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Relationship between neuropsychological deficits and cerebral perfusion abnormalities in cocaine abusers

Karen A. Tucker

Louisiana State University and Agricultural and Mechanical College

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**RELATIONSHIP BETWEEN NEUROPSYCHOLOGICAL DEFICITS AND
CEREBRAL PERFUSION ABNORMALITIES IN COCAINE ABUSERS**

A Dissertation

Submitted to the Graduate Faculty of
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy

in

The Department of Psychology

by

Karen A. Tucker

B.A., University of Louisville, 1987

M.S., University of Memphis, 1995

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ABSTRACT

The purpose of this study was to investigate the relationships between the severity of cocaine/alcohol use, neuropsychological functioning, and cerebral blood flow abnormalities. Cocaine users (n = 60) and control subjects (n = 13) were administered a battery of neuropsychological tests that yielded the following factors: Attention/Executive Functioning, Memory, Simple Motor, and Sensorimotor. Participants were assessed for decreased cerebral blood flow with single-photon emission computed tomography (SPECT).

Examination of group differences indicated that cocaine users performed significantly worse than controls on the Memory and Sensorimotor factors. The frequency/duration of cocaine use, alcohol use, and a combination of both substances were evaluated to specify which contributed the greatest to reductions in cognitive functions. Increasing frequency of recent alcohol consumption was a significant predictor of worse performance on the Attention and Sensorimotor factors. Years of alcohol use was also significantly related to the Attention factor, whereas, greater duration of cocaine use predicted poorer performance on the Memory factor.

Caucasian race was associated with better performance on the Attention/Executive Functioning, Memory, and Sensorimotor factors. The ethnic differences persisted after controlling for greater substance use among African-Americans. Increasing severity of total cerebral hypoperfusion contributed significantly only to the prediction of poorer performance on the Simple Motor

factor. There was some evidence supporting the hypothesis that the severity of hypoperfusion worsens with increasing frequency of cocaine use. Moderate alcohol use appeared to be related to a reduction in severity of hypoperfusion.

Overall, the results suggested that reductions in memory functioning in this group of cocaine users was specifically related to increasing duration of cocaine use, rather than to alcohol, or a combination of the two. Attention and sensorimotor functioning seem to be more reliant on the frequency of recent alcohol usage, contrary to the assumption that declines in these functions were due to cocaine among samples of cocaine-dependent patients. Findings suggested that simple motor performance was more affected by global hypoperfusion than the other cognitive functions. Future research is needed to evaluate whether more localized areas of cerebral perfusion deficits reveal a significant relationship between hypoperfusion and memory, attention, and sensorimotor functioning.

INTRODUCTION

Cocaine remains one of the most commonly abused illicit drugs in the United States, second only to cannabis (Substance Abuse and Mental Health Services Administration, 2000). Several studies have documented cognitive deficits associated with chronic cocaine abuse including declines in attention, memory, motor functioning, language, and executive functions (Ardila, Rosselli, & Strumwasser, 1991; Hoff et al., 1996; Horner, 1997; and Selby & Azrin, 1998). However, the severity and types of deficits noted in these studies have been largely inconsistent. The variability of results across studies is likely due to methodological differences and to the heterogeneity of personal characteristics among cocaine abusers, including abuse of other substances such as alcohol.

Deficits in neuropsychological functioning may be related to vascular alterations in the brain due to chronic cocaine abuse. Cocaine causes constriction of blood vessels and significantly reduces cerebral blood flow (Wallace et al., 1996). Studies incorporating measurement of cerebral decreased perfusion and neuropsychological functioning among cocaine abusers have tended to do so by qualitative description of perfusion deficits.

The purpose of this study is to further clarify the neuropsychological consequences of cocaine abuse. A second aim is to investigate the relationship between cognitive functioning and cerebral blood flow in cocaine abusers with an objective quantitative approach. Lastly, the association between cocaine/alcohol use and hypoperfusion was evaluated.

History and Prevalence of Cocaine Use in the United States

Cocaine hydrochloride is a white powder that is extracted from the leaves of the coca plant, *Erythroxylon coca*, found in the Andes mountains in South America (National Institute on Drug Abuse, 2001). Cocaine was introduced in the United States during the 1860s, after isolation of the active ingredient in coca leaves. By the 1880s, cocaine was commonly available in the United States in drug stores, grocery stores, saloons, and from mail-order medicine companies (Musto, 1992). Products containing cocaine were marketed as health tonics, hay fever and asthma remedies, local anesthetics, and stimulants. The popularity of cocaine soared as it was added to beverages such as Vin Mariani, a mixture of wine and coca, which earned the celebrity endorsements of Thomas Edison and Pope Leo XIII. Coca-cola offered a domestic version of the French Vin Mariani. The wine was later removed in deference to the temperance movement.

The first cocaine epidemic peaked shortly after 1900, when annual legal imports of coca leaves averaged approximately 1.5 million pounds (Musto, 1992). Knowledge about the harmful effects of cocaine became more commonplace as medical literature, newspapers, and popular magazines began circulating reports of psychosis and death. Cocaine was finally banned with the Harrison Narcotics Act (1914) and became available only with a prescription. Use of cocaine declined rapidly and remained at a low level for over 40 years.

Cocaine use increased again in the 1960s when expensive powdered cocaine gained popularity among middle and upper-middle class Americans

(National Institute on Drug Abuse, 2001). Cocaine became available in a much cheaper form, crack, in the 1980s. Cocaine abuse peaked in 1985 when it was estimated that 5.7 million Americans (3% of the population in the United States) regularly used cocaine.

During the early 1990s cocaine abuse declined and has remained at a fairly stable rate for the last few years. Despite the decrease in use, cocaine remains one of the most frequently abused illicit drugs in the United States. An estimated 1.5 million Americans were current cocaine users in 1999 (Substance Abuse and Mental Health Services Administration, 2000). This number represents 0.7 percent of the population aged 12 or older in the United States. Approximately 413,000 of these individuals used crack cocaine. An estimated two percent of the U.S. population aged 18-25 were current cocaine users. The percentage of individuals using cocaine, who meet diagnostic criteria for cocaine dependence and cocaine abuse, is unknown.

Diagnostic Considerations

Cocaine dependence is characterized by a pattern of use leading to impairment or distress involving at least three of the following criteria as elaborated in the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (American Psychiatric Association, 1994): tolerance requiring increasing amounts of cocaine to achieve intoxication; withdrawal as evidenced by dysphoric mood, sleep disturbance, clinically significant distress or impairment in social or occupational functioning; taking increasingly larger amounts than

intended; unsuccessful attempts to reduce intake; expending inordinate time and effort to obtain cocaine; neglecting important responsibilities related to work or family; and continued use despite experiencing serious negative consequences. Cocaine abuse involves a pattern of use resulting in substantial impairment or distress as demonstrated by at least one of the following in a one-year period: neglecting responsibilities at home or work; use in situations that create risk for themselves or others; or continued use despite serious negative consequences.

Cognitive symptoms of cocaine intoxication include euphoria, anxiety, alertness, impaired judgment, and an increased sense of power. Behavioral changes such as stereotyped behavior, angry outbursts, and restlessness may occur. Physiological symptoms of intoxication are increased blood pressure, pupil dilation, tachycardia, and perspiration. The diagnostic criteria for cocaine intoxication highlight the multitude of mental and physical changes related to cocaine use.

Medical and Psychological Complications Associated with Cocaine Abuse

Cocaine use disorders may induce additional psychological conditions, such as psychosis, depression, and anxiety. Psychosis during cocaine intoxication appears to be a fairly common experience in cocaine dependent individuals (Brady, Lydiard, Malcolm, & Ballenger, 1991). Fifty-three percent of patients admitted to a facility for treatment of cocaine dependence reported experiencing hallucinations (83% auditory hallucinations, 38% visual hallucinations, and 21%

tactile hallucinations). The majority of patients who reported a history of hallucinations also had delusions.

Cocaine use is associated with neurological complications, including stroke, seizures, fungal brain infections, vasculitis, and vasospasm (Pascual-Leone, Dhuna, Altafullah, & Anderson, 1990). Cardiovascular problems, including myocardial infarction, tachycardia, and hypertension, have been reported following cocaine use (Boghdadi & Henning, 1997; Willens, Chakko, & Kessler, 1994). Cocaine may cause respiratory distress and renal failure (Boghdadi & Henning, 1997). Thus, cocaine appears to have the potential to induce a wide array of medical disorders.

Cocaine's harmful effects may be caused by excessive stimulation of the central nervous system and by constriction of blood vessels (vasoconstriction). Cocaine use results in the heart beating more rapidly, an increase in blood pressure, and narrowing of the diameter of blood vessels. Arteries may be unable to supply the required volume of blood, potentially resulting in organ ischemia and organ failure. Even if reductions in blood flow are insufficient to cause a major medical event, it is possible that chronic hypoperfusion (decreased blood flow) may carry significant health risks, particularly to the brain. Wallace et al. (1996) found that cocaine abusers averaged a 30 percent reduction in cerebral blood flow for the whole brain after a typical recreational dose of cocaine.

Route of Administration and Reinforcement

The reinforcing effects of cocaine depend in large part on the route of administration (Volkow et al., 2000). The rate at which cocaine is delivered to the brain is determined by the route of administration. The more rapid the delivery to the brain, the more intense the subjective reinforcement, or "high."

The primary routes of administration used for recreational use of cocaine include intravenous injection, smoking, intranasal use (snorting), or oral (chewing). Snorting cocaine involves inhaling cocaine powder through the nostrils where it is absorbed into the bloodstream through nasal and oral tissue. A similar process occurs when cocaine is chewed, oral tissue absorbs the cocaine allowing entry into the bloodstream. Intravenous injection of cocaine delivers the cocaine directly into the bloodstream, thereby yielding more intense reinforcement. Cocaine may be smoked as a freebase cocaine or as crack cocaine in a pipe. The rate of absorption of smoked cocaine is comparable to intravenous injection, because inhaled cocaine vapor is absorbed rapidly in the lungs (National Institute on Drug Abuse, 2001).

Methods of administration with the fastest rates of delivery to the brain have the shortest duration of action. Reinforcement from the intranasal route may last 15-30 minutes, whereas, the high from smoking may last only 5-10 minutes. Frequent smoking may lead to an even shorter period of reinforcement. Briefer, more intense periods of reinforcement may increase the potential for addiction (Cone, 1995).

Neurobiology of Cocaine Abuse

Animal studies have provided insight into brain mechanisms underlying cocaine addiction. Rats and monkeys repeatedly self-administered dopamine agonists, such as cocaine and amphetamine, by pressing a lever delivering the substance into their bloodstreams (Koob & Bloom, 1988). In contrast, drugs that act as dopamine antagonists were not self-administered. Electrical stimulation studies further supported the importance of dopamine in reward.

Animals demonstrated behavioral evidence of reinforcement when regions of the brain that release dopamine are electrically stimulated. Naturally occurring behaviors that are rewarding, such as eating, drinking, and sexual intercourse, also result in release of dopamine.

The two major dopaminergic pathways in the brain are the nigrostriatal dopamine system and the mesolimbic system (Gilman, & Winans Newman, 1996). The nigrostriatal system is comprised of dopaminergic neurons in the substantia nigra and their projections to the caudate and putamen. The mesolimbic pathway consists of dopaminergic neurons in the ventral tegmental area and the projections to the nucleus accumbens, prefrontal cortex, and limbic system. The mesolimbic system appears to contain the most important projections involved in reward (Panikkar, 1999). The nucleus accumbens and the ventral tegmental area are thought to be particularly important in reward, since ablation of either area prevents reinforcement with dopamine agonists. More recent research has supported a role for the amygdala in cocaine addiction as

well. Rats self-administered cocaine delivered to the amygdala as well as to the nucleus accumbens (Hurd & Ponten, 2000; Nestler, 2001).

Acute Effects of Cocaine

Alterations in dopamine levels. When a reinforcing event occurs, large increases in dopamine are noted in the nucleus accumbens. At the cellular level under normal conditions, dopamine is released into the synaptic cleft where it binds to a transporter molecule that carries dopamine into the terminal button. When cocaine is present, this process is prevented since cocaine binds to the transporter, thereby blocking dopamine reuptake. The accumulation of dopamine in the synaptic cleft causes continuous stimulation of neurons, resulting in the euphoria associated with cocaine abuse (National Institute on Drug Abuse, 2001).

Human studies also support the role of dopamine in cocaine addiction. Volkow et al. (1997) administered intravenous cocaine at a typical recreational dose, and found that cocaine blocked between 60 to 77 percent of the dopamine transporter binding sites in the brains of addicts. Furthermore, at least 47 percent of the dopamine binding sites had to be blocked before participants had a subjective sense of high.

Although dopamine appears to play a key role in reinforcement, other neurotransmitters may be involved as well. Sora et al. (2001) proposed that cocaine's reinforcing effects are caused by blocking both dopamine and serotonin receptors at the same time. Mice were genetically altered to lack the gene for

the dopamine transporter, that allows dopamine to cross into the terminal button. Cocaine was still reinforcing to the mice, though they lacked the dopamine transporter. Sora et al. (2001) concluded that reward still occurred because the serotonin transporter was intact.

Vasoconstriction. Cocaine users have been found to demonstrate a 30 percent reduction in global cerebral blood flow following a typical recreational dose of cocaine (Wallace et al., 1996). The vasoconstrictive effects of cocaine, and cocaine's metabolites benzoylecgonine and norcocaine, appear to contribute to the increased incidence of ischemic strokes in cocaine users (Bolla, Cadet, & London, 1998). Cocaine-induced vasoconstriction may be mediated by adrenergic stimulation. When alpha-adrenergic receptors were blocked in cocaine users, the vasoconstrictive effects of cocaine were prevented (Benzaquen, Cohen, & Eisenberg, 2001).

Chronic Effects of Cocaine

Cocaine is a powerful catecholamine agonist that blocks reuptake of dopamine and norepinephrine. Blocking norepinephrine reuptake leads to excessive neurotransmitter, which stimulates the sympathetic system resulting in tachycardia and hypertension (Om, 1992). Chronic cocaine use has been associated also with acceleration of atherosclerosis (Dressler, Malekzadeh, & Roberts, 1990). Autopsy of 22 young cocaine addicts revealed that approximately 40% had significant coronary arterial narrowing defined as greater than 70% stenosis. Cocaine may induce premature atherosclerosis by increasing

the numbers of adventitial mast cells, which are large cells containing histamine (Kolodgie, Virmani, Cornhill, Herderick, & Smialek, 1991). The severity of arterial narrowing was correlated positively with the number of mast cells.

Chronic cocaine use also appears to lead to depletion of dopamine receptor availability. The number of years of cocaine abuse has been correlated with decreases in D₂ receptor availability (Volkow et al., 1997). Furthermore, reductions in glucose metabolism in frontal lobe regions receiving dopaminergic afferents have been associated with decreased D₂ receptor availability. Reductions in D₂ receptor availability may represent downregulation of postsynaptic D₂ receptors in response to repeated elevations in dopamine during cocaine use (Volkow et al., 2000). Depletion of monoamine (dopamine and serotonin) sites may make cocaine users more susceptible to development of depressive symptoms (Strickland, Miller, Kowell, & Stein, 1998).

Neuropsychological Deficits in Chronic Cocaine Abuse

Cognitive deficits related to cocaine abuse are generally more severe shortly after abstinence from cocaine. A group of cocaine dependent individuals were administered neuropsychological tests after an average of 4.9 days of abstinence (Smelson, Roy, Santana, & Engelhart, 1999). Impaired performance was found on tasks of attention, cognitive flexibility, and bilateral manual dexterity as measured respectively by Arithmetic (Wechsler, 1981), Trails B (Reitan, 1985), and Grooved Pegboard (Klove, 1963). The limited battery of tests given in this study did not explore the possibility of deficits in memory.

Horner (1997) assessed memory functioning in cocaine dependent participants after two weeks of abstinence. Immediate and delayed verbal memory were impaired, whereas, visuospatial memory was intact (Babcock Story Recall Test – Babcock & Levy, 1940; Taylor Complex Figure Test – Spreen & Strauss, 1991). The results of this study were complicated by the substantial abuse of alcohol reported among the cocaine dependent participants. Therefore, the relative contribution of cocaine and alcohol to declines in verbal memory was unclear. One study finding suggested that either cocaine, or a combination of cocaine and alcohol, was of greater relevance to verbal memory impairment. The cocaine/alcohol dependent group performed significantly worse on the verbal memory measures than the purely alcohol dependent group.

A recent study supported the conclusion that cocaine abuse plays a greater role in verbal memory deficits than alcohol abuse (Bolla, Funderburk, & Cadet, 2000). A significant dose-related association was found between amount of cocaine abuse and performance on a test of verbal learning and memory (Rey Auditory Verbal Learning Test – Rey, 1964). However, the relationship between amount of alcohol abuse and verbal learning was not significant. The relationship between cocaine abuse and poorer verbal memory was found both shortly after abstinence and again after four weeks. The slowest learning curves were demonstrated by individuals using more than three grams of cocaine per week (Strickland et al., 1993). The findings replicated those of a previous study showing a significant negative relationship between verbal memory and amount

of cocaine abuse (Bolla, Rothman, & Cadet, 1999). In addition to verbal learning deficits, the amount of cocaine abuse was related to a measure of graphomotor speed, whereas, alcohol abuse was associated with timed tasks involving visuospatial reasoning/construction, manual dexterity, cognitive flexibility, and selective attention (respectively Digit Symbol – Wechsler, 1981; Block Design – Wechsler, 1981; Grooved Pegboard – Klove, 1963; Trails B – Reitan, 1985; Stroop Color-Word – Stroop, 1935).

Visual memory was not specifically assessed in either of the studies that showed verbal memory decrements in cocaine abusers. Hoff et al. (1996) compared the performance of cocaine abusers to normal controls' on a battery of neuropsychological tests including both verbal and visual memory measures after nearly a month of abstinence (California Verbal Learning Test – Delis, Kramer, Kaplan, & Ober, 1987; Revised Visual Retention Test - Benton, 1963). There was no evidence of a decline in verbal memory, however, significantly worse visual memory was found among the cocaine users. The cocaine dependent group also demonstrated deficits on measures of confrontation naming, cognitive flexibility, and abstract reasoning/concept formation (respectively Boston Naming Test – Kaplan, Goodlass, & Weintraub, 1983; Trails B; Booklet Categories Test – DeFilippis & McCampbell 1979, 1991).

Moderate verbal memory impairment and mild visual memory deficits were noted in another group of cocaine dependent patients after one month of abstinence (Ardila, Rosselli, & Strumwasser, 1991). The discrepancy between

these results and those of the aforementioned study might be related to the different tests used to measure verbal and visual memory (Logical Memory, Associative Learning, Visual Reproduction – Wechsler Memory Scale, 1945). Other sources of variability between study results could be related to differences in exclusion criteria. Participants in the Ardila et al. (1991) study all had a prior history of significant polysubstance abuse, with cocaine being their primary drug of choice for an average of 16 months.

Robinson et al. (1999) excluded cocaine abusers with a history of dependence on other illicit drugs. They administered an extensive neuropsychological battery to three groups of participants: cocaine dependent, cocaine/alcohol dependent, and normal controls. The synthesis of cocaine and alcohol produces a toxic substance, cocaethylene, that is associated with increased morbidity and mortality (Andrews, 1997). Partly for this reason, the cocaine/alcohol dependent group was expected to demonstrate the worst global deficit scores. Instead, the solely cocaine dependent group obtained significantly worse global impairment ratings than either the cocaine/alcohol group and normal controls. Significant differences between cocaine abusers and controls were found on cognitive domains tapping attention, simple motor functioning, and psychomotor speed. In contrast with previous studies, significant differences in memory functioning were not present. Overall, the results suggested that abuse of only cocaine was more harmful than abusing both alcohol and cocaine. Alcohol was proposed to counteract the severity of the

potentially harmful vasoconstrictive effects of cocaine by acting as a vasodilator (Robinson, et al., 1999). However, some studies have shown that alcohol abuse was associated with hypoperfusion.

Conflicting results were obtained on different studies examining the question of whether abusing only cocaine was more or less harmful than polysubstance abuse involving other illicit drugs. Rosselli and Ardila (1996) concluded that the neuropsychological test performance of cocaine abusers was comparable to those of polysubstance abusers (solvent inhalation, marijuana, alcohol, and cocaine). Both groups performed significantly worse than normal controls on measures of verbal immediate/delayed memory, delayed visual memory, simple attention, and abstract reasoning/concept formation (respectively Logical Memory, Visual Reproduction - Wechsler Memory Scale; Digit Span; Wisconsin Card Sorting Test - Heaton, 1981). The generalizability of these results is uncertain since the study took place in Bogata, Colombia, and used Spanish translations for all tests.

Conclusions from a more recent study were supportive of a significant disparity between cocaine abusers and polysubstance abusers on neuropsychological tests after prolonged abstinence averaging three years (Selby & Azrin, 1998). Participants were assigned to one of four groups: normal controls, cocaine abusers, alcohol abusers, or polysubstance abusers (alcohol, cocaine, and heroin). No neuropsychological differences were found between the cocaine group and normal controls. However, polydrug users and the alcohol

group performed worse on nearly all neuropsychological measures compared to the cocaine group and normal controls. The authors proposed that cocaine abusers recover cognitive functions more fully than abusers of polysubstances or alcohol. However, the strength of their conclusion was diminished by the severe extent of alcohol abuse present in both the polydrug and solely alcohol groups, compared to the moderate level of abuse reported by cocaine abusers.

Results from Strickland et al. (1993) indicated that moderate to severe levels of cocaine abuse may be associated with neuropsychological deficits even after six months of abstinence. Deficits were described in attention/concentration, verbal learning, verbal/visual memory, and word fluency. Conclusions from the study were limited by the lack of any statistical analyses.

Overall, the results of studies investigating the effects of cocaine on cognitive functioning were equivocal. Much of the variability in findings results from a multitude of methodological and participant differences, including the amount/duration of cocaine abuse, length of abstinence, a lack of verification of abstinence, different measures being used to assess cognitive domains, concomitant substance use disorders, and different exclusionary criteria. All of this variability greatly complicates the comparison of results across different studies.

Neuroimaging and Chronic Cocaine Abuse

A variety of imaging techniques revealed structural and vascular abnormalities in the brains of chronic cocaine abusers. Cocaine may cause

stroke, vasospasm, and seizures (Pascual-Leone et al., 1990). However, even among cocaine abusers without history of neurological events or risk factors for vascular conditions (e.g., diabetes, hypertension, or head trauma), a significant proportion demonstrated “silent” abnormalities on magnetic resonance imaging (MRI). These anomalies were thought to be directly related to cocaine abuse (Bartzokis et al., 1999). Nearly 30 percent of cocaine dependent participants without a neurological history had lesions suggestive of anoxic vascular events.

In a subsequent study, Bartzokis (2000) showed that cocaine dependent participants had significantly smaller temporal lobe volumes, particularly in areas of gray matter. However, this decrease in temporal lobe volume was not evident in the hippocampus in another study (Jacobsen, Giedd, Kreek, Gottchalk, & Kosten, 2001). A study using functional MRI (fMRI) suggested that the primary motor cortex is affected by cocaine, since activation decreased by 43% in this region following administration of cocaine (Li et al., 2000).

In addition to these structural and functional changes, several studies have found vascular alterations in the brains of cocaine dependent participants. Kaufman et al., (1998) used magnetic resonance angiography (MRA), a technique that is used to measure arterial flow. They demonstrated the presence of significant vasoconstriction 20 minutes following administration. Wallace et al. (1996) quantified the degree of vasoconstriction in cocaine abusers, through the use of single photon emission computed tomography (SPECT), a technique that may be used to measure regional cerebral blood flow.

Even relatively low doses of cocaine (40mg IV cocaine hydrochloride) significantly decreased cerebral blood flow, with an average reduction of 30% for the whole brain.

The vascular changes demonstrated with SPECT may be apparent years before structural abnormalities become apparent on CT or MRI. Mena et al. (1994) reported widespread hypoperfusion (reduced blood flow) in the periventricular area in chronic cocaine abusers using SPECT, though no evidence of lesions was apparent on CT or MRI. The finding of cocaine-induced decreases in blood flow in periventricular regions was consistent with reports of the same area being particularly vulnerable to development of ischemic stroke following cocaine use (Mena et al., 1994). Examination of regional differences in the brain suggested that the frontal lobes may be more affected by vasoconstriction than other brain regions (Ernst, Chang, Oropilla, Gustavson, & Speck, 2000). The most prominent changes occurred in the gray matter.

Hypoperfusion due to cocaine abuse may be persistent, even after prolonged abstinence. Moderate to heavy cocaine abusers had significant areas of hypoperfusion after six months of abstinence (Strickland et al., 1993). It is uncertain to what degree spontaneous recovery increases cerebral perfusion. Some studies have attempted to increase perfusion with partial success in cocaine polydrug users with abstinence and a vasodilator (Holman et al., 1993).

Relationship Between Cerebrovascular Changes and Cognitive Functioning

Very little is known about how cerebral blood flow changes associated with cocaine abuse affect neuropsychological functioning. One study of chronic cocaine users showed both significant amounts of hypoperfusion on SPECT and neuropsychological deficits in attention, verbal learning, memory, and word fluency (Strickland et al., 1993). However, conclusions from this study were limited by the lack of a control group and a sample size of only eight participants.

The notion that hypoperfusion might result in cognitive deficits is supported by studies of other patient populations. Patients with occlusion of the carotid arteries, resulting in significant reductions in cerebral blood flow, showed deficits in neuropsychological functioning (Antonelli-Incalzi et al., 1997; Greiffenstein, Brinkman, Jacobs, & Braun, 1988). Furthermore, significant improvement was noted in cognitive functioning following a surgical procedure (endarterectomy) to increase perfusion. Participants in both studies demonstrated improvement in verbal memory.

Some studies of patients with different types of dementia showed that hypoperfusion was significantly related with degree of neuropsychological impairment. In a study of patients with vascular dementia, neuropsychological deficits were significantly correlated with decreases in cerebral blood flow, but not with lacunar infarctions or lesions on MRI (Sabri et al., 1999). Patients with Alzheimer's disease, frontotemporal dementia, and Parkinson's disease had a number of cognitive deficits that were related to cerebral blood flow (Boone et

al., 1999; Celsis, Agniel, Puel, & Rascol, 1987; Starkstein et al., 1997). Thus, there is some indirect evidence that chronic reduction in cerebral blood flow exerts a negative influence on cognitive functioning.

Theoretical Considerations

Cocaine users have demonstrated cognitive deficits in attention, language, memory, and motor functioning (Bolla et al., 2000; Horner, 1997). These functions are largely associated with the frontal lobes and subcortical areas (Lezak, 1983). These same regions receive projections from the major dopaminergic pathways, mesolimbic and nigrostriatal systems (Gilman, & Winans Newman, 1996). The nigrostriatal system is particularly important in the control of motor function.

Depletion of dopamine receptor availability has been correlated with years of cocaine abuse and hypoperfusion (Volkow et al., 2000). Cocaine-induced vasoconstriction may explain reductions in cognitive functioning on tasks that are reliant on brain regions involving dopaminergic pathways. In addition, the accelerated rate of atherosclerosis noted in cocaine users may contribute to reductions in neuropsychological performance.

Purpose of the Study

Results from studies examining neuropsychological test performance in cocaine abusers are conflicting and confounded with methodological problems including concomitant alcohol abuse, lack of verification of abstinence, and inadequate exclusion criteria. Findings are complicated further by participant

variables, such as severity/duration of cocaine abuse, presence of depressive symptoms, and age. Very little information is known about how reductions or abnormal increases in cerebral blood in cocaine abusers may affect neuropsychological functioning. The purpose of the study is to investigate the relationships between the extent of cocaine/alcohol use, neuropsychological functioning, and cerebral blood flow. The following hypotheses were evaluated.

Hypothesis 1: Cocaine users were expected to perform significantly worse than control subjects on neuropsychological factors involving attention/executive functioning, learning/memory, simple motor functioning, and sensorimotor functioning.

Hypotheses 2a and 2b: The frequency of cocaine use in the month preceding the study was hypothesized to predict performance on the neuropsychological factors (Attention/Executive Functioning, Memory, Simple Motor, and Sensorimotor). Cognitive performance was expected to decline as the frequency of cocaine increased (Hypothesis 2a). The number of alcoholic beverages in the month preceding the study was expected to explain additional variance in the prediction of memory functioning, with worse memory associated with an increasing number of alcoholic drinks (Hypothesis 2b).

Hypothesis 2c examined the potential influence of additional substance use (heroin and cannabis) and demographic variables (sex, race, and education) on the performance of neuropsychological factors. Heroin was not expected to be significant since a very low level of use was reported. A positive relationship

was anticipated between years of education and performance on the Attention/Executive Functioning and Memory factors.

The next group of hypotheses investigated the relationship between duration of substance use and the neuropsychological factors. Increasing years of cocaine use was expected to predict poorer performance on all of the neuropsychological factors (Hypothesis 2d), whereas, a greater number of years of alcohol use was anticipated to contribute only to lowered scores on the Memory factor (Hypothesis 2e).

Hypothesis 3: Increasing severity of cerebral hypoperfusion was expected to predict worse performance on the neuropsychological factors: Attention/Executive functioning, Memory, Simple Motor, and Sensorimotor.

Hypotheses 4a, 4b, 4c, 4d: Subjects were split into three groups on the basis of frequency of recent cocaine use. It was hypothesized that increasing frequency of cocaine consumption would be associated with greater severity of hypoperfusion (Hypothesis 4a). The study participants were also split into three groups on the basis of the reported number of alcoholic beverages drunk in the month preceding the study. As the number of drinks increased across the three groups, hypoperfusion was expected to decrease (Hypothesis 4b). Subjects were split into three groups on the basis of duration of cocaine use in years. It was hypothesized that a lengthening number of years of cocaine use would be associated with increases in hypoperfusion (Hypothesis 4c). The study participants were divided into three groups on the basis of the reported number

of years of alcohol use. As the number of years of alcohol use extended by group, it was expected that hypoperfusion would decrease (Hypothesis 4d).

Table 1 summarizes the independent and dependent variables of each hypothesis.

Table 1
Summary of Study Variables by Hypotheses

Hypothesis		Independent variable(s)	Dependent variable(s)
1		Group (cocaine, control)	Neuropsychological factors
2	a	Days cocaine/month	Neuropsychological factors
	b	Alcoholic drinks/month	Neuropsychological factors
	c	Extraneous variables Demographic variables Other drugs (heroin/cannabis)	Neuropsychological factors
	d	Years of cocaine use	Neuropsychological factors
	e	Years of alcohol use	Neuropsychological factors
3		Severity of hypoperfusion	Neuropsychological factors
4	a	Tertiles of recent cocaine use	Severity of hypoperfusion
	b	Tertiles of recent alcohol use	Severity of hypoperfusion
	c	Tertiles of years cocaine use	Severity of hypoperfusion
	d	Tertiles of years alcohol use	Severity of hypoperfusion

Note. Days cocaine = the number of days cocaine was used in the month preceding the study. Alcoholic drinks/month = the number of alcoholic beverages in the same time period. Neuropsychological factors = Attention/Executive Functioning, Memory, Simple Motor, and Sensorimotor. Severity of hypoperfusion = number of pixels indicating significantly lower global perfusion at $p < .001$.

METHOD

Participants

A total of sixty cocaine-dependent participants and 13 normal controls were enrolled into the present study. All participants were between the ages of 18 and 47. Participants in the patient group met DSM-IV criteria for Cocaine Dependence, had a history of cocaine use that exceeds a total of 14 grams during the preceding 3 months, and a history of cocaine use via an intravenous (2%) or smoked route (98%). Laboratory confirmation of cocaine use was required for cocaine using participants through urinalysis.

Exclusionary criteria were the presence of serious medical or neurological illness (e.g., history of stroke, transient ischemic attack, seizure, previous history of head injury with loss of consciousness lasting longer than 10 minutes, diabetes mellitus, renal insufficiency, or hepatic disease), prior history of thrombotic or bleeding disorders, meeting DSM-IV criteria for schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder, mental retardation, laboratory drug screen revealing the presence of any abused drug other than cocaine at the time of admission, and seropositivity for HIV.

Demographic Variables

Significant age differences were not found between the cocaine users and control subjects. However, there were significant group differences related to educational level, therefore, years of education was used as a covariate in the main analyses comparing the two groups. There were also significant differences

in the racial and gender distribution of the two groups. Table 2 presents the groups' demographic and substance use characteristics.

Table 2
Demographics and Substance Use Characteristics of Cocaine Users and Control Subjects

	Cocaine Users (n = 60)		Controls (n = 13)		
	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>	
Age	35.34	(5.06)	33.57	(5.73)	
Education	12.33	(1.30)	13.00	(1.36)	*
Sex, % male	67		31		*
Race, % white	33		70		**
Days cocaine/month	19.73	(7.68)	0	(0)	**
Alcoholic drinks/month	86.07	(121.29)	4.46	(3.97)	*
Total years cocaine	11.94	(6.22)	0	(0)	**
Sum of \$ cocaine/month	1409	(1469)	0	(0)	**
Total years alcohol	16.01	(8.27)	15.15	(8.53)	
Cannabis cigarettes/month	8.56	(24.54)	0	(0)	**
Days heroin/month	.36	(1.55)	0	(0)	**
Days since last drug use	5.74	(2.31)	N/A		

Note. Sex and race were examined with Chi-square tests. Age and educational differences were calculated with t-tests. All other differences were calculated with Mann-Whitney U. * $p < .05$. ** $p < .005$.

The correlation between the frequency of recent cocaine and alcohol use was significant ($r = .32$, $p < .01$), as was relationship between the duration of cocaine and alcohol use ($r = .36$, $p < .01$). African-Americans drank more alcoholic beverages ($M = 97.18$, $SD = 131.74$) than Caucasian subjects ($M = 32.07$, $SD = 64.44$), though this difference did not reach statistical significance with Mann-Whitney U ($U = 493.50$, $p = .06$). African-Americans also smoked cocaine slightly more frequently (Days smoked cocaine in the last month:

African-Americans $M = 17.57$, $SD = 8.59$; Caucasians $M = 13.70$, $SD = 12.40$, not significant) and for a greater number of years (Years of cocaine use: African-Americans $M = 11.63$, $SD = 6.81$; Caucasians $M = 7.00$, $SD = 7.22$).

Materials

Digit Span. Digit Span Forward (Wechsler, 1981) measures simple auditory attention, whereas, Digit Span Backwards also relies on working memory, since information must be held momentarily while it is mentally manipulated. Digit Span is one of six subtests that contribute to the Verbal IQ score of the Wechsler Adult Intelligence Scale-Revised (WAIS-R). The examiner reads number strings of increasingly longer numbers to the participant, who repeats them in the same order. The participant is then asked to repeat other strings of numbers in backwards order. Raw scores equal the total number of correctly repeated number strings.

Digit Symbol. Completion of the Digit Symbol (Wechsler, 1981) test requires visual attention, processing speed, graphomotor ability, and mental flexibility. Digit Symbol is one of five subtests that comprise the Performance IQ score of the WAIS-R. It is a timed task in which the patient must read numbers, match the number to those listed in a key, and transcribe the corresponding symbol as rapidly as possible. The raw score is the total number of symbols that were accurately transcribed.

Paced Auditory Serial Addition Task (PASAT). The PASAT (Gronwall, 1977) is a difficult task that is sensitive to cerebral dysfunction. It involves sustained

attention, divided attention, working memory, and mathematical skills. Poor performance may also reflect inadequate motivation or persistence, as it is quite challenging. A tape-recording of a voice states a single digit every 2.4 seconds for the first trial, every 2.0 seconds for the second trial, every 1.6 seconds for the third trial, and every 1.2 seconds for the fourth trial. The participant attempts to add each new number that is heard to the preceding digit. The total number of correct responses for each trial are calculated.

Auditory Verbal Learning Test (AVLT). The AVLT (Rey, 1964) relies on attention, verbal learning, organization, inhibition of interference, verbal delayed recall, and recognition memory. The examiner reads 15 items to the participant, who recalls as many items as possible across five trials. A distractor list of fifteen items is read to the participant. Immediately after hearing the new list, the participant is asked to recall the first list again. Following a delay of 20 minutes, the subject recalls the first list of words once again.

Trail Making Test. Trails A and B, which were used initially as part of the Army Individual Test Battery (1944), are timed measures that require visual scanning, visuomotor ability, sequencing, ability to inhibit an expected response, and cognitive switching. The participant completes Trails A first, which involves drawing lines to connect numbers in sequential order. Trails B is a more demanding task that involves alternately connecting numbers and letters in alphabetical and numerical order. The latter task is thought to reflect executive functioning. Trails A provides an indication of the expected level of performance

for Trails B, based on processing speed and visual scanning. Raw scores equal the number of seconds needed to complete each task.

Grooved Pegboard Test. The Grooved Pegboard Test (Klove, 1963) provides a measure of motor speed, tactile sensation, and manual dexterity for each hand. This is a timed task in which the participant inserts small metal pegs into holes on a board that are oriented in different directions. The pegs are rotated and manipulated with the fingertips. Scores consist of time to complete the task first with the dominant hand, then with the nondominant hand.

Finger Tapping Test. The Finger Tapping Test (Halstead, 1947; Reitan & Wolfson, 1993) examines motor speed and coordination. The participant uses their index finger to tap a lever attached to a number counter, as quickly as possible. Five trials, lasting 10 seconds each, are collected first with the dominant hand, then with the nondominant hand. The number of taps for each hand should yield a series of scores that are within five points of each other. If this is not the case, then a maximum of ten trials may be conducted with either hand in order to achieve consistent scores.

Cocaine use history. Lifetime cumulative amount and recent use of cocaine was assessed by self-report instruments developed specifically for use in studies of cocaine abuse and its treatment. This includes the Substance Use Index, which assesses substance use within the last month, and the Lifetime Use Index, which collects information about the number of years of substance use.

Single Photon Emission Computed Tomography (SPECT). Defects in cerebral blood flow were assessed using SPECT with Technetium-99m-d. 1-hexamethyl propyleneamine oxime (Tc-99m-HMPAO) as a tracer. Participants were injected intravenously with 20 mCi Tc-99m-HMPAO and asked to lie quietly with their eyes closed with a sleep mask and earphones in place for at least 5 minutes prior to and following injection of Tc-99m-HMPAO. The earphones were used to block out any environmental noise. SPECT images were acquired for 30 minutes with a triple-headed gamma camera, Picker PRISM 3000 XP. SPECT images were reconstructed on a UNIX workstation (SUN Ultra 60) and analyzed with Statistical Parametric Mapping (SPM96; Wellcome Institute, London, England). SPM was implemented in MEDx 3.2, a multimodal image analysis platform (Sensor Systems, Inc., Sterling, VA). Significant SPECT abnormalities ($p < .001$) were detected by comparing each cocaine subject's global activity level against the average perfusion level of the control subjects, resulting in a mean difference image of global perfusion.

Procedure

Cocaine users who presented for treatment voluntarily at the VA Connecticut Healthcare System were asked to participate in the study. Control subjects were recruited by word of mouth, placing advertisements in local newspapers, and by use of flyers placed in public areas around West Haven and New Haven, Connecticut. Participants were provided information about the study and asked to sign informed consent forms. Complete psychiatric and physical

examinations, including laboratory work, established whether participants meet inclusion/exclusion criteria. Qualified participants proceeded to having SPECT scans conducted by radiologic technicians and neuropsychological evaluations given by trained graduate school students.

Statistical Analyses

Data were examined for outliers by converting each subject's raw scores into z scores in comparison to their group (cocaine user or control). Subjects with z scores more than 3.29 standard deviations ($p < .001$) from the mean of their group were excluded. Therefore, data from two participants in the cocaine user group were discarded to better represent the vast majority of patients and to prevent distortion of results.

An exploratory factor analysis was performed to condense data generated from the 12 neuropsychological measures, thereby reducing the likelihood of Type I error related to multiple analyses. Age-corrected T-scores of all subjects ($N = 73$) were entered into a factor analysis, since this statistic requires variables to have a common metric. An oblique rotation (promax) was selected because it allows for correlations among scores that are not completely orthogonal. Factor loadings of the tests were used to create four new neuropsychological factors for all subsequent analyses.

Hypothesis 1, that significant differences in the neuropsychological factors were present among the cocaine users and controls, was evaluated with multivariate analysis of covariance (MANCOVA). Since the years of education

was significantly different among the groups, this variable was used as a covariate. Analysis of covariance was employed for follow up analyses.

Hypothesis 2 examined predictors of neuropsychological performance with multiple regression analyses. The number of days of cocaine use in the last month was expected to contribute significantly to all of the neuropsychological factors (Hypotheses 2a). The number of alcoholic drinks consumed in the last month was anticipated to be related to memory (Hypothesis 2b). Frequency of cocaine use, alcohol use, and the interaction between recent cocaine and alcohol use were entered sequentially into multiple regression analyses.

Hypothesis 2c investigated the influence of potentially confounding variables including other types of substance abuse (heroin and cannabis) and demographic variables (sex, race, and education). Heroin use was not expected to contribute significantly to performance on neuropsychological factors due to the low frequency reported in this sample of cocaine users. Education was expected to be related to factors involving memory and attention. Multiple regression analyses were conducted to evaluate the contribution of these extraneous variables to the neuropsychological factors.

Hypotheses 2d and 2e examined the relationship between the duration of cocaine/alcohol use and performance on neuropsychological factors. Years of cocaine use, alcohol use, and the interaction between duration of cocaine and alcohol were entered sequentially into multiple regression analyses.

The severity of hypoperfusion was entered into linear regression to predict performance on the neuropsychological factors (Hypothesis 3). Hypotheses 4a through 4d examined the relationship between the amount of substance use and hypoperfusion. Kruskal-Wallis tests were used to evaluate the significance of differences between groups based on days of recent cocaine use (Hypothesis 4a), recent alcohol use (Hypothesis 4b), duration of cocaine use (Hypothesis 4c), and duration of alcohol use (Hypothesis 4d). Significant findings were followed up with Mann-Whitney U tests.

RESULTS

Description of Performance on Neuropsychological Tests

The cocaine user group obtained lower mean T-scores than the controls on all but one of the 12 neuropsychological tests. However, the magnitude of the disparity between the groups ranged from being negligible to clinically relevant. More specifically, the cocaine users appeared to demonstrate mildly diminished scores (e.g., more than half a standard deviation) on measures of delayed memory (AVLT Short Delay and Long Delay). A more substantial decline of approximately one standard deviation was noted bilaterally on measures of sensorimotor functioning (Grooved Pegboard).

Table 3 presents the T-scores and the qualitative ranges for each of the neuropsychological tests by group. The initial significance level was included in this table for descriptive purposes, however, following Bonferroni correction for multiple analyses, only the Grooved Pegboard, Nondominant Hand met the required level of significance ($.05/12 = .004$).

The cocaine user group unexpectedly performed better (average range) than the controls (low average range) on a measure of simple attention (Digit Span), though this difference was not statistically significant. Examination of the individual subject's scores on Digit Span revealed that three control subjects obtained a T-score within the mildly impaired range ($T = 35$). Their performance was thought to reflect inadequate motivation on this particular test, since the

Table 3
Summary of Neuropsychological Test T-scores by Group

Measure	Cocaine Users (n = 60)			Controls (n = 13)		
	<u>M</u>	<u>SD</u>	<u>Range</u>	<u>M</u>	<u>SD</u>	<u>Range</u>
Digit Span	46.97	(10.63)	A	44.62	(8.75)	LA
Digit Symbol	48.13	(8.11)	A	49.77	(7.49)	A
Trails A	48.47	(10.81)	A	48.85	(10.85)	A
Trails B	48.50	(12.64)	A	52.92	(8.95)	A
PASAT	43.90	(8.62)	LA	47.63	(3.74)	A
AVLT						
Total	42.30	(8.85)	LA	47.55	(9.83)	A
Short Delay	42.60	(48.17)	LA	48.17	(8.13)	A*
Long Delay	40.40	(9.39)	LA	47.52	(8.24)	A*
Finger Tap						
Dominant	51.25	(12.16)	A	55.62	(9.78)	AA
Nondominant	49.98	(11.48)	A	54.23	(9.03)	A
Grooved Pegboard						
Dominant	40.35	(11.13)	LA	49.08	(13.98)	A*
Nondominant	39.87	(9.23)	MI	49.85	(12.46)	A**

Note. Range AA = above average, A = average; LA = low average; MI = mildly impaired. Group differences were calculated with t-tests. * $p < .05$, nonsignificant following Bonferroni correction. ** $p < .001$.

three subjects had obtained average scores on the remainder of tests tapping more complex aspects of attention. They were retained within the control group since the cocaine user group might also include data from individuals who were potentially affected by poor motivation.

Factor Analysis of Neuropsychological Measures

Exploratory factor analysis was performed on both the cocaine users' and control subjects' T-scores generated from the 12 neuropsychological tests.

Though several of the measures were significantly correlated, none of the

coefficients reached a level that would be indicative of multicollinearity, according to Tabachnick and Fidell (2001). Four factors yielded eigenvalues greater than one and the scree test supported the conclusion of a four-factor solution. Each of the 12 neuropsychological tests was assigned to one of the factors on the basis of a cutscore of at least .5. Most of the remaining factor loadings were in excess of .7. According to Comrey and Lee (1992), loadings greater than .71 are considered excellent. None of the tests loaded on more than one factor. All of the neuropsychological measures loaded on the same four factors, regardless of whether the control subjects were excluded from the analysis.

The four factors were interpreted as representing the following neuropsychological functions: Factor 1 - Attention/Executive Functioning; Factor 2 – Memory; Factor 3 – Simple Motor; and Factor 4 – Sensorimotor. Factor 1, Attention/Executive Functioning, accounted for 35% of the variance, and was comprised of Digit Span (simple auditory attention), Digit Symbol (visual attention and mental flexibility), PASAT (divided auditory attention), Trails A (visual attention involving searching/sequencing), and Trails B (visual attention/executive functioning). Sixteen percent of the variance was explained by the second factor, Memory. This factor included AVLT Total (word list-learning), AVLT Short Delay (verbal memory following a brief distraction), and AVLT Long Delay (verbal memory following 20 minutes). The third factor, Simple Motor functioning, accounted for 14% of the variance and was comprised of Finger-Tapping Dominant and Finger-Tapping Nondominant scores. Performance of

tests included in this factor required a purely motor response, whereas, completion of the fourth factor, Sensorimotor, necessitated both motor speed and tactile sensation/manual dexterity. The Sensorimotor Factor explained 9% of the variance and included Grooved Pegboard Dominant and Grooved Pegboard Nondominant scores.

A new variable was generated for each factor by averaging the T-scores from each neuropsychological test that loaded on the particular factor. All subsequent analyses used the results of the four factors in lieu of the 12 neuropsychological measures, allowing for fewer analyses and a reduction of potential Type I error. Table 4 summarizes the results of the factor analysis. The intercorrelation matrix in Table 5 suggested that the four factors contributed adequately unique information. The Attention/Executive Functioning and Simple Motor factors were the most highly correlated, possibly due to the timed graphomotor component of the measures of visual attention and cognitive switching that loaded on the Attention/Executive Functioning factor.

Hypothesis 1: Neuropsychological Test Performance of Cocaine Abusers and Control Subjects

Cocaine users were expected to perform worse than the controls on each of the four factors derived from the 12 neuropsychological tests (Hypothesis 1). A one-way between-subjects multivariate analysis of covariance (MANCOVA) was used to test this hypothesis, with group (cocaine user vs. control) as the independent variable. Dependent variables were the four neuropsychological factors: Attention/Executive Functioning, Memory, Simple Motor, and

Table 4
Factor Loadings of Neuropsychological Tests Using Exploratory Factor Analysis with Promax Rotation

Factor label	Factor loading				Communalities
Measure	1	2	3	4	
Attention/Executive					
Digit Span	.52	.36	.41	-.40	.64
Digit Symbol	.83	.23	.22	.31	.76
Trails A	.83	.00	.40	.27	.74
Trails B	.84	.35	.41	.22	.77
PASAT	.67	.27	.26	.33	.49
Memory					
AVLT Total	.36	.84	.21	.10	.75
AVLT Short Delay	.14	.90	.00	.00	.84
AVLT Long Delay	.32	.94	.15	.15	.89
Simple Motor Speed^a					
Tap Dominant	.42	.25	.94	.16	.90
Tap Nondominant	.32	.00	.93	.00	.90
Sensorimotor^b					
Pegs Dominant	.44	.28	.20	.85	.81
Pegs Nondominant	.42	.16	.20	.88	.83
Eigenvalues	4.5	2.1	1.8	1.2	
% of variance	35	16	14	9	Total 74%

Note. Boldface indicates highest factor loadings.

^a Finger-Tapping Test. ^b Grooved Pegboard Test.

Sensorimotor. Adjustment was made for a covariate, number of years of education. Box's M statistic was not significant, confirming homogeneity of variance-covariance matrices despite unequal sample sizes. Levene's Test was nonsignificant, thereby meeting the assumption of homogeneity of error variances of the dependent variables.

Table 5
Intercorrelations of the Neuropsychological Factors

Factor and label	1	2	3	4
1 Attention/Executive	---			
2 Memory	.34	---		
3 Simple Motor	.44	.20	---	
4 Sensorimotor	.25	.00	.00	---

The omnibus MANCOVA revealed significant differences between the cocaine users and the control group on the neuropsychological factors, Wilks' $\Lambda = .86$, $F(4,67) = 2.77$, $p = .03$. There was a modest association between group and the combined dependent variables ($\eta^2 = .14$), indicating that 14% of the multivariate variance of the neuropsychological factors was associated with the group factor. The relationship between the covariate education and the neuropsychological factors was nonsignificant.

Examination of the follow-up univariate analyses showed a contribution of group (cocaine user vs. control) to the Sensorimotor and Memory factors, with worse performance noted in the cocaine users [respectively, $F(1,70) = 5.90$, $p < .02$; $F(1,70) = 4.00$, $p < .05$]. Thus Hypothesis 1 was supported only for the Sensorimotor and Memory factors. Table 6 displays the average level of performance on each of the neuropsychological factors for both the cocaine users and the control subjects.

Table 6
Mean T-score and Range on the Neuropsychological Factors by Group

Factor	Cocaine Users (n = 60)			Controls (n = 13)		
	<u>M</u>	<u>SD</u>	<u>Range</u>	<u>M</u>	<u>SD</u>	<u>Range</u>
Attention/Executive	47.19	(7.80)	A	48.76	(4.97)	A
Memory	41.77	(8.08)	LA	47.75	(8.26)	A*
Simple Motor	50.62	(11.16)	A	54.92	(8.86)	A
Sensorimotor	40.11	(9.35)	LA	49.46	(12.72)	A**

Note. Under Range, A = average; LA = low average. * $p < .05$. ** $p < .02$.

Since significant differences existed in the racial and gender distribution among the cocaine user group and the control group, the influence of these demographic variables was examined. A 2 x 2 MANOVA was conducted with race and sex as the independent variables, and the four neuropsychological factors as the dependent variables. Group differences between cocaine users and normals were not included in this analysis, or in combination with either race or sex, since this would result in two cells with only three members apiece.

Overall, the independent variable race was significant, Wilks' $\Lambda = .71$, $F(4,67) = 6.82$, $p < .001$, but sex and the interaction between sex and race were nonsignificant. Four follow-up analyses of variance were performed on the independent variables race and sex, with each the neuropsychological factors serving as a dependent variable. There were ethnic differences for all factors except for Simple Motor Functioning: Attention/Executive, $F(1,70) = 16.62$, $p <$

.001; Memory, $F(1,70) = 12.74$, $p = .001$; and Sensorimotor, $F(1,70) = 9.00$, $p < .004$. Lower scores were obtained by African-Americans on each neuropsychological factor. Within each racial group, the cocaine users generally performed worse than the controls.

Educational achievement was comparable among Caucasian and African-American participants (Years education: Caucasian $M = 12.69$, $SD = 1.31$; African-American $M = 12.30$, $SD = 1.25$). However, the ethnic differences noted on the Attention/Executive Functioning, Memory, and Sensorimotor factors were thought to be related to discrepancies in substance use patterns.

African-Americans reported drinking approximately three times the number of alcoholic beverages than their Caucasian counterparts in the month preceding the study (African-American $M = 97.18$, $SD = 131.74$; Caucasian $M = 32.07$, $SD = 64.44$). In addition, African-Americans also reported using cocaine slightly more frequently than Caucasians (Days of cocaine use in the last month: African-American $M = 17.57$ days, $SD = 8.59$; Caucasian $M = 13.70$, $SD = 12.40$) and for a greater duration (Years of cocaine use: African-American $M = 11.62$, $SD = 6.78$; Caucasian $M = 7.02$, $SD = 7.39$). In contrast, Caucasian subjects drank more caffeinated beverages per month (Caucasian $M = 70.37$, $SD = 96.20$; African-American $M = 37.10$, $SD = 48.84$). None of the substance use variables were normally distributed, therefore, nonparametric analyses were used. Mann-Whitney U did not reveal significant ethnic differences for any substance, but the number of alcoholic drinks consumed per month approached significance ($U =$

493.50, $p = .06$). Despite the lack of statistical significance, it seems plausible that the ethnic discrepancies in substance use might be of clinical importance.

Hypotheses 2a, 2b, and 2c: Predictors of Neuropsychological Test Performance

The second group of hypotheses were made to assess the relative contribution of cocaine, alcohol, and a combination of both substances on neuropsychological test performance. As the frequency of cocaine use increased, scores were expected to decline on all the neuropsychological factors, Attention/Executive Functioning, Memory, Simple Motor, and Sensorimotor (Hypothesis 2a). Attention/Executive Functioning and Memory were expected to be the most affected, since these abilities tend to be more susceptible to decline in general. The number of alcoholic drinks consumed in the last month was hypothesized to predict performance only on the Memory factor, with more drinks associated with poorer scores, beyond the expected effects of cocaine (Hypothesis 2b). Potentially confounding variables were investigated in Hypothesis 2c. Extraneous substance use (heroin and cannabis use) and demographic variables were not expected to be significantly related to neuropsychological performance, with the exception of education, which was anticipated to be related positively to scores on the Attention/Executive Functioning and Memory factors. Heroin was not expected to affect neuropsychological functioning, since the frequency of use among this sample was very low.

Hypothesis 2a and 2b: Frequency of recent substance use and neuropsychological test performance. The reported number of days cocaine was used in the month preceding the study, the number of alcoholic beverages consumed in same period, and the interaction between the two substances were entered respectively into multiple regression analyses as independent variables. Four multiple regression analyses were run, each using one of the neuropsychological factors (Attention/Executive Functioning, Memory, Simple Motor, and Sensorimotor) as a dependent variable. Race was not initially included in these analyses, since doing so would inadvertently control for substance use. Examination of the distribution of the dependent variables and residuals indicated that the assumptions of multiple regression were adequately met.

The number of alcoholic beverages accounted for a portion of the variance associated with two factors, Attention/Executive Functioning, $R^2 = .07$, $F(1,71) = 5.7$, $p = .02$) and Sensorimotor, $R^2 = .06$, $F(1,71) = 4.37$, $p = .04$. As the number of alcoholic drinks increased, performance declined on both the Attention/Executive and Sensorimotor factors. Neither days of cocaine, nor alcoholic drinks contributed significantly to the Memory or Simple Motor factors. Contrary to expectations, the number of days cocaine was used was not significantly related to any of the neuropsychological factors.

Hypothesis 2c: Examination of potentially confounding variables. The possible contribution of extraneous variables to the neuropsychological factors

was considered in the next set of analyses. These analyses were originally intended to help rule out the potential contribution of confounding variables to significant findings between cocaine/alcohol and the neuropsychological factors. Since none of the findings with alcohol/cocaine as predictors were statistically significant, the analyses were run to determine whether controlling for unexpectedly significant confounding variables would reveal significant relationships between the variables of interest.

The analyses of potentially confounding factors included drugs of abuse other than cocaine and alcohol (cannabis, and heroin), and demographic variables (race, sex, and education). Age was not included since all of the neuropsychological test scores were converted to age-corrected scores before undergoing factor analysis. Years of education was expected to be significantly related to the Attention/Executive Functioning and the Memory factors. None of the other extraneous variables was hypothesized to affect performance on the neuropsychological factors (Hypothesis 2c).

The reported number of cannabis joints smoked in a month and the number of days heroin was used were entered into multiple regression analyses as independent variables. Four analyses were conducted, each with a neuropsychological factor as a dependent variable. Neither the cannabis, nor the heroin was a significant predictor of performance on any of the neuropsychological factors.

Sex, race, and education were entered sequentially into multiple regression analyses as independent variables. Four analyses were conducted, each with one of the neuropsychological factors as a dependent variable. Race contributed to the prediction of the Attention/Executive Functioning and Memory factors, respectively $R^2 = .19$, $F(1,72) = 16.94$, $p < .001$; $R^2 = .12$, $F(1,72) = 10.09$, $p = .002$. As with the results of MANCOVA, Caucasian race was associated with better performance on both factors. Both race and years of education accounted for a significant proportion of variability related to the Sensorimotor factor, $R^2 = .18$, $F(2,71) = 7.74$, $p = .001$. Increasing years of education and Caucasian race predicted better performance on the Sensorimotor factor. None of the demographic variables were significant predictors of the Simple Motor factor. Thus, it appeared that Hypothesis 2c, that only education would be significant among the potentially confounding variables, was incorrect.

The multiple regression analyses examining the contribution of cocaine and alcohol to neuropsychological performance were reexamined, taking the significant contribution of certain demographic variables into consideration, in the prediction of the neuropsychological factors that were significant when no statistical control was used. Hierarchical multiple regression was performed on the independent variables, Attention/Executive Functioning and Memory. Race was entered into the first block, then the number of alcoholic beverages was entered into the second block. For prediction of the Sensorimotor factor, race and education were entered into the first block, while the second block contained

the number of alcoholic drinks. The results remained the same as when the demographic variables were entered into the multiple regression analyses alone: race was a significant predictor of Attention/Executive Functioning and Memory; race and education were significant contributors to the Sensorimotor factor.

Inclusion of the control subjects in these analyses could have artifactually increased differences in race, because more control subjects were Caucasian, while a greater proportion of cocaine users were African-American. However, this possibility does not appear to account fully for the ethnic differences, since race remained a significant predictor of performance on the neuropsychological factors, even when only the cocaine users were included in the analyses.

The ethnic differences were examined also by splitting the participants into two groups according to race and reexamining findings that had been significant before correction for multiple analyses. Among African-Americans ($n = 43$), the number of alcoholic drinks contributed to the Attention/Executive Functioning factor, $R^2 = .11$, $F(1,42) = 5.21$, $p < .03$. Number of alcoholic drinks did not contribute to the Memory or Sensorimotor factors among African-Americans. When Caucasian subjects were considered separately ($n = 30$), the number of alcoholic drinks did not account for a significant proportion of variance of the Attention/Executive, Memory, or Sensorimotor factors. Larger numbers of subjects within each race are needed to evaluate this problem more fully.

The ethnic differences in substance use patterns were thought to contribute to the significant differences in neuropsychological performance.

African-Americans reported higher average consumption of alcoholic drinks during the month preceding the study than Caucasians (Number of drinks/month: African-American \underline{M} = 97.18, \underline{SD} = 131.74; Caucasian \underline{M} = 32.62, \underline{SD} = 65.51). African-American participants also reported using cocaine slightly more frequently than Caucasians (Days of cocaine use in the last month: African-Americans \underline{M} = 17.57, \underline{SD} = 8.59; Caucasians \underline{M} = 14.17, \underline{SD} = 12.34). Given the ethnic disparity in these substance use characteristics, the contribution of race was examined after first controlling for the amount of substance use.

Hierarchical multiple regression was conducted, controlling first for the number of days cocaine was used and the number of alcoholic drinks. Race was entered in the next block as an independent variable. The neuropsychological factors were the dependent variables. Race added a significant contribution to the prediction of the Attention/Executive Functioning, Memory, and Sensorimotor factors, beyond the significant variance associated with the number of alcoholic drinks found in the Attention/Executive and Sensorimotor factors.

Overall, there was no support for Hypothesis 2a, that the number of days cocaine was used would predict performance on each of the neuropsychological factors, Attention/Executive Functioning, Memory, Simple Motor, and Sensorimotor. Hypothesis 2b, that the number of alcoholic beverages would contribute to the prediction of performance on the Memory factor, appeared to be false as well. Instead, the frequency of recent alcohol use was related to the Attention and Sensorimotor factors.

Contrary to expectations (Hypothesis 2c), race was a significant predictor of performance on the Attention/Executive Functioning, Memory, and Sensorimotor factors. The ethnic disparity in substance use patterns did not appear to fully explain this difference in neuropsychological functioning, since race remained a significant predictor of performance on the Attention/Executive Functioning, Memory, and Sensorimotor factors, even after controlling for recent alcohol and cocaine use.

Hypotheses 2d and 2e: Duration of substance use and neuropsychological test performance. The relative contributions of reported years of cocaine and alcohol on neuropsychological functioning were examined in these analyses. An increasing number of years of cocaine was expected to be related to declining performance on all of the neuropsychological factors, Attention/Executive, Memory, Simple Motor, and Sensorimotor (Hypothesis 2e). A greater number of years of alcohol use was expected to explain additional variance in the prediction of poorer Memory (Hypothesis 2e).

Three independent variables, number of years of cocaine use, alcohol use, and their interaction were entered respectively into multiple regression analyses. Four analyses were conducted, each using one of the neuropsychological factors as a dependent variable. The number of years of alcohol use contributed to the Attention/Executive Functioning factor, $R^2 = .05$, $F(1,72) = 4.15$, $p < .05$. As hypothesized, an increasing number of years of cocaine use was related to poorer performance on the Memory factor, $R^2 = .05$, $F(1,72) = 3.99$, $p < .05$.

Years of cocaine use, years of alcohol use, and the interaction were not predictive of scores on the Simple Motor or Sensorimotor factors.

The potentially confounding variables identified in the last section (race and education) were examined in relationship to the number of years of cocaine and alcohol use. Race was controlled by entering this variable into the first block of hierarchical multiple regression. The number of years of alcohol use was entered as an independent variable into the second block. Years of alcohol use did not explain any additional variance in the Attention/Executive Functioning factor, beyond that associated with race, $R^2 = .19$, $F(1,72) = 16.94$, $p < .001$. Similarly, when race is first controlled before entering the number of years of cocaine use into hierarchical regression analysis, only race accounts for a significant proportion of the variance, $R^2 = .12$, $F(1,72) = 10.09$, $p < .002$.

Overall, the findings provided only partial support of Hypotheses 2d, that an increasing number of years of cocaine use would be associated with poorer performance on all of the neuropsychological factors, since it was associated only with memory. Hypothesis 2e, that escalating years of alcohol use would be related to worse performance on the Memory factor, appeared to be incorrect. Contrary to expectations, years of alcohol consumption was associated with attentional abilities. This result was consistent with the finding that the frequency of recent alcohol use was related to the Attention/Executive Functioning factor.

Hypothesis 3: Relationship Between Cerebral Blood Flow and Neuropsychological Test Performance

An increasing number of voxels indicating significant areas of cerebral hypoperfusion was expected to predict poorer performance on each of the neuropsychological factors, Attention/Executive Functioning, Memory, Simple Motor, and Sensorimotor (Hypothesis 3). Linear regression was utilized to assess the independent variable, number of voxels indicative of hypoperfusion. Four linear regression analyses were conducted, each with one of the neuropsychological factors as a dependent variable. Inspection of the distribution of the dependent variable and the residuals indicated that the assumptions of linear regression were adequately met.

The amount of hypoperfusion was a significant predictor of performance on the Simple Motor factor ($R^2 = .16$, $F(1,38) = 7.15$, $p = .01$). Severity of hypoperfusion was not significantly associated with the Attention/Executive Functioning, Memory, and Sensorimotor factors. Therefore, there was limited support of Hypothesis 3, that the amount of hypoperfusion would be significantly related to cognitive functioning.

Hypotheses 4a and 4b: Relationship Between Recent Substance Abuse and Cerebral Blood Flow Abnormalities

These hypotheses addressed the association between the frequency of cocaine/alcohol used in the last month and the severity of hypoperfusion. Data from cocaine users and normal controls who were imaged with SPECT were included in the analyses. The data were unsuitable for multiple regression

analyses, because the dependent variables were positively skewed and various transformations failed to adequately correct the sample distributions. Therefore, a nonparametric approach was assumed by dividing data from the participants into groups on the basis of the frequency of cocaine and alcohol use.

The severity of hypoperfusion was hypothesized to worsen with increasing number of days of cocaine use in the month preceding the study (Hypothesis 4a). Alcoholic beverages were expected to partially counteract the effects of cocaine, therefore, hypoperfusion was hypothesized to decrease as the number of alcoholic beverages in the last month increased (Hypothesis 4b). The 40 subjects were assigned to tertiles reflecting the number of days cocaine was used in the last month. The first tertile of subjects reported no cocaine use, since all subjects in this group were control subjects. The second tertile was referred to as Moderate Cocaine users, and the third was comprised of Heavy Cocaine users. Table 7 displays the substance use characteristics of each group.

Table 7
Substance Use Among Tertiles Based on Frequency of Cocaine Use

Group	n	Cocaine		Alcohol	
		<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>
No Cocaine	13	0 _{ab}	(0)	5.29	(4.91)
Moderate Cocaine	13	14.86 _{ac}	(4.04)	77.57	(143.54)
Heavy Cocaine	14	25.93 _{bc}	(2.40)	134.71	(159.44)

Note. Cocaine refers to number of days cocaine was used in the month preceding the study. Alcohol indicates the number of alcoholic beverages drunk within the same time period. Means with the same subscript indicate significant group differences ($p < .02$) calculated with Mann-Whitney U.

The participants were split into tertiles of alcohol use over the last month, as well. Substance use characteristics of the three groups (Low Alcohol, Moderate Alcohol, Heavy Alcohol) are presented in Table 8.

Table 8
Substance Use Among Tertiles Based on Frequency of Alcohol Use

Group	n	Alcohol		Cocaine	
		<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>
Low Alcohol	15	.87 _a	(.83)	11.53 _b	(10.68)
Moderate Alcohol	12	12.38 _a	(9.19)	7.23 _c	(10.81)
Heavy Alcohol	13	205.14 _a	(162.94)	21.71 _{bc}	(6.29)

Note. Alcohol indicates the number of alcoholic beverages drunk within the last month. Cocaine refers to number of days cocaine was used in the last month. Means with the same subscript indicate significant group differences ($p < .02$) calculated with Mann-Whitney U.

A Kruskal-Wallis one-way ANOVA by ranks revealed a significant difference in hypoperfusion among the tertiles of recent cocaine use, $\chi^2 (2) = 7.62, p = .02$. Follow up comparisons with Mann-Whitney U tests showed that both the Moderate (U = 44.50, $p < .04$) and Heavy Cocaine (U = 39.50, $p = .01$) groups had significantly more hypoperfusion than the No Cocaine group. Findings were nonsignificant for differences between the Moderate and Heavy Cocaine groups. The results supported Hypothesis 4a, that the severity of hypoperfusion worsens as the mean frequency of cocaine use increases. Table 9 displays the mean hypoperfusion by groups based on the amount of cocaine used in the month preceding the study.

Table 9
Hypoperfusion by Groups Based on Frequency of Cocaine Use

Group	n	Hypoperfusion	
		<u>M</u>	<u>SD</u>
No Cocaine	13	109.15 _{ab}	284.43
Moderate Cocaine	13	332.23 _b	456.45
Heavy Cocaine	14	690.50 _a	920.33

Note. Amount of hypoperfusion was determined by the number of pixels indicating significantly lower global perfusion at $p < .001$. Means with the same subscript differ at $p < .04$ using Mann-Whitney U.

Severity of hypoperfusion was hypothesized to decrease as the number of alcoholic beverages in the last month increased (Hypothesis 4b). Group differences in hypoperfusion were apparent among the tertiles of alcohol use, Kruskal-Wallis: $\chi^2(2) = 7.66, p = .02$. Post hoc Mann-Whitney U analyses indicated that the Moderate Alcohol group had significantly less hypoperfusion than both the Low (U = 43.00, $p = .02$) and the Heavy Alcohol groups (U = 33.00, $p = .01$). Thus, it appeared that a moderate level of alcohol consumption in this sample was associated with reductions in hypoperfusion, partially supporting Hypothesis 4b. Table 10 presents the severity of hypoperfusion among each of the groups based on alcohol use in the month preceding the study.

The three groups based on recent alcohol use were comprised of both cocaine users and control subjects. The cocaine users and control subjects were separated to examine the possibility of different group patterns of hypoperfusion

Table 10
Hypoperfusion by Groups Based on Number of Alcoholic Beverages in the Last Month

Group	n	Hypoperfusion	
		<u>M</u>	<u>SD</u>
Low Alcohol	15	550.80 _a	828.67
Moderate Alcohol	12	180.33 _{ab}	533.63
Heavy Alcohol	13	383.00 _b	512.57

Note. Amount of hypoperfusion was determined by the number of pixels indicating significantly lower global perfusion at $p < .001$. Means with the same subscript differ at $p < .03$.

in response to varying levels of alcohol consumption. Group sizes were insufficient to conduct statistical analyses. Table 11 presents separate mean levels of hypoperfusion for the cocaine users and controls by tertile of recent alcohol use.

Table 11
Hypoperfusion by Groups Based on Alcoholic Beverages in the Last Month

Group	Cocaine Users			Controls		
	<u>n</u>	<u>M</u>	<u>SD</u>	<u>n</u>	<u>M</u>	<u>SD</u>
Low Alcohol	9	776.00	(976.72)	6	213.00	(410.10)
Moderate Alcohol	5	404.60	(820.29)	7	20.14	(40.34)
Heavy Alcohol	13	383.00	(512.57)	0		

Note. Amount of hypoperfusion was determined by the number of pixels indicating significantly lower global perfusion at $p < .001$.

Inspection of the group means for both cocaine users and controls suggested that severity of hypoperfusion declines with increasing alcohol consumption.

Studies with greater numbers of subjects are needed to statistically examine this possibility.

As anticipated, the severity of hypoperfusion worsened with increasing numbers of days of cocaine use (Hypothesis 4a). Alcoholic beverages were expected to ameliorate the severity of hypoperfusion. The results provide some support of Hypothesis 4b, that hypoperfusion decreases as the number of alcoholic drinks increases. Moderate alcohol use was associated with less hypoperfusion than low alcohol use. Reductions in hypoperfusion as alcohol increased were more apparent when the cocaine users and controls were separated. However, dividing the cocaine users and the controls yielded groups that could not be statistically analyzed due to the small number of subjects within some cells. Inspection of group means suggests that hypoperfusion continues to decline as the alcohol level increases from a moderate level to a heavy level. Studies with larger numbers of participants are needed to determine whether this finding is statistically significant.

Hypotheses 4c and 4d: Relationship Between the Duration of Substance Abuse and Abnormalities in Cerebral Blood Flow

This group of hypotheses investigated the association between the number of years of cocaine/alcohol use and the severity of hypoperfusion. The assumptions of multiple regression were not met, therefore, nonparametric statistics were utilized. The 40 subjects were assigned to tertiles on the basis of the reported number of years cocaine was used. The first tertile of subjects, Low Years Cocaine, was comprised of the control subjects and seven cocaine users

with a relatively short history of cocaine use. The second tertile was labeled Several Years Cocaine, and the third tertile was called Many Years Cocaine. Table 12 displays the substance use characteristics of each group.

Table 12
Substance Use Characteristics Among Tertiles Based on Years of Cocaine Use

Group	n	Cocaine		Alcohol	
		<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>
Low Cocaine	20	1.19 _a	(2.01)	12.45 _b	(8.85)
Several Years	12	9.88 _a	(1.72)	16.56	(7.02)
Many Years	8	17.88 _a	(1.20)	19.97 _b	(9.05)

Note. Cocaine refers to the reported number of years of cocaine use. Alcohol indicates the number of years of alcohol use. Means with the same subscript differ at $p < .04$ using Mann-Whitney U.

The participants were split also into tertiles of years of alcohol use (Low Years Alcohol, Medium Years of Alcohol, High Years of Alcohol). Substance use characteristics of the three groups are presented in Table 13.

Hypotheses 4c and 4d: Years of substance use and hypoperfusion. The severity of hypoperfusion was hypothesized to worsen as the number of years of cocaine use increased (Hypothesis 4c). An escalating number of years of alcohol use was expected to be negatively associated with hypoperfusion (Hypothesis 4d). Kruskal-Wallis did not reveal significant differences in hypoperfusion among the tertiles of years cocaine use. Contrary to Hypothesis 4c, hypoperfusion did not worsen steadily as the years of cocaine use increased. Table 14 presents the mean number of pixels indicating hypoperfusion by groups based on the number of years cocaine was used.

Table 13
Substance Use Characteristics Among Tertiles of Years of Alcohol Use

Group	n	Alcohol		Cocaine	
		<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>
Low Years	13	4.73 _a	(5.10)	5.20	(6.27)
Medium Years	13	16.44 _a	(1.50)	6.88	(6.11)
High Years	14	23.73 _a	(3.44)	9.16	(7.90)

Note. Alcohol indicates the number of years of alcohol use. Cocaine refers to the reported number of years of cocaine use. Means with the same subscript differ at $p < .001$ using Mann-Whitney U.

Table 14
Hypoperfusion by Groups Based on Number of Years of Cocaine Use

Group	n	Hypoperfusion	
		<u>M</u>	<u>SD</u>
Low Years	20	247.45	(477.20)
Several Years	12	627.92	(929.69)
Many Years	8	365.12	(519.61)

Note. Amount of hypoperfusion was determined by the number of pixels indicating significantly lower global perfusion at $p < .001$.

Hypoperfusion was hypothesized to decrease as the number of years of alcohol use increased (Hypothesis 4d). Significant differences were not found with Kruskal-Wallis tests in the amount of hypoperfusion among the groups based on years of alcohol use. Therefore, Hypothesis 4d was not supported by the results. Table 15 displays the mean number of pixels indicating hypoperfusion by each of the three groups based on years of alcohol use.

Table 15
Hypoperfusion by Groups Based on Number of Years of Alcohol Use

Group	n	Hypoperfusion	
		<u>M</u>	<u>SD</u>
Low Years	13	456.23	(747.68)
Medium Years	13	455.23	(759.56)
High Years	14	254.00	(465.10)

Note. Amount of hypoperfusion was determined by the number of pixels indicating significantly lower global perfusion at $p < .001$.

Cocaine users were separated from the control subjects to evaluate whether they showed different patterns of hypoperfusion in relation to years of alcohol use. Examination of the means suggests that among cocaine users, hypoperfusion does decrease as the number of years of alcohol use increases. This observation was not subjected to statistical analysis due to the small group sizes. The control subjects demonstrated the inverse pattern, with increases in hypoperfusion as the number of years of alcohol increased. Table 16 shows the mean number of pixels indicating hypoperfusion with cocaine users and controls presented separately.

Hypothesis 4c, that hypoperfusion would increase as the number of years of cocaine use escalated, was not supported by the results. In fact, the group with many years of cocaine use actually demonstrated less hypoperfusion than the group with several years of cocaine use. Contrary to expectations, hypoperfusion did not decrease as the number of years of alcohol use

progressed. Therefore, there was no evidence that Hypothesis 4d was correct either.

Table 16
Hypoperfusion by Groups Based on Years of Alcohol Use

Group	Cocaine Users			Controls		
	<u>n</u>	<u>M</u>	<u>SD</u>	<u>n</u>	<u>M</u>	<u>SD</u>
Low Years	8	737.63	(850.26)	5	6.00	(13.42)
Medium Years	10	581.10	(831.93)	3	35.67	(61.78)
High Years	9	252.67	(503.42)	5	256.40	(442.91)

Note. Amount of hypoperfusion was determined by the number of pixels indicating significantly lower global perfusion at $p < .001$.

The groups based on years of alcohol use originally combined the cocaine users and controls due to the small sample size. The cocaine users and controls were separated and the patterns of hypoperfusion were examined across the years of alcohol use. This informal inspection suggested the possibility of a different pattern of hypoperfusion among the groups, with less hypoperfusion being found as the number of years of alcohol consumption increased among the cocaine users, and increasing hypoperfusion as the years of alcohol use extended among the control subjects. Thus, studies with larger sample sizes are needed to evaluate this possibility more fully.

Summary of the Results

Hypothesis 1 stated that there would be significant differences between the cocaine users and the control group on the neuropsychological factors, Attention/Executive Functioning, Memory, Simple Motor, and Sensorimotor.

There was a significant overall difference among the four factors between the cocaine users and the control subjects. Follow up analyses indicated that there were significant group differences on the Sensorimotor and Memory factors. Therefore, Hypothesis 1 was partially supported by the results. Significant racial differences were noted on the Attention/Executive Functioning, Memory, and Sensorimotor factors, with Caucasians performing better on each factor.

Greater frequency of recent cocaine use was expected to predict poorer performance on each of the neuropsychological factors (Hypotheses 2a). The results of multiple regression analyses provided no evidence for this hypothesis. The amount of recent alcohol use was anticipated to predict performance on the Memory factor. The results were not supportive of this conclusion, but did unexpectedly indicate a relationship between increasing amounts of recent alcohol and poorer performance on the Attention/Executive Functioning and Sensorimotor factors. As with the first analysis, Race was a potent predictor of performance on the Attention/Executive Functioning, Memory, and Sensorimotor factors. Therefore, Hypothesis 2c, that race would not predict performance on the neuropsychological factors was false.

Analyses related to Hypothesis 2d and 2e examined the relationship between the duration of cocaine/alcohol use and current neuropsychological functioning. An increasing number of years of cocaine use was expected to predict worse performance on all the neuropsychological factors, while more years of alcohol use was anticipated to predict worse performance on the

Memory factor. Consistent with the findings of recent substance use, the number of years of alcohol use was significantly related to the Attention/Executive Functioning factor. The number of years of cocaine use contributed to prediction of the Memory factor. Therefore, Hypotheses 2d and 2e were partially supported by the results.

The amount of hypoperfusion was expected to predict variance related to the four neuropsychological factors (Hypothesis 3). Instead, increasing severity of hypoperfusion contributed to the prediction of poorer performance only on the Simple Motor factor. Therefore, there was limited support of Hypothesis 3.

Hypotheses 4a and 4b examined the relationships between recent substance abuse and severity of hypoperfusion. Hypoperfusion worsened as the frequency of recent cocaine use increased, thereby, providing some support for Hypothesis 4a. Hypothesis 4b, that higher levels of alcohol would be associated with less severe hypoperfusion, was partially supported by the results. Participants who drank the fewest alcoholic beverages had the greatest amount of hypoperfusion.

Recent substance use appeared to be more relevant to the degree of hypoperfusion than the duration of use. Hypotheses 4c and 4d were not supported by the results since significant differences in hypoperfusion were not found among groups based on the number of years of cocaine use or alcohol use. Separation of cocaine users and control subjects suggested that they may

exhibit different patterns of hypoperfusion, with only cocaine users demonstrating less hypoperfusion as the years of alcohol increases.

DISCUSSION

The purpose of the present study was to investigate the relationships between the severity of cocaine/alcohol use, neuropsychological functioning, and cerebral hypoperfusion. Several studies have demonstrated cognitive deficits among cocaine abusers, including diminished attention, verbal memory, language, executive functioning, and motor speed (Ardila, Rosselli, & Strumwasser, 1991; Hoff et al., 1996; Horner, 1997). The effects of cocaine use were assumed to be the cause of the cognitive deficits. However, a large proportion of cocaine users have been found to frequently use alcohol in addition to cocaine, which could be contributing to reductions in neuropsychological performance (Selby, & Azrin, 1998). The current study evaluated the significance of possible predictors of neuropsychological functioning, including use of cocaine, alcohol, cannabis, and other potentially confounding variables.

The present study also evaluated the conclusion that hypoperfusion is associated with cognitive decline. There is some evidence to suggest that this is the case, since patients with various types of dementia have been found to have cerebral hypoperfusion (Boone et al., 1999; Celsis, Agniel, Puel, & Rascol, 1987; Starkstein et al., 1997). Studies incorporating measurement of cerebral hypoperfusion and neuropsychological functioning among cocaine abusers have generally done so by qualitative description of perfusion deficits. The present study utilized an objective quantitative approach toward the evaluation of

cerebral blood flow abnormalities and neuropsychological functioning in cocaine users.

Neuropsychological Test Performance of Cocaine Users and Control Subjects

A significant difference was found between the cocaine users and controls across the four neuropsychological factors: Attention/Executive Functioning, Memory, Simple Motor, and Sensorimotor. Follow up analyses indicated that the cocaine users performed worse than controls on the Memory and Sensorimotor factors. Therefore, the results provided some evidence for the hypothesis that cocaine users would perform more poorly than controls on the neuropsychological factors. These findings were consistent with those of some previous studies showing cognitive deficits in cocaine abusers, including verbal memory and motor functioning (Hoff et al., 1996; Horner, 1997; Smelson et al., 1999).

Predictors of Neuropsychological Test Performance

Recent substance use and neuropsychological performance. The frequency of recent cocaine use was expected to be significantly related to poorer performance on each of the neuropsychological factors, Attention/Executive Functioning, Memory, Simple Motor, and Sensorimotor. Increasing use of alcoholic beverages in the month before the study was expected to be associated with only the Memory factor. Neither of these hypotheses was supported by the results. The frequency of recent cocaine use was not significantly related to any of the neuropsychological factors. Recent

alcohol use was found to contribute to the Attention/Executive Functioning and Sensorimotor factors. Thus, the results suggested that the frequency of recent alcohol use, rather than cocaine, was related to cognitive decline in this sample of cocaine users. Therefore, the assumptions that deficits in attention/sensorimotor functioning among cocaine-dependent patients are due to cocaine use or a combination of both, appear to be fallacious.

Alternatively, perhaps the measure of alcohol consumption, reported number of drinks in the month preceding the study, was a more accurate representation of substance use than the less specific measure of cocaine use, number of days cocaine was used in the last month. Days of cocaine use was utilized instead of the reported dollar value of cocaine, since the latter value was thought to be more susceptible to extraneous factors including whether or not the individual sold cocaine, obtained cocaine by other than monetary means, or variability due to price differences.

Examination of potentially confounding variables. The relationship between neuropsychological functioning and extraneous variables was examined. Demographic variables (race, education, and sex) and other substances (heroin and cannabis) were evaluated for their predictive value. Since heroin use was very infrequent in this sample of cocaine users, it was not expected to be related to the neuropsychological factors. Only education was anticipated to contribute to the Attention/Executive Functioning and Memory factors.

Ethnicity predicted a significant proportion of the variance attributed to three of the neuropsychological factors, Attention/Executive Functioning, Memory, and Sensorimotor. Caucasian race was associated with better performance on each factor. Though ethnic differences have been found on measures of intelligence (Vincent, 1991), studies examining racial differences on tasks involving memory suggested that performance would be comparable on these measures (Fillenbaum, Huber, & Taussig, 1997; Fillenbaum et al., 1998).

Neuropsychological performance was examined separately for African-Americans and Caucasians. Within each race, the cocaine users generally performed worse than the controls. The number of alcoholic drinks was related significantly to the Attention/Executive Functioning factor only among African-Americans. Poorer performance by African-Americans on the Attention/Executive Functioning, Memory, and Sensorimotor factors did not appear to be related to differences in educational level, since this variable was comparable among the groups. However, there were ethnic differences in substance use patterns. African-Americans smoked cocaine slightly more frequently and drank more alcoholic beverages than Caucasians. The ethnic differences in amount of substance use did not appear to fully explain why African-Americans performed worse on some of the factors, since the differences persisted even after controlling for the number of alcoholic beverages and days of cocaine use.

Duration of substance use and neuropsychological test performance. The number of years of cocaine use was expected to predict performance on each of

the neuropsychological factors, whereas, the years of alcohol use was anticipated to predict performance on only the Memory factor, beyond the contribution of years of cocaine. Contrary to expectations, the number of years of alcohol use contributed to the Attention/Executive Functioning factor, which was consistent with the finding that recent alcohol use (number of alcoholic beverages/month) was related to the same factor. Significant findings suggested that the long-term effects of cocaine abuse may be more relevant to memory functioning than years of alcohol abuse. This result was consistent with those of Horner's (1997) study demonstrating greater verbal memory deficits in chronic cocaine/alcohol abusers than among patients who abused only alcohol.

Relationship Between Cerebral Blood Flow and Neuropsychological Test Performance

Severity of hypoperfusion was expected to predict poorer neuropsychological functioning. Hypoperfusion provided a significant contribution only to the Simple Motor factor, providing limited support for the assumption that hypoperfusion results in a decline in cognitive functioning. The finding that the Simple Motor factor was related to hypoperfusion was consistent with Robinson et al. (1999) who found that the most distinct difference between cocaine users and controls was on the tests included in the Simple Motor factor.

Prior to running the analyses, the Simple Motor factor was suspected to be the least likely of the neuropsychological factors to be significantly predicted by hypoperfusion, since attention and memory tend to be more susceptible to cognitive decline in general. Perhaps the severity of hypoperfusion was not

predictive of the other neuropsychological factors, due to the use of global measurement of perfusion abnormalities. It is possible that regional analyses involving more circumscribed brain areas (e.g., frontal lobes) would reveal significant differences in neuropsychological factors related to hypoperfusion.

Alternatively, perhaps the severity of hypoperfusion was significantly associated with the Simple Motor factor, because the performance of the tasks loading on that factor is partially reliant on a portion of the brain that is in close proximity to dopaminergic cell bodies. Dopaminergic cell bodies in the substantia nigra project to the caudate and putamen. These areas of the brain receive a greater concentration of cocaine, and subsequently sustain greater vasoconstriction and hypoperfusion, possibly resulting in greater decline.

Relationship Between Substance Use and Cerebral Blood Flow Abnormalities

Recent substance use and hypoperfusion. Several studies have shown significantly more hypoperfusion among cocaine users (Holman et al., 1993; Strickland, et al., 1998). However, the results of studies examining the effects of alcohol abuse on cerebral blood flow are contradictory in that there seem to be short-term increases in perfusion, but long-term decreases in perfusion (Gansler, 2000). The current results supported the hypothesis that the severity of hypoperfusion increases as the frequency of cocaine use ascends. As the amount of alcoholic beverages increased, hypoperfusion was expected to decrease, due to the vasodilatory effects of alcohol. This hypothesis was partially supported. Moderate alcohol users did show significantly less

hypoperfusion than less frequent users of alcohol. The cocaine users were subsequently separated from the controls to determine whether different patterns of hypoperfusion were evident as alcohol use increased. Though the results could not be analyzed statistically due to the small group sizes, inspection of mean levels among both groups suggested that hypoperfusion decreases as the number of alcoholic beverages increases. Larger numbers of subjects are needed to evaluate these patterns of hypoperfusion more thoroughly. This finding was consistent with Robinson et al. (1999) who showed that cocaine users performed worse on measures of motor functioning than cocaine users who also abused alcohol.

Duration of substance use and hypoperfusion. Increasing years of cocaine use was expected to be associated with greater hypoperfusion, and more years of alcohol consumption were anticipated to be related to reductions in hypoperfusion. The results provided no evidence of these hypotheses. Thus, it appears that the frequency of recent substance use may be more relevant to hypoperfusion than the duration of use. Separation of cocaine users and control subjects suggested that they may exhibit different patterns of hypoperfusion, with only cocaine users demonstrating less hypoperfusion as the years of alcohol increased. These findings emphasize the need to separate groups based on drug status before examining perfusion patterns, if sample sizes permit doing so.

Limitations of the Study

The interpretation of some findings was complicated by the significant differences in the racial distribution between the normal controls and cocaine users. This difficulty highlights the need for experimental control of racial distributions and other demographic variables between groups. The sample size of this study prohibited adequate evaluation of statistical control for race in some cases. The interpretation was further obfuscated by ethnic differences in substance abuse.

Another limitation of this study is the lack of assessment of alternative explanations for reduced cognitive functioning involving symptoms of depression, anxiety, and poor motivation. However, the cocaine user group actually performed slightly better than controls on a subtest (Digit Span) that can be sensitive to psychological distress and/or poor effort, suggesting that the cocaine user group may not have been unduly influenced by emotional or motivational variables (Lezak, 1983).

When speculating about the possible reasons why findings were or were not significant, it is necessary to first assume that the measures used to assess substance consumption, neuropsychological functioning, and cerebral blood flow accurately reflect the intended variables. Given the limited reliability of these measures, particularly in the instance of self-report of substance use, these assumptions may not be valid. Self-report measures are subject to error due to a social desirability response pattern (e.g., minimization of use) and to error

related to faulty recall. The combination of these difficulties creates noise among the data that may increase the likelihood of Type 2 error. It is possible that perfect accuracy among the self-report measures would reveal more significant findings than those reported in this study.

There is the assumption that the damaging aspect of cocaine is the drug and its metabolites. However, cocaine is often cut with other chemicals, which may be more harmful and could possibly account for neuropsychological deficits and perfusion abnormalities.

Conclusions

This sample of cocaine users demonstrated significant differences from a group of control subjects on measures of learning/memory and sensorimotor functioning. The magnitude of the differences was suggestive of relatively mild declines in functioning on these factors. It is possible that continued cocaine and alcohol abuse would result in more substantial declines, and that the inclusion of patients with relatively short histories of cocaine abuse obscured significant group differences on the attention and simple motor factors as well.

Ethnic differences were noted on measures involving attention/executive functioning, memory, and sensorimotor functioning, with African-Americans performing worse on each of the measures. The reason for this does not appear to be fully explained by the tendency for African-Americans to use more alcohol and cocaine, since the ethnic differences in cognitive performance persisted after controlling for differences in substance use. Differences in socioeconomic level

were not explored in this study, but perhaps this would help to explain the ethnic differences.

The study showed a consistent relationship between alcohol consumed and attention/executive functioning. Given the large contribution of dopaminergic pathways in the frontal lobes, an area of the brain associated with attention, it was expected that cocaine would have the greatest contribution to attention. It is possible that the trend for alcohol to be related to attention/executive functioning was due to the presence of the earliest stages of frontal atrophy. Ritchie and Schindler (1990) found that chronic alcoholics have frontal atrophy that was associated with the duration of abuse.

The significant relationship between frequency/duration of alcohol and attention suggests that previous studies showing attentional deficits in cocaine abusers may actually be related to concomitant alcohol use, rather than to the cocaine as had been assumed. These findings offer a possible explanation why previous studies of cocaine abusers have reported attention deficits inconsistently, since the amount of alcohol used among the cocaine users was variable from study to study. The results of this study suggested that reductions in memory are specifically related to the duration of cocaine use, rather than to alcohol use or a combination of the two substances. This was consistent with verbal memory deficits being one of the more reliable findings in studies of cocaine users.

Though there were significant reductions in memory and sensorimotor functioning in this sample of cocaine abusers, the only neuropsychological function associated with cerebral hypoperfusion was the Simple Motor factor. Therefore, there is limited support for the conclusion that hypoperfusion affects cognitive functioning. The lack of significant findings in regards to hypoperfusion and the other neuropsychological factors may be related to the global measurement of cerebral blood flow. It is possible that regional analysis of circumscribed brain regions would reveal significant differences in hypoperfusion among other neuropsychological factors. Further evaluation of regional areas of quantifiable hypoperfusion is needed to determine the impact of reductions in cerebral blood flow on measures of memory, attention, and sensorimotor performance.

There is a need for prospective studies of cocaine abusers to help correct for difficulties with recall of amount of substance abuse as well as to ascertain that their neuropsychological functioning represents a decline and not a premorbid level of ability. For example, cocaine users have been found to have an increased incidence of symptoms associated with a history of Attention-Deficit Hyperactivity Disorder (DSM-IV, 1994). A longitudinal design would not only control for demographic variables, but allow for stronger inferences about cognitive decline.

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VITA

Karen Ann Tucker obtained the degree of Bachelor of Arts at University of Louisville in 1987 and the degree of Master of Science from University of Memphis in 1995. She was accepted into the doctoral clinical psychology program at Louisiana State University in 1996. Karen completed her internship year at the West Haven Veterans Administration Hospital in Connecticut. She recently began a National Research Service Award postdoctoral fellowship at Yale University School of Medicine.