Reduced Frontal White Matter Integrity in Cocaine Dependence: A Controlled Diffusion Tensor Imaging Study

Kelvin O. Lim, Steven J. Choi, Nunzio Pomara, Adam Wolkin, and John P. Rotrosen

Background: *In vivo magnetic resonance studies have found that cocaine dependence is associated with T2 signal hyperintensities and metabolite abnormalities in cerebral white matter (WM). Functional neuroimaging studies have suggested that chronic cocaine use is primarily associated with frontal lobe deficits in regional cerebral blood flow and brain glucose metabolism levels; however, the effects of cocaine dependence, if any, on frontal WM microstructure are unknown. Thus, we sought to examine the effects of cocaine dependence on frontal WM integrity.*

Methods: *Diffusion tensor imaging was employed to examine the WM integrity of frontal regions at four levels: 10 mm above, 5 mm above, 0 mm above, and 5 mm below the anterior commissure–posterior commissure (AC-PC) plane. The fractional anisotropy (FA) of 12 cocaine-dependent patients and 13 age-similar control subjects was compared.*

Results: *The cocaine-dependent patients had significantly reduced FA in the frontal WM at the AC-PC plane and a trend toward reduced FA at 5 mm below the AC-PC plane, suggestive of reduced WM integrity in these regions.*

Conclusions: *These findings were consistent with the hypothesis that cocaine dependence involves alterations in orbitofrontal connectivity, which may be involved in the decision-making deficits seen in this disorder.* Biol Psychiatry 2002;51:890–895 © *2002 Society of Biological Psychiatry*

Key Words: Cocaine dependence, diffusion tensor imaging, white matter integrity, frontal lobes, fractional anisotropy, magnetic resonance imaging

Introduction

Evidence from magnetic resonance studies suggests that cerebral white matter (WM) may be vulnerable to the deleterious effects of cocaine and its metabolites. Focal WM T2 signal hyperintensities (HIs) have been reported in an early magnetic resonance imaging (MRI) case study of cocaine abusers, suggestive of WM pathology (Volkow et al 1988b). This finding has been confirmed among asymptomatic cocaine abusers, in which WMHIs were found to be relatively common in the cerebral and subinsular regions but not in the subcortical gray matter (thalamus and basal ganglia) (Bartzokis et al 1999). Proton spectroscopy studies of cocaine users abstinent for several months have shown reduced N-acetyl aspartate (NAA) (Chang et al 1999; Meyerhoff et al 1999) and increased myoinositol (Chang et al 1999) in WM, suggestive of neuronal/axonal damage and reactive glial hypertrophy or proliferation, respectively. In one of these studies, higher choline-containing compounds have been found in the frontal WM region (Meyerhoff et al 1999), suggesting that the cytoskeletal membrane of frontal WM may also be altered. It is unknown, however, whether microstructural abnormalities are present in WM among patients with cocaine dependence.

Functional neuroimaging and neuropsychological studies suggest that anterior brain structures may be susceptible to the effects of cocaine. Reduced relative cerebral blood flow (Volkow et al 1988a) and brain glucose metabolism levels (Volkow et al 1992) primarily in the frontal cortex have been reported in cocaine-dependent subjects. In neuropsychological studies, cocaine-dependent patients have been shown to exhibit deficits in abstracting and problem-solving abilities, among others (Beatty et al 1995; O'Malley et al 1992), the severity of which has been linked to greater use of cocaine (grams per week) (Bolla et al 1999). These impairments involve executive control processes, thought to be mediated by the prefrontal cortex (Hartley and Speer 2000).

Although existing structural neuroimaging studies suggest an absence of widespread cortical atrophy in cocaine

From the Nathan S. Kline Institute for Psychiatric Research (KOL, SJC, NP), Orangeburg, New York, University of Minnesota Medical School (KOL, SJC), Minneapolis, Minnesota; Department of Psychiatry, New York University (KOL, NP, AW, JPR), New York, New York; and the VA New York Harbor Health System (AW, JPR), New York, New York.

Address reprint requests to Kelvin O. Lim, M.D., Professor of Psychiatry, The University of Minnesota Medical School, 2450 Riverside Avenue, F282/2A West, Minneapolis MN 55454-1495.

Received July 31, 2001; revised November 5, 2001; accepted November 16, 2001.

0006-3223/02/$22.00
PII S0006-3223(01)01355-5

dependence (Bartzokis et al 2000; Jacobsen et al 2001b; Liu et al 1998; Pascual-Leone et al 1991), the question of whether cocaine is associated with deleterious effects in specific brain regions remains unanswered. A preliminary report from an ongoing MRI study (Langendorf et al 1996) is the only one to suggest widespread cortical atrophy, and these findings have yet to be replicated. Using linear planimetric computed tomography (CT) measurements, which may be less reliable than MRI volumetric measures, Pascual-Leone et al (1991) found an association between cocaine use and ventricular enlargement. In examining specific brain regions using MRI, some have found frontal gray matter atrophy but no temporal lobe atrophy (Liu et al 1998), whereas others found the opposite pattern of reduced temporal gray matter volume but no frontal volumetric abnormalities (Bartzokis et al 2000). Interestingly, subsequent controlled MRI studies of subcortical gray matter also found no volumetric abnormalities in the hippocampus or amygdala (Jacobsen et al 2001b), although *increased* putamen volume has been strongly associated with chronic cocaine dependence (Jacobsen et al 2001a). The variability in the findings may be due to methodological differences across studies. It is also possible that these MRI methods may lack the sensitivity to detect more subtle brain abnormalities associated with cocaine, especially in WM. Moreover, although cocaine dependence has been associated with the presence of WMHIs, WMHIs are usually found in multiple locations and may not be a specific and sensitive enough tool for identifying subtle abnormalities in frontal WM.

Diffusion tensor imaging (DTI) (Basser et al 1994) is an MRI technique that enables quantification of microstructural WM abnormalities in vivo using scalar measures of DTI, such as fractional anisotropy (Basser 1995). The sensitivity of DTI in detecting subtle WM alterations has been supported by studies of human immunodeficiency virus (HIV)-1 (Pomara et al 2001), schizophrenia (Lim et al 1999), Alzheimer's disease (Rose et al 2000), ischemic leukoaraiosis (Jones et al 1999), multiple sclerosis (Werring et al 1999), and normal aging (Klingberg et al 1999; Pfefferbaum et al 2000; Virta et al 1999).

With DTI, we sought to examine the effects of cocaine dependence on WM integrity in different levels of the frontal lobes. Using the same methods, we also explored the WM integrity in the temporal lobes, as well as the genu and splenium of the corpus callosum, to determine if cocaine affects WM in these nonfrontal regions.

Methods and Materials

Subjects

Cocaine-dependent volunteers were recruited through the mental health research program at the Department of Veterans Affairs (VA) New York Harbor Healthcare System from among participants in prior cocaine treatment studies and in addiction treatment programs. Inclusion criteria were as follows: 1) DSM-IV diagnosis of cocaine dependence within the past 6 months, based on the Structured Clinical Interview for DSM IV; 2) minimum of 6 months of self-reported continued cocaine use (intravenous, smoked crack cocaine, or both); 3) urine sample positive for benzoylecgonine within 6 months of entry; 4) ability to provide written informed consent and to comply with study procedures; and 5) men aged 18–59 years (the restriction to men was intended to eliminate potential gender-related variance in this pilot study). Potential cocaine-dependent subjects were excluded if they had 1) lifetime DSM-IV diagnosis of alcohol dependence; 2) a history of active neurologic or serious psychiatric disorders, such as psychosis, bipolar illness, major depression, organic brain disease, or dementia that had required treatment at any point; 3) a history of significant cardiovascular disease; 4) uncontrolled hypertension; 5) claustrophobia; 6) any other contraindication for MRI; 7) HIV positive status; or 8) medical conditions likely to result in structural brain changes (e.g., stroke, transient ischemic attacks, hypertension, diabetes, head trauma resulting in loss of consciousness). None of the patients suffered from dependence to any other illicit substances, aside from cocaine. Given the high comorbidity rates of alcohol and drug abuse among this population, however, this preliminary study did not exclude cocaine-dependent individuals who also engaged in the abuse of other substances.

The healthy, nonpsychiatric subjects were recruited from the community. For these control subjects, the exclusion criteria were: 1) acute medical illness, history of non–HIV-related neurologic disease; 2) current DSM-IV Axis I diagnoses, including significant alcohol or substance abuse based on a structured or semi-structured clinical interview; 3) history of psychosis; 4) loss of consciousness greater than 30 min or any loss of consciousness with neurologic sequelae; 5) claustrophobia; and 6) any other contraindication for MRI. None of the control subjects had any history of major depression or obsessive-compulsive disorder. Two control subjects had a history of hypertension, which was well controlled with medications.

All volunteers provided written informed consent. These studies were approved by the Institutional Review Boards of the VA New York Harbor Healthcare System, the New York University School of Medicine, and the Nathan S. Kline Institute for Psychiatric Research. Volunteers who sought treatment were referred for treatment. Participation in this study did not preclude ongoing treatment.

The sample consisted of 12 cocaine-dependent patients (all men) and 13 healthy nonpsychiatric control subjects (3 women). The mean age (years $\pm$ SD) of patients (44.17 $\pm$ 5.09) and control subjects (40.36 $\pm$ 6.80) were similar ($p = .174$). For the patients, the average duration of cocaine use was 17.33 years (range: 9–30 years).

Diffusion Tensor Imaging

Diffusion tensor imaging (Basser et al 1994) is an MRI method that measures the self-diffusion of water molecules caused by Brownian motion. Without any barrier to its self-diffusion, water will diffuse

uniformly in all directions; this type of diffusion would be termed *isotropic*. With barriers to water diffusion (e.g., cell membranes or fibers as in WM tracts), diffusion would be greater along the axis of the fiber and reduced in the direction perpendicular to the axis of the fiber; this type of diffusion would be termed *anisotropic*. The displacement profile of anisotropic diffusion can be visualized as an ellipsoid shape with the long axis corresponding to the axis of the fiber direction and the minor axes corresponding to the diffusion perpendicular to the fiber. This ellipsoid has both a vector direction in three-dimensional space as well as a magnitude of the diffusion in each of the three axes. Scalar measures of the tensor, such as fractional anisotropy (FA), have been developed to assess the degree of anisotropy (Basser 1995). Fractional anisotropy provides information about the degree of fiber organization and integrity, such that tissue with highly regular fibers (e.g., corpus callosum) will be reflected in higher FA.

MR Image Acquisition

All MR images were acquired with a 1.5T Siemens Vision MR system (Erlangen, Germany) at the Center for Advanced Brain Imaging in the Nathan Kline Institute for Psychiatric Research. A localizer sequence was used to orient a three-dimensional MPRAGE (magnetization prepared rapid gradient echo) volumetric acquisition (repetition time [TR] = 11.6 msec, echo time [TE] = 4.9 msec, flip angle = 12 degrees, inversion time = 300 msec, delay time = 300 msec, 120 1.5-mm sagittal slices, field of view [FOV] = 24 cm, 192 × 256 matrix), from which the anterior commissure (AC) and the posterior commissure (PC) plane was identified. All subsequent sequences including DTI were aligned to the AC-PC plane.

The DTI data were acquired using a double echo pulsed gradient echo planar imaging method to reduce eddy current effects (TR = 6 sec, TE = 100 msec, FOV = 24 cm; 128 × 128 matrix reconstructed to 256 × 256, b = 1000 sec/mm^2, 6 noncollinear gradient orientations, 20 slices, number of excitations = 4, acquisition time = 2 min, 36 sec) (Heid unpublished data); the dual echo method greatly reduces eddy currents, obviating the need for postacquisition eddy current distortion correction. An acquisition with no diffusion gradients was collected (b = 0, 2 averages), followed by acquisitions where gradients (b = 1000, 4 averages) were applied in six noncollinear directions with the following pattern (Gx,Gy,Gz): [(1,1,0), (0,1,1), (1,0,1), (−1,1,0), (0, −1,1), (1,0, −1)].

Diffusion Tensor Processing

Before processing, the raw images were inspected for evidence of artifacts. From six apparent diffusion coefficient maps, the diffusion tensor was computed for each voxel, and the eigenvalues and eigenvectors were then determined. A scalar measure, FA, was computed from the tensor. Mean diffusivity (Trace/3) was also computed to assess the average degree of water diffusion in three dimensions.

Regions of Interest

The focus of this study is to compare the integrity of WM microstructure at different frontal regions between cocaine-dependent patients and control subjects. To avoid coregistration problems between different image acquisition methods, the regions of interest (ROIs) for the DTI-derived measures were placed on the anatomical T2-weighted image (b = 0) of the DTI data set. Using software developed at the Nathan S. Kline Institute in Interactive Data Language (Research Systems Inc, Boulder, CO), circular ROIs of standard sizes were placed bilaterally in the frontal WM of four consecutive, 5 mm thick slices: 10 mm above the AC-PC plane, 5 mm above the AC-PC plane, at the AC-PC plane, and 5 mm below the AC-PC plane. For the two superior-most slices (10 mm and 5 mm above AC-PC plane), ROIs were positioned in the WM anterior and lateral to the frontal horns of the lateral ventricles. For the two most inferior slices (0 mm and 5 mm below the AC-PC plane), ROIs were positioned in the WM anterior and medial to the Sylvian fissure. The placement of ROIs on the anatomical T2-weighted images and the processed FA maps is illustrated in Figure 1. To reduce the number of comparisons, the FA and diffusivity values were averaged across hemispheres for each frontal region, yielding one mean FA and diffusivity for each of the four frontal regions.

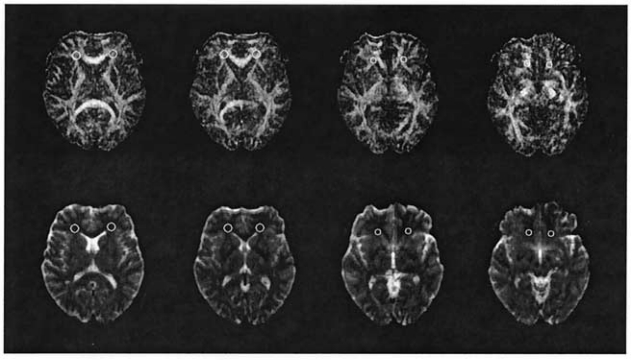

Figure 1. Region of interest placement on the fractional anisotropy maps (top) and on corresponding anatomical T2-weighted images (bottom) of the frontal white matter regions: **(A)** 10 mm above, **(B)** 5 mm above, **(C)** 0 mm below, **(D)** 5 mm below the AC-PC plane. AC-PC, anterior commissure–posterior commissure plane.

For exploratory analyses, additional ROIs were placed in the genu and splenium of the corpus callosum, as well as bilaterally in temporal WM adjacent to the hippocampus. Separate FA and mean diffusivity values were derived for the genu, splenium, and temporal WM (averaged across hemispheres).

Data Analysis

For the two dependent measures, FA and mean diffusivity, repeated measures analysis of variance (ANOVA) was performed separately with Group (patients vs. control subjects) as the between-subjects factor and Region (four frontal WM regions) as the within-subjects factor. If a significant Region × Group interaction or Group effect was present, appropriate follow-up pairwise comparisons were performed with two-tailed significance levels. Similar analysis procedures were employed to examine whether there were main effects of Group or an interaction between Group and Region (i.e., genu, splenium, and

Table 1. White Matter (WM) Fractional Anisotropy and Diffusivity Means ± SD by Group

DTI measures	ROI	Patients (n = 12)	Control subjects (n = 13)	Effect size (d)
Fractional anisotropy	Frontal WM[a]			
	10 mm above AC-PC	449.68 ± 81.99	468.65 ± 65.82	
	5 mm above AC-PC	519.64 ± 58.14	512.98 ± 58.81	
	0 mm below AC-PC	511.63 ± 46.41[c]	558.99 ± 55.58	−.921
	5 mm below AC-PC	406.36 ± 85.23[b]	480.91 ± 97.42	−.812
	Temporal WM	506.04 ± 71.41	515.56 ± 50.05	
	Genu	714.28 ± 53.02	725.05 ± 56.85	
	Splenium	851.35 ± 32.76	838.56 ± 50.40	
Mean diffusivity (trace/3)	Frontal WM			
	10 mm above AC-PC	396.99 ± 25.64	385.26 ± 26.15	
	5 mm above AC-PC	389.04 ± 23.38	381.59 ± 15.44	
	0 mm below AC-PC	382.06 ± 19.96	374.23 ± 12.31	
	5 mm below AC-PC	390.02 ± 21.90	376.28 ± 26.72	
	Temporal WM	412.19 ± 20.51	412.08 ± 12.96	
	Genu	444.28 ± 50.79	424.14 ± 28.51	
	Splenium	390.62 ± 36.27	380.14 ± 41.61	

DTI, diffusion tensor imaging; ROI, region of interest; AC-PC, anterior commissure–posterior commissure plane.
[a]Denotes a significant main effect of Group in the repeated measures analysis of variance.
[b]$p = .054$, two-tailed.
[c]$p < .050$, two-tailed.

temporal WM FA) on WM FA and mean diffusivity. Effect sizes (d) were calculated using pooled standard deviations. Alpha levels were set at .05 for all analyses.

Results

The means and standard deviations for the WM FA and mean diffusivity variables are presented in Table 1.

The repeated measures ANOVA for frontal WM FA yielded a significant effect of Group ($F = 4.394$, $p = .047$), but no significant interaction effect between Group and Region ($p = .175$). Follow-up analyses of the Group effect revealed that cocaine-dependent patients showed a significant reduction in frontal WM FA at the AC-PC plane ($t = 2.302$, $p = .031$) and a trend reduction in FA at 5 mm below AC-PC plane ($t = 2.029$, $p = .054$). There were no differences in FA between patients and control subjects at 5 mm above ($p = .828$) or 10 mm above ($p = .528$) the AC-PC plane.

The repeated measures ANOVA for mean diffusivity within the frontal WM showed no significant effect of Group ($p = .150$) or an interaction between Group and Region ($p = .876$).

For the exploratory analyses of WM FA in the three nonfrontal regions, there were no significant effects of Group ($p = .841$) or an interaction between Group and Region ($p = .686$). Similarly, no significant Group effect ($p = .222$) or interaction between Group and Region ($p = .575$) were found for mean diffusivity.

Discussion

The present study is the first to show that cocaine dependence may be associated with compromised WM microstructure in vivo. The disruption in WM integrity appears to be predominant in the inferior frontal brain regions rather than in superior frontal areas. On the contrary, no WM microstructural abnormalities were found in the temporal lobes or in the genu and splenium regions of the corpus callosum.

The findings of disrupted connectivity in the inferior frontal regions are consistent with several hypothesized anatomical circuits, suggesting a critical role for the orbitofrontal cortex in addiction-related phenomena such as drug craving, compulsive-repetitive behaviors, and maladaptive decision-making (Bechara et al 2000; Elliott et al 2000; Rolls 2000; Volkow and Fowler 2000). The orbitofrontal cortex is considered a heterogeneous region with connections to other prefrontal, visceromotor, and limbic regions, as well as to the association areas of each sensory modality (Elliott et al 2000; Ongur and Price 2000; Rolls 2000). Based on anatomy, it has been proposed that abnormalities in the anterior orbitofrontal region, with its connections to higher association areas, may contribute significantly to maladaptive decision-making processes (London et al 2000). Consistent with this suggested involvement of the orbitofrontal region, patients with bilateral lesions of the ventromedial prefrontal cortex have been found to demonstrate a propensity toward larger short-term gains without regard to future consequences (Bechara et al 2000). Similar findings have been reported among polysubstance drug abusers, who also showed a

preference for more immediate gains (Grant et al 2000). Although the functional significance of reduced inferior frontal WM integrity needs to be established in future studies, disruptions in WM connectivity in the inferior frontal region may contribute to the impaired decision-making processes evident in cocaine dependence.

Reduced WM FA among cocaine dependent patients may represent damage to axons and/or myelin, as well as possible reactive gliosis. The determination of the exact nature of the WM disruption associated with cocaine dependence, however, is beyond the scope of this study. Although the neurotoxic effects of cocaine and its metabolites (e.g., benzoylecgonine) may be responsible for these findings, the literature suggests that myelin changes may be the primary pathologic event, possibly stemming from chronic cocaine-induced hypoperfusion (Kaufman et al 1998). In animal models, chronic cerebral hypoperfusion resulted in the development of lesions specific to WM, resembling the leukoariosis seen in aged brain (Hattori et al 1992), as well as learning impairments in a passive avoidance paradigm (Kudo et al 1990). At the molecular level, chronic hypoperfusion leads to significant decreases in myelin basic protein, a marker for myelin, followed by reductions in neurofilament H, a marker of axons, as well as significant increases in glial fibrillary acidic protein, a marker of astroglia (Kurumatani et al 1998). These changes observed in the gerbil hypoperfusion model parallel the human in vivo spectroscopy WM findings in which NAA, a putative neuronal marker, is decreased and the glial marker myoinositol is increased. Most importantly, because the decrease in myelin basic protein was found to precede the decrease in neurofilament H, the change in myelin may be the initial pathologic event in frontal WM under chronic hypoperfusion, with axonal damage being secondary (Kurumatani et al 1998).

The findings of the present study are preliminary and should be interpreted with caution. The sample size in this study was relatively small, and the effects were of modest statistical significance. Replication using a larger sample is warranted. Increased susceptibility effects due to the sinuses are common in inferior axial slices in the frontal brain regions, and these effects can affect image intensity. Based on a visual assessment of susceptibility effects, we chose not to analyze image data more inferior than 5 mm below the AC-PC plane. Yet the possibility remains that susceptibility effects may still be present. As inferior frontal brain regions are becoming more important in the neuroanatomy of behavior, new methods will need to be developed to deal with this problem. In addition, given the relatively high rates of comorbidity between cocaine dependence and other substance abuse disorders, we focused on individuals for whom dependence on cocaine was the primary addiction, excluding individuals dependent on other substances. Although the findings may be more readily generalized to the average cocaine-dependent patient, the possibility that abuse of alcohol and drugs may also have contributed to reductions in frontal WM integrity in these patients cannot be dismissed.

An important limitation of this study is that the sample was restricted to male cocaine dependent patients. Gender differences in cocaine dependence have been reported with women showing less cerebral perfusion abnormalities on single photon emission computed tomography (Levin et al 1994), as well better treatment outcomes (Kosten et al 1993; Weiss et al 1997). In a single voxel proton spectroscopy study (Chang et al 1999), WM NAA/creatine ratio was reduced less in cocaine-dependent women compared with cocaine dependent men. These studies suggest that the adverse effects of cocaine are reduced in women, and further studies are needed to determine if cocaine-induced microstructural abnormalities are also present in female patients.

A greater understanding of cocaine-induced longitudinal changes in WM microstructure may also be beneficial. Reduced frontal metabolic activity has been reported to persist at 3-month follow-up and to be associated with greater average weekly dose of cocaine used (Volkow et al 1992), suggesting that cocaine-related brain injury may be longstanding and related to cumulative cocaine use; however, it remains to be determined whether successful recovery and continued abstinence impact upon WM integrity.

This work was supported in part by the Department of Veterans Affairs. We would like to thank Ms. Caroline Woo and Mr. Sandor Szilagyi for their efforts in the recruitment of subjects.

References

Bartzokis G, Beckson M, Hance DB, Lu PH, Foster JA, Mintz J, et al (1999): Magnetic resonance imaging evidence of "silent" cerebrovascular toxicity in cocaine dependence. *Biol Psychiatry* 45:1203–1121.

Bartzokis G, Beckson M, Lu PH, Edwards N, Rapoport R, Wiseman E, et al (2000): Age-related brain volume reductions in amphetamine and cocaine addicts and normal control subjects: Implications for addiction research. *Psychiatry Res* 98:93–102.

Basser PJ (1995): Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. *NMR Biomed* 8:333–344.

Basser PJ, Mattiello J, LeBihan D (1994): MR diffusion tensor spectroscopy and imaging. *Biophys J* 66:259–267.

Beatty WW, Katzung VM, Moreland VJ, Nixon SJ (1995): Neuropsychological performance of recently abstinent alcoholics and cocaine abusers. *Drug Alcohol Depend* 37:247–253.

Bechara A, Tranel D, Damasio H (2000): Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain* 123:2189–2202.

Bolla KI, Rothman R, Cadet JL (1999): Dose-related neurobehavioral effects of chronic cocaine use. *J Neuropsychiatry Clin Neurosci* 11:361–369.

Chang L, Ernst T, Strickland T, Mehringer CM (1999): Gender effects on persistent cerebral metabolite changes in the frontal lobes of abstinent cocaine users. *Am J Psychiatry* 156:716–722.

Elliott R, Dolan RJ, Frith CD (2000): Dissociable functions in the medial and lateral orbitofrontal cortex: Evidence from human neuroimaging studies. *Cereb Cortex* 10:308–317.

Grant S, Contoreggi C, London ED (2000): Drug abusers show impaired performance in a laboratory test of decision making. *Neuropsychologia* 38:1180–1187.

Hartley AA, Speer NK (2000): Locating and fractionating working memory using functional neuroimaging: Storage, maintenance, and executive functions. *Microsc Res Tech* 51:45–53.

Hattori H, Takeda M, Kudo T, Nishimura T, Hashimoto S (1992): Cumulative white matter changes in the gerbil brain under chronic cerebral hypoperfusion. *Acta Neuropathol* 84:437–442.

Jacobsen LK, Giedd JN, Gottschalk C, Kosten TR, Krystal JH (2001a): Quantitative morphology of the caudate and putamen in patients with cocaine dependence. *Am J Psychiatry* 158:486–489.

Jacobsen LK, Giedd JN, Kreek MJ, Gottschalk C, Kosten TR (2001b): Quantitative medial temporal lobe brain morphology and hypothalamic-pituitary-adrenal axis function in cocaine dependence: A preliminary report. *Drug Alcohol Depend* 62:49–56.

Jones DK, Lythgoe D, Horsfield MA, Simmons A, Williams SC, Markus HS (1999): Characterization of white matter damage in ischemic leukoaraiosis with diffusion tensor MRI. *Stroke* 30:393–397.

Kaufman MJ, Levin JM, Ross MH, Lange N, Rose SL, Kukes TJ, et al (1998): Cocaine-induced cerebral vasoconstriction detected in humans with magnetic resonance angiography. *JAMA* 279:376–380.

Klingberg T, Vaidya CJ, Gabrieli JD, Moseley ME, Hedehus M (1999): Myelination and organization of the frontal white matter in children: A diffusion tensor MRI study. *Neuroreport* 10:2817–2821.

Kosten TA, Gawin FH, Kosten TR, Rounsaville BJ (1993): Gender differences in cocaine use and treatment response. *J Subst Abuse Treat* 10:63–66.

Kudo T, Tada K, Takeda M, Nishimura T (1990): Learning impairment and microtubule-associated protein 2 decrease in gerbils under chronic cerebral hypoperfusion. *Stroke* 21: 1205–1209.

Kurumatani T, Kudo T, Ikura Y, Takeda M (1998): White matter changes in the gerbil brain under chronic cerebral hypoperfusion. *Stroke* 29:1058–1062.

Langendorf FG, Anderson DC, Tupper DE, Rottenberg DA, Weisman ID (1996): Brain atrophy and chronic cocaine abuse: Background and work in progress. *NIDA Res Monogr* 163:27–42.

Levin JM, Holman BL, Mendelson JH, Teoh SK, Garada B, Johnson KA, et al (1994): Gender differences in cerebral perfusion in cocaine abuse: Technetium-99 m-HMPAO SPECT study of drug-abusing women. *J Nucl Med* 35:1902–1909.

Lim KO, Hedehus M, Moseley M, de Crespigny A, Sullivan EV, Pfefferbaum Aea (1999): Compromised white matter tract integrity in schizophrenia inferred from diffusion tensor imaging. *Arch Gen Psychiatry* 56:367–374.

Liu X, Matochik JA, Cadet JL, London ED (1998): Smaller volume of prefrontal lobe in polysubstance abusers: A magnetic resonance imaging study. *Neuropsychopharmacology* 18:243–252.

London ED, Ernst M, Grant S, Bonson K, Weinstein A (2000): Orbitofrontal cortex and human drug abuse: Functional imaging. *Cereb Cortex* 10:334–342.

Meyerhoff DJ, Bloomer CJ, Schuff N, Ezekiel F, Norman D, Clark W, et al (1999): Cortical metabolite alterations in abstinent cocaine and cocaine/alcohol-dependent subject: Proton magnetic resonance spectroscopic imaging. *Addiction Biol* 4:405–419.

O'Malley S, Adamse M, Heaton RK, Gawin FH (1992): Neuropsychological impairment in chronic cocaine abusers. *Am J Drug Alcohol Abuse* 18:131–144.

Ongur D, Price JL (2000): The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cereb Cortex* 10:206–219.

Pascual-Leone A, Dhuna A, Anderson DC (1991): Cerebral atrophy in habitual cocaine abusers: A planimetric CT study. *Neurology* 41:34–38.

Pfefferbaum A, Sullivan EV, Hedehus M, Lim KO, Adalsteinsson E, Moseley M (2000): Age-related decline in brain white matter anisotropy measured with spatially corrected echo-planar diffusion tensor imaging. *Magn Reson Med* 44:259–268.

Pomara N, Crandall DT, Choi SJ, Johnson G, Lim KO (2001): White matter abnormalities in HIV-1 infection: A diffusion tensor imaging study. *Psychiatry Res* 106:15–24.

Rolls ET (2000): The orbitofrontal cortex and reward. *Cereb Cortex* 10:284–294.

Rose SE, Chen F, Chalk JB, Zelaya FO, Strugnell WE, Benson M, et al (2000): Loss of connectivity in Alzheimer's disease: An evaluation of white matter tract integrity with colour coded MR diffusion tensor imaging. *J Neurol Neurosurg Psychiatry* 69:528–530.

Virta A, Barnett A, Pierpaoli C (1999): Visualizing and characterizing white matter fiber structure and architecture in the human pyramidal tract using diffusion tensor MRI. *Magn Reson Imaging* 17:1121–1133.

Volkow ND, Fowler JS (2000): Addiction, a disease of compulsion and drive: Involvement of the orbitofrontal cortex. *Cereb Cortex* 10:318–25.

Volkow ND, Hitzemann R, Wang GJ, Fowler JS, Wolf AP, Dewey SL, et al (1992): Long-term frontal brain metabolic changes in cocaine abusers. *Synapse* 11:184–190.

Volkow ND, Mullani N, Gould KL, Adler S, Krajewski K (1988a): Cerebral blood flow in chronic cocaine users: A study with positron emission tomography. *Br J Psychiatry* 152:641–648.

Volkow ND, Valentine A, Kulkarni M (1988b): Radiological and neurological changes in the drug abuse patient: A study with MRI. *J Neuroradiol* 15:288–293.

Weiss RD, Martinez-Raga J, Griffin ML, Greenfield SF, Hufford C (1997): Gender differences in cocaine dependent patients: A 6 month follow-up study. *Drug Alcohol Depend* 44:35–40.

Werring DJ, Clark CA, Barker GJ, Thompson AJ, Miller DH (1999): Diffusion tensor imaging of lesions and normal-appearing white matter in multiple sclerosis. *Neurology* 52:1626–1632.