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NEUROIMAGING OF COCAINE CRAVING STATES: CESSATION, STIMULANT ADMINISTRATION, AND DRUG CUE PARADIGMS

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Cocaine craving is a cardinal feature of addiction to the drug and is clinically significant because of its potential link to relapse. Addicted patients describe the craving as a powerful, "must-have" pull that causes them to risk, and sometimes lose, their relationships, families, money, possessions, jobs, and even their lives. "Anticraving" medications are greatly needed, but despite intensive research efforts since the mid-1980s, such agents have remained elusive (1,2). This dilemma is in part a consequence of our inability to define or measure cocaine "craving" clearly. Diversity in measurement may well account for some of the variability in the data collected, as described below. In part, the problem is our nascent understanding of which brain substrate(s) an "anticraving" medication should address. Until recently, the activity of the brain during cocaine craving was a matter of inference rather than direct observations. The increased availability of powerful tools for brain imaging *in vivo* has thrust research on drug craving forward into a new era. Several laboratories have begun to measure brain activity during cocaine-craving states directly. This chapter reviews current findings, offering a framework for the results and a discussion of their theoretic and treatment implications.

IS THERE MORE THAN ONE KIND OF COCAINE CRAVING?

Despite sophisticated tools for brain imaging, the study of cocaine craving is complicated by the fact that desire for the drug can be reported under dramatically different conditions, and measurement is carried out with a range of different scales. For example, craving may be reported in association with *cocaine cessation* (3), but also in association with *cocaine administration* (4) and *cues signaling cocaine* (5,6). Brain substrates may differ across these conditions. Interestingly, changes in the mesolimbic dopamine (DA) systems of the brain have been implicated in all three conditions, but the direction of change is not the same in all three. A possible (tonic) decrease in mesolimbic (nucleus accumbens) DA has been proposed in the case of cessation/functional depletion (7–9), whereas an (episodic) *increase* in DA has been hypothesized in the case of cocaine administration (10) and response to cocaine cues (11,12). Of course, these differing DA-related states are not mutually exclusive and may interact in important ways; for example, a dose of cocaine or a cocaine-related cue may have a different brain impact in early versus late cessation, depending on the dynamic re-regulation of the affected substrates. The possible "duality" (too much DA vs. too little DA) of cocaine craving has implications not only for the design of imaging studies but also for the treatment of cocaine craving (2). If the *same* brain substrates are responsible for the craving associated with DA deficiency and the craving associated with DA excess, how can either of these craving states be treated without worsening the other? We will return to this question after a review of the neuroimaging evidence for craving across the conditions.

Neurotransmitter systems other than DA are likely to be involved in cocaine reward and motivation (13,14). For example, serotonin (15,16), glutamate (17), corticosteroids (18–20), and opioids (21,22) have each received substantial cocaine-related research attention. However, in the *neu-*

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roimaging of cocaine craving, many of the studies have used a DA-related framework for their hypotheses, interpretations, or both. The emphasis on a dopaminergic system reflects not only a long literature on DA involvement in stimulant reward and motivation (23–25) but also the availability of DA-related neuroimaging tools for humans (26). Imaging studies testing the role of other neurotransmitters and neuromodulators in cocaine craving will be a welcome addition to the field. The only currently available study in this category is included in the current review (27).

The neuroimaging studies of cocaine craving discussed below are categorized according to whether their primary focus is *cessation, stimulant administration,* or *drug cue paradigms.* In studies in which the paradigms may overlap (e.g., patients in early cessation viewing cocaine cues), this is noted, as it may be helpful in the final integration of craving results across studies and paradigms.

IMAGING OF CRAVING DURING COCAINE CESSATION

Hypotheses

Early in the cocaine epidemic, investigators hypothesized that the long-term use of cocaine resulted in a functional depletion of brain DA (9) in regions critical for the regulation of mood, motivation, thought, and concentration. Acute cocaine administration to laboratory animals or to humans elevates levels of synaptic DA (and other monoamines) by reuptake blockade (28,29). However, brain measurements in long-term users (or laboratory animals maintained on cocaine) have revealed differences from controls, such as reduced DA synthesis (30), reduced cocaine uptake (31), down-regulation of postsynaptic DA sites (32,33), and altered responses in the endogenous opioid system (34–36), differences that may reflect the homeostatic attempts of the brain to cope with a cocaine-induced flood of synaptic DA. DA transporters (DATs) in the long-term user of cocaine may also be dysregulated, although the direction of observed change varies across studies (35,37–40), potentially reflecting the oscillating nature of re-regulation (see also refs. 31,41). The DA dysregulation observed in cocaine users following cessation is supported by numerous animal studies. These studies have found alterations in accumbens DA levels (7), the threshold for rewarding brain self-stimulation (42), the metabolism of reward-relevant regions (43), DA synthesis (44), and postsynaptic DA receptors (44). Thus, on cocaine cessation, the DA systems of some cocaine users may be in a neurologically adapted, dysregulated state. The lowered mood, energy, and concentration experienced by some cocaine patients during abstinence may be related, at least in part, to a dysfunction in brain DA systems. According to this general view, the *craving* that arises during abstinence may also reflect DA system dysregulation (8). Do neuroimaging studies support this hypothesis?

Data

The results of several neuroimaging studies are consistent with the notion of DA dysregulation in cocaine cessation; we review here the studies that have also included craving measures.

Early Cessation (1 Week or Less post Cocaine)

Volkow et al. (45) found a higher rate of metabolism by positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose in cocaine users in early cessation ($\leq$1 week post cocaine) than in controls in two major regions of DA projection, the orbitofrontal cortex and the basal ganglia. In this study, craving (''none,'' ''mild,'' ''moderate,'' or ''severe'') during the week before the scan was positively correlated with (both relative and absolute) metabolic rates in the orbitofrontal cortex, and with (absolute but not relative) metabolic rates in another major mesocortical DA projection region, the prefrontal cortex.

Malison et al. (39) studied DATs with single-photon emission computed tomography (SPECT) and B-CIT, a tracer that binds to dopamine and serotonin transporters, in patients abstinent from cocaine for 96 hours or less to determine whether they exhibited the transporter elevations predicted by a neuroadaptive hypothesis. DAT increases of approximately 20% in comparison with controls were indeed detectable, although they were more modest than the DAT increases found in postmortem studies of cocaine users (37,38). An inverse relationship was noted between DAT level and depression scores, but no relationship of DAT level to craving scores (on the Cocaine Craving Scale) was found (3).

Early and Later Cessation

Long-term cocaine use can alter μ-opioid binding (34–36), which indicates an interaction of DA and endogenous opioid systems. Given the role of endogenous opioids in mood modulation, up-regulated μ-opioid receptors may contribute to dysphoria or craving in cocaine cessation. Zubieta et al. (27) used PET and ^{11}C-carfentanil (a high-affinity μ-opioid agonist tracer) to image μ-opioid-receptor binding in cocaine patients at 1 to 4 days, and then at 4 weeks post cocaine. In comparison with controls, the cocaine patients showed up-regulation of μ-opioid receptors in the caudate, thalamus, anterior cingulate, frontal, and temporal brain regions; these changes persisted for 4 weeks in all but the temporal region. On the early cessation scan, craving (Minnesota Craving Scale on the prior evening, 100-mm visual analogue scale just before the PET, or both) was positively correlated with μ-opioid binding in the amygdala and the anterior cingulate, frontal, and temporal cortex. These four regions all receive significant DA projections, consistent with DA–opioid interactions. Scores on the Beck Depres-

sion Inventory did not correlate with μ-opioid-receptor availability, which indicates that the early cessation craving was not simply a depressed mood. None of the correlations of craving with μ-opioid binding were significant for the later, 4-week scan.

Later Cessation

In abstinence extending beyond a week (imaging at 1 to 6 weeks, and again at 3 to 4 months post cocaine), neuroimaging studies from the laboratory of Volkow et al. (46) have shown that frontal metabolism is decreased in the brains of cocaine users in comparison with that in controls. Although craving (averaging 3 ± 1 on a scale of 0 to 7) was assessed as a subject characteristic in this study, no correlations with metabolic rates were reported. In a further study of the same patient sample, reductions in orbitofrontal cortex and cingulate metabolism were particularly profound, and these reductions were correlated with reductions in (striatal) DA D2-receptor availability (33). However, craving (on a scale of 0 to 10) during the week of the study did not correlate with striatal D2-receptor availability; correlations of craving with metabolic rates were not reported.

Paralleling the metabolic findings of Volkow, Childress et al. found the resting regional cerebral blood flow (rCBF) to be significantly lower in the anterior cingulate (47) and left medial orbitofrontal cortex (gyrus rectus) (48) of cocaine patients at an average of 13.5 days after cessation in comparison with controls. However, neither baseline cocaine craving nor withdrawal (self-rated on a scale of 0 to 9) at the time of the scan correlated with rCBF in these regions.

Summary of Cessation Studies

The neuroimaging data clearly show a number of differences between the brains of cocaine patients undergoing cessation in comparison with controls not using drugs. The observed differences often are clearly linked to brain DA systems. However, the relationship of these brain indices to ''cessation craving'' has been variable. At this time, correlative evidence from studies in early ($\leq$1 week) cessation, but not from those conducted at longer intervals post drug, indicates a relationship between craving and brain responses (orbitofrontal and prefrontal cortex metabolism, μ-opioid binding).

Because the ''early'' and ''late'' cessation studies were often conducted in separate populations, and with important differences across studies (e.g., monitoring of abstinence, inpatient vs. outpatient population), any conclusions must be drawn with caution. Powerful within-subject designs, including frequent scans and subjective measures across a period of prolonged abstinence, would be helpful in clarifying cessation–brain–craving relationships. If such longitudinal studies were to confirm a lack of a relationship between craving and later resting *hypo*activity (by metabolism and rCBF) in DA projection areas, such findings would have implications for both theory and treatment. For example, if low DA tone is not associated with craving, then enhancing DA activity might not help craving, and could even be problematic (49).

Even if unrelated to craving, the differences between cocaine patients and controls that are evident at both early and later time points (e.g., in DA D2 and μ-opioid receptors) may still be very important. They may reflect other functional consequences of cocaine use, or group differences that possibly predate cocaine use or even predispose subjects to such use. The latter possibility has received very recent support. In a study of Volkow et al. (50), initial liking for intravenous methylphenidate (a stimulant also acting by inhibition of reuptake of DA) in normal persons was *inversely* related to D2-receptor availability. The D2-receptor levels for normal subjects who liked methylphenidate were significantly lower than those for normal subjects who did not like the drug, and they were strikingly similar to those of long-term cocaine users in earlier studies by the same investigators (51). Reduced D2 receptors may thus be a marker for vulnerability to stimulant misuse in addition to, or perhaps even instead of, a possible consequence of misuse.

IMAGING OF CRAVING DURING STIMULANT ADMINISTRATION

Hypotheses

Administering cocaine in the laboratory is a reliable and robust trigger of cocaine desire (4), and cocaine users complain that the first dose (''taste'') of cocaine in a binge rapidly elicits profound craving, drug-seeking behavior, and a second dose. Almost two decades ago, Eikelboom and Stewart (52) modeled this behavior in rats, showing that small drug ''primes'' could motivate drug seeking and reinstate extinguished responding for drug. According to the priming hypothesis, the initial drug effect always precedes the full drug effect and comes (through classic conditioning) to trigger a druglike brain state. The state has powerful positive incentive properties, ''pulling'' the organism back to the drug.

Koob (53) has proposed a different way in which the first dose of cocaine might lead to the next. In this ''opponent process'' view, the brain responds to cocaine with homeostatic processes, some of which are the hedonic opposite of the direct effect of the drug, euphoria. The opponent response (i.e., dysphoria) emerges as the direct effects of the drug dissipate and motivates drug seeking to reduce discomfort. Clinically, patients do complain about the jittery offset of the cocaine high, and they recognize that taking another dose of the drug will alleviate this state.

So, is the craving associated with human cocaine administration more closely related to a brain state that occurs at the *onset* or at the *offset* of the drug response? Although the question is posed as a choice, these possibilities (unfortu-

nately for the task of developing medications) are not mutually exclusive. Craving of the positive, appetitive, ''primed'' variety may map onto brain responses associated with the initial effect of the drug and be followed shortly thereafter by the dysphoric craving of offset, which may map onto a later set of brain responses that are *opposite* in direction to those of drug. The exquisite temporal sensitivity of functional magnetic resonance imaging (fMRI) allows these possibilities to be examined directly, as discussed below.

What are the likely neuroanatomic and neurochemical features of the craving state(s) associated with cocaine administration? More than two decades of animal research (see refs. 25,54–56 for review) support the involvement of the mesolimbic and mesocortical DA systems of the brain in cocaine reinforcement and motivation. Thus, *a priori* neuroanatomic predictions include the familiar projections of the DA cells in the ventral tegmental area of the midbrain to the ventral striatum (nucleus accumbens), amygdala, basal forebrain, orbitofrontal cortex, and medial prefrontal/anterior cingulate cortex. And, although recent animal (13) and human (57) research leaves room for the contribution of other brain systems, DA neuronal elements (DATs, postsynaptic D2 receptors) have also been initial neuroimaging targets.

Data

Several laboratories have now imaged cocaine users during stimulant administration, but some of these studies either did not obtain a craving measure (58–61), did not analyze the craving item (62), or analyzed a craving item but did not attempt to relate it to the brain measure under study (63). The remaining four studies discussed below have been published since 1997.

Breiter et al. (64) used temporally sensitive fMRI technology with a BOLD (blood oxygen level-dependent) scan to map the brain circuitry activated during a period 5 minutes before, and 13 minutes after, cocaine (0.6 mg/kg, maximum dose of 40 mg) versus saline infusion in cocaine subjects abstinent a minimum of 18 hours. Subjective ratings (''rush,'' ''high,'' ''craving,'' and ''low'') were taken each minute throughout the experiment. ''Rush'' and ''craving'' (defined as wanting more cocaine) ratings were later correlated with the group-averaged temporal pattern of signals from each brain region meeting specified threshold and extent criteria for differential activation by cocaine. ''Craving'' ratings increased steadily from the onset of the cocaine infusion, peaking at approximately 12 minutes post cocaine. No activity in any single brain region precisely echoed the onset and late peak of ''craving'' ratings. However, significant positive correlations were obtained with regions having early-onset (during euphoria) but *sustained* activations. These included the nucleus accumbens/subcallosal cortex and some paralimbic sites (a section of the parahippocampal gyrus, a section of the posterior insula, and a section of the anterior cingulate). Signal change in the amygdala during cocaine administration was initially reported as heterogeneous (some patients showed increases and others showed decreases), not correlated with rush, and negatively correlated with craving ratings. However, in a follow-up study with cardiac gating of the fMRI signal (see below), the direction of signal change in amygdala was positive for all subjects.

In contrast to ''craving'' ratings, ''rush'' ratings peaked quickly (at 3 minutes) after infusion and then declined rapidly. Although the brain regions that correlated with ''craving'' and ''rush'' overlapped substantially, a clear dissociation was also noted. ''Rush,'' but not ''craving,'' correlated with early maximal, short-duration signals from the ventral tegmental area and basal forebrain (and sections of the cingulate). On the other hand, ''craving,'' but not ''rush,'' correlated with an early-onset but sustained signal from the nucleus accumbens/subcallosal cortex. All the activated regions showed early onset to cocaine. Thus, the primary difference between ''craving'' and ''rush'' (euphoria) substrates was not a matter of which regions were activated, but of how long. Put another way, a full orchestra is playing from the outset of cocaine administration. As the ''rush'' wanes, some instruments drop out. ''Craving'' corresponds to the strains of those that play on.

How do these data fit with the ''priming'' and ''opponent process'' hypotheses of craving in response to cocaine? Unfortunately, the fit is not completely straightforward for either view. ''Craving'' mapped onto the activity of structures (nucleus accumbens/subcallosal cortex) with an early but sustained signal. At the first level of examination, this finding seems consistent with a priming effect; the signal occurs very early and therefore looks like a direct drug effect. However, according to the priming hypothesis, ''craving'' should map better onto the brain correlates (ventral tegmental area and basal forebrain) for the direct effects of ''rush'' and euphoria. In terms of clear evidence for a simple opponent process view, no later-occurring activations *opposite* to the direction of the ''direct'' drug effects in ventral tegmental area/basal forebrain, nucleus accumbens/subcallosal cortex, or other brain regions were identified. However, because the direct drug effect was a positive signal change in virtually all brain areas, detecting opposite direction effects would necessitate the detection and interpretation of fMRI signal decreases (''negative signal change''). Because of the physiologic basis of the BOLD signal, the meaning of ''negative signal change'' is an ongoing research challenge for fMRI.* Until this issue is resolved, PET in combination

* fMRI is extremely vulnerable to movement artifact. Signals from the amygdala and other structures near the base of the brain can be affected by the slight movement, at each heartbeat, of blood entering the brain through large vessels, and unreliable or uninterpretable data can result. Cardiac gating of the fMRI signal allows the fMRI scanner to be controlled by the heartbeat, and images are collected in the intervals between beats. Under these controlled conditions, the direction of change in the amygdala was positive for all subjects (H. C. Breiter, *personal communication*).

with a ^{15}O bolus performed during and after cocaine administration offers sufficient temporal resolution (^{15}O has a half-life of 128 seconds) that it can be used to sort out ''early/direct'' from any ''later/opposed'' effects of cocaine. Another possible complication in detecting ''opposed'' drug effects is that opponent processes can be conditioned; during the course of thousands of cocaine administrations, a response may ''move back in time'' so that it becomes nearly engaged at drug onset and persists. In experienced users (the only subjects who can be given cocaine in human studies), distinguishing ''direct'' from ''opposed'' effects could be very difficult. Animal research mapping the temporal correlates of brain response to cocaine and its signals during the course of initial and repeated administrations could clarify these relationships; of course, such experiments cannot ethically be conducted in humans.

The other three neuroimaging experiments involving stimulant administration to cocaine users and measures of craving have been conducted by the Volkow team at Brookhaven Laboratories. In one of these experiments, cocaine was used as the stimulant probe; in the other two, methylphenidate was used. In the cocaine study, cocaine users were given intravenous cocaine in doses of 0.3 to 0.6 mg/kg (a dose range known to induce euphoria), administered together with a tracer dose of ^{11}C-cocaine to measure DAT occupancy (29). Subjective self-ratings were taken every minute for the first 20 minutes post infusion, and then at 10-minute intervals for the next 40 minutes. The ratings of cocaine ''high'' and ''rush'' were positively correlated with DAT occupancy, but ''craving'' (the desire for cocaine, rated on a scale from 1 to 10) and ''restlessness'' were not. Thus, as in the earlier study of Breiter et al. (64), ''craving'' did not map onto precisely the same substrate as ''rush'' and ''high.'' This variability among studies may be a consequence of differences in the way craving was measured in each study.

The results from studies of methylphenidate administration suggest that a simple DA hypothesis of stimulant effects (including craving) may be insufficient. One study compared the subjective and brain DA response of cocaine users (3 to 6 weeks post cocaine) with that of controls after an injection of methylphenidate, which (like cocaine) blocks DA reuptake (51). An intravenous injection of 0.5 mg of methylphenidate per kilogram was followed by an injection of ^{11}C-raclopride, a dopamine D2 ligand sensitive to competition by endogenous DA. Regions of interest were the striatum, thalamus, and cerebellum (as a comparison region devoid of D2 receptors). Subjective measures were taken 5 minutes before and 27 minutes after methylphenidate. ''Craving'' in response to methylphenidate was much greater in the cocaine users than the controls and was correlated with an enhanced response (reduced raclopride binding) in the thalamus. ''High'' did not correlate with either thalamic or striatal raclopride binding, but a possible correlation may have been compromised by taking the subjective measures at 27 minutes, when the high had waned. Interestingly, both the ''high'' and the DA response to methylphenidate (measured by raclopride binding) in the striatum were greater in the *controls* than in the cocaine users, as though the cocaine users' response to methylphenidate had been blunted.

In a second study of cocaine users (abstinent on average for 14 days), two sequential doses (0.5 and 0.25 mg/kg) of methylphenidate were administered 90 minutes apart, after which metabolism (measured by PET and ^{18}F-fluorodeoxyglucose), D2-receptor availability (measured by ^{11}C-raclopride), and subjective responses (27 minutes after each infusion) were determined (66). The actions of methylphenidate on brain metabolism showed substantial variability across subjects that correlated with striatal D2-receptor availability; the stimulant increased metabolism in subjects with a high level of D2-receptor availability and reduced it in subjects with a low level of D2-receptor availability. Although methylphenidate induced metabolic increases in several areas (cingulate, thalamus, cerebellum), it increased right orbitofrontal and right striatal metabolism *only* in the subjects who experienced cocaine craving (''desire for cocaine and perception of loss of control over cocaine''). This observation indicates a possible (lateralized) role for these regions in stimulant-induced craving, but it also shows that an increase in DA secondary to reuptake blockade is not in itself sufficient to induce the metabolic increases in the frontal regions. As in the prior study, ratings of ''high'' at 27 minutes post methylphenidate did not correlate with the effects of the drug on metabolism or D2-receptor availability.

Summary

The only fMRI study performed during cocaine administration showed widespread brain activation, including activation of the classic mesolimbic–mesocortical circuitry often implicated in the reinforcing and motivational effects of cocaine. Although several brain regions were commonly activated by both craving and rush, rush-associated ventral tegmental area/basal forebrain signals rapidly declined while the craving-associated signals in the nucleus accumbens/subcallosal cortex persisted. This partial dissociation suggests at least some independence of substrates for these two states. The early onset of brain activation in cocaine-induced craving is consistent with the priming hypothesis; the partial dissociation with rush/euphoria is not. The lack of apparent ''offset'' activations correlated with craving is inconsistent with a simple opponent process view, but conditioned opponent effects could occur very early in highly experienced users, so that their origins would be obscured.

Studies that use a priming dose of cocaine necessarily image both the direct effects of the drug on the system being measured (e.g., DA system) and simultaneously any cognitive–affective–craving brain activity related to the cocaine cue. This dual time course of effects may account for some of the variability or inconsistency in effects reported.

With regard to which dopaminergic neuronal elements

are involved in the craving response, the results are mixed. Cocaine-induced craving was unrelated to DAT occupancy. However, methylphenidate-induced cocaine craving was correlated with right striatal and right orbitofrontal increases in metabolism and with an enhanced response (indexed by ^{11}C-raclopride) in the thalamus in comparison with controls. These findings could support a postulated DA dysfunction in the striatal–thalamic–orbitofrontal circuit in cocaine addiction (33,67). One similarity between the craving findings in early cocaine cessation (reviewed earlier) and the craving results in stimulant administration is a positive correlation with orbitofrontal activation. As discussed in the final section, the orbitofrontal cortex is thus far the only region linked to craving in all three paradigms: (early) cessation, stimulant administration, and exposure to drug-related cues.

Based on the neuroimaging data during stimulant administration, a role of transmitters other than DA in methylphenidate-induced effects (both high and craving) seems likely. Methylphenidate alone was insufficient to increase frontal metabolism, and in other studies by the Brookhaven team, significant levels of DAT occupancy by intravenous methylphenidate did not always result in a subjective high in healthy controls (craving was not probed) (68). The studies needed to determine whether these variable effects are also likely for cocaine (namely, giving pharmacologic doses of cocaine to healthy controls) cannot be performed; primate studies offer an important alternative.

IMAGING OF CRAVING DURING COCAINE CUES

Hypotheses

A guiding hypothesis of much of the research in cue reactivity is that the powerful craving and arousal responses to drug-related cues are based on simple classic conditioning (5,6). According to this view, cocaine cues trigger cocaine-related subjective and physiologic responses, including craving, because they reliably predict the arrival of the direct effects of the drug. As both the animal and human literature has shown, however, ''simple'' classic conditioning is often anything but simple. Drug-related conditioning can result in both responses similar to those produced by the drug itself (''druglike'') and responses *opposite* to those of the drug (''drug-opposite'') (69), likely reflecting a conditioned compensatory response to drug onslaught. Both kinds of responses may be of motivational significance. Druglike responses to cues reminiscent of the drug (''Wow . . . It's like I'm feeling it already . . . and I haven't even had any yet! I can't wait!!'') may act as a powerful positive incentive, pulling the user back to the drug. If drug-opposite responses to the cues are uncomfortable (in opiate users, these include tearing, yawning, sweating, and nausea), they may also prompt drug seeking.

Is cue-elicited cocaine craving more ''druglike'' or ''drug-opposite''? Do the multiple cues surrounding the cocaine experience become linked predominantly to the brief, intense, orgasmic euphoria . . . or to the jittery, sometimes uncomfortable, offset effects of this very short-acting drug? Both links seem possible, but they would yield opposite predictions for neuroimaging and pharmacotherapies. If craving to common external (paraphernalia, other users, drug-buying locations, drug talk) or internal (e.g., drug dreams, recurrent memories of ''high'') cues is predominantly druglike, we would expect that some elements of the mesolimbic–mesocortical DA system activated by cocaine itself are also activated during cue-induced craving. In animals, cues for cocaine can indeed trigger mesolimbic DA overflow in nucleus accumbens and amygdala (70) and can activate c-*fos* (an immediate early gene) in the cingulate (71, 72), amygdala (72), and nucleus accumbens (71). Patients often describe cocaine-like effects in response to cues, including heart pounding, ear ringing, head buzzing, stomach ''flipping,'' mild euphoria, a ''taste'' of cocaine in the back of the throat, even the ''smell'' of cocaine in the room . . . and, of course, profound desire. But what do the brains of cocaine users say about the nature of cue-induced cocaine craving?

Data

As shown in Table 110.1, the first neuroimaging study in which drug cues were used to induce craving was presented in 1992 (73,74). It tested whether video-induced cocaine craving might increase endogenous DA, as indexed by competition with a D2 ligand, ^{123}I-iodobenzamide, in SPECT. The low signal-to-noise ratio of ^{123}I-iodobenzamide, the low resolution of SPECT, and timing of the cue activation (after uptake of the tracer) likely undermined the ability of this early study to detect increased DA release in response to cocaine cues. After this initial effort, imaging studies addressed the neuroanatomic rather than the neurochemical substrates of cue-induced craving.

At least six additional laboratories (Childress et al., Volkow et al., Kilts et al., Grant et al., Garavan et al., Wang et al., Maas et al.) have conducted imaging studies with cocaine cues since 1992. These studies cover a range of imaging technologies (PET with ^{15}O bolus, PET with ^{18}F-fluorodeoxyglucose, fMRI) and include several variations on the method of presenting drug cues to induce craving. The variations are useful because results obtained in only one laboratory, or with one method of cue presentation, may be more related to the specifics of the laboratory or stimuli than to the psychological state of interest (cue-induced cocaine craving). Conversely, any replication and convergence of findings across multiple laboratories and methods are very encouraging.

A survey of the data in Table 110.1 reveals several convergent findings and suggests that brain activation in response

TABLE 110.1. BRAIN IMAGING OF CUE-INDUCED COCAINE CRAVING

Laboratory	Imaging Technology	Cocaine Population	Days of Cessation	Cue Description	Results[a]
U. Pennsylvania					
Childress et al., 1992 (73,74)	SPECT, ^{123}I-IBZM competition	Treatment-seeking (n = 10; 10 controls)	Range, 6–51	15′ personalized audio followed by 10″ video (separate days for drug/nondrug)	^{123}I-IBZM not displaced from striatum
Childress et al., 1994–1999 (47,79)	PET, ^{15}O bolus (ROI)	Treatment-seeking (n = 14; 6 controls)	Average, 13.5	25′ narrative nondrug video, then 25′ cocaine video (both with soundtrack)	Limbic: amygdala + a. cingulate + OFC 0 hippocampus 0 Comparison: striatum— DLPFC 0 cerebellum 0 visual cortex 0
Childress et al., 1999–2000 (103)	PET, ^{15}O bolus (ROI)	Treatment-seeking (n = 7)	Range, 7–22	(as above)	$GABA_B$ agonist baclofen may blunt limbic activation
Listerud et al., 2000 (80)	fMRI, BOLD	Treatment-seeking (n = 7; 12 controls)	Average, 14.5 Range, 3–38	15′ nondrug video, then 15′ cocaine video	amygdala + a. cingulate +
NIDA ARC					
Grant et al., 1996 (83)	PET, FDG (ROI)	Nontreatment (n = 13; 5 controls)	36–48 h (verified)	10+ repetitions of a 2.5′ silent video plus paraphernalia; snort option (separate days for drug/nondrug cues)	DLPFC +, ^ VLPFC + m. OFC + m. temporal (amygdala) + ^ retrosplenial + temporal/ parietal + temporal + extrastriate/ striate + peristriate + cerebellum ^ r.a. OFC ^(–)
Harvard–McLean					
Maas et al., 1998 (86)	fMRI, BOLD (ROI)	Nontreatment (n = 6; 6 controls)		Alternating 2.5″ drug/ nondrug video clips from Childress tapes (faces blurred)	a. cingulate +, ^ DLPFC +, ^ cerebellum 0
Emory University					
Kilts et al., 1996–2000 (82)	PET, ^{15}O bolus (SPM)	Treatment-seeking (n = 8)	Range, 7–17	1′ guided imagery (by audiotapes of nondrug, cocaine, and angry scenarios, two trials each, same order)	r. amygdala + l. a. cingulate + l. a. insula +, ^(–) r. Nac/SCC +, ^(–) OFC 0 DLPFC 0 Cerebellum 0
Medical College of Wisconsin					
Garavan et al., 1998–2000 (84)	fMRI (AFNI)	Nontreatment (n = 17; 14 controls)		4′ nature video, followed by 4′ cocaine/sex videos; 5″ distraction task in between	amygdala + l. cingulate + caudate + parietal + frontal +

(Continued)

TABLE 110.1. *(Continued)*

Laboratory	Imaging Technology	Cocaine Population	Days of Cessation	Cue Description	Results[a]
Brookhaven Laboratories Wang et al., 1999 (85)	PET, FDG (ROI)	Nontreatment (n = 13)	Average, 7 ± 9 (self-report)	30′ family genogram interview 30′ "cocaine preparation ritual" interview with paraphernalia (separate days for drug/nondrug cues)	OFC + l. insula + r. insula cerebellum + DLPFC 0 a. cingulate
Harvard–Massachussets General Breiter et al., 1997–1998 (64)	fMRI, BOLD	Nontreatment (n = 4, retest subgroup)	18 h minimum	saline infusion in an fMRI magnet where cocaine had previously been administered	NAc/SCC + r. insula + OFC +

[a]Results legend: +, activated; 0, no difference; —, deactivated; ^, positive correlation with cocaine craving; ^(–), negative correlation with cocaine craving. When controls were studied, the summary reflects significant difference between groups for the drug cue vs. nondrug cue conditions. When no controls were studied, the effects are only for drug cue vs. nondrug cue condition in cocaine users. Because of space constraints, results are summarized and "no difference" regions are presented only as relevant to discussion in the text. Please refer to the original articles for a complete listing of neuroanatomic regions studied.
Abbreviations: SPECT, single-photon emission computed tomography; ^{123}I-IBZM, iodobenzamide, a D2-receptor ligand; PET, positron emission tomography; ROI, region of interest analysis; OFC, orbitofrontal cortex; DLPFC, dorsolateral prefrontal cortax; VLPFC, ventrolateral prefrontal cortex; fMRI, functional magnetic resonance image; BOLD, blood oxygen level-dependent technique; SPM, statistical parametric mapping technique; FDG, ^{12}F-fluorodeoxyglucose; NAc/SCC, nucleus accumbens/subcallosal cortex; l., left; r., right; a., anterior, m., medial.

to cocaine cues often occurs in a particular subset of regions activated by cocaine itself (summarized above). Because of the number of studies, the findings reviewed below are organized according to the anatomic structures that have frequently been activated during cue-induced craving.

Limbic-Related Structures

Several of the structures activated during cue-induced craving are parts of an interconnected rostral limbic system, important in motivation and affective experience. Devinsky et al. (75) describe the rostral limbic system as including "the *amygdala* and septum, and *orbitofrontal,* anterior *insula,* and *anterior cingulate* cortices, the ventral striatum including the *nucleus accumbens,* and several brainstem motor nuclei including the periaqueductal gray." We also include findings for the hippocampus, part of the caudal limbic system in Devinsky's organizational scheme. Several of these limbic structures (e.g., amygdala, anterior cingulate and orbitofrontal cortex) comprise subdivisions of functional significance, but most *in vivo* neuroimaging studies refer to the structures in their entirety because of limited spatial resolution.

Amygdala

The amygdala, located in the medial aspect of the temporal lobe, is interconnected with the other rostral limbic regions and with the hippocampus. The amygdala is critical in signal learning for biologically significant (pleasant or unpleasant) events (76,77) and has been activated by cue-induced craving in virtually all the studies able to visualize it. In the first PET study of craving, predicted increases in amygdala rCBF (measured with ^{15}O-water as the perfusion tracer) were found in cocaine patients viewing videos that induced craving (averaging 4.5 on a scale of 0 to 9 for "craving or desire for cocaine") (47,78,79) versus nature videos. This effect was not evident in controls without a cocaine history. Interestingly, baseline rCBF in the amygdala of cocaine users tended to be lower than in controls, such that increased rCBF in response to the cocaine cues did not exceed the amygdala rCBF in control subjects under the same conditions. Activation of the amygdala in this study was initially documented by a region-of-interest (ROI) analysis and has recently been confirmed by statistical parametric mapping (SPM) of the group data (Fig. 110.1, *top image*). The amygdala activation to cocaine video cues documented with fMRI (Fig. 110.2) has recently been replicated in an ongoing study (Listerud et al., *unpublished data*). In other PET studies, Schweitzer et al. (81) and Kilts et al. (82) found amygdala activation during memory of cocaine-induced craving ("How strong was the urge to use cocaine, on a scale of 0 to 10?") induced by guided drug imagery, and Grant et al. (83) found a positive correlation of medial temporal lobe activation with video- and paraphernalia-induced craving (". . . craving or urge to use cocaine, on a scale of 0 to 10"). A recent fMRI study by Garavan et al. (84) found differential activation of the temporal pole, a region surrounding the ventral amygdala, in response to cocaine versus nature video. The PET camera used in the recent ^{18}F-fluorodeoxyglucose study by Wang et al. (85) did not

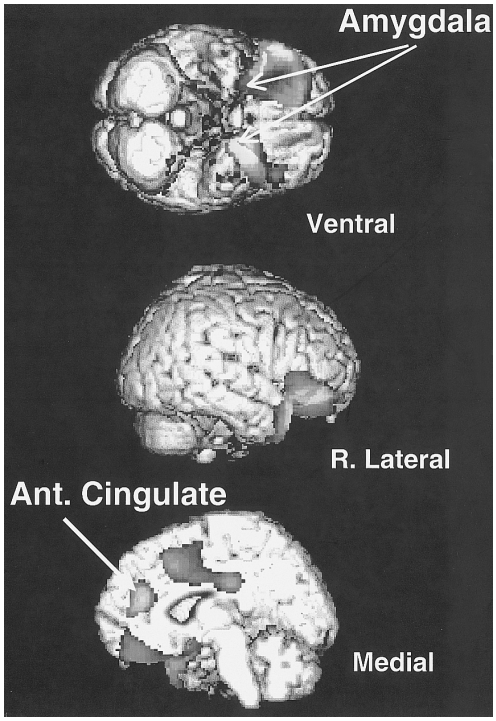

FIGURE 110.1. Amygdala and anterior cingulate activations during craving triggered by cocaine cues. Statistical parametric map (SPM 96) shows differential activation of brain regions by a cocaine video and a nondrug (nature) video; $p < .05$, corrected. See color version of figure.

permit adequate resolution of the amygdala, and susceptibility artifact in the region of the amygdala prevented reliable imaging in an earlier fMRI study by Maas et al. (86).

Anterior Cingulate

The anterior cingulate is located in the dorsomedial prefrontal cortex and is interconnected with other rostral limbic structures, including the amygdala and nucleus accumbens. Multiple roles of the anterior cingulate include selective attention and emotional reactivity to significant stimuli (75, 87). In parallel with the amygdala findings, the anterior cingulate was differentially activated during video-induced cocaine craving in our initial PET study with ^{15}O bolus (by ROI analysis and later confirmation by SPM analysis of the group data) (Fig. 110.1, *bottom image*). As with the amygdala effect, the cue-induced rCBF increase in anterior cingulate was from a resting baseline that was hypoactive relative to the baseline of controls. Unpublished fMRI data (Listerud et al.) support the anterior cingulate activation in response to cocaine versus nature cues. Studies by Maas et al. (86), Kilts et al. (82), and Garavan et al. (84) have confirmed anterior cingulate activation during cocaine cues. These studies used fMRI (84,86) and PET with ^{15}O bolus (82), imaging techniques that provide good temporal resolution. Studies by Grant et al. (83) and Wang et al. (85) did not detect increased anterior cingulate activation during cocaine cues. They both used PET with ^{18}F-fluorodeoxyglucose; because of its low temporal resolution, this technique may be insensitive to a relatively brief or nonhomogeneous activation of the anterior cingulate.

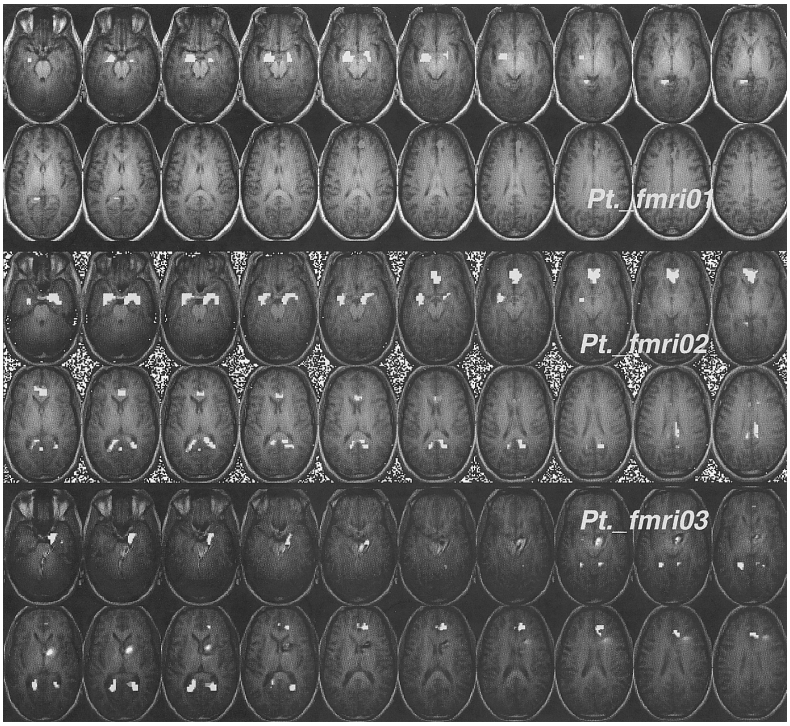

FIGURE 110.2. Functional magnetic resonance imaging of cocaine versus nature video. Individual difference maps show amygdala and anterior cingulate activation in three pilot cocaine patients. See color version of figure.

Nucleus Accumbens/Subcallosal Cortex; Striatum

The nucleus accumbens is located in the forebrain, in the ventral part of the striatum. It is a prominent terminal region for DA cells projecting from the ventral tegmental area, and much animal research points to this mesolimbic–nucleus accumbens pathway as a critical substrate for the reinforcing effects of natural rewards (88), cocaine, and other drugs of abuse (89). In humans, the size of the nucleus accumbens is about 5 mm. Thus, the nucleus accumbens falls at (or often below) the threshold of reliable detection for many early PET cameras, but it often can be localized with the precise anatomic co-registration of fMRI. The 1997 fMRI study of cocaine administration by Breiter et al. (64) contained an ''unintentional'' cue paradigm (Table 110.1). Subjects given a (double-blinded) infusion of saline solution in the fMRI magnet showed clear activation of the nucleus accumbens if they had previously received an infusion of cocaine in this novel environment. The nucleus accumbens signal to the infusion environment had the same ''early-onset, sustained'' pattern as the signals to actual cocaine administration. This striking finding suggests that a druglike response to cocaine cues can be established with a single trial.

Other striatal findings in cue paradigms are mixed. In the study performed with PET and ^{15}O bolus, the overall response of the basal ganglia to cocaine versus nature videos was an unpredicted *decrease* in rCBF, but the larger dorsal striatum (which receives primary projections from the substantia nigra) was not parsed from the smaller ventral (nucleus accumbens) portion, which receives projections from the ventral tegmental area (47,78,79). Garavan et al. (84) found activation of the dorsal striatum (caudate) with fMRI, but did not report on nucleus accumbens. Kilts et al. (82) found nucleus accumbens activation in response to guided cocaine imagery, but the activation was inversely correlated with craving self-reports.

Orbitofrontal Cortex

The orbitofrontal cortex is located in the ventromedial region of the frontal lobes. The orbitofrontal cortex is richly interconnected with DA-related regions involved in reward and stimulus–reward learning (90). Three studies (64,83, 85) found orbitofrontal cortex activation in response to cues; two did not (47,82). The remaining two studies, in which fMRI was used, did not report on the orbitofrontal cortex response (84,86) (ventral orbital regions are often difficult to image with fMRI because of artifact introduced by air in the sinus cavities). In the three studies finding an orbitofrontal cortex response to cues, the subjects were in early cessation (ranging from 18 hours to 7 days); in the two studies finding no orbitofrontal cortex activation to cues, the patients had been abstinent for longer periods. In the earlier ''cessation'' section of this chapter, we mentioned that the literature suggests that orbitofrontal cortex hyperactivity in early cocaine cessation is correlated with self-reported craving, whereas (later) orbitofrontal cortex hypoactivity is unrelated to craving. One interpretation that integrates the earlier observations with those in the explicit cue paradigms is that orbitofrontal cortex hyperactivity is associated with enhanced responsivity to cues, whether naturally occurring or presented by a laboratory experiment. Orbitofrontal cortex hypoactivity, on the other hand, clearly does not prevent cue-induced craving and may represent a different vulnerability (see summary below).

Insula

The insular cortex is located interior to the lateral sulcus. It is interconnected with several other regions activated by cocaine cues, including the amygdala and the cingulate and orbitofrontal cortex; it also reflects input from the viscera (autonomic nervous system) and sensory systems. Three laboratories have reported activation of the insula in response to cocaine-related cues, but the effects vary. Wang et al. (85) reported activation of the left insula but found a correlation of craving only with the right insula. Breiter et al. (64) reported activation of the right insula in response to the cocaine infusion environment; no correlation with craving was reported for the small subgroup in this experimental condition. Kilts et al. (82) reported activation of the left insula (in response to guided imagery), but a negative correlation with craving. Given the disparate findings, additional studies will be needed to sort out the nature and direction of cue effects in the insula.

Hippocampus

The hippocampus is located in the medial temporal lobe, posterior to the amygdala. It was not differentially activated by the cocaine videos in our PET study with ^{15}O bolus, and activation has not been reported by the other investigations. This suggests that cue paradigms generally do not make demands on explicit, declarative memory and factual recall, functions closely associated with the hippocampus (91). This is in contrast to the common finding of amygdala activation across several cue studies. Although proximal to the hippocampus and interconnected to it, the amygdala is not activated by explicit memory demands; rather, it supports functions of implicit, emotional memory (92).

Other Structures

Dorsolateral Prefrontal Cortex

The dorsolateral prefrontal cortex, best known for its role in working memory, was not differentially activated by the uninterrupted, narrative cocaine videos in our PET study (47), although craving was robust. Similarly, it was not activated by the paradigm of Kilts et al. (82) with guided imagery, by that of Wang et al. (85) with cocaine theme interviews, or by that of Garavan et al. (84) with an uninterrupted, unrepeated 4-minute video clip.

The paradigm of Maas et al. (86) did activate the dorso-

lateral prefrontal cortex; it featured brief alternating exposures to a nondrug and a cocaine video, modified from the tapes of Childress et al. (the faces were blurred to protect the patients' identities). These alternating conditions may have engaged working memory in the cocaine subjects because the same cocaine users reappeared in an ongoing drug scenario that was interrupted by the nondrug video segments. Controls are generally less engaged by cocaine stimuli and therefore would also be expected to show less engagement of working memory. A similar explanation may account for activation of the dorsolateral prefrontal cortex in the paradigm of Grant et al. (83), which featured several repetitions of the same brief cocaine video clip during the period of ^{18}F-fluorodeoxyglucose uptake. In an ongoing fMRI study (Listerud et al., *unpublished data*), activations by uninterrupted versus alternating cocaine videos are being compared within the same cocaine patients. This study will directly test the hypothesis that dorsolateral prefrontal cortex activation in cocaine users is related to the mode of stimulus presentation rather than to cue-induced craving *per se*.

Cerebellum

The cerebellum, important in motor coordination and retention of simple motor schemas, was not activated in our PET study with ^{15}O bolus in which videos were used to induce craving for cocaine (47). Similarly, it was not activated by the cues of Maas et al. (86), Kilts et al. (82), or Garavan et al. (84). The cerebellum was differentially activated in the study of Wang et al. (85), which featured a cocaine theme interview and handling of paraphernalia during the period of ^{18}F-fluorodeoxyglucose uptake. The (highly ritualized and overlearned) handling of cocaine paraphernalia may have triggered motor memories and schemas, a cerebellar function. In support of this notion, the study of Grant et al. (83) also featured handling of paraphernalia as part of the stimulus complex during the period of ^{18}F-fluorodeoxyglucose uptake, and a correlation was found between craving and cerebellar activation. This correlation would occur if handling of paraphernalia acted both as a potent conditioned cue for drug craving and as a trigger for motor memories/highly practiced motor schemas related to cocaine preparation.

Sensory/Association Cortex

In addition to the regions discussed, one imaging study has shown differential activation of visual association areas (peristriate) by cocaine cues (83), and two studies have shown differential activation of the inferior parietal lobe (83,84), which is sometimes implicated in working memory. As additional neuroimaging studies accrue, it will be easier to determine whether less common activations such as these reflect a feature of the paradigms used or a feature of the target state.

Summary

The involvement of seven laboratories in neuroimaging cue-induced craving has generated a useful database for drawing preliminary conclusions about the substrates of the state and, importantly, for generating new hypotheses that will help to refine the emerging picture. Despite the variability in imaging techniques, analysis techniques, the abstinence/treatment status of the subjects, and the varied methods used to induce cocaine desire, several convergent findings for regions of activation have been obtained. The most commonly activated regions during cocaine cues, across the laboratories, were the amygdala and anterior cingulate. Two studies that parsed the ventral (nucleus accumbens) from the dorsal striatum showed activation by cocaine cues in the ventral region; the fMRI signal from the nucleus accumbens for a ''cocaine-associated environment'' (the fMRI magnet!) was strikingly similar to that for cocaine itself. The insula has been activated in at least three cue studies, although the correlations with craving vary in direction. The orbitofrontal cortex was also activated by cues in the (three) studies of cocaine subjects in recent cessation.

The hippocampus was not regularly activated by cocaine cues, which suggests that the cue-induced state does not depend on declarative memory/factual recall. The dorsolateral prefrontal cortex was not activated in most of the cue studies but was activated by cocaine cues that were intermittent or repeated; this activation may be relatively independent of any direct connection to cue-induced craving. The cerebellum was not activated in most cue studies, although it was activated in two paradigms in which paraphernalia handling could have triggered motor memory schemas.

The brain regions activated by cocaine cue paradigms (amygdala, anterior cingulate, nucleus accumbens, insula) do substantially overlap those activated by cocaine itself in the fMRI study of Breiter et al. (64). This is consistent with the druglike phenomena (autonomic arousal, mild euphoria, sense of a cocaine ''taste'' or ''smell'') that often accompany cue-induced craving. Most cue paradigms, even those in which fMRI is used, have not yet described the temporal pattern of the signals from these regions during cues; such information would permit a more detailed comparison of cue effects with the multiple effects of cocaine (e.g., ''craving'' vs. ''rush'' substrates). No studies have yet examined the ventral tegmental area or basal forebrain in response to cues.

The orbitofrontal cortex deserves special mention in the discussion of craving and drug motivation. Orbitofrontal dysfunction in other disorders has been associated with difficulties in modulating rewarded or punished behavior (e.g., reversing or switching behavior in response to a change in contingencies) (93), impaired somatic/emotional response in anticipation of the consequences of a decision (''future insensitivity'') (94), and perseverative, compulsive behaviors (67). Clinically, some of these same difficulties have been

noted in substance abusers, which raises the possibility of a core deficit in some patients (95). Long-term users of amphetamine are impaired on a decision-making task that places demands on ventromedial prefrontal (orbital) function (96), and long-term administration of stimulants clearly erodes orbitostriatal inhibitory function in primates (93). Whether such orbitofrontal cortex deficits predate drug use in humans, predispose to it, or are a consequence of it, the news for long-term cocaine users is not good; they may be at a particular disadvantage in managing their craving for the drug. Interestingly, the reviewed studies link increases in orbitofrontal cortex activity to craving in all three paradigms: (early) cessation, stimulant administration, and response to cues (during early cessation from cocaine). A future challenge is to understand how such activations in a potentially dysfunctional orbitofrontal cortex differ (or not) from normal activation of the orbitofrontal cortex during advantageous decision making (97).

DISCUSSION

Theoretic Implications

The neuroimaging of craving states is at a very early stage, and most findings should be replicated before they are taken as either a confirmation or a challenge to theories of addiction and drug motivation. With this caveat kept in mind, some findings from the paradigms reviewed may have implications for current theories.

From the *cessation* paradigms, the preliminary imaging data provide little support for the proposition that craving (drug desire) during cessation arises primarily from a state of prolonged DA depletion or deficiency. Although the DA systems of cocaine patients do differ from those of controls, craving did not show a good relationship to these changes beyond the first week of cessation.

The *drug administration* paradigms show that DA-related regions are activated during stimulant-induced craving, but the temporal pattern of activation fits neither a simple priming (''substrates for craving are the same as the substrates for high'') nor a simple opponent process (''substrates for craving are the opposite of the substrates for high'') view. Studies of craving during methylphenidate administration indicate the possible contribution of non-DA (in addition to DA) systems.

The *cue* paradigms suggest that the regions activated during cue-induced craving often overlap the regions activated by cocaine itself (i.e., the substrate is substantially ''druglike''). Of course, these early findings do not preclude ''drug-opposite'' brain responses or conditioning in response to cocaine cues. The cue data simply suggest that across several laboratory environments (as in patients' descriptions from the natural environment), cocaine craving with a ''druglike'' substrate is likely to be evoked.

Interestingly, the current neuroimaging paradigms offer little support for the notion of a ''sensitized'' substrate, sometimes proposed as a potential mechanism for stimulant drug craving/incentive motivation. Beyond the first week of cessation, cocaine patients often exhibit resting hypoactivity in limbic and frontal regions in comparison with controls. Exposure to cocaine cues or to a stimulant can produce a significant activation in these affected brain regions, but the absolute level of brain response is often no greater than in controls, and may even be less. Of course, the appropriate test for sensitization would require comparing the current responses of cocaine patients with their own initial responses to the drug. This design is unfortunately not feasible. It does, however, highlight a limitation of all our neuroimaging studies in cocaine patients; we usually do not know their baseline before addiction on the brain variables of interest. The discovery of Volkow et al. (50) of striking baseline differences in the availability of D2 receptors in controls (based on liking vs. not liking an initial dose of methylphenidate) is fair warning that the brains of cocaine users who proceed to addiction may differ from those of (some) controls, even before cocaine use begins.

Treatment Implications

Imaging data from the stimulant administration and cue paradigms suggest that craving is often associated with relative increases in the activity of the same brain DA systems that may otherwise be hypoactive in cocaine users. Finding an ''anticraving'' agent that can modulate the periodic increases in DA in response to cues or drug primes, without worsening symptoms that may be related to chronic hypoactivity (e.g., depressed mood, low levels of energy), poses a particular challenge. Classic DA antagonists (typified by the older antipsychotics) are poor candidates for this modulatory role because they could worsen symptoms related to low levels of DA; they also carry a significant risk for extrapyramidal side effects and tardive dyskinesia.

Partial DA agonists may offer an appealing solution in the future (2,98,99). These compounds act as agonists under conditions of low DA tone (as may occur in cessation), but as antagonists when the DA concentration increases (as in response to cues or drug primes). The ''chameleon-like'' nature of partial agonists may possibly offer the cocaine patient a moment-to-moment regulation of the DA system. Unfortunately, for now, no partial agonists (D1, D2, or D3) are approved for humans, although considerable animal research has been done and preliminary safety trials are under way.

Another promising category of DA modulators are the γ-aminobutyric acid type B ($GABA_B$) agonists (100–103). These compounds may gently modulate the DA system by reducing ventral tegmental area cell firing, thereby reducing DA release in terminal regions. Roberts and colleagues (100, 101) were the first to demonstrate the blunting of cocaine motivation by the $GABA_B$ agonist baclofen (Fig. 110.3). In

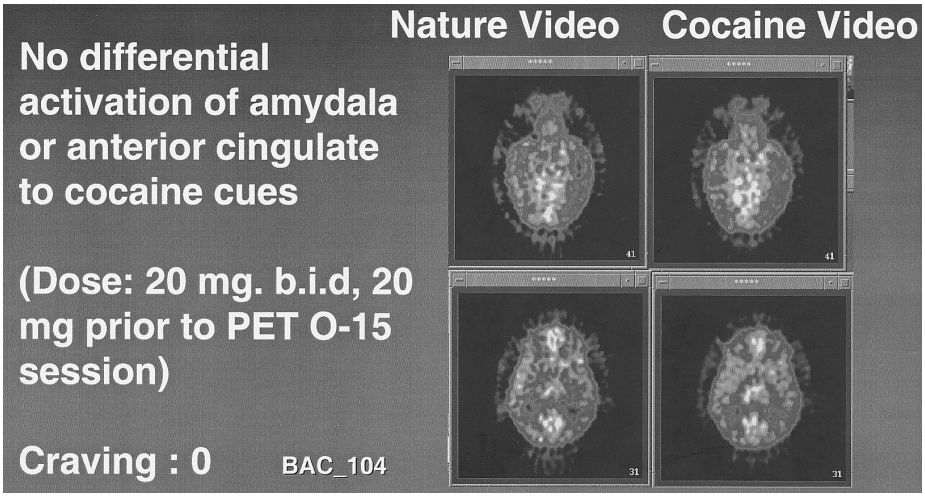

FIGURE 110.3. Baclofen, a γ-aminobutyric acid type B agonist, may blunt limbic activation and craving in response to cocaine cues. See color version of figure.

subsequent cocaine-related studies by Dewey et al. (104), the GABA transaminase inhibitor γ-vinyl-GABA also showed promise; its cocaine-related effects are reversible by a $GABA_B$ antagonist. Unpublished preliminary data from Childress et al., testing the ability of baclofen to blunt both subjective and brain responses to cocaine cues by measuring rCBF with PET and ^{15}O bolus, suggest that baclofen, although it has a relatively short half-life, may indeed confer protection against cue-induced craving and the accompanying limbic activation. These data are important because the craving/imaging paradigm is being used to test an "anticraving" medication.

Future Directions

The neuroimaging studies of cocaine craving reviewed in this chapter will soon be viewed as the "early" stage of our understanding; the imaging field is growing rapidly, as is the sophistication of the tools and their users. Advances in spatial and temporal resolution of imaging devices, and advances in image analysis, will allow the formulation of more precise hypotheses regarding craving substrates. As shown in this review, the future answers are likely to be found within temporal as well as regional patterns of activation. Although DA has played a strong role in shaping the early neurochemical hypotheses, interacting neurotransmitters and neuromodulators will soon be tested as the critical ligands become available. Until then, the combination of pharmacologic probes with neuroanatomic imaging may offer a powerful alternative.

Designs of increased rigor, with attention given to homogeneity of samples (e.g., number of days of cessation, nicotine status, treatment status, urine toxicology status, genetic status, drug use history) and careful characterization of controls, will enhance the replicability of findings across laboratories. Asking for more than one subjective response or "craving item," and asking for these at the optimal time for the paradigm, will ensure a clear test of the relationship between brain activity and subjective state. Characterizing brain activity during other, nondrug states of arousal (e.g., anger, anxiety) will help to determine the specificity of the signature of the brain for cue-induced craving. This is important because the brain structures activated in cue-induced cocaine craving are not "reserved" for this state; rather, they participate in many other states that are not related to cocaine. In this regard, measurement of the brain response during other, nondrug appetitive states (e.g., sexual desire) in subjects who do not use drugs may provide a "positive control" for cocaine craving, which is so often described in sexual terms. Imaging of the craving states for heroin, nicotine, and other drugs of abuse will also provide informative comparisons; these studies have already begun (105).

Although the path ahead is clearly challenging, finding the brain substrates of desire, both for drugs of abuse and for natural rewards, is now a matter of time and effort; the tools are increasingly available. Only a decade ago, and for all of prior human history, brain activity during subjective states was largely a matter of inference. Now, and in the future, these states can be the subject of direct measure. This represents a dramatic paradigm shift, one that enables states such as "desire" and "craving" to be the subject of rigorous scientific research. This research is a critical prerequisite to the rational, and vastly improved, treatment of disorders of desire (i.e., the addictions).

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