction learning between groups on a physiological level (Figure 1).

Neuroimaging

The four-way interaction between group, phase, time, and CS type was nonsignificant. Because fear conditioning and extinction are qualitatively distinct processes and neural responses during fear learning show a strong temporal gradation in signal intention, group differences in fear learning were investigated for each phase separately, in line with previous studies (e.g., 22, 32).

Fear conditioning. During fear conditioning, both groups displayed significant activation in the neural fear network for the CS+>CS− contrast, including the insula, dorsomedial prefrontal cortex, amygdala, and superior temporal cortex (see Table S1 in the online data supplement), reflecting fear conditioning on the neural level. Between-group analysis revealed that, compared with control subjects, cocaine users exhibited recruitment of the left amygdala and several cerebellar and occipital regions during early conditioning (Figure 2A, Table 2) and enhanced recruitment of the left insula and rolandic operculum during late conditioning (Figure 2B, Table 2). These results are consistent with the hypothesis that cocaine users exhibit neural hyperresponsivity during fear conditioning.

In addition, conditioned skin conductance responses and conditioned neural responses were significantly correlated across subjects (see Table S2 in the data supplement). An interaction analysis showed that the correlation between the skin conductance response and activity of the right amygdala and several regions within the prefrontal cortex was significantly different between groups (Figure 2C, Table 2). Follow-up tests showed a significant positive correlation in cocaine users but not in control subjects.

Extinction learning. During early and late extinction, the CS+>CS− contrast was associated with significant activation of the insula, dorsomedial prefrontal cortex, and supramarginal gyrus. The CS−>CS+ contrast was associated with significant activation of the ventromedial prefrontal cortex, the superior and middle frontal cortex, and several regions within the occipital and temporal cortices (see Table S1 in the data supplement). There were no significant between-group differences during early extinction. However, during late extinction, cocaine users showed

TABLE 1. Demographic and Clinical Characteristics of Regular Cocaine Users and Control Subjects

Variable	Cocaine Users (N=40)		Control Subjects (N=51)		p
	Mean	SD	Mean	SD	
Age (years)	31.3	7.9	31.0	8.5	n.s.
IQ	101.4	8.4	104.0	9.2	n.s.
Alcohol use (standard units per week)	19.9	35.4	4.1	3.5	<0.001
	Median	IQR	Median	IQR	
Fagerström Test for Nicotine Dependence	5.0	2.0			
Grams of cocaine use per month	7.6	5.5			
Duration of cocaine use (years)	8.8	6.4			
Frequency of cocaine use (days/month)	8.7	5.8			
Age at onset of cocaine use (years)	19.4	5.1			
Days since last use	3.0	2.0			
State anxiety score (State-Trait Anxiety Inventory)	35.0	17.0	28.0	7.0	<0.001
Shock intensity (mA)	2.8	1.4	2.4	1.8	n.s.
	N	%	N	%	
Smoker	34	86.0	0	0.0	<0.001
Lifetime history of DSM-IV depression	13	32.5	3	5.9	0.002
Lifetime history of a DSM-IV anxiety disorder	4	10.0	0	0.0	0.032

reduced activation in the dorsomedial prefrontal cortex compared with controls (Figure 3A, Table 2). This suggests that cocaine users exhibit enhanced extinction of dorsomedial prefrontal cortex fear responses.

Similar to the findings obtained during conditioning, an interaction analysis showed that the correlation between the skin conductance response and activity of the ventromedial prefrontal cortex and the parietal cortex was significantly different between groups during early extinction (Figure 3B, Table 2). Within-group analyses showed a significant negative correlation in cocaine users but not in control subjects. In addition, the correlation between skin conductance response and activation in the insula, left amygdala, and left and right superior temporal gyrus was significantly different between groups during late extinction (Figure 3C, Table 2). Within-group analysis showed a significant positive correlation in cocaine users but not in control subjects. These results suggest that reduced fear expression on a physiological level is related to enhanced ventromedial prefrontal cortex activity and reduced dorsomedial prefrontal cortex activity.

The Effect of State Anxiety and Polysubstance Use

To explore the effects of the level of substance use, light and heavy users of cocaine, cannabis, alcohol, and nicotine were compared. The neural correlates of aversive conditioning were unrelated to state anxiety, the amount and type of substance (cocaine, cannabis, alcohol, and nicotine) used, or days since last use. During extinction learning, there was a negative relation between the amount of cannabis used and responsiveness of the superior temporal, middle temporal, and inferior frontal cortex and a positive relation between the amount of cocaine used and responsiveness of the left insula, lateral prefrontal cortex, and parietal and occipital cortices (see Figure S3A,B and Table S3 in the data supplement). Nicotine and alcohol use were unrelated to the neural correlates of extinction learning. Regression analysis showed that state anxiety was negatively correlated with activation of the cerebellum during late extinction (see Figure 3C and Table S3).

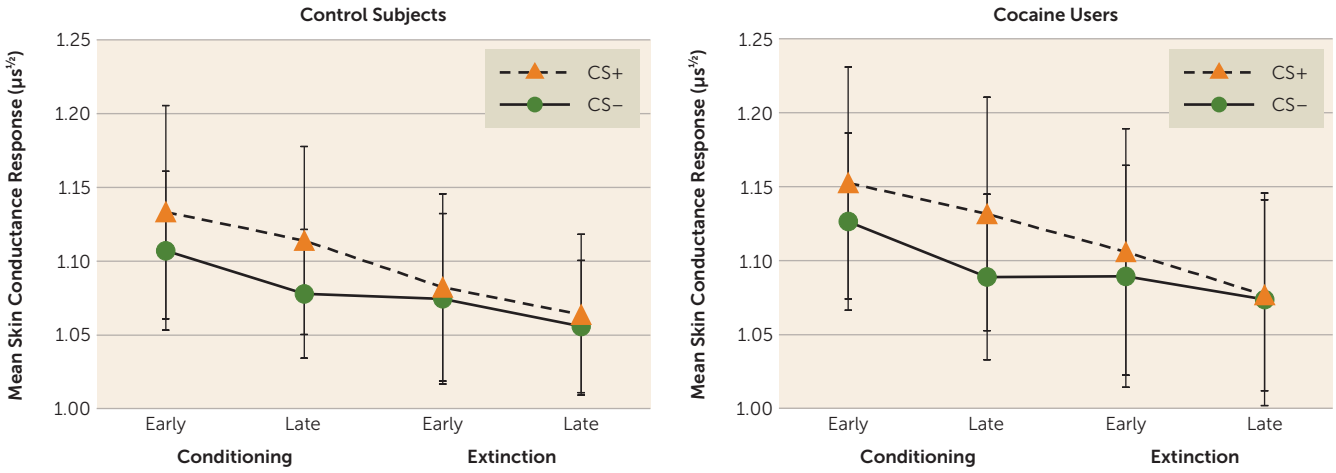
DISCUSSION

Although aversive conditioning and extinction learning have been suggested to play an important role in the development and persistence of drug abuse (5, 14, 24), this is, to our knowledge, the first study addressing the physiological and neural mechanisms underlying aversive conditioning and extinction learning in substance use disorder. Consistent with the hypothesis of enhanced aversive conditioning in substance use disorder, cocaine users showed hyperactivity of the amygdala and insula during aversive conditioning compared with control subjects. Inconsistent with the hypothesis of impaired extinction learning, cocaine users showed hypoactivation of the dorsomedial prefrontal cortex during late extinction, suggesting enhanced extinction learning compared with control subjects.

While there were no group differences in skin conductance response during aversive conditioning or extinction learning, skin conductance response and activation of the neural fear network were more strongly correlated across subjects in cocaine users than in control subjects, suggesting that the emotional response to conditioned stimuli is stronger in cocaine users than in control subjects. Overall, these findings support the postulated role of abnormal aversive learning processes in substance use disorder.

The amygdala is important for the rapid encoding of new stimulus-threat relationships (22), while the insula modulates the visceral response to conditioned stimuli (24). The dorsomedial prefrontal cortex is suggested to be involved in conscious negative appraisal of threat. These brain regions are key structures within a neural fear network, and previous studies have repeatedly demonstrated that activation of these regions is associated with fear conditioning and extinction learning (22), is enhanced in individuals with enhanced fear learning and impaired extinction learning (25), and is related to other measures of conditioned behavior, including skin conductance response (20). The finding of increased amygdala and insula activation during fear conditioning and reduced dorsomedial prefrontal cortex activation during late extinction in cocaine users therefore suggests that cocaine users exhibit enhanced fear

FIGURE 1. Mean Skin Conductance Response in Cocaine Users and Control Subjects[a]



[a] Error bars indicate standard deviation. There was a significant differential skin conductance response during early and late conditioning and early extinction, in both groups. No significant group differences in skin conductance response were demonstrated.

conditioning as well as enhanced extinction learning compared with control subjects.

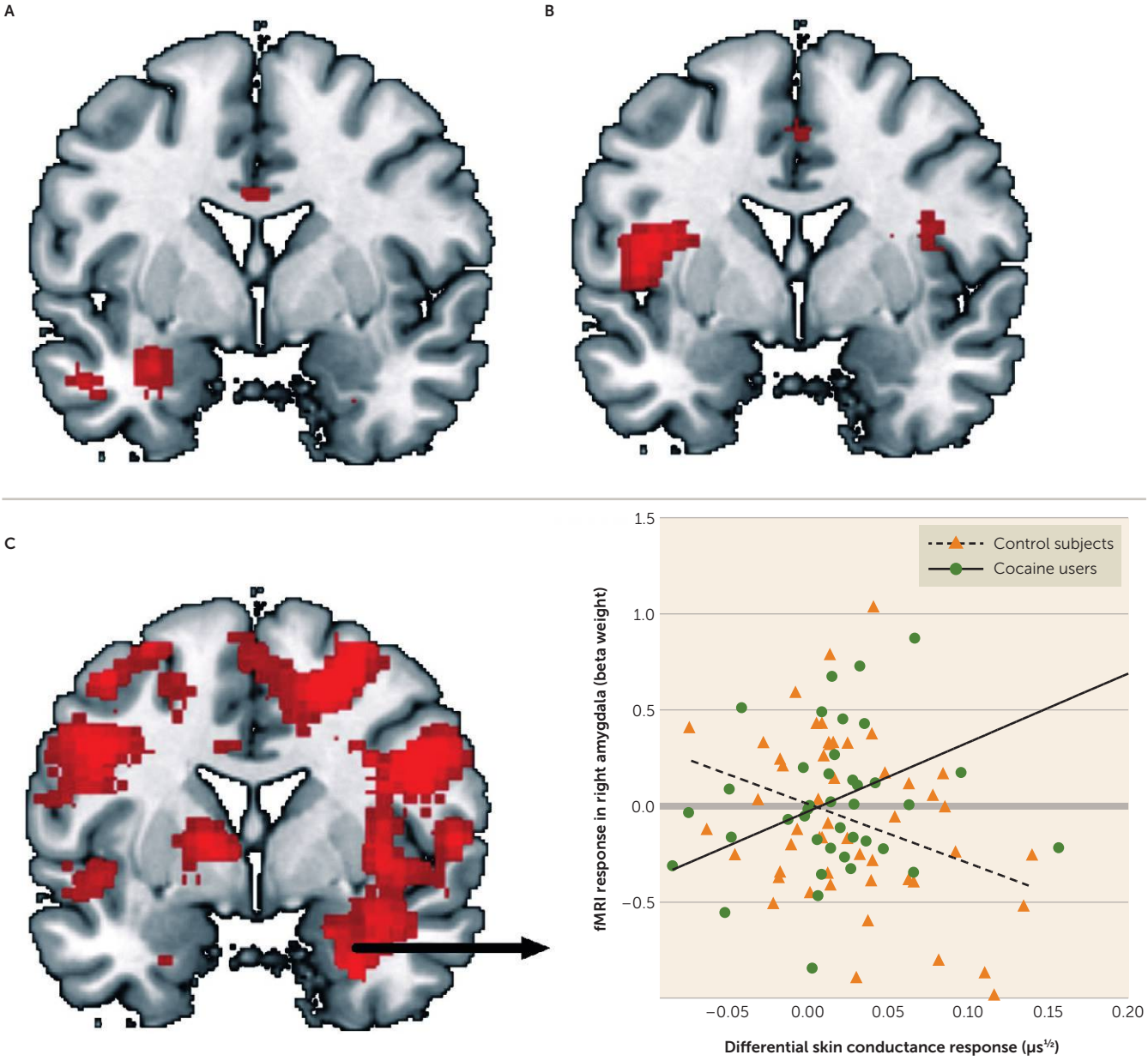
Increased amygdala activity in cocaine users during early conditioning may reflect increased attention for threat-related stimuli and enhanced aversive conditioning, followed by increased activity of the insula during late conditioning, which may reflect enhanced visceral processing. Increased responsiveness of these structures within the neural fear network are thought to underlie negative reinforcement mechanisms in substance use disorder, stress-induced relief craving, and subsequent continuation of or relapse into drug use (13, 18, 24, 33). Abnormalities in the neural underpinnings of aversive conditioning in cocaine users may therefore reflect a risk for cocaine abuse and relapse.

In contrast to our hypotheses, cocaine users showed reduced activity of the dorsomedial prefrontal cortex during late extinction, suggesting the presence of superior, and not impaired, extinction learning. While enhanced fear extinction learning may be beneficial in anxiety disorders, it may actually form a risk for the persistence of drug use, as it may underlie an inability to modify behavior in response to negative outcomes, resulting in risky behavior (34). Future studies should, however, investigate whether these difference are also present after reinstatement of the fear conditioned response. Irrespective of whether enhanced extinction of neural fear conditioned responses is good or bad, our data demonstrate that the neural underpinnings of fear extinction learning in cocaine users differ from those in patients with an anxiety disorder (16, 21, 22, 27, 35). While the relation between enhanced fear extinction learning and stress relief craving remains to be investigated, these findings may explain why cue exposure treatment, which is a successful treatment strategy in anxiety disorders, is not as effective in addiction (6).

In line with the typical observation in anxiety disorders, we found no group differences in differential skin conductance responses (16, 26, 27). Although these results could be interpreted as less efficient neural processing in cocaine users, there is substantial evidence that hyperactivation of the amygdala, insula, and dorsomedial prefrontal cortex reflects the persistence of an increased expression of conditioned fear (22). However, there are several other explanations for the dissociation between the skin conductance response and fMRI results. First, differential skin conductance responses are suggested to be more dependent on higher cognitive levels of learning, whereas differential activation of the neural fear network is suggested to be independent of higher cognitive processing (20). This would suggest that cocaine abuse is associated with abnormalities in fear conditioning and fear extinction that are mainly dependent on unconscious processes. Furthermore, the finding that the skin conductance response and fMRI data are significantly correlated in cocaine users but not in control subjects may indicate that skin conductance responses in cocaine users are less dependent on conscious processing of conditioned cues. Alternatively, it has demonstrated that the amygdala plays a critical role in the modulation of skin conductance responses to threat (36). Therefore, these results may indicate that cocaine users have a stronger emotional response to stimuli that predict an aversive outcome. In addition, several studies in anxiety disorders found that although there were no group differences in skin conductance responses during fear conditioning or extinction learning, differences were present during extinction recall (27). Thus, it could be that differences in neural processing precede differences in skin conductance responses, which can be detected only during extinction recall. Altogether, skin conductance responses may not be sensitive and fear-specific enough to detect small group differences during fear conditioning or extinction learning (37).

While sensitivity to stress has long been known to be an important risk factor for substance use and relapse (12), this is one of the first studies to investigate the potential neural mechanisms that underlie this phenomenon. We demonstrated that the neural fear network of regular cocaine users is hyperresponsive to cues that predict a negative outcome.

FIGURE 2. Neural Correlates of Aversive Conditioning and Correlation With Skin Conductance Responses in Cocaine Users and Control Subjects[a]



[a] Cocaine users exhibited hyperactivation of the left amygdala (panel A) and left insula (panel B) during early conditioning and late conditioning, respectively. The correlation between skin conductance responses and activation of the neural fear network was significantly stronger in cocaine users compared with control subjects (panel C). The scatterplot shows, for all subjects, the beta weight of the peak voxel in the amygdala (Montreal Neurological Institute coordinates [x, y, z]: 30, −4, 28) as a result of the whole brain comparison, against the differential skin conductance responses during early conditioning.

These findings emphasize that in addition to reducing drug-conditioned responses (reward craving), treatment should also try to reduce the (neural) sensitivity to stressors (relief craving). This could be achieved by means of cognitive-behavioral treatment (e.g., mindfulness-based relapse prevention [38]) or pharmaceutical treatments that target the noradrenergic stress system (e.g., propranolol [39]).

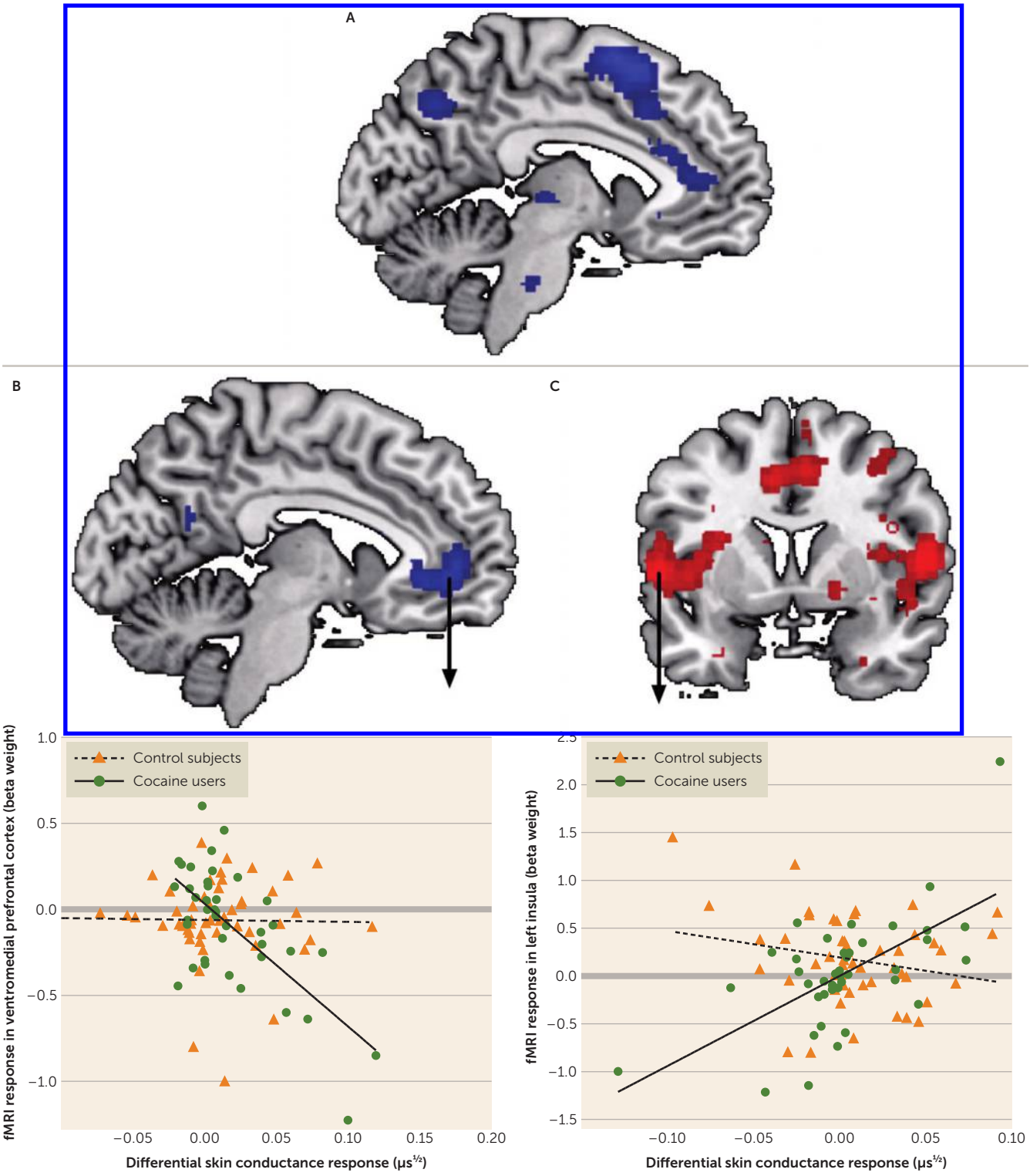
An important strength of this study is the large sample size and the assessment of the potential confounding effect of state anxiety. However, the study also has limitations. First, because only male participants were included in the study, these results may not generalize to female cocaine users. Second, because of the cross-sectional design, we need to be cautious with statements about the causality of our findings, and future studies should examine whether increased neural sensitivity for aversive events is a risk factor for cocaine abuse, a consequence of cocaine abuse, or a combination of the two. Third, most cocaine users in our sample also used cannabis,

TABLE 2. Neural Correlates of Aversive Conditioning and Extinction Group Effects and Interactions With Skin Conductance Responses[a]

Effect	Cluster Size (Voxels)	Cluster p	Voxel z	Peak Voxel MNI Coordinates			Voxel Region	Direction of Effect
Early conditioning (CS+>CS−)								
Group effects	1,032	0.016	3.48	−2	−50	−6	Vermis	CU > HC
			3.07	−6	−52	2	L lingual gyrus	
			2.69	−2	−48	18	L posterior cingulate gyrus	
			3.02	2	−44	16	R posterior cingulate gyrus	
			2.98	−4	−74	−24	L cerebellum	
			2.66	−10	−50	16	L precuneus	
	45	0.022[b]	3.15	−30	0	−22	L amygdala	CU > HC
Group-by-skin conductance response interaction	36,333	<0.001	5.27	38	−30	58	R postcentral gyrus	CU[c] / HC[d]
			5.14	−26	−20	58	L precentral gyrus	
			5.24	38	−20	56	R precentral gyrus	
			4.94	24	0	54	R superior frontal gyrus	
			4.84	4	−22	46	R middle cingulate gyrus	
			4.66	4	−32	60	R paracentral lobule	
			4.65	44	−22	14	R Heschl's gyrus	
			4.61	−18	−42	−28	L cerebellum	
	721	0.037	4.85	42	48	10	R middle frontal gyrus	CU[c] / HC[d]
			3.06	46	34	−6	R inferior frontal gyrus	
	687	0.045	4.49	−40	44	22	L middle frontal gyrus	CU[c] / HC[d]
			3.65	−40	30	22	L inferior frontal gyrus	
			3.24	−26	58	10	L superior frontal gyrus	
	139	0.001	4.07	30	−4	−28	R amygdala	CU[c] / HC[d]
Late conditioning (CS+>CS−)								
Group effects	915	0.029	3.87	−42	−2	16	L rolandic operculum	CU > HC
			3.61	−36	0	16	L insula	
Group-by-skin conductance response interaction	No significant interaction							
Early extinction (CS+>CS−)								
Group effects	No significant effects							
Group-by-skin conductance response interaction	1,368	0.004	3.92	−10	48	0	L anterior cingulate gyrus	CU[e] / HC[d]
			3.91	−28	28	−14	L inferior frontal gyrus	
			3.90	−12	46	6	L superior frontal gyrus	
			3.14	10	44	−8	R orbital frontal gyrus	
Late extinction (CS+>CS−)								
Group effects	4,691	<0.001	4.58	−10	8	62	L superior motor area	HC > CU
			3.99	14	36	20	R anterior cingulate gyrus	
			3.78	−40	2	52	L middle frontal gyrus	
			3.63	10	22	54	R superior motor area	
			3.39	18	26	46	R superior frontal gyrus	
Group-by-skin conductance response interaction	3,060	<0.001	4.49	−52	−2	6	L rolandic operculum	
			3.71	−44	−14	10	L Heschl's gyrus	
			3.63	−50	−24	28	L postcentral gyrus	
			3.59	−52	−28	28	L supramarginal gyrus	
			3.56	−58	−20	8	L superior temporal gyrus	
			3.54	−38	−20	12	L insula	
	3,670	<0.001	3.81	50	−18	26	R supramarginal gyrus	
			3.68	50	−8	−10	R superior temporal gyrus	
			3.64	56	4	8	R rolandic operculum	

[a] All results were $p<0.05$, cluster-level family-wise error corrected, with an initial height threshold of $p=0.01$, uncorrected. CU=cocaine users; HC=healthy control subjects; MNI=Montreal Neurological Institute.
[b] Corrected for the volume of the right amygdala, $p_{peak\ voxel}<0.05$.
[c] Significant positive correlation.
[d] Nonsignificant relation.
[e] Significant negative correlation.

FIGURE 3. Neural Correlates of Extinction Learning and Correlation With Skin Conductance Responses in Cocaine Users and Control Subjects[a]



[a] Cocaine users exhibited hypoactivation of the dorsomedial prefrontal cortex during late extinction (panel A). They also exhibited significantly stronger negative correlations between activation of the ventromedial prefrontal cortex (Montreal Neurological Institute coordinates [x, y, z]: 10, 44, −8) and skin conductance responses during early extinction (panel B) and significantly stronger positive correlations between activation of the neural fear network, including the left insula (coordinates: −38, −28, −12) and skin conductance responses during late extinction (panel C). The scatterplot shows, for all subjects, the beta weights of the peak voxel resulting from the whole brain analysis against the skin conductance responses during early and late extinction.

alcohol, and nicotine on a regular basis, thereby making it impossible to tell whether differences in aversive conditioning are related to cocaine, cannabis, or alcohol use or to some combination of these. Nevertheless, the exploratory analysis suggested that hyperresponsiveness of the amygdala and insula during aversive conditioning and hyporesponsiveness of the dorsomedial prefrontal cortex during late extinction learning are independent of the type or amount of substance used. Moreover, as polysubstance use is common among cocaine users in treatment (1), we expect that our sample reflects typical cocaine users. Fourth, we tested for group differences during early and late conditioning, as well as early and late extinction, while there was no phase-by-group interaction effect. Although this is in accordance with most studies in the field (22), it should be noted that such statistical flexibility could increase type I errors. Finally, while the neural pathways that underlie aversive and appetitive conditioning and extinction overlap, more research is needed to investigate whether and how enhanced neural sensitivity to aversive conditioned cues and enhanced sensitivity to drug-conditioned cues are related.

In summary, we found that cocaine use disorder is associated with hyperresponsiveness of the neural fear network during fear conditioning and extinction learning, possibly reflecting enhanced fear learning. Although the relationship between aversive conditioning and stress-induced relief craving remains to be investigated, this study is an important contribution to the understanding of the role of aversive conditioning in, and the etiology of, substance use disorder.

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