Neurochemical Predictors and Correlates of Vulnerability to Cocaine Use

Roy J. King, Jr., and Christopher Flowers

STATEMENT OF THE PROBLEM

The ultimate goal of the proposed research is to examine the neuro-chemical and behavioral factors that may predict vulnerability to cocaine craving, which is believed to be associated with relapse among abstinent cocaine abusers. In general, the proposed studies are linked through an overarching postulate that cocaine craving results from heightened mesocorticolimbic dopamine (DA) activity.

This hypothesis is explored through between-subject as well as within-subject designs. In between-subject designs, it is hypothesized that individuals prone to cocaine craving will exhibit elevated measures of dopaminergic functioning. In within-subject designs, increased craving is believed to be associated with increased dopamine activity within an individual over time. Since direct assessments of DA activity in humans are relatively limited, several indirect measures of DA function are proposed. These measures are based on animal models derived from the literature on incentive motivation and on previous studies in human sub-jects. They include cerebrospinal fluid (CSF) concentrations of homo-vanillic acid (HVA), the major metabolite of DA; CSF dopamine sulfate (DASO4) levels, reflecting central nervous system (CNS) DA activity; and real-time measurement of motor activity associated with increased DA activity. Specifically, the plan is to accomplish four specific aims.

Specific Aim 1

This project will assess the relationship between cocaine craving and variations in DA-related measures between individuals after long-term cocaine abstinence. In particular, the proposed research will test whether CSF-HVA and CSF-DASO4 levels correlate with cocaine craving. A confirmation of this hypothesis will offer more precise CNS correlates of

the subjective measures of cocaine craving, which will be useful in testing the "priming" models of craving and relapse using these biological indices.

Specific Aim 2

The project will also study the utility of using motor activity as a peripheral monitor of individual differences in CNS DA activity. Motor activity will be correlated with CSF-HVA and CSF-DASO4 in the sample of cocaine abusers. This aim will quantify the practicality of using motor activity as a reflection of CNS DA metabolism.

Specific Aim 3

In addition, the project will examine the relationships between motor activity and cocaine craving both between individuals and within individuals. In within-subject studies, the relationship between craving episodes and increased motor activity will be traced in the naturalistic setting among long-term hospitalized cocaine abusers. In addition, mean daily levels of activity and automated behavioral self-recordings of craving will be determined across subjects. The studies under the pur-view of this aim will provide information on the dynamics of cocaine craving and, in conformance with the incentive motivational model of craving, test whether heightened locomotor activity occurs with spon-taneous attacks of craving in these subjects. Findings from this work may reveal noninvasive means to identify the acute onset of cocaine craving and surrogate markers for identifying individuals at increased risk of craving cocaine.

Specific Aim 4

Finally, the project will study the relationship between Axis II personality disorder traits (as defined in the "Diagnostic and Statistical Manual of Mental Disorders," 3d. ed., rev. (DSM-III-R)) and cocaine craving. Preliminary data indicate that histrionic personality traits may predict long-term use of cocaine. Under this specific aim, it is postulated that histrionic personality disorder traits will be associated with heightened cocaine craving in long-term abstinent cocaine abusers. Moreover, using multiple regression of the Axis II personality disorder traits as indepen-dent predictors of cocaine craving, it is proposed that this association will be found to be distinctive and, thus, contribute the predominance of covariation between personality disorder and cocaine craving. A clear corollary

of this finding would be that histrionic individuals show increased craving and, thus, may be at increased risk for relapse.

BACKGROUND AND SIGNIFICANCE

Cocaine use is a major public health concern in America. In spite of numerous attempts to reduce the prevalence of cocaine abuse and dependence, long-term treatment remains a virtually intractable social problem. Even after successful detoxification, relapse remains a recurrent difficulty (Wallace 1989). One factor related to relapse into cocaine use is the continued craving that individuals experience even after long-term abstinence. Studies by Kozlowski and Wilkinson (1987) and Extein and Dackis (1987), and treatment strategies espoused by Washton and colleagues (1986) and Wesson and Smith (1985), point to craving as a substantial factor in cocaine abusers' relapse into drug use.

Treatment of stimulant abuse is typically divided into two phases: initiation of abstinence and prevention of relapse. Intense cocaine craving arises during the period of anhedonia 12 to 96 hours after the last use of cocaine, and craving can reemerge episodically months or years after its last occur-rence (Gawin and Ellinwood 1988). Thus, management of cocaine craving is crucial for prevention of relapse during detoxification and long-term treatment.

To date, several pharmacological and behavior interventions have been investigated for treating cocaine craving. Behavioral intervention strategies have focused on deconditioning or reconditioning stimuli (e.g.,environmental cues, recall of euphoria, and mood) that patients associate with craving attacks (Childress et al. 1988a, 1988b; Wallace 1989; Weddington et al. 1990). Most pharmacological interventions have been based upon the DA depletion hypothesis (Dackis and Gold 1990; Dackis et al. 1985), that proposes that withdrawal from cocaine use involves a hypodopaminergic state introducing anhedonia, which provokes craving and subsequent drug use. Proponents of this model have employed DA agonists such as apomorphine (Hollander et al. 1990), bromocriptine (Dackis et al. 1985, 1987), pergolide mesylate (Malcolm et al. 1991), amantadine (Gawin et al. 1989b), flupenthixol (Gawin et al. 1989a), and desipramine (Gawin et al. 1989b) without clear indications of therapeutic efficacy.

Although a dysphoric component possibly related to hypodopaminergia probably exists as a component of craving, human and animal evidence (Stewart 1984; Wise and Bozarth 1987) have directed recent research to focus on the relationship between the craving experience and the rewarding and reinforcing effects of cocaine. Some studies suggest that the rewarding effects of cocaine are mediated by an enhancement of mesolimbic/ meso-cortical DA function (Pettit et al. 1984; Ritzetal. 1987). As a result, behavioral and pharmacological therapies based on alleviating the effects of the positive reinforcement associated with cocaine-induced hyperdopa-minergic functioning seem a more plausible means of extinguishing cocaine craving and preventing relapse. However, before such inter-ventions can be developed, the relationships between cocaine craving and neurochemical and behavioral factors known to be involved in cocaine abuse must be carefully examined. Clarification of the relationships between dopaminergic functioning, motor activity, mood states, personality features, and cocaine craving will serve as a foundation upon which to build a comprehensive and efficacious treatment strategy. Thus, the proposed research is of particular clinical significance for developing treatments to prevent relapse among cocaine abusers.

Individual Differences in Cocaine Craving and Dopaminergic Activity (Specific Aim 1)

Cocaine craving as a medical phenomenon has yet to be distinguished as an event arising from a fundamental set of conditions. Moreover, the use of craving as a medical construct has been confounded by its connota-tions in common language. In most connotations, craving refers to a strong desire or intense longing. Typically, craving is used to describe two distinct states that often are not carefully distinguished: aversive craving associated with the anhedonic effects of drug withdrawal and appetitive craving, a desire to reinstate the euphoric effects of the drug. Although some inconsistent findings exist in the literature on cocaine craving, the research discussed here focuses on craving as a motivational state associated with the positive reinforcing qualities of cocaine. The behavioral, psychopharmacological, and neurochemical evidence supporting this model of cocaine craving is presented.

Individual differences in vulnerability to cocaine craving have been suggested by animal models of cocaine self-administration and human studies, but they have yet to be demonstrated directly. The conditions in which cocaine craving arises and the time course for

development of craving also remain unmeasured. Several means have been proposed to measure cocaine craving at a single point in time, but few have charac-terized changes in craving intensity over a period of time. Methods to assess cocaine craving include a 29-item self-administered test (Gawin and Kleber 1986), a 13-item withdrawal symptom scale (Tennant and Sagherian 1987), a 20-point analog scale (Kosten et al. 1987), the Brief Psychiatric Rating Scale (Giannini and Billet 1987), the Addiction Severity Index (ASI) (McLellan et al. 1980), and the Beck Depression Inventory (O'Brien et al. 1988).

More recently, Voris and colleagues (1991) and Halikas and colleagues (1991) have focused on describing the craving episode, and they have demonstrated the reliability and validity of measurements of cocaine craving. Employing a 20-point visual scale, Voris and colleagues (1991) found statistical reliability among 25 patients' self-assessments of intensity of craving, mood, energy, and general health measured on successive days. This evidence suggests that the experience of craving and related variables can be reliably measured by self-assessment techniques. Halikas and colleagues (1991) described cocaine craving in terms of three dimensions: intensity, frequency, and duration. Data gathered from 234 questionnaires completed by 35 subjects indicate cocaine craving to be infrequent (< 2 times per day), of short duration (<20 minutes), and of variable intensity. A test of internal consistency revealed that the three measurements described the same construct, a=0.826. Also, the intensity, frequency, and duration of craving components each correlated positively with cocaine-use dreams. These data suggest that craving is a robust construct related to individual psychological and cortical functioning; they pave the way for more detailed descriptions of cocaine craving and the associated behavioral and psychosocial variables. These scales and inventories serve as a foun-dation upon which an automated assessment of cocaine craving was constructed to measure mood covariants and the time course of cocaine craving. This information will be useful to construct a dynamic model of cocaine craving that can be readily incorporated into the corpus of neurochemical and psychiatric knowledge concerning cocaine abuse.

Most neurochemical models of cocaine craving have focused on fluc-tuations in dopaminergic functioning as the underlying mechanism to account for variations in craving. Until recently, theoretical investigation of the postacute period of cocaine administration has been influenced primarily by the dopamine depletion hypothesis, which asserts that a hypodopaminergic state underlies the dysphoric aspects of abstinence leading to anhedonia, craving, and subsequent

drug use (Dackis and Gold 1985; Gawin and Kleber 1986). This postulate has been supported by empirical work in animal models (Karoum et al. 1990; Robertson et al. 1991) and studies of human subjects measuring glucose metabolism (Volkow et al. 1991) and DA receptor activity (Volkow et al. 1990), but it has yet to be demonstrated directly. However, this hypothesis is contra-dicted by research in which cocaine craving appears to be accompanied by a rise in dopaminergic functioning (Martin et al. 1989), and by findings that craving is induced by elevated DA (Jaffe et al. 1989).

Psychostimulants such as cocaine generate a relatively weak withdrawal syndrome and elicit responses in animals that suggest these agents serve as positive reinforcers (Stewart 1984; Wise and Bozarth 1987). Therefore, alternative hypotheses explaining the presence of craving have been proposed. One interesting interpretation is that craving states are mediated by the incentive motivational properties of both external and internal events (Marlatt 1987). Marlatt dissociates craving from the dysphoric effects of withdrawal and conceptualizes drug craving following abstinence as a motivational state that seeks to reproduce the primary appetitive quality of the original state induced by cocaine use. Marlatt specified the realm of craving to be a desire to experience primary and secondary reinforcers. Even though this model of craving as "a motivational state associated with a strong desire for an expected positive outcome" (Marlatt 1987, p. 43) is still speculative, such a scheme fits readily into the corpus of basic research in the psychopharmacology of cocaine.

Evidence establishing the dopaminergic system as integral to incentive motivation and reward-dependent conditioning (LeMoal and Simon 1991) suggests enhanced dopaminergic activity may mediate the positive reinforcement associated with cocaine use. In animals, dopaminergic activity in the nucleus accumbens (NACC) increases when subjects are presented with a conditioned stimulus previously associated with cocaine (Blackburn et al. 1989). Increases in dopamine have also been shown to potentiate responding for other reward-related stimuli (Cador et al. 1991), presumably by enhancing the animal's motivation for weak cues (Kelley and Delfs 1991; Robbins et al. 1989). While some disparate opinions exist (Ettenberg et al. 1982; Pettit et al. 1984), the preponderance of evidence from studies exhibiting the reduction or elimination of the reinforcing effects of psychostimulants through 6-hydroxydopamine lesions of the ventral tegmental area (VTA) and NACC (Roberts et al. 1980) or pharmacological blockade of the dopaminergic system (Bozarth and Wise 1981; De Wit and Wise 1977; Roberts and Koob 1982; Spyraki

et al. 1982) also emphasize the dopaminergic pathway as fundamental to the positive reinforcing effect of cocaine.

Recently, the association between mesolimbic DA activity and incentive motivation processes has been extended to individual differences in psychostimulant reactivity in rats. In a series of studies, Hooks and colleagues (1991a, 1991b) have investigated individual differences in rats divided into high responders (HR) and low responders (LR) based on their locomotor response to a novel environment. Studies of these subtypes of rats show neurochemical differences between these two groups, including elevated baseline and cocaine-induced mesolimbic DA levels in the HR group. For instance, following exposure to a novel environment, HR and LR rats show differences in NACC and prefrontal 3,4-dihydroxyphenylacetic acid (DOPAC)/DA ratios (Piazza et al. 1991) and corticosterone elevations (Piazza et al. 1990).

In other studies, reactivity in the mesolimbic DA system predicted individual responsiveness to both the initial effects of amphetamine as well as the more prolonged sensitization to this psychostimulant (Piazza et al. 1989, 1991). There was also a significant correlation between rats' locomotor responses to novelty and to cocaine administration (10 mg/kg dose, $r = 0.65$, $p < 0.005$; 15.0 mg/kg dose, $r = 0.92$, $p < 0.0001$) (Hooks et al. 1991a).

Following 15.0 mg/kg cocaine administration, HR rats experienced a larger NACC DA response and a greater increase in locomotor activity than LR rats. Correlations were demonstrated between rats' locomotor responses to novel environment and dopaminergic response to cocaine. However, HR and LR rats did not express detectable differences in their basal concentrations of DA, suggesting that differences in dopaminergic responsiveness to cocaine is unlikely to be mediated by baseline-dependent effects. Nevertheless, changes in both pre- and postsynaptic dopaminergic mechanisms are believed to be involved. Both DA type 1(D1) and type 2 (D2) receptor sites undergo priming, which could provide a mechanism for the strong enhancement of the effectiveness of an agonist (supersensitivity) and for making otherwise ineffective doses effective at causing a response (Criswell et al. 1989; Morelli et al. 1989). Individual differences in D1 or D2 DA receptor functioning may sustain individual differences in the priming of incentive motivational states or the quality of reinforcement, which would influence the induction and maintenance of cocaine craving.

Studies of human subjects suggest that individual differences in mesocorticolimbic DA functioning exist in humans as well, as reflected by variations in the observable manifestations mentioned above. In humans, the CNS dopaminergic system seems to be a crucial mediating element for motivational excitement (Wise 1988). CSF-HVA levels of cocaine-dependent subjects were not significantly different from those of control subjects, although cocaine abusers with heightened craving had higher HVA levels (Knoblich et al. 1992). This evidence, combined with the data from animal subjects discussed above, suggests that abusers experiencing heightened craving may be a subtype of cocaine abusers who have heightened dopaminergic responsiveness and increased susceptibility to cocaine.

It is not the intention of this proposed study to uncover the mechanisms underlying individual differences in responsiveness to psychostimulants, but rather to examine the behavioral concomitants (differences in motor activity and histrionic features) associated with these underlying mechanisms. Measurement of CSF-HVA and DASO4 levels in larger samples of cocaine-abusing and control subjects is necessary to confirm or refute the model supported by previous findings (Knoblich et al. 1992) and by animal studies (Hooks et al. 1991b). Comparison of baseline CSF-HVA and DASO4 levels in cocaine-abusing and control subjects could reveal whether differences in mesocorticolimbic DA system activity exist in humans and whether these differences reflect individual differences in dopaminergic activity, DA-mediated cocaine craving, or both.

Motor Activity as Potential Indicator of DA Metabolism (Specific Aim 2)

Since the sum of the evidence from animal and human studies suggests that individual differences in motor activity mediated by the mesocorti-colimbic DA system may predict individual differences in vulnerability to psychomotor stimulants, the second specific aim of this research focuses on the relationships between a noninvasive real-time measure of DA activity and a measure of motor activity that is sensitive enough to distinguish individual differences. Much evidence exists from animal studies to support the viability of this measure. For instance, under baseline conditions, Pradhan and colleagues (1990) have shown that variations in spontaneous locomotor motility correlate highly with DA and its metabolite levels in the striatum. Moreover, cocaine adminis-tration is known to elicit locomotor activity (Post and Contel 1983) and to increase extracellular DA in the NACC (Kalivas and Duffy 1990; Pettit et al. 1990).

As discussed above (Specific Aim 1), studies in animal models suggest that dopaminergic systems mediate individual differences in locomotor activity related to psychostimulant administration. Specifically, findings by Hooks and colleagues (1991a,b) and Piazza and colleagues (1989, 1990) propose that individual differences in locomotor response are mediated by the mesocorticolimbic DA system. In an experiment examining the role of NACC DA in individual differences, HR rats exhibited a 250 percent higher basal DA concentration (6.45±1.01nM, n= 6) than LR rats (2.58±0.16 nM, n = 7) (Hooks et al. 1992). Following intraperitoneal (IP) cocaine administration, HR rats had both a greater locomotor response and increase in absolute DA concentration compared to LR rats. Together these findings suggest that measures of motor activity potentially may be used as surrogate markers for CNS dopaminergic activity in humans.

In support of this concept, there have been several studies demonstrating a correlation between motor activity and CSF-HVA levels in human subjects. For example, Banki (1977) showed a significant correlation between CSF-HVA and nurse-rated motor activity in a large sample of patients. In general, manic or hypomanic patients who have higher motor activity than depressed patients also have higher levels of CSF-HVA (Post et al. 1973). Evidence indicates that measurement of motor activity may offer a noninvasive, real-time reflection of DA output. In the present proposal, a measurement of wrist motor activity (described below) will be tested as a potential marker for CNS dopaminergic activity. If significant correlations are found between cocaine abusers' CSF-HVA and/or CSF-DASO4 levels and wrist activity measures, this method may provide a peripheral noninvasive measure reflecting CNS dopaminergic activity.

Conditioned Locomotor Activity and Cocaine Craving (Specific Aim-3)

Since cocaine craving appears to be associated with heightened dopaminergic functioning (as discussed above in Specific Aim 2), it seems reasonable that the onset of a craving episode would be associated with a real-time measure of a change in dopaminergic functioning (i.e.,motor activity). As suggested above, animal studies have shown that locomotor activity is correlated with a propensity to self-administer psychostimulants. In human studies as well, changes in DA-related mood states might be expected to be associated with motor activity. Wolff and colleagues (1985) observed decreased daytime

motor activity levels in 27depressed patients in their depressed states as compared with their manic or euthymic states. Affectively ill subjects exhibited lower mean daytime motor activity levels during their euthymic periods (measured by a self-contained wrist apparatus) than a group of volunteer normals housed in the same ward. These results suggest that motor activity may reflect interpersonal and intrapersonal variation across mood continua. Measures of wrist motor activity may prove to be a reflection of acute variations in dopaminergic functioning and a source for objective studies of craving within and between individuals that could advance the understanding of the temporal relationships between craving and dopaminergic activity. More signifi-cantly, activity monitoring may provide a noninvasive means for diagnosis and prognosis in the treatment of cocaine abuse.

Relationship Between Personality Disorder and Cocaine Craving (Specific Aim4)

Recent models of personality broadly propose relationships between DSM-III-R Axis II personality disorders and patterns of drug use (Cloninger 1987; King 1986). In general, studies indicate a relationship between the impulsive personality disorder cluster including antisocial, borderline, narcissistic, and histrionic disorders, and both alcohol and drug abuse. For example, Kosten and colleagues (1982) showed that opiate addicts had higher frequencies of antisocial, borderline, and histrionic personality disorders.

Recent evidence demonstrated significant relationships between histrionic traits and cocaine use (King et al. 1991). In a sample of 70 male poly-substance abusers in a long-term drug rehabilitation program, histrionic personality disorder traits were uniquely associated with measures of lifetime abuse by the ASI ($r = -0.52$, $p < 0.0001$). Post hoc correlation with individual traits also suggested that histrionic individuals had used cocaine longer ($r = 0.41$, $p < 0.0004$). In separate studies, significant correlations have been shown between CSF-HVA and indices of cocaine craving (Knoblich et al. 1992) and histrionic ($r = 0.35$, $p < 0.05$) and antisocial ($r = 0.36$, $p < 0.05$) personality disorder features (unpublished data). Similarly, in a study of long-term abstinent cocaine abusers (Knoblich et al. 1992), CSF-HVA was positively correlated with a composite craving score ($rs = 0.61$, $p < 0.05$).

These observations are in accordance with the proposed model of the interaction of abused drugs with personality and neurochemistry.

That is, individual differences in mesolimbic DA activity, which may be temperamentally based, could lead to differences in histrionic, prosocial, and emotionally expressive behavior. Those who are readily excited by social cues (i.e., histrionic individuals) might be more sensitive to the rewarding aspects of cocaine consumption, specifically the dopaminer-gically mediated activating effects as manifested by increased activity, talkativeness, and emotionality. Because of this increased sensitivity, such individuals might be more likely to crave cocaine and continue long-term use even after treatment. Furthermore, because the acute effect of cocaine appears to be a blockade of DA reuptake at the nerve terminal, frequent or prolonged use might lead to enhanced histrionic behavior under the influence of the drug, thereby exaggerating those very personality traits presumed to be risk factors for cocaine use. Thus, individuals might, over a period of time, begin to acquire the self-concept of being social or histrionic under chronic use. Also, one may find the self-administration of cocaine rewarding enough to overcome the anticipated dysphoric effects after the drug has worn off. As a result of this motivation, such a person would be particularly prone to developing cocaine craving as a result of appetitive desires.

By seeking specific associations between cocaine craving and personality disorder traits, the proposed study expects to clarify the relationships between histrionic personality traits and propensity to crave cocaine. Figure 1 shows the hypothesized relationships between the biological indices associated with dopaminergic functioning and measures of cocaine craving. Mean hourly activity, CSF-DASO4, and CSF-HVA are believed to be measures reflecting individual variations in CNS dopa-minergic functioning. Findings from animal and human studies suggest that these measures are related to individual differences in susceptibility to cocaine craving. In the present studies, this susceptibility is measured by a variety of craving indices.

PRELIMINARY DATA SUPPORTING THE SPECIFIC AIMS

Automated Craving Measures: Behavioral Studies (SpecificAim 1)

In order to determine craving changes within individuals, procedures have been developed to track and record these variations over time. For 5consecutive days male cocaine-abusing subjects carried a pocket computer and responded to questions each time they heard a programmed

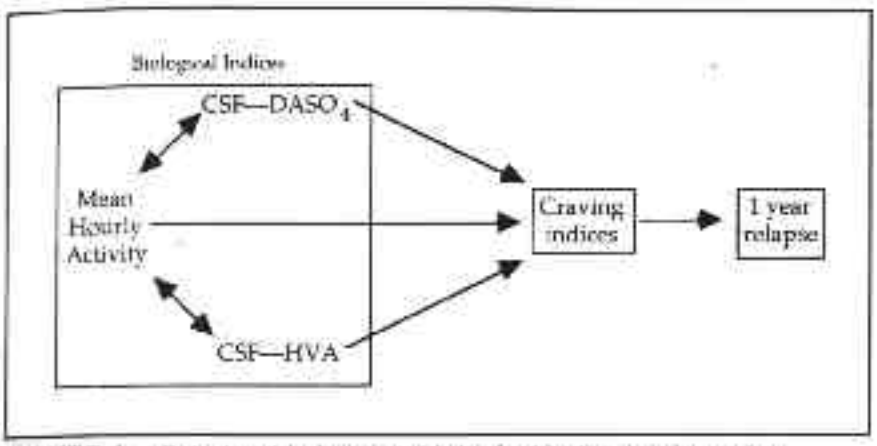

FIGURE 1. *Relationship between biological indices and cocaine craving.*

signal. Seven times during the course of each day each subject was asked if he experienced craving since his last report. If so, the subject was instructed to rate his urge to use cocaine (1 to 10), subjective of cause for the urge, degree of control over the urge (none to extreme), and means of resisting the urge. Using 10-point scales, the subject was asked to describe three aspects of mood: sad to happy, anxious to relaxed, and excited to calm. Finally, the subject was asked to rate the chance of craving in the next 3 hours. To ascertain whether cocaine craving arises with a circadian or ultradian rhythm, the total number of craving attacks occurring within each hour interval was tabulated. A Kolmogorov-Smirnov goodness-of-fit test of the distribution of craving attacks (N=48) over a 24-hour period demonstrated craving to be nonuniformly distributed over time ($p = 0.007$). A histogram of the distribution of craving attacks over time shows that craving occurred more often after 10:00 (figure 2). Table 1 shows the frequency of self-reported attributions of craving attacks to various causes. Most commonly, subjects attributed these craving attacks to the experience of bad mood and physical feelings.

The relationships between fluctuations in mood and onset of craving also were explored. Time course changes of mood in periods of craving versus periods of no craving were tabulated and graphed on a 10-point ordinal scale. Figure 3 compares changes in mood before, during, and after periods of craving versus periods of no craving and demonstrates

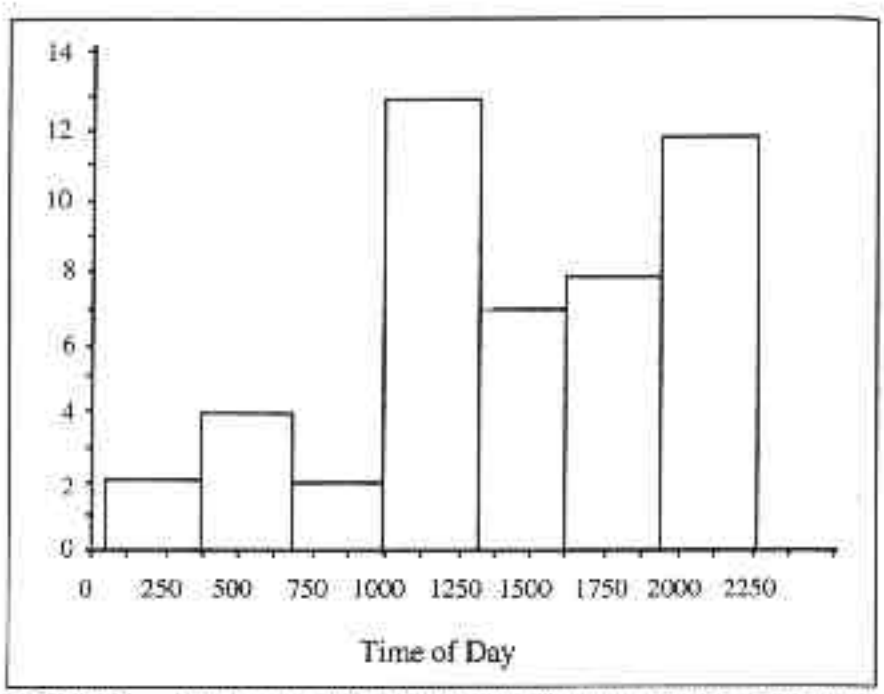

FIGURE 2. *Histogram of the distribution of craving attacks by the time of day.*

TABLE 1. Frequency of attributed causes of cocaine-craving attacks.

Attribution	Percentage of Attacks
Bad mood	43
Physical feelings	38
Flashbacks	35
Stressful interactions	27
Memories	19
Bad news	13
Sensory reminders	6

that subjects tend to be happier and more relaxed before craving attacks, sadder and more excited and anxious during craving periods, and tend to feel likely to crave again in the next 3 hours after craving episodes.

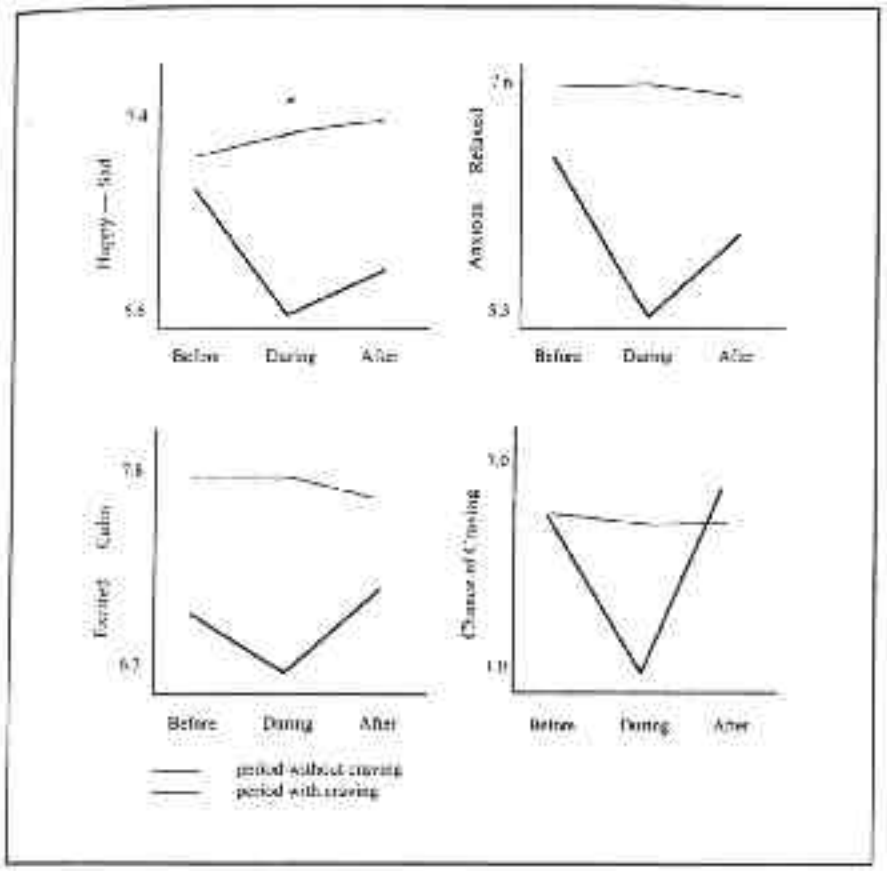

FIGURE 3. *Comparison of the changes in mood before, during, and after periods of craving versus periods of no craving.*

To determine which of the mood variables assessed before or during a craving attack could predict craving, multiple stepwise regression analyses were performed. Regression analysis to predict craving using the mood variables and chance of craving before the episode yielded the excited-calm scale as the only variable that entered significantly (multiple R= 0.23; F(1,115) = 6.2; p = 0.014). Using the mood variables happy-sad, excited-calm, and anxious-relaxed and the chance-of-craving scale during the craving event to predict craving revealed that only anxious-relaxed and chance of craving entered significantly (multiple R = 0.69; F(2,114)= 52.4; p< 0.0001; ß chance of craving = -0.52; ßanxious-relaxed = -0.38).

Individual Differences in Craving Related to Dopamine Function (Specific Aim 2)

Strong preliminary data show a relationship between cocaine craving in long-term abstinent cocaine addicts and CSF levels of HVA. In this study (Knoblich et al. 1992), nine cocaine-dependent males from a long-term inpatient drug treatment program and nine community controls underwent diagnostic interviews followed by the Personality Diagnosis Examination (PDE) (Loranger et al. 1987) and lumbar puncture. On the day of the lumbar puncture, all subjects were rated using the Hamilton Rating Scale for Depression (HRSD) (Hamilton 1967).

In order to test the hypothesis that craving would be positively associated with HVA, three craving indices were a priori selected. These were frequency of pleasant thoughts of cocaine during the past month, frequency of craving episodes during the past month, and intensity of desire for cocaine during the past week. To minimize the possibility of type I error due to multiple tests, a composite craving score was computed adding the three ranged-normalized craving indices. A one-tailed Spearman rank correlation was used to demonstrate a positive association between the composite craving score and HVA; a Mann-Whitney nonparametric test of means compared HVA levels between the cocaine-dependent and control subjects.

Results demonstrated that patients diagnosed with cocaine dependence did not differ significantly in levels of CSF-HVA from normal controls, with the mean CSF-HVA levels being 267 (±66) picomolars (pmol)/ml and 267 (±85) pmol/ml respectively. Within the group of abusers, however, the dopamine metabolite was positively correlated with the composite craving score ($rs = 0.61$, $p < 0.05$). Post hoc, the association was seen in questions referring to frequency of pleasant thoughts of cocaine ($rs = 0.70$, $p < 0.02$) (see figure 4) and approached significance with frequency of craving episodes ($rs = 0.59$, $p = 0.051$) in the past month. CSF-HVA was associated neither with other measures of cocaine use nor with depression (see table 2).

Motor Activity, CSF Dopamine, and Craving (Specific Aim 3)

Much of the animal data predict that various forms of locomotor activity measures may be important reflections of the underlying status of activity in the DA system. Since locomotor activity may be more readily

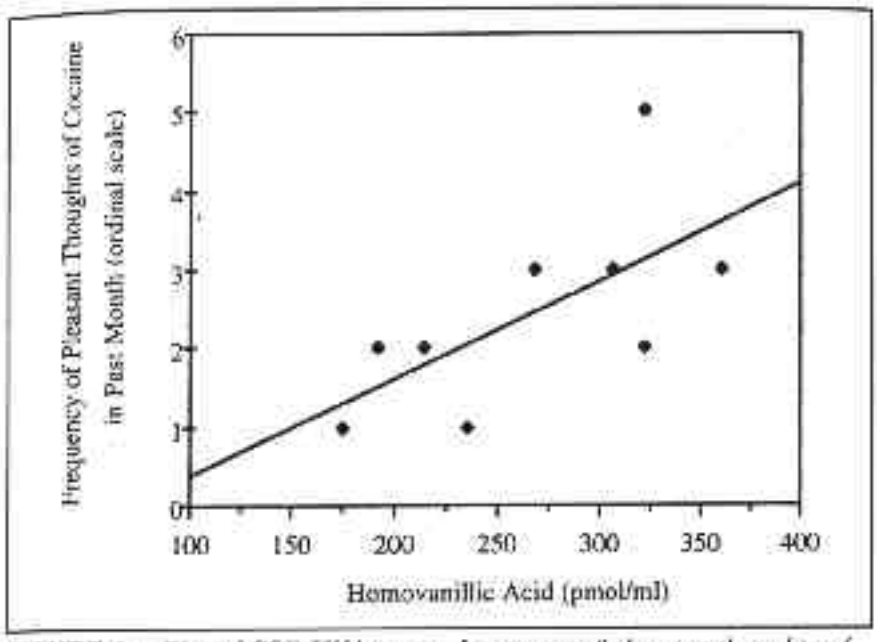

FIGURE 4. *Plot of CSF HVA versus frequency of pleasant thoughts of cocaine in the past month.*

monitored than the dynamics of the DA system, measuring associated motor activity in humans might be quite useful in testing the hypotheses outlined in this proposal. In previous work, theoretical models of DA activity have been sought that mathematically predict chaotic instability over time in manifest behavior (King et al. 1981, 1984). These are nonlinear, dynamic models of DA activity that predicted the appearance of both oscillations and chaos in variables coupled to the DA system. Natural extensions of these models would also predict oscillation and chaos in motor activity under certain conditions.

Motivated by these models, empirical studies were designed to analyze tonic individual differences in motor activity (King et al. 1988). On the basis of the model of histrionic traits as expressions of a heightened dopaminergic responsiveness, it is hypothesized that histrionic traits would be correlated with locomotor activity. Indeed, in a study of individuals who presented with a diagnosis of panic disorder and were recruited to undergo a clinical trial for reduction of panic attacks, histrionic traits were found to be significantly correlated with average

TABLE 2. *Correlations of cocaine use, craving, and depression indices with CSF-HVA in male cocaine abusers.*

Item	Mean±SD	Range	Corr with CSF-HVA
Frequency of pleasant thoughts of cocaine in the past month	2.4±1.2	1-5	0.70**
Frequency of craving episodes in the past month	1.9±1.2	1-4	0.58*
Intensity of desire for cocaine in the past week	3.3±5.1	0-15	0.50
Typical daily consumption (gms)	1.9±2.1	0.25-7.0	0.31
HRSD score	3.4±4.1	0-10	0.20
Total years of cocaine use	6.2±5.8	1-20	-0.02

KEY: CSF-HVA = cerebrospinal fluid homovanillic acid; HRSD = Hamilton Rating Scale for Depression; * = $p = 0.051$; ** = $p < 0.02$.

daily locomotor activity ($r = 0.35$, $p < 0.025$, one-tailed Pearson's, N-=33). Subsidiary findings from that study also showed high 8-week retest reliability in motor activity ($r = 0.73$). This indicates that locomotor activity in the sample is stable over time and, therefore, is a good variable to assess individual differences.

Locomotor activity was measured using a solid state microcomputer monitor worn on the belt; the associated motion sensor consists of six liquid mercury switches attached to the lateral thigh. Preliminary studies used an updated technique with watch-size wrist monitors with activity sensed by transducers, digitized, and counted in 15-second epoch bins. In a pilot study of a small sample of eight volunteers, the bipolar mood measure happy/sad correlated with locomotor activity averaged during the 30-minute period surrounding the mood recording. In this group of subjects the intraindividual correlations between happy/sad and activity ranged from -0.37 to 0.96. A nonparametric sign test demonstrated that these correlations were significantly greater than 0 ($p < 0.035$). This pilot work shows the

feasibility of monitoring mood states and locomotor activity on a real-time scale.

Axis II Personality Traits and Cocaine Use (Specific Aim 4)

The overlap between the key Axis II traits related to incentive motivation and cocaine use has been investigated in a series of studies using the PDE to assess Axis II traits. The PDE rates each of 11 Axis II personality disorders according to an ordinal scale of severity through a semistructured interview. To show construct validity for the proposed models, it was necessary to assess the reliability of the PDE. Table 3 shows the internal consistency (Chronbach alpha), the interrater reliability (interclass r), and the 6-month retest reliability for each of the Axis II scores from the PDE in the subject pool. As can be seen, each of the cluster B Axis II traits demonstrates high reliability and temporal stability.

TABLE 3. Personality Disorders Examination reliability data.

Diagnostic Category	Chronbach a	F interclass	Interclass r	6-mo. retest reliability
	(N = 289)	(N = 229)	(N = 22)	(N = 48)
Paranoid	0.71	40	0.95	0.74
Dependent	0.74	96	0.98	0.80
Avoidant	0.74	191	0.99	0.65
Antisocial	0.87	188	0.99	0.95
Schizoid	0.50	12	0.85	0.54
Schizotypal	0.68	25	0.92	0.72
Compulsive	0.62	92	0.98	0.71
Histrionic	0.73	38	0.95	0.75
Narcissistic	0.68	46	0.96	0.47
Borderline	0.80	117	0.98	0.76
Passive-aggressive	0.67	69	0.97	0.55

Recent work has shown relationships between histrionic traits and cocaine use (King et al. 1991). Using the structured interview for assessing personality disorder traits according to the DSM-III-R, a group of 200 male subjects (40 community controls, 70 patients in a long-term drug rehabilitation program, and approximately 90 other male psychiatric controls) were rated according to the severity of their Axis II disorder traits using the PDE. A principal component of analysis was performed on these 11 dimensions of Axis II traits, which demonstrated the presence of two unrotated components with eigenvalues greater than 1. Table 4 shows the factor loadings for each of the Axis II personality traits on these two factors.

Clearly, factor 1 is a general psychopathology factor involving a multitude of interpersonal and affective problems. It is highly loaded for borderline, paranoid, and narcissistic personality disorder traits. Factor 2 is bipolar, loaded at one extreme on histrionic personality traits and in the other direction on schizoid personality traits. In a subset of this group

TABLE 4. Personality Disorders Examination principal components analysis (N = 200).

Diagnosis Category	Factor 1	Factor 2
Paranoid	0.86	0.10
Dependent	0.69	-0.26
Avoidant	0.79	0.27
Antisocial	0.67	-0.13
Schizoid	0.46	0.80
Schizotypal	0.79	0.37
Compulsive	0.66	0.11
Histrionic	0.65	-0.50
Narcissistic	0.83	-0.32
Borderline	0.89	-0.05
Passive-aggressive	0.70	-0.20

(N= 72) who completed the ASI (McLellan et al. 1980), these two factor scores were correlated with measures of lifetime abuse of drugs. Lifetime abuse of cocaine was strongly associated with the second bipolar (his-trionic versus schizoid) factor ($r = -0.52$, $p < 0.0001$). Neither of the factors correlated with any of the other drugs of abuse, including opiates, amphetamines, marijuana, or ethanol.

On the basis of post hoc correlations with individual traits, those who are histrionic appear to have a longer use of cocaine ($r = 0.41$, $p < 0.0004$). Another demonstration of the interrelation among incentive motivation, DA activity, and personality was performed using community control subjects. In this preliminary study, 26 volunteers who were screened using the DSM-III-R Structured Clinical Interview (SCID), found to be free of Research Diagnostic Criteria (RDC) diagnoses, and were screened with the PDE to rule out Axis II personality disorder diagnoses, underwent a lumbar puncture. Log CSF levels of HVA were then correlated with the cluster B personality disorder traits as measured by the PDE. As shown in table 5, log HVA was significantly correlated with histrionic and antisocial per-sonality disorder features in this sample of control subjects. As hypothe-sized, histrionic traits were related to putative measure of incentive motivation. Moreover, mild antisocial traits also appeared to aggregate with heightened DA activity. Given the family studies data showing that antisocial and histrionic personality traits may overlap in familial trans-mission (Cloninger 1987), this study demonstrates that those traits may also overlap in this biological measure. It was concluded that these observations are in accordance with the proposed model of the interaction of abused drugs with personality and neurochemistry.

TABLE 5. HVA correlations with cluster B personality traits in normal subjects (N = 26).

Personality Trait	Correlation with log HVA
Histrionic	0.35*
Antisocial	0.36*
Narcissistic	0.19
Borderline	0.30

KEY: * = $p < 0.05$, one-tailed Pearson's.

DESIGN AND EXPERIMENTAL METHODS

Hypotheses Restated

The basic hypothesis for this proposal is that individual differences in the degree of vulnerability to cocaine craving are mediated by individual differences in the mesocorticolimbic DA system. As a result, individual differences in cocaine craving should be predictable by differences in measures of the mesocorticolimbic DA system, namely CSF-DASO4 and CSF-HVA. Moreover, it is hypothesized that individual differences in craving also are observable in other personality and behavioral measures known to be associated with the mesocorticolimbic DA system, specifi-cally histrionic features and motor activity. These measures may serve as noninvasive markers for susceptibility to cocaine craving and relapse after treatment. The findings from the proposed research could provide clinical measures that would help define patient subpopulations at increased risk of cocaine craving during abstinence. The assessment of covariance in motor activity and automated self-report measures of cocaine craving within individuals also could offer means to predict when an individual is at increased risk to crave. Such measures could help maintain patient abstinence from cocaine use and help prevent relapse after treatment.

General Design and Methods

Subject Selection. A total of 70 subjects for the proposed studies will be drawn from the patient population of a long-term, inpatient, drug rehabili-tation unit. All subjects are to be screened on the basis of two exclusionary principles: Subjects cannot have been diagnosed with AxisI disorders other than drug and alcohol dependence, and they cannot have any major medical problems, including a positive human immunodeficiency virus (HIV) status that would influence their participation in the study.

Fifty experimental subjects will be selected on the basis of a history of cocaine dependence taken from the history on admission. Twenty controls will be drawn from members of the patient population who are abusers of drugs other than cocaine. These patients are to be free of psychotropic medications, including cocaine, during the course of the study as verified by random breath and urine analysis. All subjects will have been inpatients on the ward and abstinent from drug use for a minimum of 6 weeks. Data from previous studies of patients on the same ward (Knoblich et al. 1992) demonstrated that nine

subjects who volunteered to receive a lumbar puncture were free of psychotropic medications, including cocaine, for an average of 28 weeks (ranging from 12 to 60 weeks).

Patients and controls will be age-matched since it is possible that dopaminergic functioning decreases with age (Gerner et al. 1984). Potential subjects will be informed of the nature of the research and their responsibilities, and they will be encouraged to inquire about the project. All selected subjects will certify their compliance with the proposed research guidelines by reading and signing consent forms.

Measurement of Dopaminergic Functioning. Twenty-five cocaine-dependent and 10 control subjects selected according to the criteria stated above will undergo lumbar puncture to measure CSF-HVA and CSF-DASO4 as assessments of dopaminergic functioning. These subjects will fast and remain in bed overnight before undergoing a lumbar puncture performed in the lateral decubitus position at 8:00. A 25 cc aliquot of CSF will be collected, immediately frozen, and stored at -80°C until the time of analysis. HVA will be measured using amperometric detection as previously described (Bankiewicz et al. 1990). Samples will be thawed and vortexed, and 300 micromolars (μM) of each sample will be mixed with 50 pmol of internal standard 3-ethoxy, 4-hydroxyphenylglycol (EHPG). Samples will be analyzed in a single run if possible. In previous studies, the intra-assay coefficient of variation (CV) was approximately 5 percent for each of the compounds of interest (Knoblich et al. 1992). In general, the interassay CV is approximately 10 percent. Measurement of DASO4 will be performed using a modification of high-performance liquid chromatography (HPLC) with the electrochemical detection procedure described by Mefford and colleagues (1983).

Measurement of Craving and Mood. Subjects will characterize their cocaine craving episode by self-assessments of their craving experiences using written questionnaires and a palmtop computer. Previous studies have demonstrated both reliability (Voris et al. 1991) and validity (Halikas et al. 1991) of these self-assessment procedures. Since craving appears to be relatively infrequent and of short duration (Halikas et al. 1991), patients will respond to questions administered by a pocket computer at 35 time points over a consecutive 5-day period. The computer will be programmed to beep seven times during the course of each day at times selected to coordinate with free times in the patients' therapy schedules.

At each interval, the subject will be asked about craving experience since the last report. If craving is reported, ratings are requested for the urge to use cocaine (1 to 10), subjective cause for the urge, degree of control over the urge (none to extreme), and means of resisting the urge. Next the subjects will be asked to rate four mood variables (10-point scale): happy-sad, anxious-relaxed, excited-calm, and agreeable-angry. These bipolar mood states were included in those found by Lorr and Wunderlich (1988) in studies of 210 high school boys that confirmed the presence of five mood factors in semantic space: cheerful-depressed, energetic-tired, good natured-grouchy, confident-unsure, and relaxed-anxious. Finally, the subject will also be asked to rate the chance of craving in the next 3 hours.

Answers to each question are registered by touching responses listed on the computer screen. Data will then be compiled and prepared for statis-tical analysis. Subjects will also complete an instrument to measure lifetime cocaine use (Gawin and Kleber 1986) and the ASI (McLellan et al. 1980) to assess drug use patterns.

Measurement of Personality, Psychiatric Diagnosis, and Drug Use. Each subject will be administered the PDE to determine diagnoses and symptoms assessment (Loranger et al. 1987), the SCID to screen for AxisI personality disorders (Endicott and Spitzer 1978), and the Eysenck Personality Inventory (EPI) (Eysenck and Eysenck 1964) to assess personality traits such as sociability, impulsivity, and neuroticism. On the day of the lumbar puncture subjects will be rated by one interviewer using the HRSD (Hamilton 1967). The results will be compiled for later statistical analysis.

Measurement of Activity. For the duration of the study each subject will wear an activity monitor on the wrist of the nondominant hand (Redmond and Hegge 1985). This device weighs about as much as a digital wristwatch, and poses about as much hazard to subjects. The activity monitor contains a piezoelectric accelerometer to measure wrist motion in three axes. This transducer provides a linear transformation of physical movement into an electronic signal that lends itself to analog processing, filtration, calibration, and adjustment using standard linear circuitry.

Relationship Between CSF Dopamine Metabolites and Cocaine Craving (Specific Aim 1)

Protocol. The clearest demonstration in humans of a relationship between CNS DA neurochemistry and cocaine craving would be the concurrent measurement of craving and DA activity. Twenty-five subjects who meet the exclusionary criteria, who also meet the SCID inclusionary criteria for cocaine dependence, and who have spent a minimum of 6 weeks off psychotropic or abused medications will be recruited. A separate sample of 10 control subjects who have never used cocaine and meet the other selection criteria will be recruited to form a contrast group of nonabusers of cocaine.

One week before the lumbar puncture all subjects will undergo an assessment of cocaine craving using the ASI to measure lifetime use and the QCH to record the indices of recent cocaine craving. They will also undergo an independent assessment of cocaine craving with the auto-mated behavioral questionnaire on the palmtop computer. The computer data will be used to create a sum score of number of cocaine craving attacks per day for each cocaine-abusing subject or, for those in the control group, the number of craving attacks for that individual's dominant substance of abuse.

Data Analysis. To demonstrate reliability of the measure for craving attacks, the number of attacks per day for the first 2 days of recording will be correlated across the 25 individuals with the number of attacks noted during the last 3 days of recording. Furthermore, the average number of craving attacks per day will be correlated with the composite craving score from the QCH to determine convergent validity.

The specific hypotheses to be tested are that CSF-HVA and CSF-DASO4 correlate with subjective measures of cocaine craving. Thus, the Ztrans-form of the three individual dimensions of the quantitative cocaine history that assess craving (current desire, imaginations of pleasant thoughts during the past month, and level of craving during the past month) will be added together and correlated with both CSF-HVA and CSF-DASO4. For the purpose of power calculation, a minimal correla-tional coefficient of 0.55 is assumed; this is compatible with published pilot data. For a power of 85 percent chance of detecting such a difference, a sample size of 25 subjects is required.

After testing the first-order correlation coefficients between craving and DA metabolite measures, multiple regressions will be performed using CSF-HVA and CSF-DA as dependent measures to be predicted by the self-report craving score and the frequency of craving recorded during the computerized behavioral assessment. This information will yield an estimate of the comparative utility of the two independent measures in predicting neurochemical differences.

Central DA Associations of Wrist Motor Activity

Protocol. A total of 25 cocaine abusers who participated in the lumbar puncture study (specific aim1) will be monitored for wrist motor activity before the tap. For the activity monitoring, the volunteers will wear the wrist actimeter on the nondominant arm. They will wear the monitor from 7:30 a.m. to 7:30 p.m. for a period of 5 consecutive days in order to ensure homogeneity of counting time. The actimeter will collect activity counts in 15-second epochs.

Data Analysis. For these 25 subjects, the stability of activity over time will be estimated by correlating the first 2 days of recording with the last 3days of recording in total mean hourly activity. CSF measures relevant to DA turnover, namely CSF-HVA and CSF-DASO4, will be used as esti-mates of CNS-DA activity. A multiple regression will be performed correlating these two metabolites with mean hourly wrist activity, indi-cating both the raw correlation coefficients and the relative contribution of CSF-HVA and CSF-DASO4 levels to variations in wrist motor activity. This study should indicate whether or not mean hourly wrist reflects variations in CNS DA functioning across individuals. Although the CSF-HVA and CSF-DASO4 measures are taken at a single time point (8:00), because of the slow clearance of these metabolites through the CSF the measures may in fact reflect a temporal integration of DA activity. Thus, it is plausible that the hourly averages in wrist motor activity may mirror CSF-DA metabolite levels.

Within-Subject Associations Between Motor Activity and Craving Attacks (Specific Aim3)

Protocol. The purpose of this aim is to investigate whether changes in motor activity occur within a person during naturally occurring craving attacks while under the conditions of long-term abstinence. For this study, the full sample of 50 recruited cocaine addicts (specific aim2) will wear the wrist monitor and use the palmtop computer to assess craving frequency and intensity. All 50 subjects will be

instructed to press the event marker on the monitor at the time the individual is first aware of a craving attack. The data will be recorded for 5 consecutive days.

Data Analysis. In this within-subject design, locomotor activity will be averaged over the 15-second bins for a 30-minute interval preceding a reported craving episode and over the 30-minute interval following a craving episode. These two measures will be compared with motor activity before and after a neutral period, at the same time on a different day, randomized to either the previous day or the day following the craving event. Thirty-minute intervals have been chosen to serve as a preliminary measure of the mean motor activity for the periods imme-diately preceding and following craving. Since the protocol measures motor activity every 15 seconds, this interval may be adjusted in future studies to provide better approximations of motor activity surrounding the onset of craving.

A repeated-measures analysis of variance (ANOVA) will be performed to test whether there is an increase in activity during a craving attack compared with two consecutive 30-minute periods at the same time on a nonevent day. It is hypothesized that there will be an increase in motor activity during a craving attack that may reflect a CNS release in DA during naturalistic craving events.

Studies Testing the Relationship Between Cocaine Craving and Axis II Personality Disorder Traits (Specific Aim 4)

Protocol. In this section, the full cohort of 50 cocaine-abusing subjects will be used. These experiments will refine the relationship between cluster B personality disorder traits that have been linked to enhanced DA turnover (histrionic personality disorder traits) and cocaine craving. The inclusion and exclusion criteria are the same as those outlined in the general methods section. The 50 subjects will be long-term cocaine abstinent (> 6 weeks). All of them will be given the PDE to assess AxisII personality disorder traits; the Eysenck Personality Inventory to measure personality traits such as sociability, impulsivity, and neuroti-cism; the ASI; the QCH for recording patterns of drug use; and the SCID for formal psychiatric diagnoses. In addition, all subjects will wear the wrist activity monitor and carry the palmtop computer to rate the temporal occurrence of a cocaine craving attack.

Data Analysis. Because of the large sample size, data analyses in this section will be optimally used to reduce the number of cocaine

craving variables studied. In particular, a principal component analysis with varimax rotation will be performed on the three craving variables from the QCH, the average number of daily craving attacks, and the average reported intensity of urge of craving for the craving attacks. The resulting factors with eigenvalues > 1 will be correlated with histrionic traits with the expectation that there will be a positive association between the factor scores and histrionic traits. A multiple regression will also be performed tofind the best predictors for histrionic personality traits among the craving factors. For these experiments, a minimal correlation coefficient of 0.40 isexpected to correlate histrionic traits with the craving factors. At 85per-cent power of detecting such difference, a sample size of 53 is required.

Expected Results

Each of the specific aims and hypotheses of the proposed research has been designed to examine the neurochemical and behavioral factors that influence cocaine craving. Previous findings, literature on animal models of incentive motivation, and some findings in human subjects by other researchers suggest that heightened corticomesolimbic DA activity mediates cocaine craving. Between subjects, individuals prone to cocaine craving are expected to demonstrate elevated measures of dopaminergic functioning. Baseline levels of CSF-HVA and DASO4 measured in cocaine-abusing subjects should correlate with the frequency of craving recorded using the palmtop computer and a composite score of the three individual dimensions of cocaine craving (current desire for cocaine, imaginations and pleasant thoughts of cocaine during the past month, and level of cocaine craving during the past month) assessed on the QCH.

Such findings would support previous work that has shown that, within a group of nine long-term abstinent cocaine abusers, CSF-HVA was positively correlated with the composite craving score from the QCH ($r_s=0.61$, $p < 0.05$), but was not associated with other measures of cocaine use or with depression (Knoblich et al. 1992). The multiple regression using CSF-HVA and CSF-DA as dependent measures may also demonstrate the ability of levels of CSF-DA metabolites to predict the likelihood that individuals will crave cocaine, which may prove a useful tool for prognosis and treatment.

Personality features shown to be associated with CSF-HVA and cocaine use may also correlate with the frequency and degree of cocaine craving. Previous findings that histrionic individuals appear to have a longer use of cocaine ($r = 0.41$, $p < 0.0004$) (King et al.

1991) and that log HVA was significantly correlated with histrionic and antisocial personality disorder features in a sample of control subjects suggest that factor scores derived from a principal component analysis and the three craving variables from the QCH will correlate positively with histrionic traits from the PDE. These observations would be in accordance with the proposed model of the interaction of abused drugs with personality and neurochemistry.

This study also proposes to assess the ability of a noninvasive, readily accessible measure, peripheral motor activity, to reflect CNS-DA activity both between individuals and within a subject over time and to investi-gate whether changes in motor activity occur within a person during naturally occurring craving attacks. Substantial evidence in the literature on animal models of incentive motivation indicates that locomotor activity is associated with CNS dopaminergic activity. Thus, it is expected that CSF-HVA and CSF-DASO4, as estimates of CNS-DA activity, will correlate average wrist activity in human subjects. Within subjects wrist motor activity is expected to be elevated during periods when subjects experience craving compared with periods when they do not. Such findings would be of particular significance for the design and implementation of noninvasive means for performing prognostic assess-ments of cocaine abusers experiencing craving, which could reduce relapse among abstinent individuals.

PUBLIC HEALTH SIGNIFICANCE

The treatment of cocaine abuse remains an important but difficult task for this socially devastating condition. In recovering abstinent individuals, cocaine craving has been associated with relapse. An important inroad into discovering novel methods of treatment is the investigation of biological factors that predict differences between individuals in cocaine craving. Results from animal research indicate the importance of the corticomesolimbic DA system in the reward/reinforcing effects of cocaine self-administration.

This proposed study will apply these concepts from animal studies to investigate the relationship between DA function and cocaine craving in long-term abstinent cocaine abusers. As previously discussed, research in human subjects, in concert with the data from animal models, suggest a cluster of interrelationships between motor activity, CNS dopaminergic functioning, personality features, and cocaine craving. The present research focuses on elucidating these

relationships in both between-individual and intra-individual paradigms. It is hoped that this work will generate potential measures such as motor activity and CSF DA metabolite levels that can be used as baseline measures in longitudinal studies of high-risk individuals prior to substance abuse. Furthermore, the findings may reveal motor activity to be an acute noninvasive measure of CNS dopaminergic activity, a reflection of individual propensity to experience craving, or both. Such findings could lead to the development of a useful tool for the prevention of relapse among abusers of cocaine and other substances.

However, there remain some specific concerns about the measures to be tested as correlates of cocaine craving. First, lumbar CSF-HVA and CSF-DASO4 may not strongly reflect DA activity in the regions of interest, the corticomesolimbic system. To the extent that large sample sizes allow for some component of CSF-DA measures to reflect variations in incentive motivation, this problem can be partially overcome. Imaging studies utilizing specific markers of DA activity in localized regions may be the method of choice for reducing such problems. However, CSF measures and the monitoring of motor activity may offer insight into the optimal craving measures to be used in future studies.

An additional conceptual limitation arises from the multiple systems per-spective of neurobiological functioning. As with models from depression (Potter et al. 1991), monoamine systems can be perturbed in a variety of ways to produce similar effects. Interactions between DA and serotonin may be important in the regulation of cocaine self-administration. Furthermore, interactions with opiate systems (Mello 1991) may also be relevant to cocaine use in animal models. Although the methodology is not sufficient to address opiate interactions, other monoamine metabolites such as 5-hydroxyindoleacetic acid (the major metabolite of serotonin) will be measured through HPLC analysis. Thus, these studies will offer additional pilot data potentially exploring the relationships among serotonergic and dopaminergic functioning and cocaine craving.

Early theoretical investigation of cocaine craving has been influenced primarily by the DA depletion hypothesis, which asserts that a hypo-dopaminergic state underlies the dysphoric aspects of abstinence leading to anhedonia, craving, and subsequent drug use (Dackis and Gold 1985; Gawin and Kleber 1986). Another model of cocaine craving (Marlatt 1987) dissociates craving from the dysphoric effects of withdrawal, and conceptualizes it as a motivational state initiated by

external or internal events that reproduces the primary appetitive quality of the state induced by drug self-administration. Much contention and confusion exists concerning these two models of cocaine craving.

The proposed study builds on previous research in human subjects and animal models and could clarify the importance of appetitive and aversive components in cocaine craving. The relationships between personality features, mood, motor activity, and cocaine craving will help distinguish these components of craving within individuals during periods of craving compared to periods without craving and/or expose individual differences that predict the likelihood to crave.

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AUTHORS

Roy J. King, Jr., M.D., Ph.D.

Christopher Flowers, M.D.

Department of Psychiatry
Stanford University Medical School
Stanford, CA 94305

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