

Functional Magnetic Resonance Imaging of Cocaine Craving

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Objective: Identification of brain activity associated with craving is important for understanding the neurobiology of addiction.

Method: Brain activity was measured in cocaine addicts and healthy subjects by functional magnetic resonance imaging (fMRI) while the subjects watched videotapes designed to elicit happy feelings, sad feelings, or the desire to use cocaine. The subjects indicated the onset of drug craving or emotional response, allowing comparison of groups before and after such feelings.

Results: Robust activation of the anterior cingulate was evident in patients watching cocaine-cue tapes but not in patients watching happy or sad tapes or in healthy subjects under any condition. Anterior cingulate activation preceded the reported onset of craving and was evident in patients who did not report craving. In contrast, patients showed less activation than healthy subjects during the cocaine-

cue tapes in areas of the frontal lobes. After the reported onset of craving, cocaine-dependent subjects showed greater activity than healthy subjects in regions that are more active in healthy subjects when they watch sad tapes than when they watch happy tapes, suggesting a physiologic link between cocaine-cue responses and normal dysphoric states. Dynamic aspects of regional brain activations, but not the location of activations, were abnormal in cocaine-dependent subjects watching sad tapes, suggesting more general affective dysregulation. Patients showed low activation of sensory areas during initial viewing of all videotapes, suggesting generalized alteration in neuroresponsiveness.

Conclusions: Cocaine cues lead to abnormally high cingulate and low frontal lobe activation in cocaine addicts. Addicts also show more general abnormalities in affect-related brain activation.

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While psychosocial and genetic factors are central to the etiology of addictive disorders, craving is the pathological motivational state that usually precedes the seeking and taking of drugs. Understanding the neurobiological basis of craving is thus essential for understanding the pathophysiology of addiction. Moreover, measuring physiologic correlates of craving, instead of relying on self-report, could provide a better index of treatment response. Comparing the neurobiology of craving to that of more common emotional states is relevant for a basic scientific understanding of the regulation of affect and motivation and may help determine the relationship between craving and other affect-related states.

Functional brain imaging can identify specific brain regions that become active with presentation of drug-use cues and/or with the experience of craving. Such information can point to the neural circuitry underlying craving and may allow comparisons among addictive disorders, as well as between addictive disorders and other psychiatric conditions. Previous studies have used three methods to induce craving: videotapes of people using drugs, directed recall of past drug experiences, or pharmacologic stimulants. Activation of the anterior cingulate has been found

with both video cues and pharmacologic stimulants (1–4). Activation of both the dorsolateral cortex (2, 5) and the orbitofrontal cortex (4–6) has been found in two different video-cue studies. Individual video-cue studies have shown activation of the amygdala and the temporal pole (3) and retrosplenial, peristriate, and temporal/parietal areas (5). Of two studies using pharmacologic stimulation, one showed activation of the nucleus accumbens and subcallosal cortex (1), and the other indicated activation of the striatum, cerebellum, and thalamus (4).

This collection of observed craving-related activations has been seen as having at least two physiological links. First is an association between craving and differential activation of limbic structures important in motivation and affect (3). Second is a relationship in which many of these regions are part of, or receive input from, the mesoaccumbens dopamine pathway that appears in animal studies to be important for the reinforcing effects of cocaine (1). It is interesting, however, that these are not the brain regions most consistently activated in imaging studies of emotion in healthy individuals. The most consistent finding in these studies has been activation of the medial frontal cortex in the superior frontal gyri following

presentation of stimuli that evoke either happy or sad emotions (7–9). Activations have also been reported in the thalamus, hypothalamus, caudate, claustrum, and putamen (7, 8), and activation of the amygdala has been reported but primarily in response to fear-associated stimuli (10, 11). The remarkably limited overlap between the regions apparently active during normal happy and sad emotional responses and those active during the pathological affect-motivational state of craving suggests a fundamental neurobiological difference between craving and normal emotional states. To our knowledge, however, no previous study has directly compared brain activation during craving to that during other emotional states. Nor have brain activation responses by cocaine-dependent patients to cues evoking happy or sad emotions been evaluated to determine if susceptibility to craving is associated with other abnormalities in emotional response. In the present study we addressed both of these questions by comparing brain activation responses in cocaine-dependent and healthy subjects exposed to cocaine-cue videotapes and to tapes designed to elicit happy or sad emotions.

Method

The subjects were 21 right-handed healthy individuals (13 female, eight male; mean age=33 years, range=24–60) and 11 right-handed cocaine-dependent patients (three female, eight male; mean age=34 years, range=20–42). All gave written informed consent to participate. The patients all had recently been admitted (days before scan: mean=14.9 days, range=4–23) to an inpatient drug dependence treatment unit, met the DSM-III-R criteria for cocaine dependence, and reported regular use of cocaine up to the time of admission. Four patients also met the criteria for substance-induced mood disorder with depressive features, and a fifth met the criteria for generalized anxiety disorder. The healthy subjects denied any more than occasional social use of alcohol or illicit drugs, and they reported no use of psychoactive substances during the 72 hours before functional magnetic resonance imaging (fMRI). None of the subjects was taking prescription drugs with effects on the central nervous system, had a history of neurological illness or injury, had a history of psychiatric illness other than cocaine dependence, or had abnormalities shown by structural MRI.

Stimulus Videotapes

Each videotape consisted of an actress seated, looking at and talking directly to the camera (viewer). In the happy tape, the actress smiled frequently and spoke cheerfully about happy memories of growing up on a farm and then of a family reunion. In the sad tape, the actress spoke sadly about the deaths of close family members, crying throughout. In the cocaine tape, the actress spoke briefly about recent perceived injustices, expressed anger and frustration, described the desire to get high, removed drug paraphernalia from a paper bag, chopped a fake rock of “crack” cocaine, twice smoked some and pretended to get a rush, commented repeatedly how good the “shit” was, and invited or teased the viewer about getting high him- or herself. One actress made a happy, a sad, and a cocaine tape. A second actress made a sad and a cocaine tape. There were therefore a total of two sad tapes, two cocaine tapes, and one happy tape. The tapes were from 3.0 to 4.5 minutes in length and were preceded and followed by 30-second baseline periods of gray illumination. The subjects indicated the

onset and progressive increases in emotional responses by button pushes during tape viewing. Immediately after each tape, the subjects described the nature of their emotional responses and rated the peak and average intensities of their responses from 0 to 10. The cocaine-dependent patients were asked whether or not they felt the urge to use cocaine immediately after each tape and to rate the peak and average intensities of this feeling from 0 to 10. The tapes were presented in one of two sequences, each to one-half of the subjects: 1) sad tape A, cocaine tape B, happy tape, sad tape B, cocaine tape A or 2) happy tape, sad tape B, cocaine tape A, sad tape A, cocaine tape B.

The subjects were told that the experiment involved measurement of brain responses related to emotions that might be triggered by watching videotapes and that they were to indicate when they first began to feel any emotional response and when that response became moderate or very strong. The cocaine-dependent patients were also told that some of the tapes might make them feel like using cocaine. The subjects were not told before or after a tape what emotion that actress was attempting to portray. There was a 2.5-minute rest between tapes.

fMRI

Each subject's head was stabilized by a band across the forehead. Video goggles were placed over the subject's eyes and headphones over the ears. By using a 1.5-T GE Signa MRI system with resonant gradients for echoplanar imaging, conventional T₁-weighted spin echo sagittal anatomical images (TE=11 msec, TR=667 msec, field of view=24 cm, slice thickness=5 mm, gap=0, 256×128 data matrix) were acquired for slice localization. Next, eight T₁-weighted oblique axial slices (TE=13 msec, TR=500 msec, field of view=40×40 cm, slice thickness=8 mm, gap=1 mm, 256×192 data matrix) were acquired parallel to the plane transecting the anterior and posterior commissures, covering the brain from the inferior temporal sulcus to the most superior portion of the cortex, to serve as underlays for functional images collected at the same locations. Functional images were obtained by using a single-shot echoplanar gradient-echo sequence (flip angle=60°, TE=60 msec, TR=2600 msec, field of view=40×20 cm, 128×128 data matrix, slice thickness=8 mm, skip=1 mm). Head movement was evaluated by measuring changes in the center of mass of the functional images over time. If the motion exceeded 1 voxel in the x or y direction from the beginning to the end of the study, the subject was dropped from the data set (one patient was dropped). If the motion exceeded 0.5 voxel from the beginning to the end of a particular tape, that tape was dropped from the data set (one sad tape and one cocaine tape from one patient and one cocaine tape from another patient were dropped). Otherwise, motion was corrected by using SPM 96 software. The corrected images were spatially filtered by using a Gaussian filter with a full width at half maximum of 6.5 mm. Data are presented for axial-oblique imaging slices 4 mm below and 4, 12, 24, and 32 mm above the plane of the anterior and posterior commissures (referred to as z levels).

Changes in echoplanar imaging signal were evaluated in three pairs of successive epochs (Figure 1). The first comparison was between the 30-second pretape baseline (baseline 1) and the initial period of tape viewing before the self-report of emotional response (emotion 0). The second comparison was between the initial period of emotional response (emotion 1) and the immediately preceding period of tape viewing before the self-report of emotional response (emotion 0). The third comparison was between the final 45 seconds of tape viewing (independent of report of emotional response) (emotion 2) and the posttape baseline (baseline 2). The onset of emotional response varied from subject to subject, leading some subjects to have longer periods of tape viewing before the report of emotion (emotion 0) and shorter periods of watching the tape after reporting the onset of emotion (emotion 1). In order to maintain sufficient comparability among

FIGURE 1. Timeline of Epochs Used in Comparisons of Brain Activations in Cocaine-Dependent Patients and Healthy Comparison Subjects During Viewing of Video-tapes Designed to Evoke Cocaine Craving, Happiness, and Sadness^a

Before Tape	Viewing of Tapes (3.0–4.5-minute duration)				After Tape
	Before emotional response		After emotional response		
Baseline 1	Emotion 0	Emotion 0	Emotion 1	Emotion 2	Baseline 2
30 sec	13–45 sec	13–45 sec	13–45 sec	45 sec	30 sec
Duration of Epoch					

^a The first emotion 0 was compared to baseline 1, and the second emotion 0 was compared to emotion 1. The duration of tape viewing before the report of emotional response determined whether the two emotion 0 periods were distinct, partially overlapping, or the same. The same is true for emotion 1 and emotion 2, although the tapes were long enough, and the emotional responses generally early enough, that overlap between these two was infrequent.

subjects in data sampling, comparisons were not made if either epoch to be compared was less than 13 seconds long (five images), and images acquired only during the first or last 45 seconds of long epochs were considered. Three healthy subjects reported the onset of emotion so quickly that there were not the required five images in the emotion 0 period (one during cocaine tape A and two others during cocaine tape B), as did one patient subject during sad tape B. Data from these subjects were not used in the contrast between emotion 0 and baseline 1 or the contrast between emotion 1 and emotion 0, but they were used in the analysis of the difference between emotion 2 and baseline 2. One healthy subject reported the onset of emotion too late to have enough images for the contrast of emotion 1 and emotion 0 for cocaine tape A, and one patient reported too late during the happy tape. Some healthy subjects did not report any emotional response to one or two tapes (five to the happy tape, two to sad tape A, two to sad tape B, and one to cocaine tape A). The same was true for some patients (three to the happy tape, four to sad tape A, three to sad tape B, three to cocaine tape A, three to cocaine tape B). These subjects therefore did not contribute to the contrast of emotion 1 and emotion 0. One healthy subject did not report any emotional response to any tape and was dropped from the data set (as one would drop a subject whose performance on a cognitive activation task was so low as to raise doubts about whether he or she was doing the task). Technical problems (ghosting) led to the loss of data for one healthy subject during cocaine tape B, one patient during cocaine tape A, and two patients during sad tape B.

Thus, in total, for the contrast of emotion 1 and emotion 0 there were 14 healthy subjects and seven patients for the happy tape, 17 healthy subjects and six patients for sad tape A, 17 healthy subjects and five patients for sad tape B, 17 healthy subjects and five patients for cocaine tape A, and 16 healthy subjects and seven patients for cocaine tape B. For the contrasts involving emotion 0 minus baseline 1 and emotion 1 minus baseline 2, there were 19 healthy subjects and 10 patients for the happy tape, 19 healthy subjects and 10 patients for sad tape A, 19 healthy subjects and seven patients for sad tape B, 18 healthy subjects and seven patients for cocaine tape A, and 18 healthy subjects and 10 patients for cocaine tape B. The mean/median durations of the emotion 0 and emotion 1 epochs were 38.7/41.6 seconds and 26.0/41.5 seconds for the happy tape, 39.3/39.0 seconds and 30.9/41.6 seconds for sad tape A, 30.2/36.4 seconds and 31.2/

41.6 seconds for sad tape B, 29.9/39.0 seconds and 27.8/36.4 seconds for cocaine tape A, and 37.2/41.6 seconds and 34.2/41.6 seconds for cocaine tape B.

The data analysis followed several steps. First, three t maps were created for each subject for each tape, 1) comparing the signals during emotion 0 and baseline 1, 2) comparing emotion 1 and emotion 0, and 3) comparing emotion 2 and baseline 2. These first-order statistical maps and the anatomic images from individual subjects were transformed into a proportional three-dimensional grid (12) in order to combine data across subjects. The t maps were used only to compute standard linear contrast measures (13). Under the null hypothesis of no effect, the expected value of the mean of this contrast across subjects is equal to zero. We then used a randomization procedure to generate a distribution of task-related t values in order to estimate the significance of the observed linear contrast at each voxel (14–16). This procedure creates the population distribution for each voxel by repeatedly calculating the value of the contrast when the t values of one-half the subjects, randomly chosen, have a reversed sign. This randomization was performed 1,000 times, generating a sampling distribution of the linear contrast measures. The observed linear contrast measure, calculated without sign reversal, was assigned a p value on the basis of its position in this distribution. All reported p values were derived from this procedure. A voxel was considered to show a significant difference between conditions (or groups, see next paragraph) only if it and two of the four voxels with which it shared a border met the significance criterion.

This procedure was followed for the two sad tapes together, the two cocaine tapes together, and the happy tape, in the healthy and patient groups separately, in order to identify the activation topography of each emotional condition in each subject group. Next, the statistical significance of differences between the cocaine and sad tapes and between the cocaine and happy tapes for the cocaine addicts was evaluated. These randomizations were done by switching t values of the cocaine and sad tapes (or the cocaine and happy tapes) in randomly chosen subsets of one-half the subjects. Finally, the statistical significance of differences between healthy and patient groups for the cocaine, sad, and happy tapes was evaluated. These randomizations were done by switching the group assignments in randomly chosen subsets of one-half of the subjects, a procedure unaffected by differences in the size of the subject groups compared.

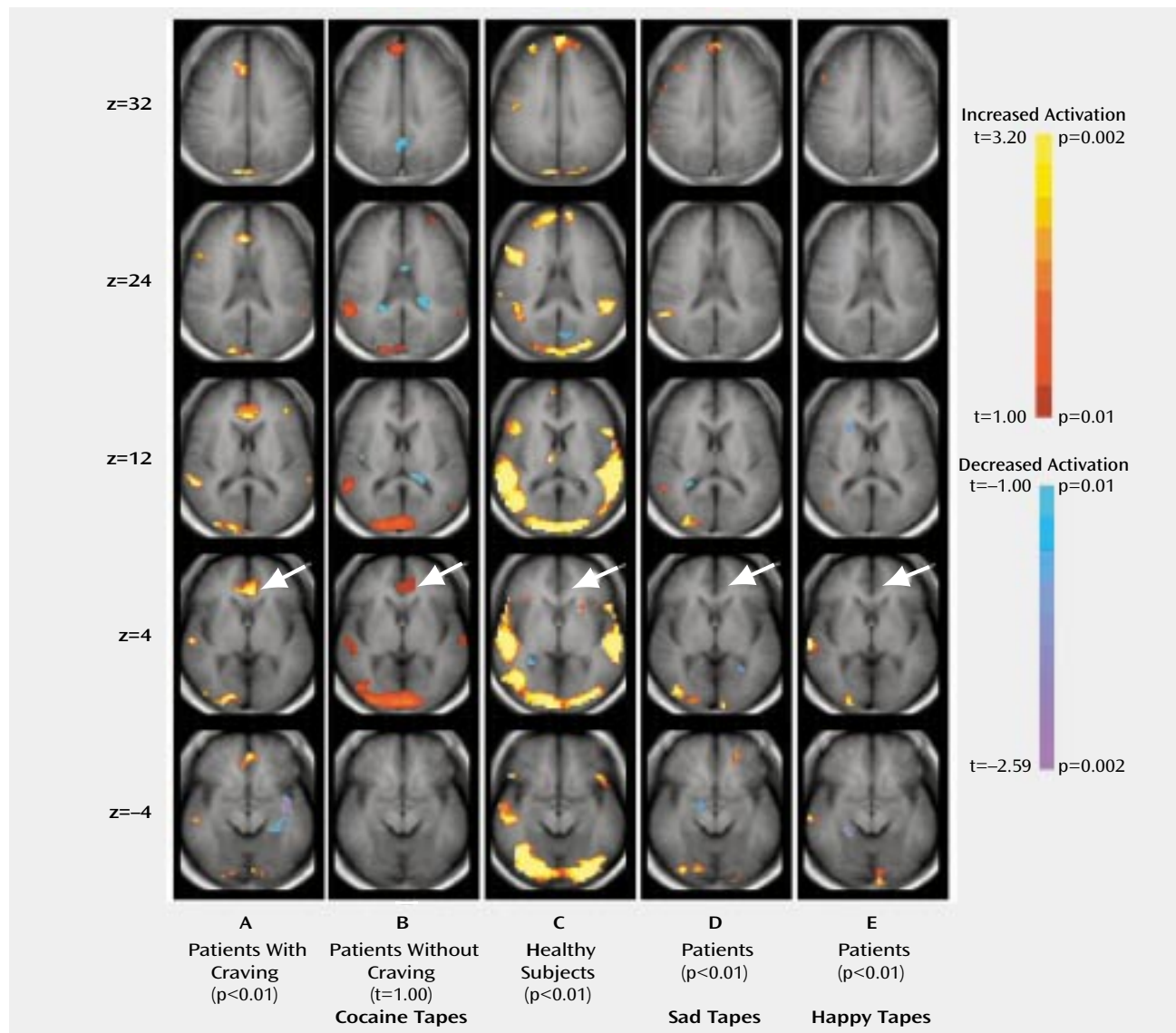
Because of differences between the patient and healthy groups in gender mix, we also compared male healthy subjects to male addicts separately. The results reported are for the comparisons of the mixed-gender groups, but only intergroup differences that were also significant for the comparisons of male subjects are labeled and discussed as significant.

Results

Subjective Responses

The subjective emotional responses were robust and comparable in the healthy subjects and patients for all tapes. For the cocaine tapes the mean intensity ratings of the patients and healthy subjects, respectively, were 5.6 (range=0–10) and 5.6 (range=0–8), for the happy tapes they were 5.5 (range=0–7) and 4.1 (range=0–7), and for the sad tapes the ratings were 6.5 (range=0–9) and 6.9 (range=0–10). The intensity of the response to the cocaine tapes was comparable to the intensity of the responses to the happy and sad tapes in both groups. Healthy subjects described their responses to the cocaine tapes as curiosity,

FIGURE 2. fMRI Images Comparing Regional Brain Activations During Initial Videotape Viewing and at Baseline in 11 Cocaine-Dependent Patients and 20 Healthy Comparison Subjects Who Watched Videotapes Designed to Evoke Cocaine Craving, Happiness, and Sadness^a



^a The epochs involved are defined in Figure 1; the images represent emotion 0 minus baseline 1. The numbers of patients and healthy subjects varied among tapes. The z values indicate the distance in millimeters below or above the plane of the anterior and posterior commissures. The arrows point to anterior cingulate activity in cocaine addicts watching cocaine-cue tapes and the absence of such activity in all other conditions. The left hemisphere is on the right side of each image. The p values on the color bars refer to columns A, C, D, and E; t values refer to column B. See text for details of the data analysis.

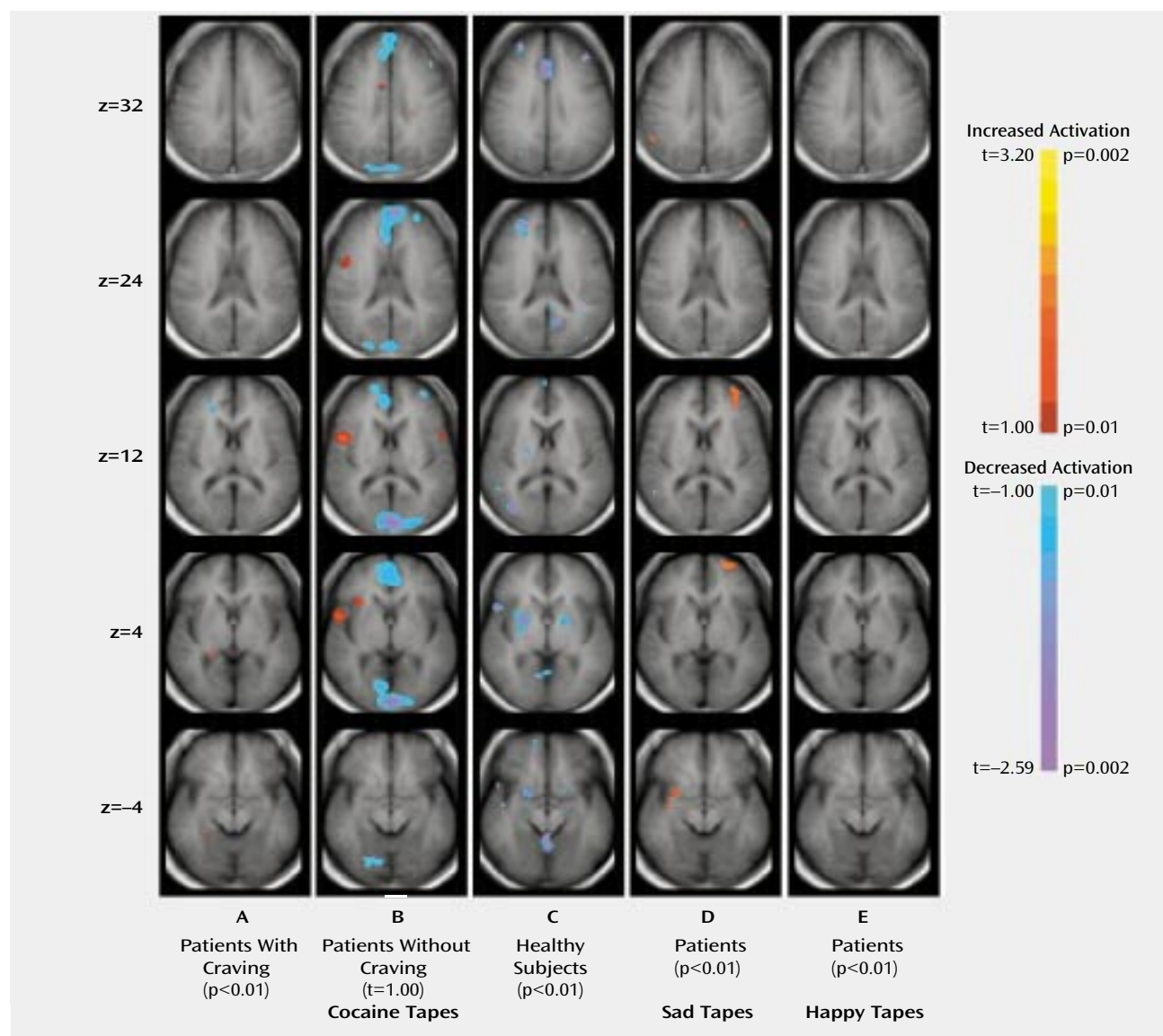
disgust, or pity. None of the cocaine subjects reported craving during the sad or happy tape, but eight of the 11 reported high levels of craving during the cocaine tapes, and two reported a cocaine-like "rush." One of these subjects said that his ears popped while he was watching one of the cocaine tapes, an experience he had often had when using cocaine but not at other times.

Activations Specific to Cocaine Addicts Watching Cocaine-Cue Tapes

Figure 2 shows areas of significant ($p \leq 0.01$) signal increase from the pretape baseline to the initial period of

tape viewing before the self-reported onset of craving or emotional response (emotion 0 minus baseline 1). The five columns show data for the cocaine patients watching the cocaine tapes who did or did not go on to report craving responses, the healthy subjects watching the cocaine tapes, and the cocaine-dependent patients watching the sad and happy tapes. Figure 3 and Figure 4 are parallel presentations of signal change from the period of tape watching before the onset of self-reported onset of craving or other emotions to the period of self-reported craving or emotion (emotion 1 minus emotion 0, Figure 3) and from

FIGURE 3. fMRI Images Comparing Regional Brain Activations During Initial Self-Reported Craving or Emotional Response and in Immediately Preceding Period in 11 Cocaine-Dependent Patients and 20 Healthy Comparison Subjects Who Watched Videotapes Designed to Evoke Cocaine Craving, Happiness, and Sadness^a



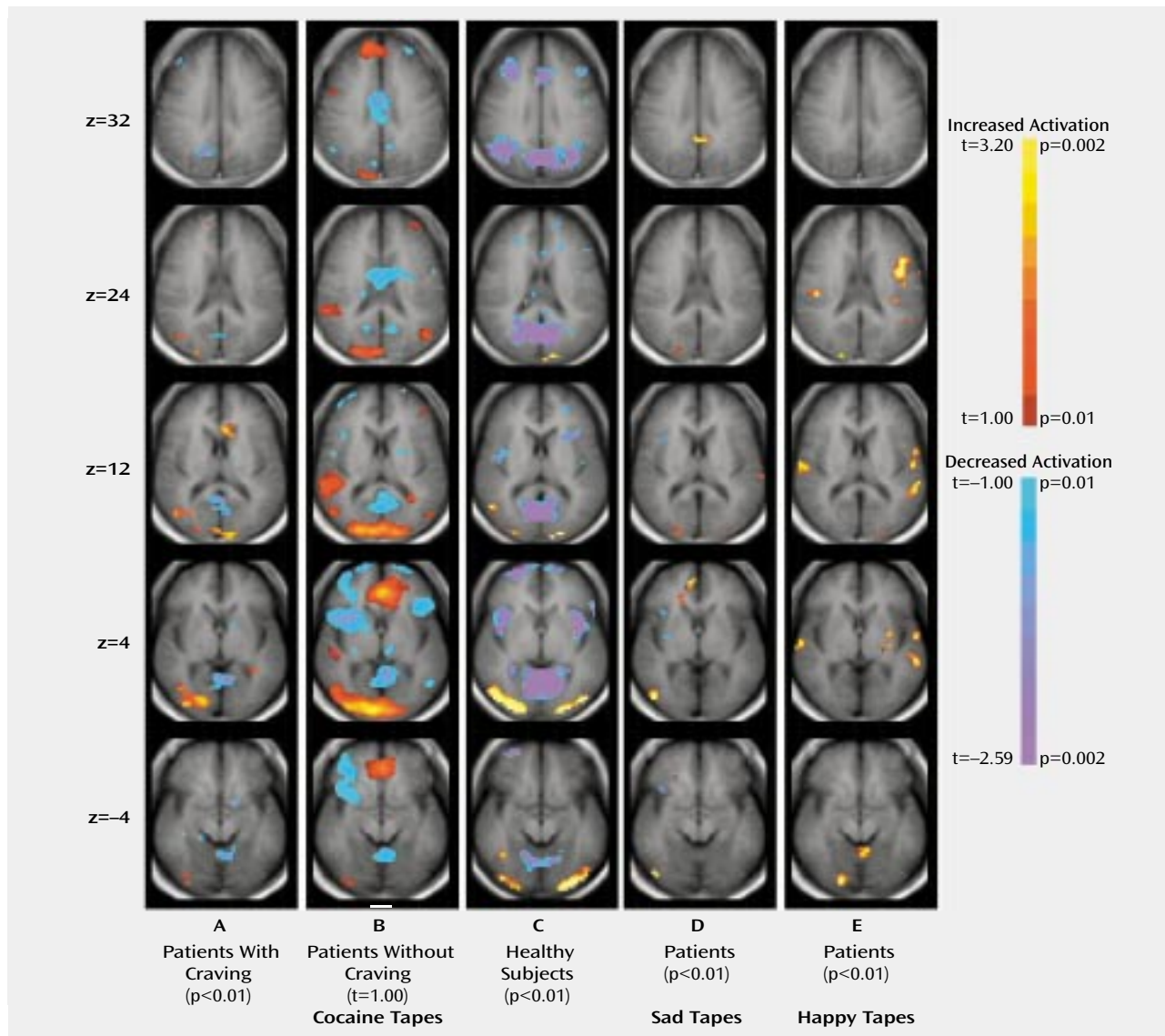
^a The epochs involved are defined in Figure 1; the images represent emotion 1 minus emotion 0. The numbers of patients and healthy subjects varied among tapes. The z values indicate the distance in millimeters below or above the plane of the anterior and posterior commissures. The left hemisphere is on the right side of each image. The p values on the color bars refer to columns A, C, D, and E; t values refer to column B. See text for details of the data analysis.

the final period of tape viewing to the posttape baseline (emotion 2 minus baseline 2, Figure 4). Table 1 lists the brain regions showing significant differences between the cocaine-dependent patients and the healthy subjects as determined by the randomization procedure described in the Method section. Note that some of these analyses indicate significant intergroup differences in regions in which neither group alone showed a significant change in activity.

Activations before reported onset of emotional response (emotion 0 minus baseline 1). During initial viewing of the cocaine tapes before the self-reported onset of craving or other emotions, the cocaine-dependent patients

and healthy subjects showed very different activations (Figure 2, columns A–C). The patients who went on to report craving showed marked activation of the anterior cingulate (column A, z=-4 to z=24), which was completely absent in the healthy subjects even when the significance threshold was lowered to p=0.05. Statistical comparison of signal changes in the patients (column A) and the healthy subjects (column C) showed this intergroup difference in the anterior cingulate to be significant (p<0.005, N=28). It is interesting that the anterior cingulate activation is also clearly evident in the three patients who said they did not experience craving (column B, z=4 and z=12). The absence of these anterior cin-

FIGURE 4. fMRI Images Comparing Regional Brain Activations at the End of Videotape Viewing and at the Posttape Baseline in 11 Cocaine-Dependent Patients and 20 Healthy Comparison Subjects Who Watched Videotapes Designed to Evoke Cocaine Craving, Happiness, and Sadness^a



^a The epochs involved are defined in Figure 1; the images represent emotion 2 minus baseline 2. The numbers of patients and healthy subjects varied among tapes. The z values indicate the distance in millimeters below or above the plane of the anterior and posterior commissures. The left hemisphere is on the right side of each image. The p values on the color bars refer to columns A, C, D, and E; t values refer to column B. See text for details of the data analysis.

gulate activations in healthy subjects during the cocaine tapes is in striking contrast to their robust activation of auditory and visual processing areas and of portions of the superior frontal gyrus thought to be involved in emotional response (column C, $z=4$ to $z=32$) (8, 9). Indeed, the signal increase during the cocaine tapes was significantly greater in the healthy subjects than in the patients in the right ($p<0.01$, $N=28$) and left ($p<0.05$, $N=28$) inferior occipital gyrus and the right ($p<0.05$, $N=28$) and left ($p<0.01$, $N=28$) inferior frontal and posterior lateral orbital gyri at $z=-4$; the right and left superior temporal gyrus ($p<0.05$, $N=28$) at $z=-4$ and $z=4$; in the right thalamus ($p<0.005$, $N=28$) and the left superior frontal

gyrus ($p<0.05$, $N=28$) at $z=12$; and the right middle frontal gyrus ($p<0.05$, $N=28$) at $z=32$.

There was no evidence of activation of the anterior cingulate in the cocaine-dependent patients during either the happy or sad tapes (Figure 2, columns D and E). Statistical analyses confirmed that the signal change in the anterior cingulate was significantly greater during the cocaine tapes than during either the happy ($p<0.01$, $N=10$) or sad ($p<0.01$, $N=10$) tapes in the cocaine addicts.

Activations after reported onset of emotional response (emotion 1 minus emotion 0). When the epoch immediately after the self-report of emotion or craving

TABLE 1. Brain Regions Showing Significant Differences^a in Activation Between Cocaine-Dependent Patients and Healthy Comparison Subjects Who Watched Videotapes Designed to Evoke Cocaine Craving and Sadness

Region	Group With Greater Activation During Cocaine Tapes			Group With Greater Activation During Sad Tapes		
	Emotion 0 Minus Baseline 1 ^b	Emotion 1 Minus Emotion 0 ^c	Emotion 2 Minus Baseline 2 ^d	Emotion 0 Minus Baseline 1 ^b	Emotion 1 Minus Emotion 0 ^c	Emotion 2 Minus Baseline 2 ^d
Anterior cingulate	Patients ^{***}		Patients ^{**}			
Superior frontal gyrus	Healthy subjects (left side) [*]		Patients (left side) ^{**}	Healthy subjects ^{**}		
Middle frontal gyrus	Healthy subjects (right side) [*]		Patients ^{**}	Healthy subjects (right side) ^{***}	Patients ^{***}	Healthy subjects (right side) [*]
Inferior frontal gyrus	Healthy subjects ^{**}		Patients (right side) ^{**}		Patients (right side) ^{***}	Healthy subjects ^{***}
Posterior lateral orbital gyrus	Healthy subjects ^{**}					
Superior temporal gyrus	Healthy subjects [*]			Healthy subjects ^{**}	Patients (right side) ^{**}	Healthy subjects ^{***}
Middle temporal gyrus			Patients ^{**}	Healthy subjects ^{***}		
Superior occipital gyrus			Patients ^{**}			
Middle occipital gyrus		Patients (right side) ^{**}		Healthy subjects [*]		
Inferior occipital gyrus	Healthy subjects ^{**}		Healthy subjects [*]			
Lingual gyrus		Patients (left side) ^{**}	Patients ^{**}	Healthy subjects [*]		Healthy subjects ^{**}
Thalamus	Healthy subjects (right side) ^{***}					
Caudate				Healthy subjects [*]		
Globus pallidus/putamen					Patients (left side) [*]	
Hippocampus		Patients (right side) ^{**}			Patients (right side) [*]	
Nucleus accumbens/posterior orbital gyrus			Healthy subjects ^{**}			

^a See text for description of data analysis.^b Activity during the initial period of tape viewing before self-reported onset of craving or emotional response as compared to the baseline activity before tape viewing.^c Activity during the initial period of self-reported craving or emotion as compared to activity during the immediately preceding period of tape viewing before emotional response.^d Activity during the final period of tape viewing as compared to the posttape baseline activity.* $p < 0.05$. ** $p < 0.01$. *** $p < 0.005$.

(emotion 1) during the cocaine tapes is compared to the immediately preceding period before the report of emotion or craving (emotion 0), one general difference between the patients (Figure 3, column A) and healthy subjects (column C) is evident. The healthy subjects showed signal decreases in several areas but no areas of significant signal increase, just as was the case in those subjects after the self-reported onset of sad and happy feelings (unpublished data, 1999). Decreased signal was evident both in areas that had shown an initial increase (emotion 0 minus baseline 1) and in areas that had not. The patients, in contrast, showed evidence of signal decrease only near or in the right middle frontal gyrus (column A, $z=12$). The differences between patients and healthy subjects (increases in the patients and/or decreases in healthy subjects) were statistically significant ($p < 0.01$, $N=24$) in the right hippocampus ($z=4$), the right middle occipital gyrus ($z=12$ and $z=24$), and the left lingual gyrus ($z=-4$).

Activations after extended tape viewing (emotion 2 minus baseline 2). Subtraction of the posttape period from the final epoch of tape viewing identified areas that

persisted and/or increased in activity as the tape progressed and then decreased in activity after the tape stopped. While viewing the cocaine tapes, both the patients and healthy subjects showed significant persistent activity of visual sensory and association areas (Figure 4, columns A and C, $z=-4$, $z=4$, $z=12$, $z=24$), which was significantly greater in the healthy subjects in the inferior occipital gyrus ($p < 0.05$, $N=28$). However, while several nonsensory areas in the healthy subjects were significantly less active during the final period of tape viewing than they were after the tape ended, the patients showed persistent and/or increased activity in these areas during the final segments of the tape. These differences between the patients and healthy subjects were statistically significant ($p < 0.01$, $N=28$) bilaterally in the lingual and middle temporal gyri, in the right inferior frontal gyrus, and in the left superior frontal gyrus (all at $z=4$) and bilaterally in the anterior cingulate, middle frontal gyrus, and superior occipital gyrus (all at $z=24$).

The patients but not the healthy subjects had lower activity during the final period of tape viewing than during

the posttape baseline in a region including the nucleus accumbens on the left (Figure 4, column A, $z=-4$), leading to a significant ($p<0.01$, $N=28$) intergroup difference here as well. The signal change in this area in the patients during the cocaine tapes was also significantly different from that in the patients during the sad tapes ($p<0.01$, $N=10$). Here then is another activation change that appears selectively in cocaine addicts watching cocaine tapes.

Activation Abnormalities in Cocaine Addicts During Happy and Sad Tapes

Activations before reported onset of emotional response (emotion 0 minus baseline 1). During viewing of the happy and sad tapes, the patients showed significantly less activation than the healthy subjects in the superior temporal gyrus bilaterally on multiple imaging slices (p values ranging from <0.05 to <0.01 across slices, $N=29$), the middle temporal gyrus bilaterally (right greater than left) on multiple slices ($p<0.005$ to $p<0.05$, $N=29$), the lingual gyrus bilaterally at $z=-4$ and $z=4$ ($p<0.05$, $N=29$), the middle occipital lobe bilaterally at $z=-4$, $z=4$, and $z=12$ ($p<0.05$, $N=29$), and the middle frontal gyrus on the right at $z=12$, $z=24$, and $z=32$ ($p<0.005$ to $p<0.01$, $N=29$). In addition, the patients showed less activation than the healthy subjects during the happy tape in the right medial temporal lobe at $z=-4$ and $z=4$ ($p<0.05$, $N=29$), and during the sad tapes the patients showed reduced activation in the medial superior frontal gyrus ($z=-4$ and $z=4$, $p<0.01$, $N=29$) and the caudate bilaterally ($z=4$, $p<0.05$, $N=29$). These regions of underactivity in the patients, relative to the healthy subjects, during the initial viewing of the happy and sad tapes are similar to the regions of relative underactivity in the patients during the initial viewing of the cocaine tapes.

Activations after reported onset of emotional response (emotion 1 minus emotion 0). With the onset of self-reported emotional responses the patients differed markedly from the healthy subjects on the sad tapes but not the happy tape. Coincident with the onset of reported sad feelings, activity widely decreased in the healthy subjects (unpublished data) but increased in several areas in the patients, leading to significant intergroup differences in multiple regions, including the superior temporal gyrus ($z=-4$, $p<0.01$, $N=23$) and the inferior frontal gyrus ($z=-4$ to $z=24$, $p<0.005$, $N=23$) on the right, the middle frontal gyrus bilaterally ($z=4$, $z=12$, and $z=24$, $p<0.005$, $N=23$), the hippocampus on the right ($z=-4$, $p<0.05$, $N=23$), and the globus pallidus and putamen on the left ($z=4$, $p<0.05$, $N=23$).

Activations after extended tape viewing (emotion 2 minus baseline 2). When activity levels during the final viewing periods of the happy and sad tapes were compared to the posttape baselines, many of the areas of relative underactivity in the patients seen in the contrast involving emotion 0 minus baseline 1 were again apparent. In addition, the patients showed significantly less tape-re-

lated activation than the healthy subjects bilaterally in the inferior frontal gyrus ($z=-4$, $z=4$, $z=12$, $p<0.005$, $N=29$).

Discussion

In the present study we found that cocaine addicts watching cocaine-cue videotapes had regional brain activations that were not present in healthy subjects watching the same tapes and were not present in either cocaine addicts or healthy subjects watching tapes that evoked happy or sad feelings (unpublished data). These activations thus appear to be specifically associated with the drug-taking experiences of the addict subjects. One prominent activation (anterior cingulate) was evident before the subjects reported the onset of craving as well as in the cocaine-dependent subjects who did not report experiencing craving. This raises questions about the relationship between brain activations and subjective experience and about possible advantages of using physiological rather than subjective responses to evaluate clinically relevant abnormalities in emotional state or cognitive processes. The addicts also differed from the healthy subjects in activation responses while watching tapes that induced happy or sad feelings. This suggests that the abnormalities in affective responses may in some way be related to their addictions. Finally, the cocaine addicts showed lower than normal activations of auditory and visual sensory areas during the initial viewing of all videotapes. This suggests possible generalized alterations in neuronal responsiveness following prolonged and extensive cocaine use. It could represent a true hypo-responsivity, an elevated response during the baseline period to the auditory and visual stimulation associated with the scanning procedure, or an uncoupling of neuronal activity and blood flow in these specific regions.

The earliest activation specific to the cocaine addicts watching the cocaine tapes was in the anterior cingulate. This activation was seen throughout the rostral-caudal extent of the anterior cingulate in the addicts but was minimal or absent throughout this region in the healthy subjects watching the cocaine tapes and in the addicts watching the happy or sad tapes. Activations of this structure in cocaine addicts have been observed in four previous studies, two that used cocaine-cue videotapes (2, 3) and two that involved pharmacologically produced cocaine or cocaine-like effects (1, 4). This activation is thus an established feature of the physiological response of cocaine addicts to cocaine cues. To our knowledge, the present study is the first to demonstrate that this activation precedes the self-reported onset of craving. Moreover, cingulate activation was also seen in cocaine-dependent patients who did not go on to report feelings of craving. The anterior cingulate is part of the limbic affect-response system, and its activation could reflect an immediate and marked affective response to cocaine cues. This response could be the basis of findings that surgical lesioning of the

anterior cingulate can decrease drug taking in patients (17, 18). Activation of the anterior cingulate occurs when subjects perform tasks that generate mutually conflicting response inclinations and require response inhibition (19). More than in any other situation in the current study, the addicts watching the cocaine-cue tapes were faced with an internal response conflict and the potential need to inhibit response tendencies. Such activation could be similar in the individuals who did and the individuals who did not go on to experience craving.

During the initial viewing of the cocaine tapes before the reported onset of craving, the patients showed less activation than the healthy subjects in multiple areas within the frontal lobes. In some of these same areas, activation was lower in the patients when they watched the cocaine tapes than when they watched the sad tapes. These observations raise the intriguing possibility of inhibition of frontal activation in addicts responding to cocaine cues, perhaps because of alteration of the normal activation balance between limbic (i.e., cingulate) and frontal regions.

After the self-reported onset of craving in the addicts, and other emotions in the healthy subjects, during viewing of the cocaine tapes (emotion 1 minus emotion 0 or emotion 2 minus baseline 2), nine regions were more active in the patients than in the healthy subjects: the right hippocampus, the anterior cingulate, the left superior frontal gyrus, the middle frontal gyrus, the lingual gyrus, the right inferior frontal gyrus, the middle temporal gyrus, the right middle occipital gyrus, and the superior occipital gyrus. The first five of these regions were more active during sad than happy emotional responses in the healthy subjects, while only the middle temporal gyrus was more active during happy than sad responses (unpublished data). These similarities suggest a physiological link between the cocaine-cue response in addicts and dysphoric affective states in healthy subjects.

In addition to the differential activation related to cocaine cues, the addicts showed differences from the healthy subjects while viewing the sad tapes. The patients showed increased activity after the self-reported onset of sad feelings while the healthy subjects showed decreases. The right hippocampus, already implicated in the craving response (see preceding) and in the dysphoric response in healthy subjects (unpublished data), was more active in the patients than the healthy subjects during the initial period of self-reported sadness. The right dorsolateral prefrontal cortex showed robust activation in the healthy subjects during the viewing of the sad tapes before the onset of self-reported feelings of sadness, but decreased activity after the onset of self-reported emotion (unpublished data). The cocaine-dependent subjects showed less activity in this region than did the healthy subjects before the self-reported onset of emotion but significantly more activity after the onset of feelings of sadness. Thus, the regions activated during exposure to sadness-inducing stimuli are not abnormal in location, but the time course

and modulation of their activity appears to be abnormal. Differences between groups in activation dynamics during the happy tape were similar but less marked, perhaps because the availability of only one happy tape decreased the sensitivity of this comparison.

Four of the cocaine-dependent patients met criteria for substance-induced mood disorder with depressive features, and two of these were among the eight patients who reported craving responses while watching the cocaine tapes. The very facts that depression is common among cocaine addicts, that depressed mood regularly follows short-term use, and that antidepressant medications can reduce drug craving suggest a neurobiological association between cocaine use and depression. It is not surprising, then, that we should find overlap among regions active in the response of cocaine addicts to cocaine cues and regions active in healthy subjects in response to sadness-evoking stimuli. Nor is it surprising that we should find abnormalities among addicts in response to sadness-evoking stimuli. Indeed, these observations provide clues to the neural systems that are the basis for the various associations among cocaine use, cocaine addiction, and dysphoric mood states. However, more work is needed to sort out the neurobiological similarities and differences between the craving and dysphoria responses in addicts and between dysphoria in addicts and in patients with mood disorders unrelated to substance use. Imaging of patients with depressions unrelated to substance use, however, suggest that there are substantial differences between activation abnormalities in patients with depressions unrelated to substance use and the abnormalities we observed in cocaine addicts. For example, repeated studies have shown less activation of the anterior cingulate in depressed patients than in healthy subjects (20–22), while we found greater activation of this region in addicts than in healthy subjects.

In summary, cocaine-dependent subjects show highly specific activation of the anterior cingulate in response to cocaine cues. This activation precedes the self-reported onset of feelings of craving, and it is evident in patients who have only recently begun treatment but do not report craving while watching a cocaine-cue video. At the same time, they show lower than normal activation of the frontal lobe, suggesting an imbalance between limbic and frontal cortical activity. After the onset of feelings of craving, cocaine-dependent subjects show activations of the right hippocampus and left superior frontal gyrus that are not seen in healthy subjects watching cocaine tapes but are evident in healthy subjects watching sad tapes. This suggests an association between craving and normal dysphoric states. Dynamic aspects of regional brain activations, but not the location of the activations, are abnormal in cocaine-dependent subjects while they watch the sad tapes, suggesting more general affective dysregulation in these patients.

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