# Neuropsychological Abnormalities in Cocaine Abusers: Possible Correlates in SPECT Neuroimaging

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## INTRODUCTION

Neuropsychological abnormalities in cocaine dependence fall into two broad categories: mood and cognitive disorders. The mood disorders include both acute anhedonic symptoms, which are associated with cocaine abstinence, and sustained depressive disorders, which occur at about five times the community rates (32 percent versus 6percent) (Gawin and Kleber 1986; Rounsaville et al. 1991). The neurobiology of these mood disorders may be related to abnormalities in catecholamine receptors and reuptake carriers induced by chronic cocaine usage. These changes are probably reversible, although they may leave a permanent diathesis towards underlying psychiatric disorders. For example, cocaine-associated panic disorders appear to lead to spontaneous panic attacks in many individuals for years after they stop taking cocaine (Aronson and Craig 1986; Louie et al. 1989; Rosen and Kosten 1992). Cognitive disorders appear to be related to neuronal loss.

In order to examine these two disorders associated with chronic cocaine usage, single photon emission computed tomography (SPECT) neuro-imaging has been employed. Correlates of mood dysfunction might be examined using iodinated probes for dopamine (DA) receptors and the DA reuptake carrier; both the receptors and the reuptake carrier can be affected by chronic cocaine use in animal models (Alburges et al. 1993). Correlates of cognitive deficits can be examined with agents that assess blood flow such as technetium-99-hexamethyl-propylamine oxime (HMPAO) (Holman et al. 1989; Holmes et al. 1985).

## SPECT CEREBRAL BLOOD FLOW STUDIES AND COGNITIVE FUNCTIONING

In a series of studies, Holman and colleagues (1991, 1993) have shown that cocaine-dependent patients may have patchy perfusion defects in cerebral cortical blood flow. These defects appear to be relatively persistent over several weeks after cessation of cocaine use, although recent work suggests a potential improvement in blood flow of up to 30percent during 4 weeks of treatment with the partial opioid agonist buprenorphine (Holman et al. 1993; Mendelson et al. 1995). Other investigators have noted these perfusion defects in cocaine-dependent patients, but because of the small number of subjects in most studies, the general prevalence of these defects among cocaine abusers is unknown (Strickland et al. 1991; Tumeh et al. 1990; Volkow et al. 1988).

### Brain Perfusion Defects

In the first study by Holman and colleagues (1991), 18 male polydrug abusers who had used an average of 2.2 grams (g) of cocaine per week for an average of 7.7years were examined. Seven of the 18 meet current abuse or dependence criteria for alcoholism, and 7 met dependence cri-teria for opioids. The subjects reported their last use of cocaine from 1 to 16 days prior to the SPECT study, and nine of the subjects were positive for cocaine metabolites on the study day. The neuropsychological test battery included the Wechsler Memory Scale and its subtests of digit span and visual reproduction, the Stroop Color Word Test, the Rey-Osterreith Complex Figure Test, the California Verbal Learning Test, the Wisconsin Card Sorting Test, and the Luria Three-Step Motor Sequence Test. The imaging protocol used a brain imager with a resolution of 8.2millimeters (mm) and imaging was done using 20 millicuries (mCi) of HMPAO. Perfusion defects in cortical regions were identified as any area with less than 60percent of the maximum cerebellar activity, as determined from computer-generated isocount maps. The defects were then described as large if they involved more than 1 centimeter (cm) of cortex. Sixteen of the 18 cocaine-dependent subjects had abnormal brain perfusion patterns with the most frequent perfusion abnormalities seen in the parietal cortex (16/18), temporal cortex (15/18), frontal cortex (14/18), and basal ganglia (11/18). Only one subject had large focal deficits without additional small perfusion deficits. Amount or frequency of previous cocaine use was not associated with the number or size of these focal defects, although the two subjects who had no defects on scanning reported only infrequent

alcohol use. All of the other subjects reported moderate to severe alcohol abuse or dependence, suggesting an association of defects with combined alcohol and cocaine abuse, an issue addressed later in this chapter.

The subsequent study by Holman and colleagues (1993) included 10 cocaine-dependent polydrug abusers who were imaged with HMPAO 2 to 3 days after admission to an inpatient treatment facility and then again at 7to 8 days and 17 to 29 days after beginning abstinence from illicit drugs. Beginning on day 10, the patients also received buprenorphine (a mixed opioid agonist/antagonist), which was continued until the end of the study. The details of image acquisition and analysis were the same as the previous study, but with some simplification in the categorization. The cortical regions were classified as "abnormal" if the activity ratio was less than 0.6and "borderline" if they fell between 0.6 and 0.72 relative to cerebellar activity. In the abnormal zones, regional cerebral blood flow increased 11percent ± 9 percent at 7 to 8 days and 24 percent ± 9 percent at 17 to 29days after initiation of treatment. In the borderline cortex areas, the increase in cerebral blood flow was 5 percent on day 7 to 8 and 11 percent on day 17 to 29. Blood flow showed virtually no change in the normal areas. The increase in cerebral blood flow did not vary significantly by location in the cortex. An interesting conclusion of the investigators was that the perfusion defects observed in these chronic cocaine- and opioid-dependent patients were partially reversible with short-term abstinence and treatment using buprenorphine. Overall, the amount of improvement across subjects was variable, but all patients showed an increase in cerebral blood flow in abnormal regions during the 3 to 4 weeks of the study, with a range of increase between 11 and 37percent.

Holman's work has suggested that these perfusion deficits are more common in patients dependent on cocaine and either alcohol or opioids than on cocaine alone. In a 20-subject study, the authors' research group has found that patients dependent on alcohol and cocaine are more likely to have perfusion deficits than those dependent on cocaine alone (Woods et al., submitted). In the frontal and parietal cortex of cocaine- and alcohol-dependent patients, blood flow is particularly reduced and the mean decrease is four times greater than the variation in blood flow across normal subjects. The "pure" cocaine abusers showed no differ-ences from normals. The role of cocaethylene in producing these lesions is of interest, since the authors' studies have shown a potentiation of cocaine's cardiovascular effects by alcohol. With alcohol plus cocaine, cocaethylene is formed,

and heart rates and blood pressures are higher and sustained twice as long as with cocaine alone (McCance-Katz et al. 1993). Thus, alcohol abuse in the context of heavy cocaine dependence may predispose to the development of these perfusion defects.

## Mechanisms Leading to Perfusion Defects

In acute cocaine administration studies, the authors and other investigators have found a decrease in cortical cerebral blood flow and general metabolic activity as assessed by fluorodeoxyglucose studies using positron emission tomography (PET) (London et al. 1990; Pearlson et al. 1993; Wallace et al. 1994). The blood flow study by Pearlson and colleagues (1993) involved the administration of 48 milligrams (mg) of intravenous (IV) cocaine to eight abstinent cocaine users in a double-blind, crossover design. The investigators examined blood flow using SPECT and 20 mCi of HMPAO. The cocaine produced significant decreases in frontal cortical and basal ganglia blood flow, which corre-lated negatively with increases in self-ratings of rush and high. The sta-tistically significant mean percentage changes by region were 6.5percent in the left caudate, 5.5-percent in the left putamen, 9.9 percent in the inferior cingulate, and 9percent in the right frontal area. Changes within individual patients included decreases in blood flow of up to 25percent during cocaine administration.

Subjective responses, including high and rush, were also significantly elevated after cocaine administration. Because HMPAO has more than 80percent first-pass extraction with an estimated 90-second time window reflecting regional cerebral blood flow changes, this activity corresponds rather closely to the time of peak subjective effects, which for IV cocaine is typically 3 to 5 minutes after administration. Thus, a reasonably close correspondence might be expected between the blood flow measures and these subjective responses. However, it is not clear what these blood flow changes reflect, since these regional cerebral blood flow changes could reflect direct effects of cocaine on cerebrovasculature. The regional locali-zation that was observed makes this nonspecific blood flow alteration unlikely. All of the regional changes were observed in areas connected neuroanatomically to the dopaminergic system. Thus, cocaine in humans may produce regional decreases in cerebral blood flow corresponding to sites enriched in dopaminergic terminals.

A similar study by Wallace and colleagues (1994) calculated absolute changes in blood flow during cocaine administration. Four male

cocaine abusers were given IV cocaine at 0.5 milligrams per kilogram (mg/kg) followed by an injection of HMPAO to assess regional cerebral blood flow. Arterial levels of the HMPAO metabolite were also measured in order to calculate absolute blood flow, which was compared for placebo injection versus cocaine injection. Substantial decreases of up to 40per-cent in whole brain blood flow were detected during acute cocaine injec-tion with regional differences in blood flow similar to the findings of Pearlson and colleagues (1993). These greater changes in absolute blood flow suggest that the relative blood flow changes calculated in com-parison to cerebellum in the Pearlson study (1993) underestimated the decrease in blood flow caused by cocaine. The actual decreases in blood flow within particularly vulnerable areas in the basal ganglia and cortex appear to be as much as twofold greater than those estimates made by Pearlson. The implication of this greater reduction in blood flow is that the pathophysiological consequences for highly localized perfusion deficits could be substantial. Particularly with repeated cocaine dosing or in the presence of cocaethylene, which has a substantially longer half-life than cocaine itself (McCance-Katz et al. 1993), blood flow reductions could be substantial and sustained.

In these controlled studies by Wallace and colleagues (1994), it was further observed that all four of the subjects had patchy cortical perfusion deficits when administered placebo rather than cocaine. These deficits were similar to those previously observed by Holman in cocaine abusers (1991, 1993). When cocaine was acutely administered, these patchy perfusion deficits had a further reduction in blood flow, which in many cases leads to complete reduction in blood flow for small focal defects. Again, the implication for the pathophysiology of persistent blood flow defects in cocaine abusers is obvious. In subjects who already have cerebral perfusion deficits from chronic cocaine abuse, the hypoperfusion is enhanced by acute cocaine administration. This enhancement of chronic perfusion deficits by acute cocaine administration suggests the pathophysiology that leads to the development of structural brain deficits in cocaine abusers (Jacobs et al. 1989; Klonoff et al. 1989). These structural brain lesions have been noted in patients who present to the emergency room typically after very large dosages of cocaine. These doses might produce severe and persistent cerebral vasoconstriction and perfusion deficits. Thus, a vascular basis for neuronal loss is evident.

While direct vasoconstriction of cerebral blood flow by cocaine may decrease cerebral perfusion (Isner and Cholski 1990), another effect of

cocaine that may decrease cerebral perfusion has been described by Rinder and colleagues (1994) based on platelet adhesion. Platelets are granular cells lacking a nucleus, but still having active metabolism (Marcus 1969). When a blood vessel is injured, platelets aggregate at the site and form a viscous plug prior to formation of a clot. Aggregation of platelets is produced by small amounts of thrombin as well as by adeno-sine diphosphate (ADP), which is released from the platelets themselves. As part of their structure, platelets include dense granules and a-granules. The dense granules contain large amounts of serotonin leading to vaso-constriction as well as ADP, which recruits other platelets and activates the a-granules. Release of the dense granules occurs in the early stages of this clot formation and can be blocked by aspirin, which inhibits cyclo-oxygenase, a key enzyme for the adhesive process. The a-granules are involved in the next phase of platelet aggregation and thrombus forma-tion. They are activated by ADP and release fibrinogen, thrombospon-din, and prostaglandins. Platelets that have already partially released some of their a-granules attract other platelets, leading to the formation of platelet thrombi. The a-granule includes a membrane protein called P-selectin, which becomes an integral part of the platelet membrane when the a-granule is released. P-selectin mediates adhesion of these platelets to leukocytes and serves as a marker for platelet activation. P-selectin positive platelets can be identified and quantified using monoclonal antibody assays.

Using this antibody assay, Rinder and colleagues (1994) found that platelets of chronic cocaine abusers are in a partially activated state, making them substantially more adherent to each other and to blood vessel walls. In a series of 92 baseline and 18 ADP-stimulated blood studies, the percentage of P-selectin positive platelets was significantly higher in cocaine abusers at baseline (12 percent versus 5 percent in normals), and the cocaine abusers' platelets had a significantly smaller response to ADP activation (3.5 percent versus 22 percent in normals). This lower percentage of activation simply reflects the already partially activated state of the platelet pool (e.g., the baseline differences from normals) due to a-granule release in the cocaine abusers' platelets. Because of this activation, any stimulus leading to dense granule release in these platelets results in rapid and substantial platelet clumping and thrombus formation in small cerebral blood vessels. This critical action of cocaine was recently confirmed by Kugelmass and colleagues (1993). This platelet clumping may also be reversible by aspirin, leading to a resolution of the cerebral perfusion defects noted earlier with SPECT scans. Figure 1 shows perfusion defects in a cocaine abuser reversed by 4weeks of aspirin treatment. Row (a) images were taken before treat-ment; row (b) shows blood flow following 2 weeks of treatment with 325-mg aspirin per day.

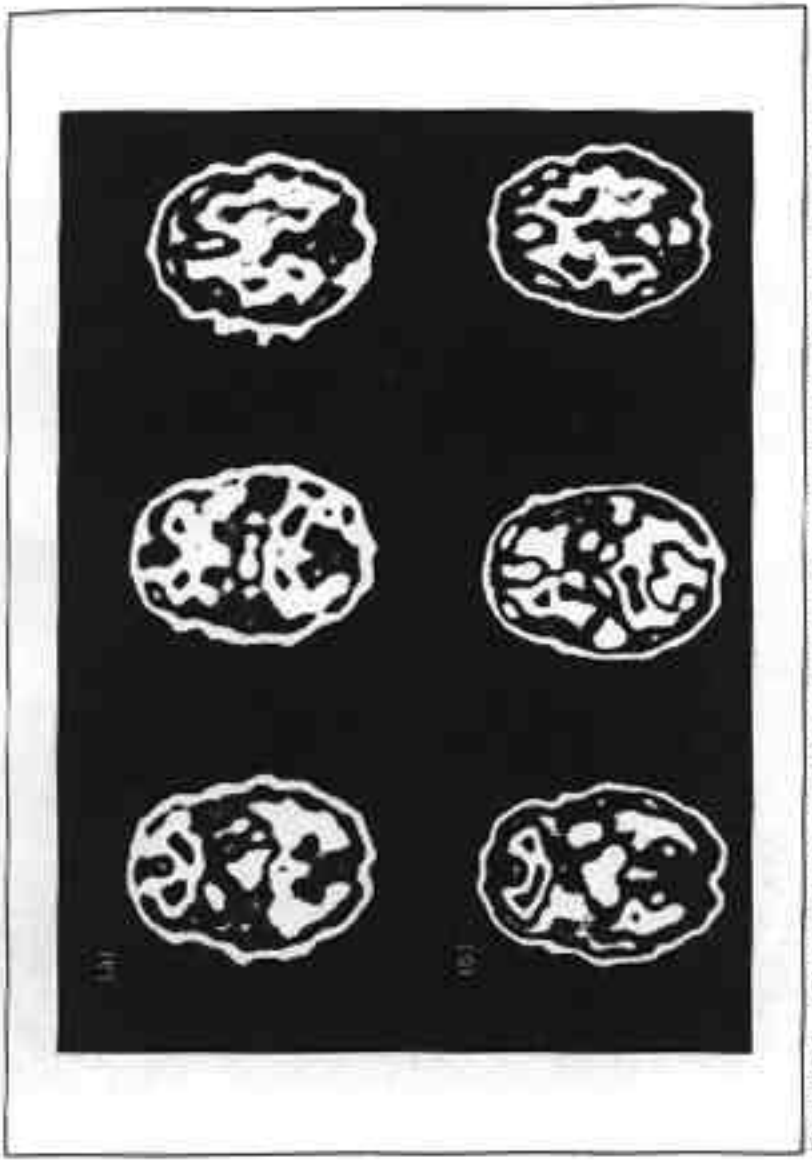

**FIGURE 1.** *Change in cerebral blood flow in cocaine abusers following 2 weeks of aspirin treatment.*

## Neuropsychological Deficits

The functional consequences of these cerebral perfusion deficits have not been directly shown, but several studies have demonstrated neuropsycho-logical deficits in chronic cocaine dependence. O'Malley and colleagues (1990, 1992), in two separate studies, have shown that chronic cocaine-dependent patients who have been abstinent for up to 18months can show persistent difficulty in tasks requiring concentration and recent memory. Herning and colleagues (1990) have had similar findings and, most recently, others (Bauer 1993; Roberts and Bauer 1993) have demonstrated abnormalities in a variety of motor tasks suggestive of Parkinsonian symptoms in abstinent cocaine-dependent patients.

Holman and colleagues' SPECT neuroimaging studies (1991, 1993) found no specific correlation between areas of neuroanatomical abnormalities and specific neuropsychological deficits, but found that the patients with perfu-sion deficits had overall neuropsychological impairment on a variety of tests. All the subjects showed abnormalities on psychometric testing, with 5 of the 18 subjects having moderate deficits. The most common deficits involved spatial learning and organization in 12 out of 18 subjects. There was no detailed correspondence between the site of the perfusion defects and the character of the neuropsychological defects. No attempt was made to relate the number and severity of perfusion defects to the number of neuropsychological tests showing impairment. Thus, there does not appear to be a precise correlation between specific neuropsychological impairments and specific cerebral perfusion deficits, but there is an overall association between psychological impairment in memory and concentration and the occurrence of multiple cerebral perfusion deficits.

The association between the degree of neuropsychological impairment and cerebral blood flow was examined in a study of methadone-maintained cocaine abusers by Woods and colleagues (1991). In this study, human immunodeficiency virus (HIV)-negative and HIV-positive patients who did not have clinically diagnosed acquired immunodeficiency syndrome (AIDS) and were not treated with azidothymidine (AZT) were examined and compared. Two interesting associations were demonstrated. Among the HIV-negative patients, the ratio of blood flow in the striatum to the whole brain was inversely correlated with the percentage of 13 neuropsycho-logical tests showing impairment ($R = -0.77$, $p < 0.05$). Thus, more impairment was associated with reduced blood flow. A second

interesting finding was the relationship of striatal blood flow to the percentage of neuropsychological tests showing impairment for the HIV-positive patients. Previous neuroimaging studies have suggested that the identification of blood flow deficits is difficult in HIV-positive cocaine abusers, because both conditions can be associated with patchy cortical blood flow deficits (Holman et al. 1991). However, in the early stages of HIV infection of the central nervous system (CNS), the basal ganglia and striatum frequently show metabolic hyperactivity rather than the blood flow deficits that are observed with chronic cocaine abuse. This association between increased striatal blood flow and greater levels of neuropsychological impairment was observed in the Woods study (Woods et al. 1991) (R=0.55). Thus, cocaine-abusing methadone patients who were HIV negative shared a strong negative correlation between striatal blood flow and neuropsycho-logical impairment, while those who were HIV positive showed a strong positive correlation between striatal bloodflow and neuropsychological impairment. This finding is of particular importance in differential diag-nosis during the early stages of HIV infection among IV cocaine users, since brain infection with the AIDS virus is an indication for initiation of chemotherapies such as AZT.

## SPECT RECEPTOR STUDIES AND AFFECTIVE DISTURBANCES

### Postsynaptic DA Receptors

While cerebral blood flow deficits in cocaine abusers appear to be associated with cognitive dysfunction, the underlying neuropathology for affective disturbances may reside in receptor changes induced by chronic cocaine. Cocaine binds to the DA transporter and blocks reuptake of DA back into the presynaptic dopaminergic neuron, leading to an accumu-lation of DA in the synapse. This accumulation of DA in the synapse can have opposite effects on the pre- and postsynaptic neurons. The post-synaptic neuron's DA receptors may be downregulated from chronic stimulation. The animal studies on this issue have not clearly demon-strated downregulation of dopamine type 2 (D2) receptors, but have consistently found downregulation of dopamine D1 receptors (Alburges et al. 1993). In studies using a carbon-11 labeled D2 antagonist in humans, Volkow and colleagues (1990) demonstrated a reduction in D2 receptors during acute abstinence among chronic cocaine abusers. Other human studies by Childress (1995) used SPECT imaging with the ligand iodo-benzamide (IBZM) to examine the D2 and possibly D3 receptor during sustained abstinence among cocaine abusers. While these

studies have not involved comparisons with matched normal controls, the DA receptors do not appear to be downregulated in these patients. No SPECT studies have examined DA receptors during acute abstinence from cocaine. However, in primate studies the authors have demon-strated that IBZM has good specific affinity for the D2 receptor in the caudate and that it is readily displaceable by haloperidol, a potent D2 antagonist (Innis et al. 1992). This ligand, IBZM, can also be displaced by the endogenous DA that is released by amphetamine administration. This amphetamine effect can be blocked by the administration of reser-pine, which depletes endogenous DA (Innis et al. 1992). Human studies with a D2 ligand using SPECT in cocaine abusers are being started.

DA Transporters

The authors' most recent work with SPECT involves imaging the DA transporter using [123I]-methyl-3ß-(4-iodophenyl) trophane-2ß-carboxylate (iodinated ß-CIT), a cocaine analog in which the ester linkage has been removed between the tropane and benzene rings. Binding to dopaminergic cells in the striatum appears highly specific and can be displaced by other cocaine analogs or GBR 12909, another DA transporter ligand. Binding of CIT in the striatum is not displaced by citalopram, a serotonin reuptake inhibitor. In normal human subjects, CIT takes approximately 24 hours to reach maximal binding in the striatum and remains stable there for about 1day.

In human studies, the authors have examined regulation of the DA transporter and the percentage of transporter occupancy using cocaine displacement. Transporter regulation was examined by comparing cocaine addicts to healthy controls and by comparing binding after acute versus sustained drug abstinence within the same subjects scanned at 1, 14, and 28 days after stopping cocaine. The rationale for these studies are that although preclinical research demonstrates conflicting results about the effects of chronic cocaine administration on the DA transporter, post-mortem studies in humans have shown an increase of 50 to 100percent among cocaine abusers dying of overdose (Little et al. 1993; Staley et al. 1992, 1993).

The subjects in the present study comparing cocaine abusers to normals included five male and three female cocaine-dependent patients with a mean age of 32 years. They smoked an average of 6 g per week of cocaine and had been abstinent for 30 to 96 hours prior to the first imaging session. They were compared to age- and gender-matched controls. Using V3", which is defined as the ratio of specific

striatal binding over nonspecific occipital binding, the authors found that the cocaine-dependent patients had much greater amounts of CIT binding, as shown in figure 2. In comparing specific patients with their matched controls, in only one case was the control subject slightly higher in CIT binding. In the most dramatic difference, a cocaine-dependent patient had a V3" of 15.0 while a matched healthy control had a V3" of 10.8, indicating a 40percent increase in DA transporters.

When the authors compared acute versus sustained abstinence among six patients examined serially over 2 to 4 weeks after stopping cocaine abuse, a reduction in CIT binding was found. In every subject, there was a reduc-tion in binding from initial imaging until the followup. Upon initial imaging the average V3" was 11.6; this measurement decreased about 20percent over the 2- to 4-week followup. This drop was slightly less than the 30 percent difference between the healthy controls and the cocaine abusers at the initial imaging. Thus, normalization in the number of reuptake carriers appears to take 2 to 4 weeks, which corresponds very well with the time course of depressive symptomatology following dis-continuation of cocaine (Satel et al. 1991; Weddington et al. 1990).

In studies with CIT, the authors have determined whether euphorigenic dosages of cocaine occupy measurable levels of DA transporters in human cocaine abusers. In this preliminary study, the authors adminis-tered cocaine to five cocaine abusers who smoked an average of 6g of cocaine per week. The IV cocaine administration studies used dosages of-20 and 40 mg while monitoring both physiological and subjective responses. In these studies, specific displacement of CIT was only about 25percent with a cumulative cocaine dose of 60 mg. This dosage of cocaine produced substantial euphoria and physiological effects on heart rate and blood pressure. An unusual characteristic of these studies was that maximal displacement of CIT did not occur for about 40 to 60-minutes after cocaine administration. Since the subjective effects of cocaine peaked within a few seconds and subsided within 15 minutes, this temporal dissociation suggested an underestimate of the percentage of reuptake carrier occupied by cocaine in order to produce euphoria. In order to produce the 40 to 100 percent upregulation of reuptake carriers as well as the substantial downregulation of postsynaptic DA receptors, a much greater percentage in occupancy of reuptake carriers would be expected during chronic and repeated cocaine usage. Since these studies involved only two relatively modest dosages of cocaine, it is possible that repeated higher dosages of cocaine over more sustained periods of time might occupy a substantially greater proportion of reuptake carrier.


**FIGURE 2.** *CIT binding in healthy control and cocaine addict.*

Affective Disturbances

The substantial neuroreceptor and transporter abnormalities that appear to persist during cocaine abstinence may have their clinical correlates in affective disturbance. A study by Weddington and colleagues (1990) found that over the course of a 30-day inpatient stay, Beck Depression Inventory scores declined from a mean of 9 to 2. Satel and colleagues (1991) found that depression scores declined from a mean of 15 to about 8 after 10 days, with a secondary peak at about day 14 when the scores rose to 12. During this period, craving for cocaine went from a high of 80 out of 100 down to a low of 5 by day 30 (Weddington et al. 1990). In both of these studies, the majority of the decline occurred during the first 2 weeks of hospitalization and included substantial reductions in anxiety, depression, hostility, fatigue, and general physical symptoms. One symp-tom that appeared to show greater persistence among inpatient cocaine abusers was difficulty falling asleep, which continued for about 3weeks. In the Satel study (Satel et al. 1991), serial blood samples were also obtained three times weekly for prolactin, growth hormone, and homo-vanillic acid, a DA metabolite. None of these hormonal measures differed from those of normal subjects. Both studies concluded that symptoms after inpatient cessation of

uncomplicated cocaine addiction were relatively mild and decreased linearly over the first month.

Both of these inpatient studies have several limitations. First, these symptoms of cocaine abstinence may be somewhat more persistent in an outpatient setting where cues associated with cocaine use recur and there-by increase both anxiety and cocaine craving (Gawin and Kleber 1986). Second, both studies involved relatively small numbers of subjects, with 12 cocaine-dependent patients in the Weddington study and 22 patients inthe Satel study. Third, further studies need to examine correlations between the amount of receptor dysregulation and subjective dysphoria and cocaine craving. Since the Satel study found no hormonal abnor-malities in these subjects, it is possible that patients with documented neurobiological abnormalities on SPECT or other scanning will show more severe symptoms during abstinence. Future studies can examine these correlates as researchers accumulate data from more brain-scanned subjects.

## Future Prospects for SPECT

Future receptor imaging work with cocaine abusers might focus on sensitization and noradrenergic receptors as well as on tolerance from chronic cocaine abuse. Recent studies by the authors' group suggest significant dysregulation of noradrenergic systems during cessation of cocaine use (McDougle et al. 1994). During an inpatient stay, 14 subjects were given 2 mg/kg of intranasal cocaine three times daily for a 3-day period. One or 2 days after the last dose of cocaine, subjects received a double-blind, randomized IV infusion of yohimbine at 0.4-mg/kg. These cocaine treated subjects had significantly greater placebo corrected methoxyhydroxyphenylglycol (MHPG) response to yohimbine and rated themselves as significantly more nervous following yohimbine than following placebo. When these challenges were repeated 2 weeks later, cocaine-treated subjects reported significantly less nervousness. In addition, at the initial yohimbine challenge, 71 percent of the subjects developed a panic attack, whereas none of them developed a panic attack during the challenge session 2 weeks later. These results suggest an underlying dysregulation in noradrenergic function and a vulnerability to panic/anxiety during early cocaine cessation in cocaine dependence. Thus, future studies using SPECT imaging might examine whether noradrenergic receptors are upregulated by chronic cocaine use. Because this upregu-lation may occur on presynaptic receptors, which have a relatively lower density than postsynaptic receptors, these changes induced by cocaine may be difficult to detect with SPECT imaging.

However, the general concept of receptor upregulation as a possible correlate of the sensitization associated with cocaine holds promise for the future of SPECT receptor imaging.

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