Neuropsychiatric Effects of Cocaine Use Disorders

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Individuals who use cocaine report a variety of neuropsychiatric symptoms that are yet to be adequately targeted with treatment modalities. To address this problem requires an understanding of these symptoms and their neurobiological origins.

Our paper reviewed the existing data on the neuropsychiatric implications of cocaine. We conducted a Medline search from 1984–2004 using terms, such as "cocaine", "cocaine addiction", "cocaine abuse", "cocaine neuropsychiatry" and "dual diagnosis". The search produced additional reference materials that were used in this review, although we focused on data that have likely clinical implications.

The literature evidence suggested that, whereas acute cocaine overdose is potentially fatal, the ingestion of mild-to-moderate doses could result in fatal or nonfatal neuropsychiatric events. Also, chronic cocaine use may be associated with deficits in neurocognition, brain perfusion and brain activation patterns. Some of these deficits were unresolved with periods of abstinence ranging from 3–200 days. Taken together, these studies suggest the need for further investigations to fully characterize the neurobiological substrates of cocaine use disorders (CUDs) with the future possibility of more efficient treatment modalities.

Key words: cocaine addiction ■ neuropsychiatry ■ cocaine abuse ■ drug neurobiology

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INTRODUCTION

Cocaine use disorders (CUDs) have continued to be a public health problem characterized by multiple neuropsychiatric sequelae.[1-5] Although the neuropsychiatric complications of cocaine partially account for the morbidity and mortality in CUDs, their role in the transition from initial to compulsive use is controversial.[6-10]

Potentially lethal neuropsychiatric effects of cocaine include suicidal behaviors,[11] violent psychoses,[12] strokes,[13,14] seizures[15] and encephalopathies.[16] Also, cocaine's toxic effects on the cardiac,[17-19] vascular,[20,21] thermoregulatory,[22,23] and respiratory[24] systems can present as or with acute neuropsychiatric symptoms. Indeed, the complex manifestations of cocaine can pose substantial problems in differential diagnoses and resuscitative treatment.

Intriguingly, a number of clinically silent neuropsychiatric complications have been described in long-term cocaine users. Examples include mental distress,[25,26] altered frontolimbic excitability,[27,28] psychomotor,[29,30] neurocognitive,[31] neurochemical,[32] and neuroischemic alterations.[3,33] These subtle complications of cocaine are ill understood mechanistically, although they could be related to neuroadaptation,[10] direct toxicity[34] or neuroischemia.[33] Recently, researchers have been vigorously investigating the neuropsychiatric effects of cocaine because of the treatment implications. Thus far, the prospects are promising. This paper reviews the current state of neuropsychiatric research that deals with CUDs and their potential clinical relevance.

COCAINE OVERDOSE

Fatal and near-fatal cases of cocaine overdose are not uncommon.[35-38] The dose of cocaine that might result in fatal outcomes depends on an individual's weight, height and general health status. Also, fatal outcomes may occur irrespective of the frequency of use or route of administration.

Cocaine induces a multisystem response characterized by vasoconstriction, tachycardia and tachyp-

nea. As a result, clinicians need a high index of suspicion to manage cocaine overdoses effectively. For instance, severe hemodynamic compromise can lead to target organ damage in the heart, bowels, skeletal muscles, liver, kidneys and the brain.

Also, cocaine has a direct deleterious effect on cardiac repolarization. Massive doses can produce angina pectoris, myocardial necrosis and/or sudden death even among individuals with no cardiac risk factors, such as young adults. Low doses may result in malignant arrhythmias in individuals with cardiac risk factors.[18,39,40] Apparently, the growing awareness of the cardiac effects of cocaine is persuading active users to report chest complaints immediately to the ambulance service or the emergency departments.

Cocaine overdose is associated with seizures, status epilepticus, headaches and strokes. Typically, there might be a new-onset seizure or an exacerbation of an existing seizure disorder. Cocaine-related, new-onset focal seizures in humans should prompt a search for cerebral hemorrhage.[41] Cocaine should be considered in the diagnostic work up of strokes in young adults.

Acute renal failure is a serious complication of cocaine overdose. The kidney shutdown might be secondary to massive muscle necrosis and myoglobinemia. The patient might exhibit mental status alterations. In long-term cocaine users, this acute failure may be superimposed on chronic renal arteriopathy and hypertension.[37,42]

Acute agitation in cocaine overdose can manifest as garrulousness, excitement, restlessness and confusion. Patients with suspected overdose of cocaine should be transported urgently to the nearest emergency department using an advanced life-support ambulance, when possible. The patients' family, ambulance service personnel, law enforcement officers and physicians need to be aware that attempts to control cocaine agitation with physical restraints and neck hold can result in lethal complications.[43-45]

Table 1. Summary of the results of studies evaluating neuropsychologic performances in cocaine abusers

Authors	Cocaine Subjects Studied	Cognitive Domains with Significant Deficits among Cocaine Users	Cocaine Variable Correlating with the Observed Deficit(s)
Ardila et al., 1991[79]	N=37	Verbal memory Attention	Lifetime cocaine use
O'Malley et al.,1992[80]	N=20 (inpatients)	Concentration Verbal memory Nonverbal problem-solving	Dose of cocaine used; Recent use
Mittenberg et al.,1993[81]	N=16	Verbal memory	Dose of cocaine used
Berry et al., 1993[82]	N=16 (inpatients)	Memory Visuospatial Concentration	Recent use of cocaine
Hoff et al., 1996[83]	N=38 (inpatients)	Spatial memory Perceptual motor speed Cognitive flexibilty	3–4 years of continuous use
Gillen et al., 1998[84]	N=19 (outpatients and inpatients)	Visual memory Verbal generation Sequencing	None*
Smelson et al., 1999[85]	N=35	WAIS arithmetic Grooved pegboard Trails B	None*
Bolla et al., 1999[78]	N=30 (community sample)	Visuomotor tracking Information processing Mental flexibility	Dose of cocaine used
Rosselli et al., 2001[86]	N=42	Attention Memory Executive function	None*

* The study reported no cocaine variables correlating with the observed cognitive deficits

An overdose of alcohol and cocaine frequently needs more intense care in the emergency department than cocaine-only overdose. Worse episodes of violent acts, cardiotoxicity and sudden death occur with coalcohol overdose as compared to cocaine overdose alone. In the presence of alcohol, cocaine forms a highly toxic metabolite, cocaethylene.[46-50]

CNS EFFECTS OF "RECREATIONAL" COCAINE USE

Psychiatric Effects of Cocaine

Acute euphoria. The acute psychiatric effects of cocaine include a brief "rush," excitability, hypervigilance and anxiety. Cocaine euphoria can positively reinforce drug-taking behavior. In "recreational" cocaine use, psychiatric status and safety depends on the degree of emotional instability, physical exhaustion, behavioral agitation, sleep alterations and suicidal behavior.[12,51]

Cocaine can induce psychotic symptoms that have included delusions, hallucinations or both. Brady and coworkers examined 55 patients who were consecutively admitted for cocaine treatment and found that approximately 50% reported that they had experienced a short-lived psychosis. In the study, the risk factors for cocaine psychosis included male gender, a greater duration of use and a greater use in the 12 months before admission.[52] However, it is important to note that studies conducted with treatment samples may embody a bias.[53]

Among cocaine's most feared complications are suicidal, parasuicidal and homicidal behaviors. Studies worldwide have linked cocaine to intentional and unintentional injuries. Cocaine exacerbates suicidal and omnipotent fantasies, making the prevention of self-harm an important treatment focus. Suicidal intent is a common psychiatric complaint related to cocaine presentation in the emergency department.[54] Roy compared the characteristics of 124 cocaine-dependent patients who had never attempted suicide with the characteristics of 84 patients who were admitted with cocaine dependence and suicide attempt. The study found a 33% risk of suicide attempt among patients with recent cocaine use. Compared to cocaine users who had never attempted suicide, cocaine users who had attempted suicide reported more suicide risk factors across lifespan.[11] Autopsy studies that were conducted in New York also implicated recent cocaine use in suicide deaths[55] and motor vehicle fatalities.[56]

Cocaine abstinence. Cocaine withdrawal is associated with negative affect states, such as apathy, anxiety, irritability, depression and suicidal thoughts.[57-60] Among cocaine-withdrawn patients, severe depression and/or suicidality appeared to correlate with prior depression or long-term.[61,62] In some studies, severe abstinence symptoms significantly increased premature drop-out from cocaine treatment[61] and enhanced the subjective response to cocaine.[62] Interestingly, Kampman and colleagues used cocaine withdrawal assessment and intake urine toxicology results to predict treatment attrition,[63] suggesting a potential strategy in selecting patients for focused treatment intervention.

Neurologic Complications of Cocaine

In the past two decades, abundant preclinical and clinical data on the neurologic side effects of cocaine have appeared.[64-66]

Gestational effects of cocaine. From preliminary studies, the fetal effects of cocaine have included autonomic hyperarousal,[67] delayed CNS development[68,69] and attentional deficits after birth.[70] However, caution must be used to attribute in utero effects to cocaine alone because of the prevalence of cigarette smoking, anemia, malnutrition and infectious diseases among cocaine-using pregnant women. Indeed, the occurrence of cocaine-induced teratogenicity and "crack babies" has been questioned.[71] Excellent reviews on prenatal cocaine exposure are available,[72-74] and this subject is beyond the scope of this paper.

Effects in adult cocaine users.

a) Neurovascular effects of cocaine. Neurologic complications of cocaine among adults include headaches, fainting attacks, cerebrovascular accidents, CNS vasculitis and encephalopathies.[75] Ischemic or hemorrhagic strokes can occur within three hours of cocaine use.[16] Peterson and colleagues completed a three-year prospective study of 31,081 admissions in an inner-city trauma unit. Neurovascular events were approximately 3% of 979 admissions related to cocaine and the incident population was aged ≤45 years.[76]

b) Delirium and seizures. Delirium and seizures are significant contributors to cocaine's morbidity and mortality.[13-16,77] Cocaine-associated delirium is a medical emergency. Hospitalization may be required for close monitoring and to exclude infection, trauma and CNS bleeding. Similarly, cocaine-induced seizures should be diagnosed only after excluding common causes of seizures. Cocaine provokes seizures (partial or generalized) independent of the route of drug administration.

c) Movement disorders. Movement disorders in long-term cocaine users include resting tremors, stereotypy, dystonia and chorea. Cocaine-induced hand tremors differ from physiologic tremors of 9 Hz found in normal individuals at rest. Physiologic tremors are worsened during sympathoadrenergic arousal but not during action or intention. Cocaine is

associated with low-frequency (4–6Hz) tremors that are not present during movement or intention.[29] Unlike alcohol tremors, cocaine tremors are not associated with cerebellar signs.

Cocaine tremors are not visible to the naked eye. Bauer used an accelerometer to study chronic cocaine users at 100 days of monitored abstinence and found evidence of rest tremors.[30] Generally, cocaine can worsen preexisting movement disorders, including antipsychotic-induced movement disorders.[65]

Neuropsychologic Complications of Cocaine

Bolla and colleagues have studied the neurocognitive effects of chronic cocaine abuse among 51 community-based adult volunteers (30 cocaine-using and 21 control subjects). The drug-using group reported using cocaine at least four times per month for at least one year, with an average dose of 2.3 g per week for about 6.7 years, and urine toxicology screening was positive for cocaine metabolites at the time of admission. The study compared the heavier cocaine users, intermittent users and control subjects with respect to their performances on neuropsychologic batteries. The result showed a correlation of heavier use of cocaine with greater impairment in visuomotor tracking, speed of information processing and other areas of neuropsychologic functioning[78] (Table 1).

Other studies also found an association between chronic cocaine use and deficits in neurocognitive domains, such as visual, spatial memory, perceptual motor speed, mental flexibility, verbal generation, attention and concentration[79-86] (Table 1). Because these studies were conducted following periods of abstinence of two weeks to six months, the observed deficits are unlikely to be due to acute effects of cocaine. Some of the studies suggested that cocaine use variables, including lifetime use, quantity used, peak dose, and frequent and recent use, were significant predictors of neurocognitive deficits.

Importantly, alcohol has well-documented neurocognitive effects. Concurrent use of alcohol and cocaine is common, suggesting the possibility of confounding in studies of the neurocognitive effects of cocaine. To address this question, investigators have compared the neuropsychologic performances of cocaine users versus cocaine-alcohol users although not all studies used a control group of non-drug-using individuals. Nevertheless, these studies were able to demonstrate some cognitive effects of cocaine even after accounting for the neurocognitive effects of alcohol[87-90] (Table 2).

For example, Robinson and coworkers found that the cognitive profiles of cocaine users and cocaine-alcohol users were similar.[88] But Bolla and colleagues found that the cognitive effects of cocaine and the cognitive effects of alcohol were different. The study by Bolla et al. suggested that cocaine affected performances on block design, Trails B and Stroop, whereas alcohol affected reaction time on go-no-go

Table 2. Results of studies evaluating neuropsychologic performances in cocaine abusers vs. cocaine-alcohol abusers

Authors	Number of Subjects	Duration of Abstinence Prior to Initial Testing (Days)	Comparison of Neurocognitive Deficits among the Drug Users	Cocaine Variables Showing Significant Association with Cognitive Impairment
Brown et al., 1994[87]	Cocaine: N=64 Alcohol: N=64	28 days	Similar profiles among drug-abusing groups	None*
Robinson et al., 1999[88]	Cocaine: N=30 Alcohol: N=30 Controls N=30	96 days	Profiles similar except for worse motor skills in the cocaine group	None*
Bolla et al., 2000[89]	Cocaine: N=29 Alcohol: N=27 No controls	1–3 days	Differential neurocognitive effects†	Dose used
Di Sclafani et al., 2002[90]	Cocaine: N=20 Alcohol: N=37 Controls N=29	35 days	Similar profiles among drug-using groups	Quantity used; Duration of peak dose

* The study reported no cocaine variables correlating with the observed cognitive deficits; † Cocaine affected performances on block design, Trails B and Stroop tests, whereas alcohol affected reaction time on go-no-go test and Ray Auditory Verbal Learning test, learning rate and total

test and Ray Auditory Verbal Learning Test, learning rate and total, indicating that alcohol use might worsen neurobehavioral function in patients with CUDs.[89]

IMAGING STUDIES OF COCAINE USE DISORDERS

Brain Blood Flow Studies

Cerebral blood flow is a valuable indicator of brain function. Global and regional brain perfusion has been investigated in cocaine users at rest or during experimental cocaine administration, with and without the performance of mental tasks. These studies are briefly summarized below.

Transcranial Doppler (TCD) studies. TCD provides a noninvasive and economical imaging of blood flow in the CNS. Herning and coworkers used TCD to investigate 50 cocaine-using individuals and 25 control subjects. The participants were community-based volunteers who were studied within three days and again on day 28 of monitored abstinence. The study reported a statistically significant brain perfusion deficit in the anterior and middle circulations among the chronic cocaine users but not among the control subjects. Also, cocaine users showed an elevated cerebral vascular resistance as measured by the pulsatility index. The reported pulsatility index was comparable to those of elderly patients at risk for cerebrovascular events and remained unchanged at one month of monitored abstinence, indicating that the deficits were probably due to the chronic effects of cocaine.[91]

Single photon emission computed tomography (SPECT) studies. The SPECT examination illustrates cerebral circulation using computer-generated images. The SPECT is a safe imaging technique that involves less expense and lower resolution than the positron emission tomographic (PET) scan.[92]

Tumeh and colleagues conducted a rest SPECT study that revealed blood flow deficits in the frontal and temporal regions among 11 (seven were asymptomatic) out of 12 patients who had acknowledged using cocaine on daily basis.[93] A SPECT study by Ernst and coworkers investigated 25 abstinent cocaine users and 15 control subjects. The cocaine users showed significant hypoperfusion in the putamen and temporal cortex as compared to control subjects.[94] Interestingly, the SPECT scans by Levin and colleagues revealed fewer brain perfusion abnormalities in women than in men who used cocaine on long-term basis.[95]

More recently, Gottschalk and colleagues used SPECT to compare the cerebral blood flow parameters of three study groups—namely, alcohol and cocaine patients (n=12), cocaine-only patients (n=20) and control subjects (n=20). Six participants had used cocaine four days prior to being scanned and the others were drug-free at the time of the study. Hyperperfusion was noted in the frontal cortex of 10 patients who had cocaine-use histories compared with 0 control subjects ($p<0.005$). The cocaine users also showed hypoperfusion in the temporal and parietal cortices. Concomitant cocaine and alcohol use appeared to worsen the hypoperfusion deficits among the cocaine users.[96]

In their 1993 study, Strickland and coworkers combined SPECT with neuropsychologic examination of cocaine-using individuals who were abstinent for six months. In this cohort, the chronic cerebral blood flow changes correlated with decrements in neurocognitive functioning.[97]

A study by Adinoff and colleagues evaluated 13 abstinent cocaine-dependent and 15 healthy comparison subjects. The cocaine group had completed 21–55 days of monitored abstinence prior to the study. The participants were scanned at rest and were then required to perform a gambling task that was designed to assess decision-making, which taps orbitofrontal cortex function. The observed scores in the gambling task did not differ significantly between cocaine-dependent patients and normal controls, although the performances showed a significant correlation with the blood flow in the anterior cingulate and the left dorsolateral prefrontal. The cocaine-dependent subjects had a lower left dorsolateral prefrontal cortex than the healthy comparison subjects.[98]

Recently, Tucker and coworkers used a similar design to study 17 abstinent cocaine-dependent patients whose mean period of abstinence was 4.6 days. The study reported that perfusion within the anterior cingulate gyrus, middle frontal gyrus, medial frontal gyrus and superior frontal gyrus was negatively correlated with better performance in the Iowa Gambling Task. Tucker et al. noted that the cohort spent a great amount of time making card selection and suggested that the poor performance at the gambling task may be due to cognitive difficulties rather than impulsive response pattern.[99]

Magnetic resonance angiography (MRA). Kaufman and colleagues have used MRA to study blood flow in healthy male volunteers aged 29 years who were administered with either 0.4 mg/kg or 0.2 mg/kg of cocaine in a double-blind design. The study provided direct evidence that cocaine-induced cerebral vasoconstriction in a dose-related way and stratification of the subjects by prior cocaine use increased the strength of the association.[100]

OTHER IMAGING STUDIES IN COCAINE USE DISORDERS

Computed Tomography (CT)

The popularity of CT in addiction research has

diminished considerably because of its resolution power and the risk of ionizing radiation. In 1991, a planimetric CT study found significant cerebral atrophy among 35 habitual cocaine abusers as compared to 16 self-reported first-time users and 54 control subjects.[101]

Magnetic Resonance Imaging (MRI)

MRI is a noninvasive imaging modality that is based on the physical properties of water in the tissues. The MRI is not associated with health concerns related to ionizing radiation.

MRI studies during acute cocaine infusion. Recently, Bartzokis and colleagues conducted a clinical trial that involved 11 patients who were acutely administered with cocaine and studied with MRI. The study reported a positive correlation between the frontal and temporal cortical volumes and euphoric effects of cocaine.[102]

MRI studies during early cocaine abstinence. The 2002 MRI study by Bartzokis and colleagues examined 37 male cocaine-dependent patients who were recently admitted for cocaine treatment and 52 healthy controls. The study found some evidence of brain maturation arrest (absence of white-matter expansion) among chronic cocaine users but not among the control subjects. The limitations of this study included subject selection. The subjects were predominantly men aged 19–47 years, with 43% reporting ongoing or prior alcohol abuse.[103]

Franklin and colleagues used the technique of voxel-based morphometry to examine 13 recent cocaine users and 16 cocaine-naïve individuals. The cocaine users reported an average of 13-year history of cocaine use and an average of 15-day cocaine use in the 30 days prior the study. The whole-brain analysis revealed a decreased gray matter density in the medial orbitofrontal, anterior cingulate, insular and superior temporal cortices in cocaine-dependent subjects as compared with control subjects. Interestingly, no white-matter differences were reported.[104]

The T1-weighted MRI study by Matochik and coworkers was driven by the hypothesis of a region of interest based their PET study. They scanned 14 cocaine abusers who were abstinent for 20 days and 11 in the nondrug-using comparison group. The average duration of cocaine use was about eight years and the frequency of use was at least four times per month. The study found a statistically significant frontal cortical tissue loss among abstinent cocaine users as compared to nondrug-using control subjects. Intriguingly, no frontal cortex white-matter differences were noted. The investigators suggested that these brain alterations were probably induced by cocaine.[105]

MRI studies during prolonged cocaine abstinence. Strickland and coworkers have used MRI to study cocaine-using individuals who were abstinent for six months and found no abnormalities.[97] Chang and colleagues studied African-American multiple-substance-abusing men with cocaine as their drug of choice (n=26). The duration of cocaine use was about seven years and the last use was 47 months. Although the MRI study found no changes, the proton magnetic resonance spectroscopy revealed biochemical changes suggestive of lost neuronal cell integrity. The result of this study may not be generalizable to patients with CUDs alone.[32]

Diffusion Tensor Imaging (DTI)

The DTI is utilized to study the integrity of axonal microstructure and is based on directional flow properties of water in the axons. Lim and colleagues evaluated cocaine abusers using the DTI and noted significant white-matter loss in the frontal lobe, implying a possible link between deranged connectivity and craving and decision-making deficits in these individuals.[106] More DTI studies are needed to resolve the issue of white-matter loss in CUDs.

MRI Imaging of Cocaine Users Performing Cognitive Tasks

Fein and coworkers have compared prefrontal cortical volume reduction in 20 normal control subjects, 17 cocaine-only and 29 cocaine-alcohol subjects. The drug using subjects were abstinent for six weeks. Although the drug-using patients showed no

Table 3. CUDs: initial clinical assessment

Intake Screening
History (psychiatric, medical and neurologic)
Drug and sexual history
Physical, including neurologic examination
Laboratory screens
- urine toxicology
- urinalysis
- complete blood count
- blood chemistries
- thyroid function
- serology
- HIV counseling and testing

Neuropsychologic Testing
(see text)

Rating Scales and Inventories
- Addiction Severity Index
- Quantitative Substance Use Inventory
- Cocaine Selective Severity Scale
- Symptom Checklist-90
- Hamilton Depression Inventory
- Mini-Mental Status Examination
- Abnormal Involuntary Movements' Scale
- Global Assessment of Functioning

group differences, the observed frontal cortex changes correlated with impaired cognitive performances, indicating that brain function may be affected by changes in frontal cortex volume associated with cocaine dependence with or without alcohol dependence.[107]

Kaufman and colleagues used MRI to test the hypothesis of inhibitory dyscontrol in CUDs. The study found that activity in the anterior cingulate was significantly reduced during the go-no-go test, a test of response inhibition, implying that the anterior cingulate may be a treatment target in CUDs.[108]

Positron Emission Tomographic (PET) Imaging

PET imaging has revolutionized research in psychiatry by making in vivo visualization possible at molecular level. The PET combines the CT and nuclear scanning and involves an intravenous injection of a radioactive tracer that emits a radioactive substance. The PET cameras are used to record the signals emitted by the tracer. The PET cameras are expensive and their reimbursement remains a major issue.

PET studies during acute cocaine infusion. Volkow and coworkers investigated the molecular substrates of cocaine euphoria using PET imaging. They reported that the subjective effects of cocaine at doses commonly used in humans (0.3–0.6 mg/kg) were significantly correlated with the level and rate of dopamine transporter occupancy.[109]

PET studies during early cocaine abstinence. In a series of seminal PET studies, Volkow and colleagues have elucidated the role of frontal lobe in CUDs. The early studies revealed decrements in prefrontal blood flow during acute withdrawal[110] as well as alterations in postsynaptic dopamine receptor availability in long-term cocaine users. Subsequent studies revealed that brain metabolism in CUDs was time-dependent and regional, with higher activity in the basal ganglia and orbitofrontal cortex within the first week, but not within 2–4 weeks among the cocaine-withdrawn subjects as compared to the non-drug-using controls.[111]

PET studies during prolonged abstinence. Using an expanded time frame, Volkow and colleagues found no global differences in the brain metabolism between the cocaine users and the control subjects following 1–6 weeks of abstinence and again following about three months of verified abstinence. However, the left frontal cortex was significantly lower in cocaine users even at four months of abstinence.[112] These results have been replicated and confirmed in persistent cocaine abusers[113,114] and appeared to link compulsive drug use to the frontal lobe's failure to exert executive control over brain regions involved in drive and emotion[115,116] and indicated a possible role for pharmaceutical augmentation of frontal lobe in CUDs.

Recently, Bolla and colleagues used functional PET imaging to examine 13 abstinent cocaine abusers and 13 control subjects who were required to perform the Iowa Gambling Task, a test of decision-making. The patients were studied following an average of 25 days of monitored abstinence and showed a significantly impaired activation of the orbitofrontal cortex as compared to the control subjects, which suggested possible deficits in working memory and planning.[117]

Imagining Studies in Cocaine Craving

Imaging studies of brain substrates in cocaine craving have also been insightful regarding the neurobiology of CUDs. The studies have used paradigms, such as external cues in videotapes or internal cues in script-guided imagery. The external models have relied on videotapes of cocaine cues or some versions of emotion face assessment task. Interestingly enough, studies that used external cues, but not the study that used imagery, revealed greater prefrontal cortex activation in cocaine abusers than in control subjects.[118] In their study, Wexler and colleagues used cocaine-cue videotapes to illustrate regional activations in the amygdala, subcallosal gyrus, nucleus accumbens and anterior cingulate cortex in cocaine abusers but not in control subjects.[119]

Furthermore, functional brain imaging appears to support a role for the frontal cortex, and cerebellar and limbic structures in the neural activity in cocaine craving.[120-122] In their [F18] fluorodeoxyglucose (FDG) PET study of cue-induced craving, Wang and coworkers showed that cocaine theme interview, but not the neutral interview, produced activations in the orbitofrontal and left insular cortex.[123]

The accumulating evidence supports a role for limbic neuronal hyperexcitability in cocaine craving. For example, reexposure to drug cues resulted in an increased activation in the amygdala among cocaine-using individuals as well as decrements in activation in the prefrontal cortex. This appears to indicate that the amygdala might be ineffectively inhibited by the frontal lobe in cue-induced craving,[124] suggesting an important treatment target.

Taken together, the brain imaging studies suggest that CUDs are associated with functional, structural, cellular and molecular alterations. Cocaine use appears to induce regional brain dysfunction in the prefrontal cortex (executive), anterior cingulate cortex (internal monitoring of performance, error detection and performance adjustment) and the basal ganglia (movement and cognition). In addition, suboptimal inhibitory control of the amygdala by the prefrontal cortex may have a role in cocaine craving.[125]

COMORBIDITY OF COCAINE USE AND MENTAL DISORDERS

Comorbid mental illnesses are common in and can worsen CUDs. The factors responsible for morbidity appear to differ among cocaine users with mental illness as compared to cocaine users without mental illness.[126-129]

Patients with schizophrenia have a high lifetime cocaine use.[131] The concomitant use of cocaine markedly increases suicidal risk, treatment nonadherence, psychosocial maladjustment, readmissions to inpatient drug treatment centers and the rates of incarceration in schizophrenia patients.[130] Cognitive deficits and imaging abnormalities in schizophrenia[132] are likely to be worsened by concurrent use of cocaine.

Cocaine use coexists with and is often diagnosed as bipolar disorder or attention deficit hyperactivity disorder, particularly when the affective symptoms are mild.[133] Cocaine use increases the risk of suicide[134] and complicates remission in bipolar disorders.[135] The cognitive deficits in bipolar disorder, manic type, are trait- and state-dependent.[136] The imaging deficits and cognitive dysfunction that have been described in bipolar disorders may be worsened with co-occurring CUDs.[137]

Another common psychiatric comorbidity in CUDs is depression. Differentiating substance-induced depression from primary depression may be difficult.[138] Recent reports have suggested that individuals with CUDs and depression are retained in treatment at higher rates than individuals with CUDs and no depression.[139] Conversely, individuals with CUDs and ADHD are less likely to complete treatment than individuals with CUDs and no Axis-I diagnosis.[140] A diagnosis of depression in CUDs is associated with poorer psychosocial function, greater mental distress and psychiatric functioning. In addition, treatment-seeking, cocaine-using individuals may have other psychiatric disorders, including other substance use disorders, anxiety and personality disorders.

CLINICAL IMPLICATIONS OF NEUROPSYCHIATRY OF CUDS

Diagnosis

It is important to elicit the substance use history in a nonjudgmental manner. Also, collateral information may be critically important. Cases of suspected cocaine overdose should receive a careful medical, neurologic and psychiatric evaluation and a 12-lead electrocardiogram. Resuscitation may require a venous access and urethral catheterization. The urine specimen should be sent for analysis and screening for commonly used drugs.

The toxicology screening should examine for cocaine and its primary metabolites, benzoylecgonine and ecgonine methyl ester, in human urine. Laboratory aids, such as a complete blood count, liver function tests, serum electrolytes and creatine kinase, urine analysis and neuro-imaging studies, may be indicated. Medications that can prolong the Q-T interval must be carefully weighed in CUDs.[141,142]

Neuropsychiatric evaluation in CUDs should examine self-analysis, decision-making, problem-solving, synthetic integration, working memory, information processing and other areas of neuropsychologic functioning (Table 3).

A complete biopsychosocial assessment must be cognizant that social maladies, including prostitution, crime, incarceration, infectious diseases, neonatal drug exposure and adverse employment outcomes, are prevalent in CUDs.[143-146] Also, the exchange of sex for crack-cocaine is a leading route for HIV transmission. In their 1992 study, Khalsa and colleagues found that approximately 92% of subjects who reported having sex in the past year used condoms on an irregular basis.[147] Indeed, the constellation of psychiatric and neurologic complications of cocaine is no less significant than the sociobehavioral consequences, and it has been suggested that cocaine abuse itself is a neuropsychiatric disorder.[148]

Treatment

Neuropsychologic treatment planning. Indeed, the occurrence of neurocognitive dysfunction in CUDs is underrecognized.[149] Few cocaine rehabilitation programs have taken into account the patients' cognitive deficits, although the extent that cognition improved during abstinence is unknown. Thus, the advisability of rigorous counseling during cocaine rehabilitation is uncertain. Indeed, cognitive remediation has been shown to be effective in schizophrenia, suggesting that treatment outcomes in CUDs may be improved with behavioral treatment plans guided by neuropsychologic assessments.[150-153] Moreover, the awareness of cocaine-related neuropsychologic impairments might enhance staff attitudes as well as treatment engagement and retention.[149]

Psychosocial treatment approaches. Psychosocial treatment of CUDs has not reported desirable remission rates. Some drug programs have advocated harm reduction and encouraged a shift away from change and total abstinence, a theoretical position that has been praised for its practicality and equally criticized for implicit pessimism.[154]

Total abstinence programs might kindle power struggles between therapists and their patients who succumbed to the potent reinforcing effects of cocaine. Frequent admissions for cocaine treatment can familiarize patients with the treatment milieu and its lingo, and this might lead the patients to skip

the individual therapy and self-help group sessions. Conversely, patients who have remained in treatment because of pressures from family, friends or the legal system may feel inspired to cheat on urine toxicology specimens. It is possible that an effective pharmacologic treatment of CUDs might help these patients to wage a more successful struggle against the drug habit.

Emerging pharmacologic treatment approaches. Pharmacologic treatment for CUDs was reviewed recently.[155-157] Novel approaches that specifically target cocaine reward, cocaine craving and cue reactivity are being developed. Preventive approaches include cocaine vaccines as well as strategies to improve cerebrovascular perfusion. These treatments are yet to be adequately studied longitudinally.

CONCLUSION

Adverse health consequences of cocaine are yet emerging, owing to the ease of procuring the drug nowadays.[158] Through a number of approaches, greater light is being shed on the pattern of neuropsychiatric effects of cocaine. The growing evidence should strengthen our understanding of the neurobiology of cocaine and improve our therapeutic armamentarium in the management of drug use disorders.

In summary, molecular, cellular, structural and functional changes are commonly seen in the complex presentation of CUDs. The emerging data should stimulate vigorous awareness campaigns involving patients, their families and providers. The evidence indicates that frontal lobe dysfunction may be an important treatment target in CUDs. Intriguingly, individuals who are diagnosed with the neuropsychiatric effects of cocaine, particularly those in inner cities, are entangled in the intricacies of disparate health outcomes that might hold them accountable for poor decision-making. Therefore, our understanding of cocaine-induced brain alterations could be improved through further research with the promise of effective pharmacologic interventions for reversing the brain alterations in this disease.

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