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Limbic Activation During Cue-Induced Cocaine Craving

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Abstract

Objective—Since signals for cocaine induce limbic brain activation in animals and cocaine craving in humans, the objective of this study was to test whether limbic activation occurs during cue-induced craving in humans.

Method—Using positron emission tomography, the researchers measured relative regional cerebral blood flow (CBF) in limbic and comparison brain regions of 14 detoxified male cocaine users and six cocaine-naive comparison subjects during exposure to both non-drug-related and cocaine-related videos and during resting baseline conditions.

Results—During the cocaine video, the cocaine users experienced craving and showed a pattern of increases in limbic (amygdala and anterior cingulate) CBF and decreases in basal ganglia CBF relative to their responses to the nondrug video. This pattern did not occur in the cocaine-naive comparison subjects, and the two groups did not differ in their responses in the comparison regions (i.e., the dorsolateral prefrontal cortex, cerebellum, thalamus, and visual cortex).

Conclusions—These findings indicate that limbic activation is one component of cue-induced cocaine craving. Limbic activation may be similarly involved in appetitive craving for other drugs and for natural rewards.

Craving for a drug is a cardinal feature of addictive disorders and is clinically significant because of its potential to trigger drug use and relapse (1). The cocaine epidemic in the United States has prompted an intensive, largely unsuccessful search for medications to treat cocaine craving (2,3). This search has likely been complicated by a heterogeneous target: drug desire that emerges during cocaine cessation (4) may well have a different brain substrate than desire induced by cocaine itself (5) and the cues that signal it (6). Noninvasive brain imaging studies have recently begun to examine the brain substrates of both withdrawal-based craving (7,8) and cue-induced craving (9–11) in humans. We present here a hypothesis-guided imaging study of cue-induced cocaine craving in which we used evocative video cues from our prior work, which measured peripheral and subjective correlates of that state (6,12–14).

Human cocaine users often experience profound desire for the drug when they encounter cues (people, places, paraphernalia, etc.) associated with cocaine (6,15). Cue-induced cocaine craving is sometimes accompanied by a number of signs and symptoms similar to the effects

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of cocaine itself, including generalized arousal, palpitations, light-headedness, ear ringing, chest tightness, the “taste” of cocaine in the back of the throat, and even euphoria (1). The druglike nature of these responses led us to hypothesize that brain structures activated during cocaine craving may be among those activated by cocaine itself, including the dopamine-innervated limbic regions implicated in cocaine's pleasurable effects (16–18). Consistent with this hypothesis, cocaine itself triggers craving (5). Further, signals for rewards—whether cocaine (19–21), food (22), or sex (23)—reliably activate limbic brain regions in rats.

We tested whether limbic-related regions (the amygdala, anterior cingulate, temporal pole, hippocampus, and orbitofrontal cortex) may be differentially activated during cue-induced cocaine craving by measuring regional cerebral blood flow (CBF) (24) in cocaine-dependent patients and cocaine-naive comparison subjects during exposure to non-drug-related and cocaine-related videos in a single positron emission tomography (PET) session. Several comparison regions (the basal ganglia, cerebellum, dorsolateral prefrontal cortex, thalamus, and visual cortices) were also monitored to determine regional specificity of the cue effects. Initial resting regional CBF was used for subsequent baseline comparison of the two groups, to determine their comparability before exposure to the cue.

METHOD

The subjects were 20 right-handed men who gave written informed consent to participate after hearing and reading a description of the study procedures. The 14 cocaine patients were in treatment at either the Philadelphia VA Medical Center or the Treatment Research Center at the University of Pennsylvania School of Medicine. All patients met the DSM-III-R criteria for cocaine dependence; they reported an average of 8.1 years of cocaine use and 3.4 prior treatment admissions for the disorder. On average, 13.5 days had elapsed since their last reported use of cocaine. The patients’ average age was 37, and 86% (N=12) were African American, reflecting the local treatment demographics for cocaine dependence. On screening interview, all subjects acknowledged a prior history of cocaine craving in response to real-world cocaine cues.

The critical selection factor for comparison subjects was lifelong abstinence from cocaine. Since media advertising for paid medical experiments attracts local drug users, the six comparison subjects were instead recruited by approaching men whose cocaine-free history was known to the research staff through at least one collateral source. These comparison subjects self-reported no history of cocaine use, and all gave cocaine-free urine samples during screening. With these stringent screening criteria, the comparison group was younger (mean age=27 years) than the patient group (unpaired t test, two-tailed: $t=-3.16$, $df=19$, $p<0.05$) and had more formal education (mean=15.5 years versus 12.9 years) ($t=2.46$, $df=19$, $p<0.05$); two (33%) of these six subjects were African American. The comparison subjects and patients did not differ on report of monthly income, history of regular alcohol use, or alcohol use within the past 30 days (all p values >0.05).

Exclusion criteria for both groups included diagnoses of current alcohol dependence, current or past history of opiate dependence, formal thought disorder, organicity, or neurological abnormalities detected on structural magnetic resonance imaging (MRI). PET data from three additional study candidates were excluded because of cyclotron failure during image acquisition, claustrophobia preventing the MRI necessary for coregistration, and unusable arterial data.

Scans

On the day of scanning, just before the PET session, an intravenous line was placed in the subject's left arm to permit continuous infusion of ^{15}O-labeled water, the flow tracer. An intra-

arterial catheter was placed in the subject's right arm to permit the blood sampling (at 2.5-minute intervals during each scan) that was necessary for kinetic modeling of flow. To minimize movement during scanning, the subject's head was stabilized in a rigid, foam-lined head holder. Six sequential 10-minute PET scans were obtained during an 86-minute session featuring an initial resting baseline, a non-drug-related video, a second (recovery) baseline, and a cocaine-related video. Both initial baseline and recovery baseline scans were obtained during resting conditions (eyes and ears open; room lighting reduced by half). Two contiguous scans were obtained during each of the videos; counts were later averaged for each video prior to flow conversion.

Each video was 25 minutes in length and was begun 5 minutes in advance of PET scanning. Both videos contained a soundtrack. The nondrug video featured a nature story/travelogue from public television; the cocaine video featured the simulated purchase, preparation, and smoking of crack cocaine. Because craving and arousal often persist beyond the cocaine video, it was necessarily presented after the nondrug video. Immediately after the PET session, each patient had a supportive “talk-down” with a trained clinician.

Behavioral Measures

Self-ratings of cocaine-related states were obtained with the use of a modification of the Within Session Rating Scale for Cocaine (available from the first author on request), a 10-item scale asking about the high, craving, and withdrawal related to cocaine and to other drugs, along with items probing “wish for rush,” “wish to get rid of bad feelings,” relaxation/tension, and global well-being. The questions were asked by a trained research assistant, and each item was rated aloud by the patient on a scale ranging from 0 (not at all) to 9 (the most ever). The scale was administered before and after each video, and change scores (postvideo minus prevideo) were used for the statistical analyses.

Image Analysis

The CBF for each region of interest was determined through a multistage process involving cross-registration of each subject's MRI with the functional PET image (25). In brief, the PENN-PET 240H camera (UGM, Philadelphia) (spatial resolution=5.5 mm full width at half maximum in all directions near the center of the field) imaged brain activity with the steady-state method, with a constant infusion of ^{15}O-labeled water as the flow tracer. Radioactive counts corrected for axial nonuniformity, scatter, and attenuation were reconstructed with 2-mm sampling in all three directions, resulting in 64 transaxial slices. The PET images and MRI for each subject were then rotated and resliced in planes parallel to a line connecting the anterior commissure to the posterior commissure. Anatomical regions of interest based on the atlas of Talairach and Tournoux (26) were hand-drawn on the relevant MRI slices by a trained investigator (P.D.M.) and were subsequently transposed onto the resliced PET images. Whole brain boundaries were used to transpose the set of regions of interest onto the images of each scan condition. Cross-registered scans were checked and corrected for misalignments indicating subject movement between the scans of a session. The mean counts per pixel in the regions of interest were imported into a relational data base for conversion into absolute flows with the use of the arterial blood curve and a standard kinetic model (flow=[decay constant * count concentration for region of interest]/[arterial counts – (count concentration for region of interest/partition coefficient)]). Absolute flows for each region were further normalized (to whole brain flow) for use in the statistical analyses. The resulting relative flow measures are useful where the primary question is regional distribution of CBF, as in this study.

Normalized regional CBF was determined for regions of interest (the amygdala, anterior cingulate, temporal pole, hippocampal complex, and orbitofrontal area) within the brain's limbic circuitry, long thought to be important for integrated emotional experience and

emotional learning (27–30). (The nucleus accumbens is unfortunately too small in humans for resolution with the current PET technology.) The comparison regions were either outside traditional limbic circuits (cerebellum, visual cortices, and dorsolateral prefrontal cortex) or in known afferent relation (thalamus) or efferent relation (caudate and lenticular nuclei) to them. Activity in the thalamus and in visual cortices served as a monitor for comparability of the two stimulus videotapes in sensory load and visual attention, respectively. Data on all regions except the cerebellum were collected bilaterally.

Data Analysis

Change in subjective state during the videos (postvideo minus prevideo) was compared both within the patient group (paired t tests, two-tailed) and between the patient group and the comparison group (one-way analysis of variance [ANOVA]) for each of the scale items.

Change in relative regional CBF in response to the two videos (cocaine video minus nondrug video) was compared within the cocaine patients (paired t tests, two-tailed) and between the patients and the comparison subjects (repeated measures ANOVA, with group as a between factor and laterality as a within factor) for both limbic and comparison regions of interest. Initial baseline activity was also compared (one-way ANOVA) between patients and comparison subjects, as prior literature has suggested limbic hypoactivity during cocaine cessation (4,31–33). Correlations (Pearson's r, t transform) were used to examine the relationship between video-related changes in regional CBF and clinical status variables or resting flow.

We selected an alpha level of $p<0.05$ for both the subjective and regional CBF analyses, with the explicit prediction that cocaine cues would induce a positive, appetitive state and limbic activation in the cocaine patients. In specificity designs such as this one, where a number of null results (e.g., effects on aversive subjective ratings and nonlimbic regional CBF) are explicitly predicted, a correction for multiple comparisons could inflate the rate of null findings and thus was not used.

RESULTS

Cue-Induced Subjective Effects

Cocaine craving, high, and wish for rush increased significantly during the cocaine video for the cocaine patient group (figure 1), characterizing an appetitive, druglike desire state. As expected, the cocaine-naive comparison subjects did not report cocaine craving or other cocaine-related responses and thus differed significantly from the cocaine patients on these items. Changes in wish to get rid of bad feelings, cocaine withdrawal, relaxation/tension, and global well-being did not differ significantly either within or between groups (all p values >0.10).

Regional CBF During Video Stimuli

Relative blood flow response to the two videos was analyzed within and between patients and comparison subjects (figure 2) and with respect to laterality. For limbic regions, the cocaine patients showed reliable increases in relative regional CBF in the amygdala (mean=0.125, SD=0.072), anterior cingulate (mean= 0.066, SD=0.090), and temporal pole (mean=0.060, SD=0.050) during the cocaine video compared with the nondrug video. The comparison subjects did not show significant changes between videos by this comparison (all p values >0.10).

The cocaine patients differed significantly from the comparison subjects in relative flow increases in the amygdala and anterior cingulate. The cue effect in the patients was often larger

for the left amygdala (mean relative increase=0.150, SD=0.090) than for the right amygdala (mean=0.106, SD=0.090), although this change fell short of significance (group-by-laterality interaction F=2.92, df=1, 18, p=0.10). Changes in regional CBF in response to the cocaine video in the amygdala and anterior cingulate did not correlate with age (r=–0.29, df=12, p=0.31, and r=0.00, df=12, p=0.99, respectively) or with years of education (r=0.05, df=12, p=0.86, and r=0.40, df=12, p=0.15, respectively), the two demographic variables on which the patients differed from the comparison subjects. Activation of the amygdala and anterior cingulate during the two videos is illustrated by the images from a cocaine patient in figure 3.

The amygdalar and cingulate response in cocaine patients was a change (differential increase) in regional CBF in response to the cocaine video, although the patients' relative regional CBF was not greater than that of the comparison subjects in response to the same video. This pattern reflects the lower initial values for both of these regions in the patient group (see Baseline Regional CBF). Initial hypoactivity neither blunted nor enhanced activation by the cocaine video; the two variables were statistically unrelated (r=–0.08, df=12, p= 0.78, and r=–0.37, df=12, p=0.20, for correlations with change in the amygdala and anterior cingulate, respectively).

Response to the videos in the hippocampal complex was not different either within or between groups (both p values >0.60). Although the orbitofrontal region did not demonstrate significant within- or between-group effects, it showed a group-by-laterality interaction (F=4.78, df=1, 18, p<0.04), with patients tending to activate the right side and comparison subjects the left side.

With regard to comparison regions, the only significant change in response to the cocaine video was a robust reduction in basal ganglia (caudate and lenticular) regional CBF in the cocaine patient group (figure 2). The change in caudate flow was significantly different between the patients (mean=–0.105, SD=0.090) and comparison subjects (mean=0.011, SD=0.050).

Baseline Regional CBF

Baseline regional CBF was comparable in patients and comparison subjects across nonlimbic regions, but it was significantly lower in the patient group for a limbic region, the anterior cingulate (F=10.28, df=1, 18, p=0.004, repeated measures ANOVA). Resting anterior cingulate flow in the patient group did not correlate with several cocaine-related measures (cocaine use in the past 30 days, r=–0.30, df=12, p=0.21; days since the last use of cocaine, r=–0.22, df=12, p=0.45; number of prior treatment episodes, r=–0.35, df=12, p= 0.13). There was a significant negative correlation of resting anterior cingulate flow with years of cocaine use (r=–0.50, df=12, p<0.03), but this correlation did not remain significant (r=0.16, df=12, p=0.63) when age was controlled (34).

Baseline differences in regional CBF for other regions did not reach statistical significance, although resting amygdalar regional CBF was also lower in the patient group. Prior research found the orbitofrontal region to be hyperactive immediately following cocaine cessation (7) and hypoactive several weeks later (35), but the patients in the current study were scanned in between these time points and did not differ from the comparison subjects in resting orbitofrontal activity.

There were significant main effects of laterality (left greater than right, which is common in a right-handed population) at baseline for several structures (anterior cingulate, temporal pole, hippocampal complex, orbitofrontal area, dorsolateral prefrontal cortex, and visual cortices; all F values ≥5.46, df=1, 18, all p values <0.05), but these generally did not differ between patients and comparison subjects (the hippocampal complex was the only exception, F=5.88, df= 1, 18, p<0.03).

DISCUSSION

The findings of this study support the hypothesis that cocaine craving is associated with differential activation of limbic structures that are thought to be important in motivation and affect. Limbic regions demonstrated a significant increase in regional CBF in response to the cocaine video within the cocaine patient group, and the regional CBF increases in the amygdala and anterior cingulate were reliably different from the pattern in the comparison subjects. The relative specificity of these regional CBF increases in cocaine patients is suggested by the absence of increases in nonlimbic comparison regions and by the absence of similar limbic activation in the comparison subjects in response to the cocaine video. The regional specificity of activation, and its restriction to the cocaine patients, also makes it unlikely that increases in regional CBF in response to the cocaine video were simply a function of the ordering of the videos or time in the scanner. The nondifferential activation of the thalamus and visual cortices by both videos points to their general comparability on sensory dimensions and indicates that the increases in limbic regional CBF in response to the cocaine video were not attributable to gross differences in sensory load or visual attention.

Coactivation of the amygdala and anterior cingulate during cue-induced craving is consistent with the importance of these two regions in affective behavior and in emotional learning (36). The amygdala is critical for learning the relationships between biologically significant stimuli (food, sexual partners, pain) and the signals for them (37), and in animal studies it has been shown to play a similar role in processing signals for cocaine (20,21,38,39). The anterior cingulate shares reciprocal connections with the amygdala (40,41) and has, among diverse functions, a known role in mood and emotional responsivity (42–44). Both structures are anatomically linked with the nucleus accumbens (40,41), a brain region important for the reinforcing properties of cocaine (16–18) and natural rewards (22,23) in animals. These interconnected regions allow the organism not only to experience the pleasure of rewards but also to learn the signals for them (critical for survival). Cocaine's supranormal stimulation of this reward circuitry results in robust, entrenched incentive learning. As shown in this study, the subjective (incentive motivational) and associated limbic effects of cocaine signals are preserved despite hypoactivity in parts of the same circuit (35,45,46) and despite other potential effects of chronic cocaine in the brain (47–50).

The drop in basal ganglia regional CBF during craving may also reflect the influence of these interconnected limbic structures (51), perhaps representing active inhibition of reward-irrelevant responses. The lack of hippocampal activation during craving suggests the subordination of explicit (factual) memory (52) to an amygdala-driven emotional state (53). The developing brain signature of cue-induced craving is thus consistent with its clinical phenomenology: the drug user is gripped by a visceral emotional state, experiences a highly focused incentive to act, and is remarkably unencumbered by the memory of negative consequences of drug taking.

Our findings in the amygdala are supported by the recent report of positive correlations between changes in cue-induced craving and changes in glucose metabolism (another index of synaptic activity) in the medial temporal lobe (10). On the other hand, the current paradigm induced craving without differential stimulation of the dorsolateral prefrontal cortex, a “working memory” region (54,55) activated by drug-related videos both in the cited glucose metabolism study and in a recent cue study using functional MRI to index regional blood flow (11). The videos in these studies were either repeated (10) or intermittent (11), making potentially greater demands on working memory than the narrative videos used in the current study. Neither our own nor the functional MRI cue findings (11) support a role for the cerebellum in cue-induced craving, as proposed by the glucose metabolism correlative study (10).

Our interpretations of the data should be taken in the context of our study's possible limitations. Although we propose that the limbic activation observed in the cocaine patients during the cocaine video reflects, at least in part, an increase in druglike cocaine desire, we cannot, of course, completely rule out the possibility that the cocaine video produced other, unmeasured or less specific subjective responses. For example, imaging studies have shown amygdalar activation in response to a variety of emotional stimuli (56,57), and the anterior cingulate has a known role in selective attention (40,41). However, alternative explanations such as anxiety or distress are unsupported by the pattern of findings in the current study, as there was no difference in relaxation/tension, global well-being, or the wish to get rid of bad feelings between the two video conditions. It is also theoretically possible that some difference between the patients and the comparison subjects other than cocaine history could account for the differential limbic activation in response to the cocaine video, but the pattern of demographic and clinical status variables argues against this interpretation. Finally, the possibility that seeing a second video of any type affects cocaine patients differently than comparison subjects—and in the very specific way predicted by the hypotheses—cannot be ruled out with the current design, but this explanation is less straightforward than attributing differences to the intended explicit difference between the two groups, i.e., their experience with cocaine.

Since cocaine itself can also prime a focused state of desire (5), imaging studies with the drug might be expected to confirm limbic activation. Limbic activation has indeed been demonstrated in four animal studies (58–61) and in a recent human study using functional MRI (62). Cocaine's rapid temporal dynamics (63) and/or local vasoconstrictive actions may have prevented a demonstration of limbic effects in several other studies (64–69). Cocaine's multiple, and sometimes opposed, actions in the brain remain a significant technical challenge for in vivo imaging.

The finding of some overlap in hypoactive limbic structures with those activated during cue-induced craving suggests that the cocaine patients' resting state could modulate the response to cues. Although this study did not find a significant correlation between resting limbic flow and the limbic response to cues, group size may have limited the ability to detect a correlation. The overlap between hypoactive and cue-activated limbic structures may also help explain the frustrated search for medications to prevent cocaine relapse. "Antiwithdrawal" agents intended to restore or enhance the dopaminergic tone of hypoactive limbic regions may actually generate an internal state experienced as craving and/or may enhance the response to external cocaine cues (70). Conversely, "anticraving" agents that block limbic dopamine receptors may reduce cue-related craving (71), but their blunting of mood and motivation makes compliance problematic (72). Medications that target either specific receptor subgroups (73,74) or dopamine-modulating transmitter systems (75–77) may offer more promise.

In sum, the current findings in cocaine patients offer both a foundation and a strategy for studying the brain substrates of drug desire, a hallmark of drug dependence disorders. Both the results and the strategy may be generalizable not only to craving for other drugs of abuse but also to the appetitive states associated with natural rewards such as food and sexual activity.

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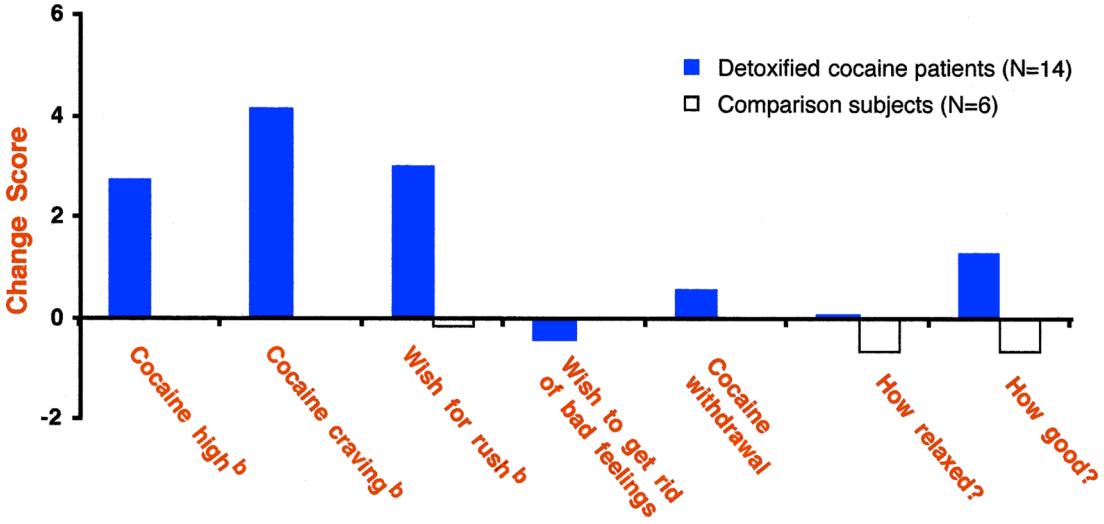

FIGURE 1. Changes in Subjective Responses to a Cocaine-Related Video Among Detoxified Cocaine Patients and Cocaine-Naive Comparison Subjects[a]

[a] Scores represent the change from resting baseline for items self-rated on a 10-point (0 to 9) scale.

[b] Changes differed both from the patients' own baseline responses (all t values ≥3.70, df=12, p values ≤0.003) and from the responses of the comparison subjects (one-way ANOVA: for craving, F=17.13, df=1, 18, p=0.0006; for high, F=5.87, df=1, 18, p<0.03; for wish for rush, F=6.27, df=1, 18, p=0.02).

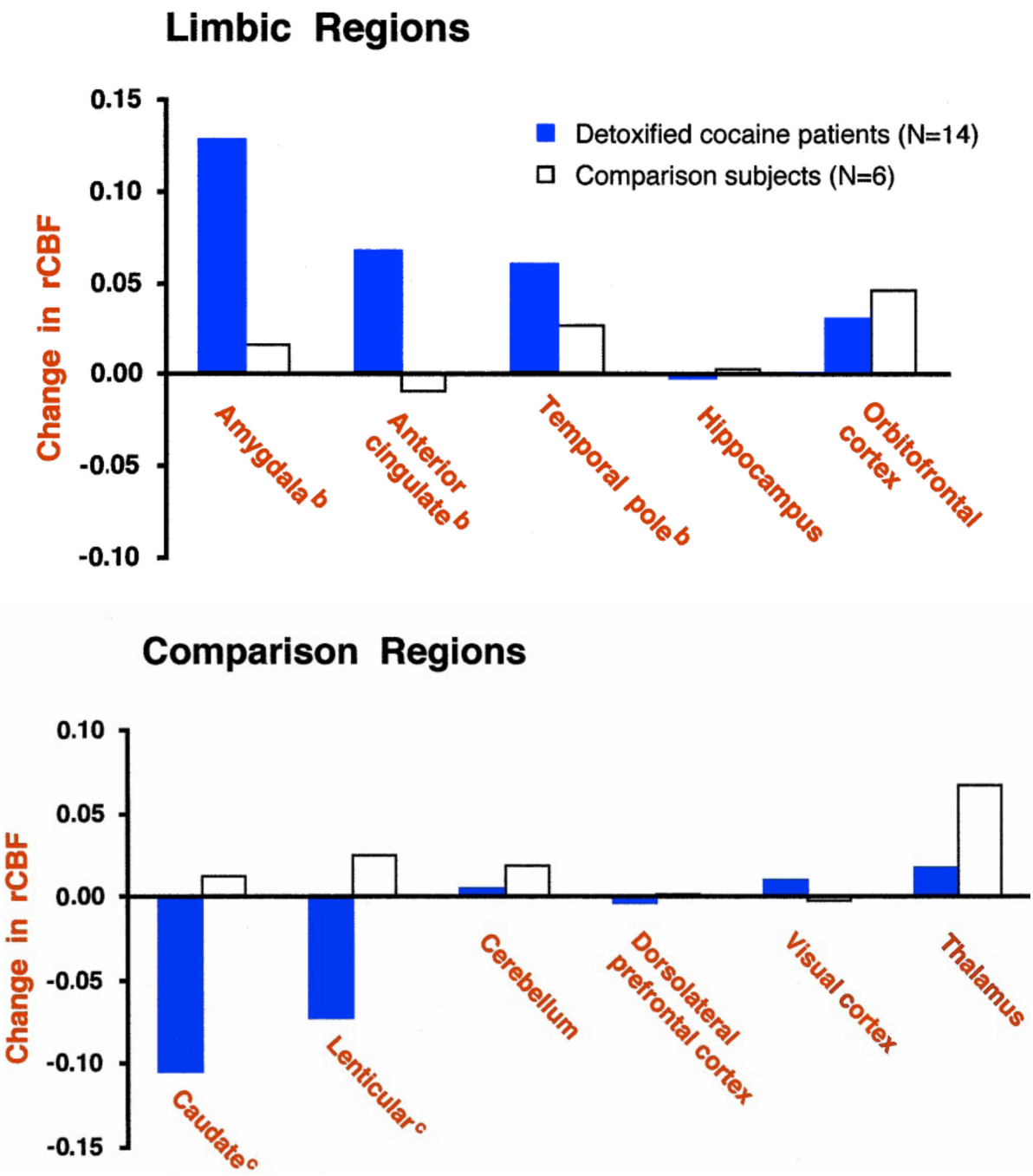

FIGURE 2. Changes in Relative Regional Cerebral Blood Flow (rCBF) in Limbic and Comparison Brain Regions of Detoxified Cocaine Patients and Cocaine-Naive Comparison Subjects in Response to a Cocaine-Related Video[a]

[a] Values represent the change in regional CBF between a non-drug-related (nature) video and a cocaine-related video. Regional CBF in the cocaine patients showed a pattern of differential limbic increases and basal ganglia decreases in response to the cocaine video; this pattern did not occur in comparison subjects without a cocaine history. For these analyses, the hippocampus included the adjacent entorhinal cortex, the orbitofrontal cortex included the rectal gyrus, and the visual cortices included both primary and association cortices.

[b] There were significant changes in regional CBF in response to the cocaine video for the amygdala and the anterior cingulate both within the patient group ($t=6.42$, $df=12$, $p=0.00002$, and $t=2.75$; $df=12$, $p<0.02$, respectively) and between the patients and the comparison subjects ($F=6.37$, $df=1, 18$, $p<0.02$, and $F=4.62$, $df=1, 18$, $p<0.05$, respectively). Within the cocaine group there was also a significant change in regional CBF for the temporal pole ($t=4.45$, $df=12$, $p=0.0007$).

[c] Within the cocaine group there were significant reductions in regional CBF in response to the cocaine video for the caudate ($t=4.56$, $df=12$, $p=0.0005$) and the lenticular nuclei ($t=2.31$, $df=12$, $p<0.04$) There was also a significant difference in caudate regional CBF between the patients and the comparison subjects ($F=9.46$, $df=1, 18$, $p=0.007$).

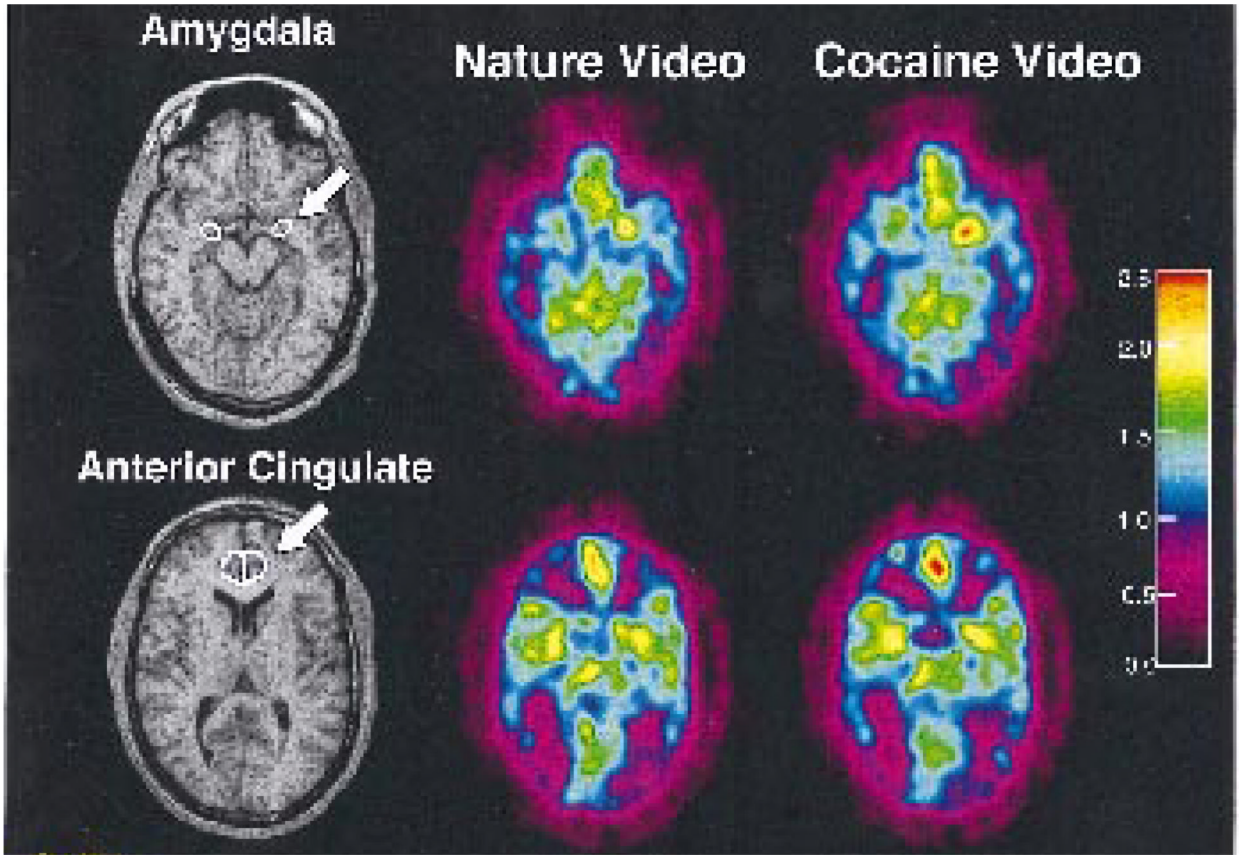

FIGURE 3. Transaxial Images Illustrating the Differential Increase in Relative Regional Cerebral Blood Flow (CBF) in the Amygdala and Anterior Cingulate of a Detoxified Cocaine Patient During a Non-Drug-Related (Nature) Video and a Cocaine-Related Video[a]

[a] Anatomical regions of interest were first localized on the patient's MRI (the first image in each row); region templates were subsequently superimposed on ^{15}O PET images, yielding radioactive count files for conversion to normalized (relative) regional CBF. The middle and final images in each row show relative regional CBF as measured by PET. The range on the arbitrary color scale is from 0.0 to 2.5 times background activity; whole brain average regional CBF is 1.0 on the scale. Areas with greatest relative regional CBF are shown in red; activity in the amygdala and in the anterior cingulate differentially increased during the cocaine video.