Clinical and MRI Evaluation of Psychostimulant Neurotoxicity

George Bartzokis, Mace Beckson, and Walter Ling

PSYCHOSTIMULANT NEUROTOXICITY AND CLINICAL
MEDICATION TRIALS

Human and animal data have demonstrated that psychostimulants can
cause central nervous system (CNS) neurotoxicity. In addition to
gross neurotoxic effects such as infarcts and seizures (Ritz and George
1993; Rodnitzky and Keyser 1992), more subtle cellular toxicity has
also been demonstrated and is especially evident in the dopaminergic
neurotransmitter system (Gibb et al. 1993).

The Dopaminergic System is believed to be of central importance to
the brain processes involved in the development of human addiction
to psychoactive substances (Parsons et al. 1991; Robinson and
Berridge 1993). Study of animal models of addiction has revealed
that mesocorti-colimbic dopaminergic pathways are necessary for the
establishment of repetitive self-administration of psychoactive drugs
such as cocaine, opiates, and alcohol (Koob and Bloom 1988).
Repetitive self-adminis-tration will not occur following disruption of
dopaminergic transmission, including lesions to the nucleus
accumbens. This nucleus, anatomically distinct in rats but indistinct
from the ventral striatum in man, receives dopaminergic input from
presynaptic neurons whose cell bodies reside in the ventral tegmental
area (VTA) of the midbrain (Fallon 1988). Cocaine and other
psychostimulants bind to the dopaminergic transporter of the
presynaptic nerve terminal, thereby blocking reuptake and increasing
dopaminergic synaptic transmission (Gawin 1991). This presumably
applies to all dopaminergic systems, including mesocorticolimbic pro-
jections believed responsible for the repetitive behaviors of addiction
as well as the nigrostriatal dopamine system responsible for the
coordination of complex movements.

The search for a medication to ameliorate or reverse the clinical
syndrome of cocaine addiction, including withdrawal, craving, and
relapse, has taken on great urgency in the context of both a high
prevalence of cocaine depen-dence and the limited efficacy of
established treatment strategies (Adams et al. 1986; Kosten et al.
1987). Clinical trials of medications that affect the dopaminergic

systems have been and continue to be conducted to evaluate the potential therapeutic usefulness of such agents. Except for gross neurological abnormalities (e.g., clinical evidence of stroke), these studies generally do not evaluate for the more subtle indicators of neurotoxic damage. Thus, the subject samples recruited for these trials may be hetero-geneous with respect to the functioning and pharmacologic responsiveness of the dopaminergic system. This problem would be compounded by the fact that most trials are short in duration and enroll patients early in their abstinence. These factors may limit any recovery from neurotoxic damage in individuals for whom reversibility of such damage is possible.

The inclusion of highly heterogeneous groups of patients in clinical trials in the absence of any measures of neurotoxicity could greatly hinder the effort to develop pharmacologic treatments in at least two ways. First, heterogeneity of the population reduces the power of clinical trials to detect medication efficacy. Second, the opportunity to detect subgroups of patients in whom a pharmacologic intervention is either especially efficacious or possibly countertherapeutic could be missed if quantitative assessments of neurotoxicity are not done a priori.

The following sections review a hypothesis suggesting new avenues of inquiry into the impact of neurotoxicity on medication trials. The data presented are preliminary and, although supportive of the thesis of neurotoxicity in psychostimulant-addicted populations, they should be interpreted with caution.

Mechanisms of Basal Ganglia Neurotoxicity

Catecholamine metabolism produces free radicals (Halliwell and Gutteridge 1985, 1988) and psychostimulants greatly increase catechol-amine metabolism. Animal data support the hypothesis that the increased levels of catecholamines cause psychostimulant neurotoxicity through free radical mechanisms and that these toxic effects are persistent (Gibb et al. 1993). Metabolic abnormalities, which do not improve with long periods of abstinence, have also been observed in the basal ganglia dopaminergic terminals and in the cortex of cocaine addicts (Baxter et al. 1992; Volkow et al. 1992, 1993), and these abnormalities have been shown to be interrelated (Volkow et al. 1993). One study also reported increased urinary lipoperoxides (breakdown products from oxidative damage of membrane polyunsaturated lipids) in abusers of cocaine (Knight et al. 1988).

The basal ganglia, a region rich in catecholamine terminals, are at high risk for neurotoxicity caused by psychostimulants because increased oxidative stress results from increased dopamine metabolism. Bursts of increased dopamine metabolism increase free radical production and can cause neurotoxicity (Halliwell and Gutteridge 1985, 1988; Gibb et al. 1993). An important additional risk factor for basal ganglia oxidative damage is the high levels of iron present in these structures (Hallgren and Sourander 1958; Morris et al. 1992). As shown in figure 1, iron can catalyze the transformation of free radicals into highly reactive hydroxyl radicals capable of causing neurotoxicity by denaturing biomolecules and initiating lipid peroxidation (Halliwell and Gutteridge 1985, 1988).

Some animal data indicate that amphetamines are more likely to be neurotoxic than cocaine alone (Bennett et al. 1993) or result in different neurotoxicity patterns than cocaine (Ellison and Switzer 1993). Some investigators have even reported a lack of evidence of neurotoxic effects of cocaine in controlled animal experiments (Goodman and Sloviter 1993; Bennett et al. 1993). As these investigators have pointed out, however, this finding should not be interpreted as evidence of lack of toxicity in human addicts because of differences between human and animal physiology, as well as differences between human drug use patterns and animal psychostimulant exposure in laboratory paradigms.

The extent of neurotoxicity in humans can be increased by multiple factors. In the context of cocaine use, even limited exposure to amphetamines can have severe neurotoxic consequences (Kleven and Seiden 1991). Addicts rarely limit themselves to the abuse of a single substance, and, in addition, cocaine is often "cut" with amphetamines. Cocaine may be especially neurotoxic once it enters the CNS (Gu et al. 1993). By bypassing hepatic metabolism, human crack users can achieve very high CNS cocaine levels. Thus, cocaine-induced neurotoxicity may be especially relevant for crack users. In addition, animal data indicate that dopamine metabolism may be markedly increased by significant interactions between cocaine and environmental stress (Kalivas and Duffy 1989). Such interactions would suggest that the psychosocial stressors addicts endure could also increase the likelihood of deleterious effects from cocaine. Finally, considering that human addicts use cocaine for months to years versus the limited exposure in most animal experi-ments, there is an increased likelihood that neurotoxicity is a significant component of the human psychostimulant dependence syndrome.
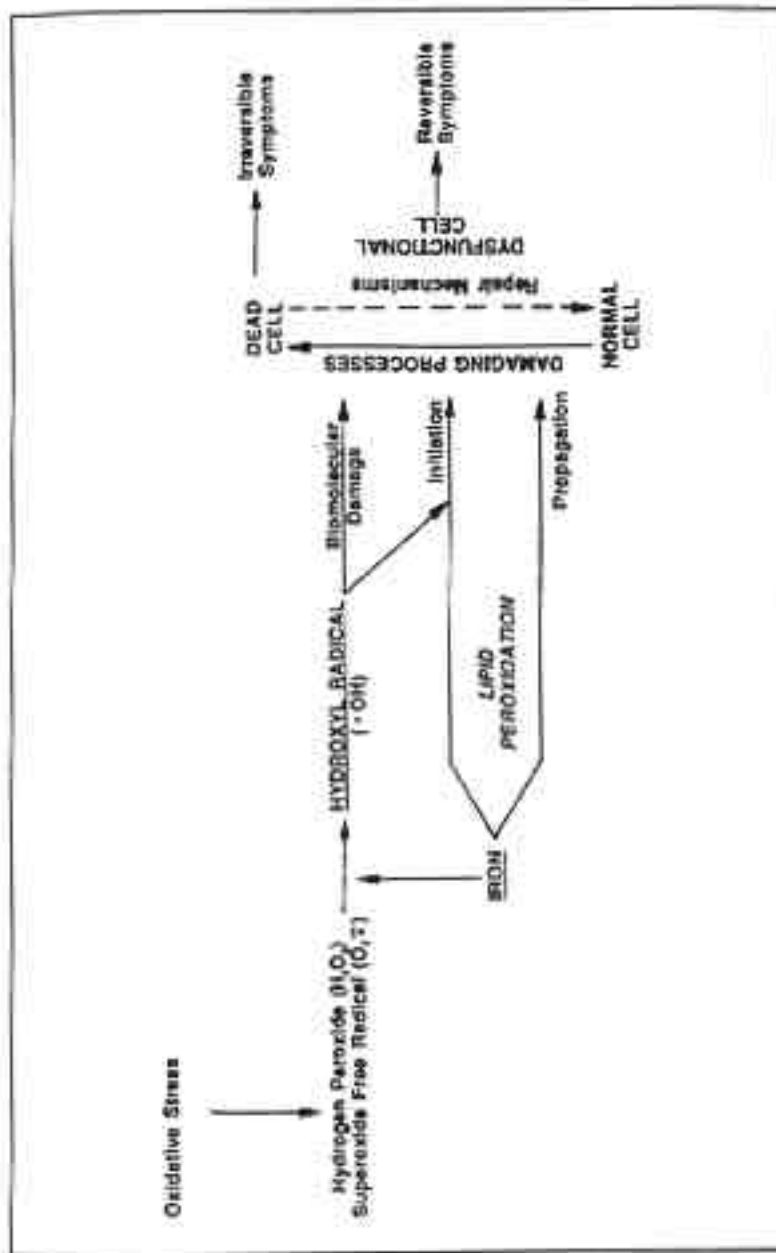
FIGURE 1.

Clinical Evidence of Basal Ganglia Neurotoxicity

Despite the fact that evaluation of neurotoxicity in humans is hampered by the lack of microscopic specimens, evidence is beginning to emerge. Clinical manifestations of subtle neurotoxicity such as deficits in concen-tration and memory (O'Malley et al. 1992; Berry et al. 1993) have been reported. Persistent extrapyramidal movement disorders such as dystonia, chorea, and tics, which are clearly associated with amphetamine and neuroleptic exposure (Rodnitzky and Keyser 1992; Bartzokis et al. 1990), have also been reported with cocaine abuse (Habal et al. 1991; Bauer 1993; Daras et al. 1994). The prevalence of choreoathetoid movements in the cocaine-addicted population is unknown, and it is probably under-appreciated since Daras and colleagues (1994) report that the addicts themselves are aware of the association between crack binges and choreo-athetoid movements, referring to the phenomenon as "crack dancing."

Extrapyramidal movement abnormalities in the cocaine-addicted population may be a useful way of evaluating neurotoxicity in subjects participating in clinical medication trials. A controlled assessment of choreoathetoid movements in cocaine addicts has not been published. Following are preliminary results of an ongoing pilot study on choreo-athetoid movements in male inpatients admitted to the Alcohol and Drug Treatment Program of the West Los Angeles VA Medical Center for treatment of primary cocaine dependence. All patients evaluated were male, with an average age of 41 (range 30 to 60), and had a diagnosis of cocaine dependence according to criteria in the "Diagnostic and Statistical Manual of Mental Disorders," 4th ed. (DSM-IV). Patients were excluded on the basis of a concomitant current or past diagnosis of dependence on other substances, but were not excluded for history of abuse of other sub-stances with the exception of amphetamines. A group of normal controls matched in age, race, and sex to the patient group was also examined. Control subjects had no history of major illness, exposure to neuroleptic medications, severe head trauma (defined as loss of consciousness greater than 15 minutes), or disease or neurologic impairment on routine admis-sion clinical exam. By self-report, the control subjects denied a history of drug dependence or abuse, but some did admit to limited experimentation with cocaine years before the assessment.

Choreoathetoid movements were evaluated using the Abnormal Involuntary Movement Scale (AIMS) and were rated according to the Schooler and Kane (1982) criteria developed for rating tardive

dyskinesia (TD). All but one of the patients were evaluated an average of 8 days after last use. The last patient had been in recovery for 6 years, had a history of severe cocaine dependence similar to the inpatients', and was selected as the first of a new cohort of patients in recovery to evaluate the long-term extrapyramidal sequelae of cocaine dependence.

Nine of the 15 cocaine-dependent patients evaluated were found to have "probable TD" according to Schooler and Kane (1982) criteria, while only 3 of 10 controls met the rating criteria for "probable TD." The amount of movement observed was subtle and none of the patients had severe choreo-athetoid movements of the kind that sometimes is seen in emergency rooms and has been referred to as "crack dancing" (Daras et al. 1994). Interest-ingly, the quantitative differences approached significance between patients and controls only in the body (limbs plus body) AIMS subscore (table 1).

TABLE 1.   AIMS in cocaine-dependent patients and normal controls.

	Cocaine patients (N = 15) Mean (SD)		Normal controls (N = 10) Mean (SD)		T	P
Face	3.07	(1.90)	2.80	(1.32)	0.37	0.71
Body	1.67	(1.72)	0.50	(0.71)	2.02	0.055
Total	4.73	(2.58)	3.30	(1.70)	1.54	0.14

Improvement of the choreoathetoid movements during continuous abstinence from cocaine was evaluated. Ten of the inpatients were available to be reexamined an average of 19 days from the first evalua-tion, the entire interim occurring in an inpatient setting, including random urine toxicologic monitoring. As a group, the patients had a decrease in their AIMS scores, which almost reached statistical significance for the total AIMS score (table 2).

Although the data suggest that there are some withdrawal-associated changes in AIMS scores, the choreoathetoid movements are probably not simply an acute withdrawal phenomenon since half of the 10 subjects still had enough movement to be rated as "probable TD" an average of 4weeks from last use. A study of subjects who have been in recovery for long periods and have a history of severe dependence could address the question of whether the extrapyramidal neurotoxicity has permanent sequelae in some patients.

TABLE 2.   Choreoathetoid movements in 10 patients withdrawing from cocaine.*

	AIMS score change Mean (SD)		T	P
Face	-0.3	(1.2)	-0.82	0.434
Body	-0.4	(1.5)	-0.84	0.423
Total	-0.7	(1.1)	-2.09	0.066

KEY: * = Cocaine-dependent patients examined an average of 1-week, and reexamined 4 weeks, from the day of last use.

Evidence of Neurotoxicity From Human Brain Imaging Studies

In human studies of cocaine addicts, gross anatomic evidence of neuro-toxicity in the form of increased ventricular brain ratio and cortical atrophy has been observed with magnetic resonance imaging (MRI) and x-ray computed tomography (CT) (Pascual-Leone et al. 1991; Morgan et al. 1993). Some anatomic abnormalities are associated with brain func-tional changes such as decreased sensitivity of individuals with enlarged ventricles to the effects of cocaine itself (Morgan et al. 1993), a phenom-enon also observed in animal models (Schenk et al. 1991). In addition, using positron emission tomography (PET), independent research groups have observed persistent functional abnormalities in striatal dopamine metabolism and cortical glucose metabolism in cocaine addicts (Baxter et al. 1992; Volkow et al. 1992), and these abnormalities have been shown to be interrelated (Volkow et al. 1993).

MRI is an imaging modality that provides excellent resolution and contrast and is essentially a risk-free noninvasive procedure that can assess CNS neurotoxicity. Recently, magnetic resonance spectroscopy and functional magnetic resonance imaging have shown great potential for providing additional biochemical and functional data in a research setting. The discussion is limited to neurotoxicity information obtainable with MRI instruments that are widely available and could be used in the context of medication trials.

Clinical MRI instruments can evaluate both biochemical and structural brain changes. Structural changes such as increased ventricular volumes and lesions such as strokes and CNS bleeds have been reported. More subtle evidence of neurotoxic tissue changes can be evaluated by quantifying tissue relaxation times. Transverse

relaxation times (T2) reflect differences in the immediate molecular environments of water protons and can thus provide biochemical information. T2 lengthening is often associated with increased water content, and T2 shortening in the basal ganglia is often associated with increased iron levels. As noted in this chapters introduction, iron is a possibly important risk factor because it catalyzes free radical-mediated neurotoxic processes (Halliwell and Gutteridge 1985, 1988).

Small differences in water content can have a large impact on T2 values as water T2 is > 1,000 milliseconds (ms) compared with normal brain T2 of < 100 ms. Thus, the inclusion of even a few voxels with increased water content in a region of interest could greatly increase the average T2 measure for the region. An increase in tissue iron would have to be very large to be detected in the context of increased water content since it would have to more than offset the T2 increase caused by increased water concentration. The converse is also true. Increased tissue water will be underestimated if the tissues also contain an increase in iron levels. Since most pathologic tissue changes such as those that may be caused by neuro-toxicity increase the water content of brain tissue, it is likely that neuro-toxicity will result in increased T2 even in the presence of increased iron levels.

Cocaine-dependent patients were examined to investigate whether gross anatomic and T2 evidence of neurotoxicity could be observed using a clinical 1.5 Tesla MRI instrument. Thirteen of the patients who were evaluated with the AIMS agreed to undergo an MRI examination. Despite the fact that the subjects had no history of major illness or severe head trauma and no evidence of disease or neurologic impairment on routine admission clinical exam, two were noted to have severe structural pathology. The first of these, a 53-year-old male, had a very large number of multiple, diffuse, confluent lesions in a classic watershed distribution (figure 2). The second, a 32-year-old male, had a silent occipital stroke (figure 3). The patient group also seemed to have an apparent increase in the prevalence of small hyperintense lesions in the ventral putamen, globus pallidus regions on qualitative evaluation of the scans (figure 4). These lesions were most apparent on coronal scans and corresponded to an area supplied by the anterolateral branches of the mid and anterior cerebral arteries, often a site of intracerebral hemorrhages in this population.
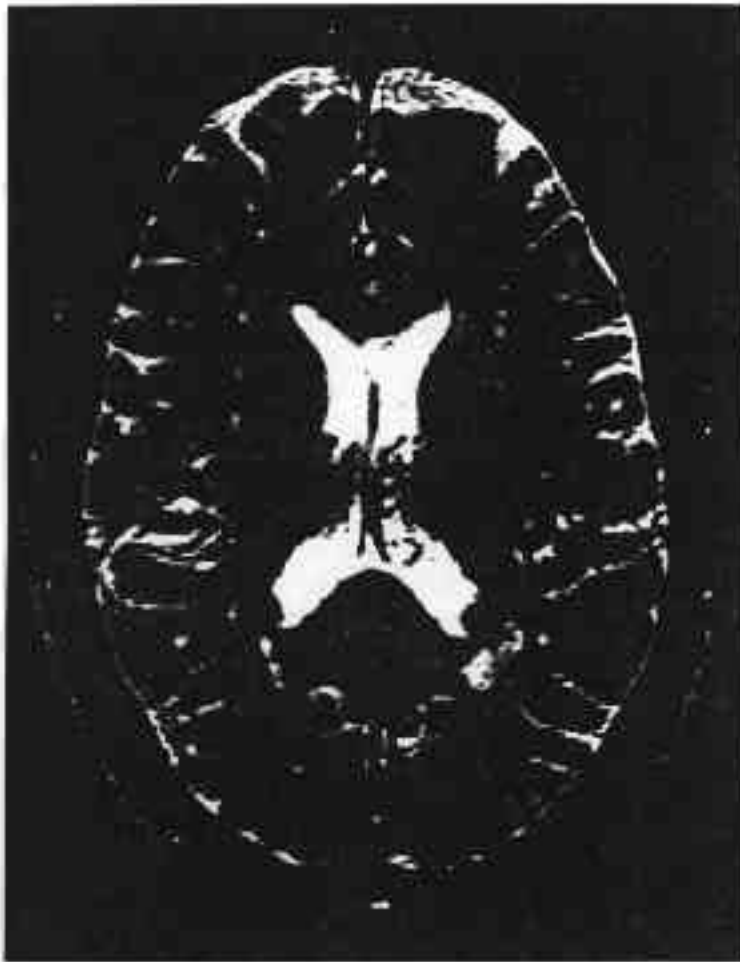
FIGURE 2. *55-year-old cocaine addict with confluent white matter lesions.*

SOURCE: Bartzokis et al. 1994.

FIGURE 3. *37-year-old cocaine addict with right occipital stroke.*

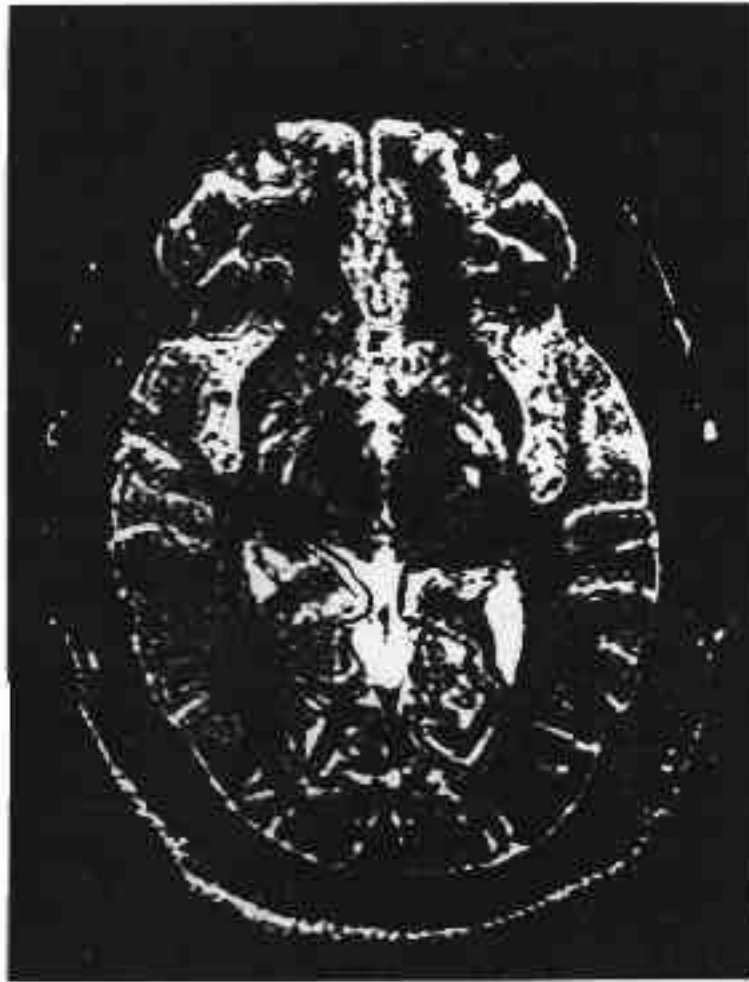SOURCE: Bartzokis et al. 1994.

FIGURE 4. *39-year-old cocaine addict with ventral putamen/globus pallidus hyperintense lesions.*

SOURCE: Bartzokis et al. 1994

In addition to examining for gross pathology, the average T2 relaxation time of the pixels in the structures of interest (caudate, putamen, and globus pallidus) was measured as described previously (Bartzokis et al. 1994a). Three structures were evaluated for evidence of relationships between clinical evidence of basal ganglia neurotoxicity (choreoathetoid movements as quantified by AIMS) and basal ganglia T2. Preliminary analyses show that cocaine-dependent patients demonstrated an almost statistically significant correlation between AIMS and putamen T2 relaxation times (figure 5). The correlation reached statistical significance on the right ($r = 0.599$, $p = 0.03$), and almost were statistically signafcant overall ($r=0.56$, $p = 0.06$) and on the left ($r = 0.506$, $p=0.08$). Interestingly, this association was largely due to body (trunk and extremities) AIMS subscores, which approached statistical signifi-cance by themselves at the $p = 0.1$ level on the left, right, and overall ($r=0.52$, $p = 0.07$; $r = 0.50$, $p=0.08$; $r = 0.48$, $p = 0.09$). These corre-lations were not present in the control group or when both controls and cocaine-dependent patients were evaluated together.

Future Directions

As noted above, T2 changes are not specific. The basal ganglia contain high levels of iron that may play a role in neurotoxic processes and could also affect T2 relaxation times. The difficulties of evaluating tissue iron and water in vivo with specificity are not insurmountable. The T2 short-ening effect of ferritin (the iron storage protein that contains up to 90per-cent of non-heme iron in brain (Hallgren and Sourander 1958; Morris et al. 1992) is field-dependent (Bartzokis et al. 1993). This means that MRI is better at detecting T2 shortening caused by ferritin at higher magnetic field strengths (1.5 Tesla (T) and above). At 0.5 T the effect of ferritin is low enough to make it useful as a way of estimating background field-indepen-dent influences on T2 (Bartzokis et al. 1993) and evaluating subtle changes in water content (Bartzokis et al. 1994a, 1994b).

Tissue iron can be evaluated in vivo with specificity by using the unique property of ferritin to shorten T2 in a field-dependent manner (Bartzokis et al. 1993, 1994a, 1994b). This can be done by measuring T2 on two instruments of differing field strengths. The T2 value obtained from the low field-strength instrument reflects the field-independent properties of the tissue. Subtracting the field-independent effects measured by the low field-strength instrument from the effects detected by the high field-strength instrument (composed of both the field-independent tissue effects plus the field-dependent effects of ferritin) produces a measure
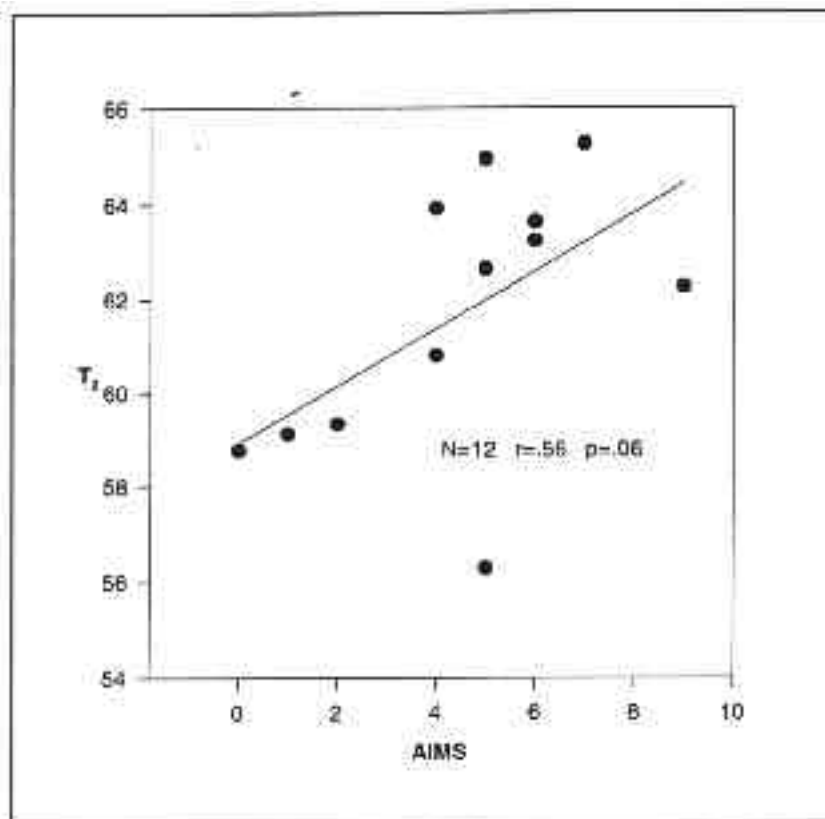
FIGURE 5. *Scatter plot of AIMS score versus putamen T_2 in cocaine addicts.*

that is directly proportional to ferritin levels and is specific for ferritin (Bartzokis et al. 1993, 1994a, 1994b). This approach provides the opportunity to obtain specific measures of both brain water levels and brain iron stores in vivo. Such data may significantly aid efforts to eval-uate both a possible risk factor (high iron levels) and extent of damage (increased water content) in clinical populations and improve the under-standing of amphetamine- and cocaine-mediated neurotoxicity in sub-stance abusers.

CONCLUSIONS

Psychostimulant-induced neurotoxicity has been observed in a variety of human and animal models. Assessing the issue of neurotoxicity and its impact on treatment outcome of cocaine and amphetamine abusers is therefore indicated. Future work should include the continued develop-ment of methodology to evaluate neurotoxic

damage in psychostimulant dependent patients. Such methodology would be incorporated in medi-cation trials for the treatment of substance (particularly psychostimulant) dependence disorders. Some measures such as the AIMS and other stan-dardized clinical assessments can be presently incorporated on a large multicenter scale. More rigorous methods for measuring extrapyramidal movements (Bartzokis et al. 1989; Wirshing et al. 1991), gross brain pathology, and changes in water and iron levels could be evaluated selectively in specialized centers. Identifying and measuring neurotoxic damage mediated by cocaine and amphetamines would help clarify the toxic mechanisms, suggest novel medication strategies, and elucidate the relationship of patient CNS characteristics and associated treatment re-sponse. Such understanding could yield neurobehaviorally based patient-treatment matching and consequently enhance treatment outcome for substance dependence disorders.

REFERENCES

Adams, E.H.; Gforer, J.C.; Roose, B.A.; and Kozel, N.J. Trends in prevalence and consequences of cocaine use. Adv Alcohol Subst Abuse 6:49-71, 1986.

Bartzokis, G.; Aravagiri, M.; and Oldendorf, W.H. Field dependent transverse relaxation rate increase may be a specific measure of tissue iron stores. Magn Reson Med 29:459-464, 1993.

Bartzokis, G.; Garber, H.J.; Marder, S.R.; and Oldendorf, W.H. MRI in tardive dyskinesia: Shortened left caudate T2. Biol Psychiatry 28:1027-1036, 1990.

Bartzokis, G.; Mintz, J.; Sultzer, D.; Marx, P.; Herzberg, J.S.; Phelan,C.K.; and Marder, S.R. In vivo evaluation of age-related increases in brain iron using MRI. AJNR 15:1129-1138, 1994a.

Bartzokis, G.; Sultzer, D.; Mintz, J.; Marx, P.; Phelan, C.K.; and Marder,S.R. MRI suggests increased brain iron in Alzheimer's disease. Biol Psychiatry 35:480-487, 1994b.

Bartzokis, G.; Wirshing, W.C.; Hill, M.A.; Cummings, J.L.; Altschuler,L.; and May, P.R.A. Comparison of electromechanical measures and observer ratings of tardive dyskinesia. Psychiatry Res 27:193-198, 1989.

Bauer, L.O. Motoric signs of CNS dysfunction associated with alcohol and cocaine withdrawal. Psychiatry Res 47:69-77, 1993.

Baxter, L.R.; Melega, W.P.; Yu, D.C.; Barrio, J.R.; Huang, S.; and Phelps, M.E. "Abnormal Presynaptic Dopamine Neuron Function in Heavy Cocaine Abusers Determined with PET and [18F] Fluro-Dopa." Paper presented at the 31st annual meeting of the American College

of Neuropsychopharmacology, San Juan, Puerto Rico, December 6-10, 1992.

Bennett, B.A.; Hyde, C.E.; Pecora, J.R.; and Coldfelter, J.E. Differing neurotoxic potencies of methamphetamine, mazindol, and cocaine in mesoencephalic cultures. J Neurochem 60:1434-1452, 1993.

Berry, J.; van Gorp, W.G.; Herzberg, D.S.; Hinkin, C.; Boone, K.; Steinmann, L.; and Wilkins, J.N. Neuropsychological deficits in abstinent cocaine abusers: Preliminary findings after two weeks of abstinence. Drug Alcohol Depend 32:231-237, 1993.

Daras, M.; Koppel, B.S.; and Atos-Radzion, E. Cocaine-induced choreo-athetoid movements ("crack dancing"). Neurology 44:751-752, 1994.

Ellison, G., and Switzer, R.C., III. Disimilar patterns of degeneration in brain following four different addictive stimulants. Neuroreport 5:17-20, 1993.

Fallon, J.H. Topographic organization of ascending dopaminergic projections. Ann NY Acad Sci 537:1-9, 1988.

Gawin, F.H. Cocaine addiction: Psychology and neurophysiology. Science 251:1580-1586, 1991.

Gibb, J.W.; Johnson, M.; Stone, D.M.; and Hanson, G.R. Mechanisms mediating biogenic amine deficits induced by amphetamine and its congeners. In: Erinoff, L., ed. Assessing Neurotoxicity of Drugs of Abuse. National Institute of Drug Abuse Research Monograph 136. NIH Pub. No. 93-3644. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1993. pp. 226-241.

Goodman, J.H., and Sloviter, R.S. Cocaine neurotoxicity and altered neuropeptide Y immunoreactivity in the rat hippocampus: A silver degeneration and immunocytochemical study. Brain Res 616:263-272, 1993.

Gu, J.; Yassini, P.; Goldberg, G.; Zhu, W.; Konat, G.W.; and Wiggins,R.C. Cocaine cytotoxicity in serum-free environment: C6 glioma cell culture. Neurotoxicology 14:19-22, 1993.

Habal, R.; Sauter, D.; Olowe, O.; and Daras, M. Cocaine and chorea. Am J Emerg Med 9:618-619, 1991.

Hallgren, B., and Sourander, P. The effect of age on the non-haemin iron in the human brain. J Neurochem 3:41-51, 1958.

Halliwell, B., and Gutteridge, J.M.C. The importance of free radicals and catalytic metal ions in human diseases. Molec Aspects Med 8:89-93, 1985.

Halliwell, B., and Gutteridge, J.M.C. Iron as biological pro-oxidant. ISI Atlas Sci Biochem 1:48-52, 1988.

Kalivas, P.W., and Duffy, P. Similar effects of daily cocaine and stress on mesocorticolimbic dopamine neurotransmission in the rat. Biol Psychiatry 25:913-928, 1989.

Kleven, M.S., and Seiden, L.S. Repeated injection of cocaine potentiates methamphetamine-induced toxicity to dopamine-containing neurons in rat striatum. Brain Res 557:340-343, 1991.

Knight, J.A.; Piper, R.K.; Smith, S.E.; and Crockett, H.H. Increased urinary lipoperoxides in drug abusers. Ann Clin Laboratory Sci 18:374-377, 1988.

Koob, G.F., and Bloom, F.E. Cellular and molecular mechanisms of drug dependence. Science 242:715-723, 1988.

Kosten, T.R.; Rounsaville, B.J.; and Kleber, H. A 2.5 year follow-up of cocaine use among treated opioid addicts: Have our treatments helped? Arch Gen Psych 45:18-23, 1987.

Morgan, J.M.; Cascella, N.G.; Stapleton, J.M.; Phillips, R.L.; Yung,-B.C.K.; Wong, D.F.; Shaya, E.K.; and London, E.D. Sensitivity to subjective effects of cocaine in drug abusers: Relationship to cerebral ventricle size. Am J Psychiatry 150:1712-1717, 1993.

Morris, C.M.; Candy, J.M.; and Leith, A.B. Brain iron homeostasis. JInorganic Biochem 47:257-265, 1992.

O'Malley, S.; Adamse, M.; Heaton, R.K.; and Gawin, F.H. Neuropsycho-logical impairment in chronic cocaine abusers. Am J Drug Alcohol Abuse 18:131-144, 1992.

Parsons, L.H.; Smith, A.D.; and Justice, J.B. Basal extracellular dopamine is decreased in the rat nucleus accumbens during abstinence from chronic cocaine. Synapse 9:60-65, 1991.

Pascual-Leone, A.; Dhuna, A.; and Anderson, D.C. Cerebral atrophy in habitual cocaine abusers. Neurology 18:131-144, 1991.

Ritz, M.C., and George, F.R. Cocaine-induced seizures and lethality appear to be associated with distinct central nervous system binding sites. JPharmacol Exper Ther 264:1333-1343, 1993.

Robinson, T.E., and Berridge, K.C. The neural basis of drug craving: An incentive-sensitization theory of addiction. Brain Res Rev 18:247-291, 1993.

Rodnitzky, R.L., and Keyser, D.L. Neurologic complications of drugs. Psychiatr Clin North Am 15:491-503, 1992.

Schenk, S.; Hoger, B.A.; Peltier, R.; and Shelton, K. Supersensitivity to the reinforcing effects of cocaine following 6-hydroxydopamine lesions to the medial prefrontal cortex in rats. Brain Res 547:227-235, 1991.

Schooler, N.R., and Kane, J.M.Research diagnoses for tardive dyskinesia. Arch Gen Psychiatry 39:486-487, 1982.

Volkow, N.D.; Flower, J.S.; Wang, G.J.; Hitzemann, R.; Logan, J.; Schlyer, D.J.; Dewey, S.L.; and Wolf, A.P. Decreased dopamine D2

receptor availability is associated with reduced frontal metabolism in cocaine abusers. Synapse 14:169-177, 1993.

Volkow, N.D.; Hitzemann, R.; Wang, G.J.; Flower, J.S.; Wolf, A.P.; Dewey, S.L.; and Handlasman, L. Long term frontal brain metabolic changes in cocaine abusers. Synapse 11:184-190, 1992.

Wirshing, W.C.; Cummings, J.L.; Dencker, S.J.; and May, P.R.A. Electro-mechanical characteristics of tardive dyskinesia. J-Neuropsychiatry Clin Neurosci 3:10-17, 1991.

ACKNOWLEDGMENTS

AUTHORS

George Bartzokis, M.D.
The Research Service
West Los Angeles VA Medical Center
Los Angeles, CA 90073

UCLA Department of Psychiatry
Los Angeles, CA 90074

Harbor-UCLA Department of Radiology
Torrance, CA 90509

Mace Beckson, M.D.
The Psychiatry Service
West Los Angeles VA Medical Center
Los Angeles, CA 90073

UCLA Department of Psychiatry
Los Angeles, CA 90074

Walter Ling, M.D.
The Psychiatry Service
West Los Angeles VA Medical Center
Los Angeles, CA 90073

UCLA Department of Psychiatry
Los Angeles, CA 90074

Click here to go to page 318