Neuropsychological Effects of Chronic Methamphetamine Use on Neurotransmitters and Cognition: A Review

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Methamphetamine use is on the rise, with an imminent upsurge of abuse and dependence reported across the United States. Currently, preliminary evidence suggests that methamphetamine dependence may cause long-term neural damage in humans, with concomitant deleterious effects on cognitive processes such as memory and attention. This selective review provides an outline and synthesis of studies that assess the neurotoxic mechanisms of methamphetamine, as well as those that evaluate the cognitive sequelae of methamphetamine abuse.

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Among the illicit stimulants, cocaine and the amphetamines are the most widely abused. While cocaine use has had a national distribution and an overall decrease since the early 1990s, the use of amphetamines, particularly methamphetamine, has been increasing and spreading eastward from its endemic centers in the western and southwestern parts of the United States.[1–3] The use and effects of methamphetamine command increasing attention from researchers and drug treatment professionals, as well as from drug enforcement officials and state and national legislators. Using the University of California's MELVYL MEDLINE database, a search for journal articles indexed under "methamphetamine" reveals a doubling of the number of articles from the year 1990 through the year 2000. One hundred six articles are indexed for 1990, whereas 212 articles are found for 2000. In contrast, the number of articles indexed under "cocaine" remained essentially constant over the same time period, at approximately 1,000 per year. From 1994 to 2000, the number of underground methamphetamine labs that were seized by the U.S. Drug Enforcement Agency (DEA) increased 590%, with 6,394 lab seizures reported.[4] Similarly, the amount of the drug seized by the DEA also increased, from 289 kg in 1996 to 3,163 kg in 2000.[4,5] Several acts of national legislation, such as the Comprehensive Methamphetamine Control Act of

1996 and the Methamphetamine and Club Drug Anti-Proliferation Act of 2000, have focused specifically on the growing problem of methamphetamine abuse. This article provides an overview of some of the relevant clinical and historical features of methamphetamine abuse, followed by a discussion of the drug's effect on different neurotransmitter systems. Particular attention is given to the issue of methamphetamine-induced neurotoxicity. Lastly, the effects of methamphetamine on cognition are also assessed, with particular reference to neurotoxic effects.

Unlike cocaine, methamphetamine is a synthetically derived drug, and its synthesis requires only rudimentary laboratory equipment (See Figure 1). Until the enactment of recent legislation, the requisite reagents used to make methamphetamine could be purchased in drugstores, hardware stores, and chemical supply houses. According to the DEA, among the controlled substances manufactured underground in the United States, methamphetamine is the most prevalent, and it is one of the commonly abused controlled substances that can be made in the home.[6] For many years, methamphetamine has been manufactured in small "mom-and-pop" labs that can be readily concealed in a shed, storage garage, or large vehicle such as a minivan. Prior to the late 1980s, illicit manufacture of methamphetamine was the purview of white motorcycle gangs who used the chemical phenyl-2-propanone (P2P) to make the drug, which was legal at the time, as the major precursor. Federal controls were placed on P2P with the implementation of the Federal Chemical Diversion and Trafficking Act of 1988. Subsequently, underground chemists began using ephedrine and pseudoephedrine as the main precursors in methamphetamine synthesis. The use of ephedrine and pseudoephedrine is simpler and more efficient than the P2P-based process, as it produces a higher yield of the psychoactive D-isomer of the drug. Additionally, Mexican poly-drug trafficking organizations began manufacturing and distributing methamphetamine in the mid-1990s. These organizations created "superlabs" in Mexico and southern California that were capable of producing 10 pounds or more of high-purity methamphetamine in 1 to 2 days. The superlabs are in marked contrast to the more numerous and widely distributed mom-and-pop labs, which maintain a share of the U.S. market. Because of the varied manufacturing patterns, the purity of street methamphetamine can vary widely, even within a circumscribed geographic area.[3]

Methamphetamine is typically ingested (usually dissolved in a beverage, such as a soft drink or coffee), smoked (vaporized), snorted, or injected intravenously. The amount used at a single administration can vary more than tenfold, depending on individual tolerance, route of administration, and purity. Among chronic users, dosing patterns tend to be either administrations of low doses or cycles of high-dose bingeing that lasts for days, followed by a period of abstinence.

Amphetamines have a longer duration of action than cocaine (8–13 hours versus 1–3 hours) and may be more rapidly addicting.[7] Methamphetamine has higher lipid solubility than the unsubstituted amphetamine, and thus larger amounts of the drug rapidly and efficiently cross the blood-brain barrier. Approximately 45% of a methamphetamine dose is metabolized into amphetamine, and both drugs are primarily excreted renally.[8] In animal models the pharmacological effects of methamphetamine depend greatly upon the dose and pattern of administration. In rat models, for instance, different effects are seen with administration of a single dose, repeated administration of low doses at long intervals, repeated administration of high doses at short intervals, or high-dose runs superimposed on chronic low-dose administration.[9] In methamphetamine-naïve humans, low doses produce a sense of heightened alertness, attentiveness, and energy. Higher dose intoxication produces a sense of well-being, euphoria, and enhanced self-esteem that can approach hypomania and grandiosity. Initially, sexual activity and pleasure may be increased, although longer use is associated with impaired sexual functioning. Appetite is suppressed. Adverse effects include restlessness, insomnia, bruxism, and excessive weight loss. Suspiciousness may occur and can

FIGURE 1. Chemical diagrams

Methamphetamine   Amphetamine   Cocaine
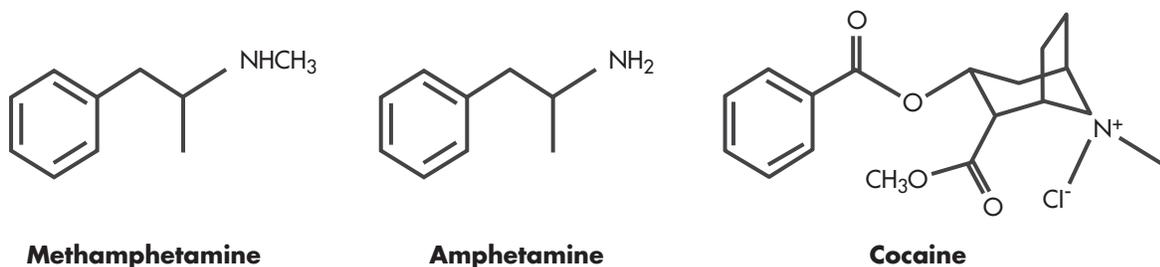
develop into a full paranoid psychosis that is indistinguishable from acute paranoid schizophrenia. The psychosis may extend beyond the period of acute intoxication, and some experts believe that it may recur or become chronic, despite abstinence from drug use.[10–12] A preoccupation with minutiae and details can arise, leading to compulsive repetitious behaviors. Skin picking is not uncommon and is, at times, accompanied by tactile hallucinations and delusions of parasitosis. Abrupt cessation of long-term use produces withdrawal, which can last for days and may be accompanied by dysphoria, irritability, and agitation.[13]

Effects on Neurotransmitter Systems

Acute administration of methamphetamine increases extracellular dopamine (DA) levels through the reverse transport of DA and by the displacement of DA from vesicular stores.[14,15] Methamphetamine also impacts serotonergic, noradrenergic, and glutamatergic systems through interactions with 5-HT transporters, monoamine transporters, and *N*-methyl-D-aspartate (NMDA) receptors. Repeated administration of the drug to rodents or nonhuman primates decreases striatal concentrations of DA and DA metabolites in several brain regions.[16–18]

Dopamine

The neurotoxic effects of methamphetamine lead to alterations in levels of DA, with increased levels correlating with subsequent decreases in DA neurotransmission.[19] Conversely, DA receptor antagonists or synthesis inhibitors attenuate methamphetamine-induced neurotoxicity.[19,20] DA uptake inhibitors attenuate methamphetamine-induced deficits in DA neuronal activity, suggesting that the dopamine transporter (DAT) is critical to the mediation of neurotoxicity.[21–23] However, Yuan et al.[24] found that the depletion of DA with reserpine or alpha methyl paratyrosine (AMPT), with the process held at normal temperatures, did not protect against the neurotoxic effects of methamphetamine. Although the DAT may function in damage mechanisms, the role for endogenous DA seems less defined.

In a number of findings, damage has been observed in animals exposed to methamphetamine, particularly the degeneration of DA nerve terminals, with reductions in DAT activity, tyrosine hydroxylase activity, and vesicular monoamine transporter-2 (VMAT) protein levels.[21,23,25–27] Human imaging studies have shown reductions in DAT levels.[28–30] Alterations in both humans and animals occur within days of drug exposure and may persist for months or years.[18,28,31]

Serotonin

In addition to DA, other neurotransmitters are affected by methamphetamine use, including 5-HT and cholinergic systems. The mechanism of methamphetamine damage to 5-HT fibers is unknown, and the release of DA is believed to be an intermediate step in the cause of 5-HT degeneration.[32,33] Blocking DA synthesis prevents 5-HT degeneration.[34,35] The relationship between DA release and 5-HT fiber damage is complex and may involve other neurotransmitter systems.[36]

After exposure to methamphetamine, marked effects may take place in the serotonergic system. Zhou et al.[37] reported that, within hours of methamphetamine injection in monkeys, region-specific dose effects were observed, with the frontal cortex and hippocampus affected at lower amphetamine doses and the striatum and parietal cortices at higher doses. Targets of methamphetamine insult included 5-HT pathways (e.g., medial forebrain bundle, cingulum bundle, indusium griseum, fornix, and stria terminalis). In contrast, the temporal cortex, hypothalamus, and brainstem were relatively spared. Unlike studies on DA, few studies imaging the serotonin system have been performed in humans, and none have been conducted with methamphetamine using subjects.[38]

Other Neurotransmitters

The excitatory neurotransmitter glutamate may function in methamphetamine-induced neurotoxicity, with acute administrations of methamphetamine producing marked and prolonged increases in glutamate release.[39,40] NMDA glutamate-receptor antagonists decrease methamphetamine-induced DA overflow and prevent reduction in tyrosine hydroxylase activity.[41–43]

Studies have investigated how nitric oxide (NO) functions in methamphetamine-induced neurotoxicity. Abekawa et al.[44] examined the effect of NO synthesis inhibition on methamphetamine-induced dopaminergic and serotonergic neurotoxicity in rats. Their findings revealed that toxic doses of methamphetamine significantly decreased contents of DA, dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) in the striatum; and contents of 5-HT were greatly reduced in the striatum, nucleus accumbens, and medial frontal cortex. However, coadministration with the NO synthase inhibitor, N-omega-nitro-L-arginine methyl ester (LNAME), lowered the methamphtetamine-induced decreases in the striatum in contents of DA, DOPAC, and HVA but did not alter the decreases of 5-HT in the nucleus accumbens, medial prefrontal cortex, or striatum. Therefore, it is conceivable that methamphetamine-induced dopaminergic neurotoxicity, but not serotonergic neurotoxicity, may be related to NO formation that

is caused by the activation of postsynaptic DA receptor. Hence, DA, glutamate, and perhaps NO may all function in the neurotoxic effects of methamphetamine on the DA system.

Imaging Studies

Imaging techniques, such as proton magnetic resonance spectroscopy (MRS), have been used to assess the presence of neuronal damage in human subjects. A noninvasive magnetic resonance imaging (MRI) technique, MRS uses certain pulse sequences to yield chemical spectra that reflect relative concentrations of specific neurotransmitters, or their metabolites, in preselected brain volumes. Using proton MRS, one can obtain measures of N-acetylaspartate (NAA), choline (Cho), myoinositol (mI), and creatine (Cr) content. NAA is present in axons, dendrites, and the cell bodies of healthy neurons, and its levels are thought to be a measure of neuronal viability.[45] In a wide range of studies, abnormally low levels of NAA and abnormally high levels of mI (a glia marker) and Cho have been linked to neuronal damage.[46] Using MRS, Ernst et al.[46] reported uncharacteristically low NAA in the basal ganglia of methamphetamine-dependent subjects. They also observed an inverse correlation between the prefrontal white matter NAA values and years of use, with evidence of abnormally high Cho and mI in the frontal grey matter. In a subsequent MRS study of recently abstinent subjects, Nordahl et al.[47] found evidence of abnormally low normalized NAA (i.e., NAA/Cr) levels and higher normalized Cho (i.e., Cho/Cr) levels in the anterior cingulum (ACC), with no evidence of such findings in the primary visual cortex that served as the control region. Taylor et al.[48] also found evidence of low NAA in the anterior cingulum and a trend toward a low NAA value for the basal ganglia. These findings have been interpreted as consistent with neural damage to the frontostriatal regions. Using MRI analyses, Bartzokis et al.[49] reported no overall tissue loss in frontal gray and white matter. Postmortem confirmation and longitudinal within-subjects studies are necessary in order to confirm these results. Using positron emission tomography [F-18]-fluorodeoxyglucose (FDG PET) techniques, London et al.[50] and Volkow et al.[30] examined brain glucose metabolic changes in methamphetamine-dependent subjects.

Duration of Neurotoxicity

An emerging body of studies aims to establish the duration of methamphetamine damage on neuronal regions and processes. In this section, we review recent studies that were conducted on humans and monkeys and revealed findings pertinent to the continual long-term effects of methamphetamine use. In a study performed on monkeys to assess the persistence of methamphetamine exposure effects, Harvey et al.[51] used in vivo and postmortem techniques. Following a 1-month exposure to methamphetamine, postmortem characterization revealed extensive decreases in the immunoreactivity (IR) profiles of tyrosine hydroxylase, DAT, and VMAT-2. These decreases were observed in the striatum, medial forebrain bundle, and ventral midbrain dopamine (VMD). When assessed at 1.5 years by stereological methods, IR deficits were not associated with a loss of VMD cell number. At 1.5 years, IR profiles of methamphetamine-exposed monkeys, throughout the nigrostriatal dopamine system, appeared to be similar to those of controls, although some regional deficits persisted. The lack of VMD cell loss suggests that the magnitude and extent of dopaminergic deficits may represent transient impairment.

Recent studies conducted on humans suggest that permanent degeneration of the DA system does not occur, and normalization of dopaminergic deficits may take place over time. In their investigation of the postmortem brains of methamphetamine users, Wilson et al.[52] reported lower levels of the DA nerve terminal markers and the DA transporter in the nucleus accumbens, caudate, and putamen. They also suggested that lower levels of striatal DA transporter might explain the rationale for the dose escalation and dysphoria that are frequently found in methamphetamine abusers. They did not, however, find decreased levels of the enzyme 3,4-dihydroxyphenylalanine (DOPA) decarboxylase or VMAT, which is found in patients with Parkinson's disease who have permanent degeneration of their nigrostriatal DA system.

In a study that used positron emission tomography (PET) to measure DA transporter binding, Volkow et al.[53] found evidence of DAT normalization in a paired study of five subjects that were initially examined in early abstinence and then in late abstinence (1.5 to 2 years). These latter findings suggest that chronic exposure to methamphetamine does not necessarily cause permanent deficits or damage to the DA system in human users. In the presentation of her data, however, Dr. Volkow reported that the five subjects still had cognitive deficits following normalization of their DA transporter binding values.

In summary, findings for neuroanatomical, neurochemical, and imaging data support the conclusion that methamphetamine abuse causes damage to multiple transmitter systems that are distributed throughout the brain. Whether the ensuing damage is permanent or reversible over time has not yet been determined.

Cognitive Effects of Methamphetamine Abuse

Drugs that affect the monoaminergic system, such as amphetamine and cocaine, can alter both behavioral and

cognitive processes in many ways. Although numerous studies have examined the effects of cocaine on cognition,[54–60] less is known about the long-term cognitive effects of methamphetamine use. As methamphetamine use has been shown to damage both DA and 5-HT systems, the cognitive effects may differ qualitatively from those resulting from cocaine use, which has a differential effect upon these systems.[61] Earlier studies reported that acute doses of methamphetamine administered to drug-naive subjects produced improvements in cognitive processing.[62–64] Studies using sleep-deprived individuals revealed that administration of amphetamines reduced reaction times and improved performance.[62] Other investigations have reported similar results in non-fatigued individuals.[65] Fleming et al.[66] observed that single doses of dextroamphetamine reduced reaction times on a continuous performance test but had no significant effect on other attentional measures. Additional studies reported improvements in verbal memory performance as a result of the administration of methamphetamine.[64] In contrast to the improvements cited above, some investigations found no cognitive improvements associated with amphetamine administration.[65,67]

More recent studies have shown that long-term methamphetamine use is associated with impaired performance on a number of cognitive tasks.[68–71] Volkow et al.[71] tested a group of methamphetamine-dependent subjects and found that they exhibited performance deficits in both verbal memory and motor function. Simon et al.[70] observed that the methamphetamine users in their study did not differ from controls on global Intelligence Quotient (IQ) measures, though they did perform significantly worse on tests of memory recall. The methamphetamine group in this same study had difficulty with tests that measured manipulation of information (i.e., Digit Span Task and Trail Making Part B), but had no problems on tasks that measured psychomotor speed separately (i.e., Trail Making Part A). The methamphetamine group also displayed deficits in abstract reasoning and task shifting strategies. In their study, Ornstein et al.[72] reported that methamphetamine-dependent subjects displayed specific deficits in shifting categories on a computerized task shifting experiment when compared with chronic heroin users and non-substance using control subjects.

Clinically, methamphetamine-dependent individuals appear distractible and exhibit difficulties in sustaining attention. Our lab has examined the attentional performance in a group of methamphetamine-dependent individuals, using a sensitive, computerized battery of selective attention tasks to better understand the nature and specific properties of their cognitive dysfunction.[69] A single-trial Stroop priming task; a task switching ex-

periment, with response conflict trials; a spatial priming task; and a go-no-go task were all used in the assessment. When compared with controls, the methamphetamine-dependent individuals displayed more consistent patterns of difficulties in suppressing irrelevant task information. These deficits became apparent in both reaction time measures and accuracy rates. Although the methamphetamine-dependent individuals exhibited deficits in the explicit components of the tasks, they had preserved attentional priming, which is a noteworthy dissociation in attentional performance. Priming is an implicit component of cognitive processing that remains intact in some disorders, even when other cognitive abilities are impaired, such as in global amnesia. In disorders such as schizophrenia, however, priming does not remain undamaged.[73–74]

Dopaminergic Systems and Cognition
The dopaminergic system often exhibits modulatory effects on many cognitive functions, including memory, attention, task switching, and response inhibition.[74] Recent studies in humans and animals revealed that DA depletion in the mesostriatum can lead to both a slowing in reaction time and deficits in overall task performance.[75] Dopaminergic systems within the prefrontal cortex (PFC) are vital to the formation of attentional sets and switching behavior, with DA neurotoxic lesions of the PFC disrupting the establishment of attentional sets.[68,75,76] Deficits in task switching have been observed in patients with Parkinson's disease.[77–79] This suggests that, functioning in the mesostriatum, DA may also play a role in the creation of attentional sets.[80] As previously discussed, long-term methamphetamine use can impair the DA system in both humans and animals. Therefore, the logical assumption is that methamphetamine-induced damage to DA systems may contribute to some of the cognitive deficits observed in methamphetamine-dependent subjects.

Serotonergic Systems and Cognition
The depletion of central 5-HT in rats has been shown to increase the level of premature responding that is independent of the ability to detect and respond accurately to visually displayed targets.[81] Harrison et al.[81] proposed that 5-HT depletion in animals may increase impulsivity by altering 5-HT-DA interactions and, possibly, removing the inhibitory effects of 5-HT on DA neurotransmission. Others have suggested that lower 5-HT levels may actually enhance attentional focus under other conditions, although reduced serotonin levels may increase impulsive responses and errors of commission in some circumstances.[82,83] In an attentional search task that required the suppression of a distracting stimulus,

Coull et al.[82] found that subjects on a tryptophan-depleted diet ignored the distractor more promptly than those in the placebo control group. Data from their study suggests that reduced serotonin levels may contribute more to impulsive patterns of responses rather than to deficits in selective attention. Reduced serotonin levels in humans have been linked to impaired long-term memory performance.[84,85] Memory performance in 27 tryptophan-depleted healthy subjects was assessed at immediate and delayed intervals, with specific memory impairments emerging in the delayed condition.[85] In contrast, no short-term memory, perceptual, or psychomotor deficits were observed.

Methamphetamine-dependent subjects show cognitive patterns that are similar to those of subjects who have been on tryptophan-depleted diets.[68] Rogers et al.[68] used a novel computerized decision making task in order to compare the decision making behavior of 1) chronic amphetamine abusers, 2) chronic opiate abusers, 3) patients with focal lesions of orbital frontal cortex or dorsolateral/medial prefrontal cortex, and 4) tryptophan-depleted normal volunteers. Chronic amphetamine abusers and patients with damage to the orbito-frontal cortex—but not other sectors of the PFC—showed suboptimal decisions and deliberated for significantly longer periods of time before making choices. Subjects with lower plasma tryptophan performed similarly to subjects with histories of amphetamine abuse. Such a discovery is salient, as studies conducted on animals have revealed reduced levels of 5-HT due to high-dose methamphetamine administration.[31] Limbic regions that are innervated by 5-HT projections are especially sensitive to the effects of repeated amphetamine administration in animal studies,[17,31] thus one mechanism for altered decision making associated with chronic amphetamine abuse in humans might be the altered serotonergic modulation of the ventral PFC and its interconnected structures. Increased impulsivity and impaired judgment that are associated with methamphetamine use may be linked to the depletion of both DA and 5-HT neurotransmitter systems.

Electrophysiological Studies

Disrupted attentional processing as a result of methamphetamine use has been detected using electrophysiological techniques in both animals[86] and humans.[87,88] Effects of repeated administration of methamphetamine in rats were examined using electrophysiological techniques to measure an attentional component (P3-like potential) of the event-related potential (ERP) while the animals were performing an active discrimination task.

The rats were trained to press a bar after cessation of a target tone (1000 Hz) that lasted for 800 ms and to withhold an overt response to the standard tone (2000 Hz). Following a series of injections with saline or methamphetamine, ERPs were recorded in rats. In the rats that received methamphetamine, the amplitude of an attention-related ERP (the P-3 like potential) decreased without alterations in latency. These results are consistent with alteration in catecholaminergic neurotransmission that is induced by repeated methamphetamine administration. Human subjects were used in a study in which auditory ERPs were recorded for 15 methamphetamine-dependent individuals during a selective attention test.[87] Attention-related negative ERP components were reduced and latency was delayed when compared to normal controls, which suggests impairment in auditory information processing. Another experiment revealed abnormal electrophysiological activity in methamphetamine-dependent subjects who exhibited reduced P3a amplitude and delayed P3b latency, both markers of selective attention.[88] The authors suggested that these findings might be linked to the dysregulation of functioning that is related to impairment of the frontal cortex.

The prevalence of methamphetamine abuse has reached epidemic proportions throughout the United States. The review of relevant literature supports the assertion that cognitive impairments exhibited by methamphetamine- dependent individuals may be the result of the neurotoxic effects of multiple neurotransmitter systems that are distributed throughout the cortex. Deficits in attentional inhibition, increased impulsivity, and impaired task-switching strategies may all be consequences of collective damage to the DA and 5-HT systems. A convergence of evidence from behavioral studies in humans, animal research, and the field of neuroimaging is needed to further examine the neural basis of cognitive deficits in methamphetamine-dependent individuals. Increased knowledge of how neural regions and cognitive functions are affected by excessive methamphetamine use could benefit both pharmacological and therapeutic treatment interventions. Targeted and longitudinal research that uses neuroimaging techniques, along with sensitive measures of cognitive function, will have profound implications for the neuroscience of drug addiction, which could subsequently guide pharmacological and treatment interventions.

References

1. Anglin M, Burke C, Perrochet B, et al: History of the methamphetamine problem. J Psychoactive Drugs 2000; 32:137–41

2. Office of National Drug Control Policy: National Drug Control Strategy 2001—ONDCP (Web Page). 16 August 2001; Available at http://www.whitehousedrugpolicy.gov/publications/policy/ndcs01/chap2.html#5. (Accessed 13 November 2001)

3. Community Epidemiology Work Group: Epidemiologic Trends in Drug Abuse Advance Report, June 2001 (Web Page). 3 August 2001; Available at http://165.112.78.61/CEWG/AdvancedRep/601ADV/601adv.html. (Accessed 13 November 2001)

4. U.S. Drug Enforcement Agency: Drug trafficking in the United States (Web Page). September 2001; Available at http://www.dea.gov/pubs/intel/01020/index.html. (Accessed 13 November 2001

5. U.S. Drug Enforcement Agency: Drug trafficking in the United States (Web Page). September 1999; Available at http://www.dea.gov/pubs/intel/99024/99024.html. (Accessed 13 November 2001)

6. Marshall DR. Methamphetamine trafficking, use, abuse and clandestine drug laboratories. Senate Judiciary Committee testimony (Web Page). 28 July 1999. Available at http://www.dea.gov/pubs/cngrtest/ct072899.html. (Accessed 13 November 2001)

7. Gonzalez Castro F, Barrington E, Walton M, et al: Cocaine and methamphetamine: differential addiction rates. Psychol Addict Behav 2000; 14:390–396

8. Cho AK, Kumagai Y: Metabolism of amphetamine and other arylisopropylamines in Amphetamine and Its Analogs: Psychopharmacology, Toxicology, and Abuse, Cho AK, Segal DS. San Diego: Academic Press, 1994

9. Segal D, Kuczenski R. Repeated binge exposures to amphetamine and methamphetamine: behavioral and neurochemical characterization. J Pharmacol Exp Ther 1997; 282:561–573

10. Sato M, Chen C, Akiyama K, et al: Acute exacerbation of paranoid psychotic state after long-term abstinence in patients with previous methamphetamine psychosis. Biol Psychiatry 1983; 18:429–440

11. Iwanami A, Sugiyama A, Kuroki N, et al: Patients with methamphetamine psychosis admitted to a psychiatric hospital in Japan: a preliminary report. Acta Psychiatr Scand 1994; 89:428–432

12. Yui K, Goto K, Ikemoto S, et al: Monoamine neurotransmitter function and spontaneous recurrence of methamphetamine psychosis. Annals New York Academy of Sciences 1996; 81:415–429

13. American Psychiatric Association: Diagnostic and statistical manual of mental disorders: DSM-IV-TR, 4th edition, text revision. Washington, DC: American Psychiatric Association, 2000

14. Liang NY, Rutledge CO: Evidence for carrier-mediated efflux of dopamine from corpus striatum, Biochem Pharmacol 1982; 31:983–992

15. Sulzer D, Maidment NT, Rayport S: Amphetamine and other weak bases act to promote reverse transport of dopamine in ventral midbrain neurons. J Neurochem 1993; 60:527–535

16. Ricaurte GA, Schuster CR, Seiden LS: Further evidence that amphetamines produce long-lasting dopamine neurochemical deficits by destroying dopamine nerve fibers. Brain Res 1984; 303:359–364

17. Seiden LS, Ricaurte GA: Neurotoxicity of methamphetamine and related drugs, in Psychopharmacology: the third generation of Progress, Meltzer H. Edited by New York, Raven Press

18. Wagner GC, Ricaurte GA, Seiden LS, et al:. Long-lasting depletions of striatal DA and loss of DA uptake sites following repeated administration of methamphetamine. Brain Res 1980; 181:151–160

19. O'Dell SJ, Weihmuller FB, Marshall JF: Methamphetamine-induced dopamine overflow and injury to striatal dopamine terminals: attenuation by dopamine D1 or D2 antagonists. J Neurochem 1993; 60:1792–1799

20. Axt KJ, Commins DL, Vosmer G, et al: Alpha-methyl paratyrosine pretreatment partially prevents methamphetamine-induced endogenous neurotoxin formation. Brain Res 1990; 515:269–276

21. Fumagalli F, Gainetdinov RR, Valenzano KJ, et al: Role of dopamine transporter in methamphetamine-induced neurotoxicity: Evidence from mice lacking the transporter. J Neurosci 1998; 18:4861–4869

22. Marek GH, Vosmer G, Seiden LS: Dopamine uptake inhibitors block long-term neurotoxic effects of methamphetamine upon dopaminergic neurons. Brain Res 1990; 513:274–279

23. Schmidt CH, Gibb JW: Role of the dopamine uptake carrier in the neurochemical response to methamphetamine: Effects of amfonelic acid. Eur J Pharmacol 1985; 109:73–80

24. Yuan J, Callahan BT, McCann UD, et al: Evidence against an essential role of Endogenous brain dopamine in methamphetamine-induced dopaminergic neurotoxicity. J Neurochem 2001; 77:1338–1347

25. Bowyer JF, Davies DL, Schmued L, et al: Further studies of the role of hyperthermia in methamphetamine neurotoxicity. J Pharmacol Exp Ther 1994; 268:1571–1580

26. Hotchkiss AJ, Gibb JW: Long term effects of multiple doses of methamphetamine on tryptophan hydroxylase and tyrosine hydroxylase activity in rat brain. J Pharmacol Exp Ther 1980; 214:257–262

27. Ricaurte GA, Guillery RW, Seiden LS, et al: Dopamine nerve terminal degeneration produced by high doses of methamphetamine in the rat brain. Brain Res 1982; 235:93–103

28. McCann UD, Wong DF, Yokoi F, et al: Reduced striatal dopamine transporter density in abstinent methamphetamine and methcathinone users: Evidence from positron emission tomography studies with (C-11)-WIN-35,428. J Neurosci 1998; 18:8417–8422

29. Sekine Y, Iyo M, Ouchi Y, et al: N Methamphetamine-related psychiatric symptoms and reduced brain dopamine transporters studied with PET. Am J Psych, 2001; 158:1206–1214

30. Volkow ND, Chang L, Wang GJ, et al: Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. Am J Psychiatry 2001; 158:377–382

31. Ricaurte GA, Schuster CR, Seiden LS: Long-term effects of repeated methylamphetamine administration on dopamine and serotonin neurons in the rat brain: A regional study. Brain Res 1980; 193:153–163

32. Johnson M, Stone DM, Hanson GR, et al: Role of the dopaminergic nigrostriatal pathway in methamphetamine-induced depression of the neostriatal serotonergic system. Eur J Pharmacol 1987; 135:231–234

33. Sonsalla PK, Gibb JW, Hanson G.R: Roles of D1 and D2 dopamine receptor subtypes in mediating the methamphetamine-induced changes in monoamine systems. J Pharmacol Exp Ther 1986; 238:932–937

34. Stone DM, Stahl DC, Hanson GR, et al: The effects of 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenediox-

yamphetamine (MDA) on monoaminergic systems in the rat brain. Eur J Pharmacol. 1986; 128:41–48

35. Schmidt CJ, Ritter JK, Sonsalla PK, et al: Role of dopamine in the neurotoxic effects of methamphetamine J Pharmcol Exp Ther 1985; 233:539–544

36. Callahan BT, Cord BJ, Ricaurte GA: Long-term impairment of anterograde axonal transport along fiber projections originating in the rostral raphe nuclei after treatment with fenfluramine or methylenedioxymethamphetamine Synapse 2001; 40:113–121

37. PUB:Zhou FC, Bledsoe S., Methamphetamine causes rapid varicosis, perforation and definitive degeneration of serotonin fibers: An immunocytochemical study of serotonin transporters. Neuroscience NET, 1996; 1

38. McCann UD, Szabo Z, Scheffel U, et al: Positron emission tomographic evidence of toxic effect of MDMA ('Ectasy') on brain serotonin neurons in human beings. Lancet 1998b; 352:1437–1445

39. Abekawa T, Ohmori T, Koyama T: Effects of repeated administration of a high dose of methamphetamine on dopamine and glutamate release in rat striatum and nucleus accumbens. Brain Res 1994; 643:276–281

40. Nash JF, Yamamoto BK: Methamphetamine neurotoxicity and striatal glutamate release: comparison to 3,4-methylenedioxymethamphetamine. Brain Res 1992; 581:237–243

41. Sonsalla PK, Nicklas WW, Heikkila R: Role for excitatory amino acids in methamphetamine-induced nigrostriatal dopaminergic toxicity. Science 1989; 243:398–400

42. Sonsalla PK, Riordan DE, Heikkila RE: Competitive and noncompetitive antagonists at N-methyl-d-aspartate receptors protect against methamphetamine-induced dopaminergic damage in mice. J Pharmacol Exp Ther 1991; 256:506–512

43. Weihmuller, FB O'Dell, SJ Marshall, JF: MK-801 protection against methamphetamine-induced striatal dopamine terminal injury is associated with attenuated dopamine overflow. Synapse 1992; 11:155–163

44. Abekawa T, Ohmori T, Koyama T: Effects of nitric oxide synthesis inhibition on methamphetamine-induced dopaminergic and serotonergic neurotoxicity in the rat brain. J Neural Transm 1996; 103:671–680

45. Pfefferbaum A, Adalsteinsson E, Spielman D, et al: In vivo brain concentrations of N-acetyl compounds, creatine, and choline in Alzheimer disease. Arch Gen Psychiatry 1999; 56:185–192

46. Ernst T, Chang L, Leonido-Yee M, et al: Evidence for long-term neurotoxicity associated with methamphetamine abuse a H-MRS study. Neurology 2000; 54:1344–1349

47. Nordahl TE, Salo RE, Poissin K, et al: Low N-acetyl-aspartate and high choline in the anterior cingulum of recently abstinent methamphetamine dependent subjects: a Proton MRS study. Presented at the Annual Meeting of Soc Neuroscience, 2001

48. Taylor MJ, Alhassoon OM, Schweinsburg BC, et al: MR spectroscopy in HIV and stimulant dependence. J Int Neuropsychol Soc 2000; 6:83–85

49. Bartzokis G, Beckson M, Lu PH, et al: Age-related brain volume reductions in amphetamine and cocaine addicts and normal controls: implications for addiction research. Psychiatry Re 2000; 98:93–102

50. London E, Dong Y, Simon SL, et al: Brain metabolism during early abstinence from methamphetamine abuse. Presented at the Annual Meeting of the Am College of Neuropsychopharmacology, 2001

51. Harvey DC, Lacan G, Tanious SP, et al: Recovery from methamphetamine induced long-term nigrostriatal dopaminergic deficits without substantia nigra cell loss. Brain Res 2000; 871:259–270

52. Wilson JM, Kalasinsky KS, Levey AI, et al: Striatal dopamine nerve terminal markers in human, chronic methamphetamine users. Nat Med1996; 2:699–703

53. Volkow ND, Chang L, Wang GJ, et al:Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. J Neurosci, 2001; 21:9414–9418

54. Bolla KI, Funderburk FR, Cadet JL:Differential effects of cocaine and cocaine alcohol on neurocognitive performance. Neurology 2000; 54:2285–2292

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

56. Gillen RW, Kranzler HR, Bauer LO, et al: Neuropsychologic findings in cocaine-dependent outpatients. Prog Neuro psychopharmacol Biol Psychiatry 1998; 22:1061–1076

57. Horner MD: Attentional functioning in abstinent cocaine abusers. Drug Alcohol Depend 1999; 54:19–33

58. Robinson JE, Heaton RK, O'Malley SS: Neuropsychological functioning in cocaine abusers with and without alcohol dependence. J Int Neuropsychological Soc 1999; 5:10–19

59. Rosselli M, Ardila A: Cognitive effects of cocaine and polydrug abuse. J Clin Exp Neuropsychol 1996; 18:122–135

60. Smelson DA, Roy A, Santana S, et al: Neuropsychological deficits in withdrawn cocaine-dependent males. Am J Drug Alcohol Abuse 1999; 25:377–381

61. Fleckenstein A, Gibb J, Hanson G: Differential effects of stimulants on monoaminergic transporters: pharmacological consequences and implications for neurotoxicity. Eur J Pharmacol 2000; 406:1–13

62. Kornetsky C, Mirsky AF, Kessler EK, et al: The effects of d-amphetamine on behavioral deficits produced by sleep loss in humans. J Pharmacol 1959; 127:46–50

63. Seashore RH, Ivy AC: Effects of analeptic drugs in relieving fatigue. Psychological Monographs 1953; 67:1–16

64. Soetens E, Casaer S, D'Hooge R, et al: Effect of amphetamine on long-term retention of verbal material. Psychopharmacology 1995; 119:155–162

65. Grinspoon L, Hedblom P: The Speed Culture. Harvard University Press, Cambridge, Mass 1975

66. Fleming K, Bigelow LB, Weinberger DR, et al: Neuropsychological effects of amphetamine may correlate with personality characteristics. Psychopharmacol Bull 1995; 31:357–362

67. Burns JT, House RF, Fensch FC, et al: Effects of magnesium pemoline and dextroamphetamine on human learning. Science 1967; 155:849–851

68. Rogers RD, Everitt BJ, Baldacchino A, et al: Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depeleted normal volunteers: evidence for monoaminergic mechanisms. Neuropsychopharmacology 1999; 20:322–339

69. Salo R, Nordahl TE, Possin K, et al. Reduced cognitive inhibition in methamphetamine dependent individuals. (Abstract presented at Society of Neuroscience, San Diego, CA 2001)

70. Simon SL, Domier C, Carnell J, et al: Cognitive impairment in individuals currently using methamphetamine. Am J Addict 2000; 9:222–231

71. Ornstein TJ, Iddon JL, Baldaccino AM, et al: Profiles of cognitive dysfunction in chronic amphetamine and heroin abusers. Neuropsychopharmacology 2000; 23:113–126

72. Squire LR, Zola-Morgan S: Memory: brain systems and behavior. Trends Neurosci 1988; 4:170–175

73. Tulving E, Schacter DL: Priming and human memory systems.

Science. American Association for the Advancement of Science 1990; 4940:301–306

74. Cohen JD, Servan-Schreiber DS: A theory of dopamine function and its role in cognitive deficits in schizophrenia. Schizophr Bull 1993; 19:85–104

75. Baunez C, Robbins TW: Effects of dopamine depletion of the dorsal striatum and further interaction with subthalamic nucleus lesions in an attentional task in the rat. Neuroscience 1999; 92:1343–1356

76. Roberts AC, De Saliva MA, Wilkinson LS, et al: 6-Hydroxydopamine lesions of the prefrontal cortex in monkeys enhance performance on an analog of the Wisconsin Card Sort Test: possible interactions with subcortical dopamine. J Neurosci 1994; 14: 2531–2544

77. Alexander, GE, DeLong ME, Strick PL: Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Ann Rev Neurosci 1986; 9:357–381

78. Cools AR, van den Bercken JHL, Horstinck NW, et al: Cognitive and motor shifting aptitude disorder in Parkinson's disease. J Neurol Neurosurg Psychiatry 1984; 47:443–453

79. Harrington DL, Haaland KY: Sequencing in Parkinson's disease. Brain 1991; 114:99–115

80. Downes JJ, Roberts AC, Sahahkian BJ, et al: Impaired extradimensional shift performance in unmedicated and medicated Parkinson's disease: evidence for a specific attentional dysfunction. Neuropsychologia 1989; 26:1329–1343

81. Harrison AA, Everitt BJ, Robbins TW: Central 5-HT depletion enhances impulsive responding without affecting the accuracy of attentional performance: interactions with dopaminergic mechanisms. Psychopharmacology 1997; 133:329–342

82. Coull JT, Sahakian BJ, Middleton HC, et al: Differential effects of clonidine, haloperidol, diazepam and tryptophan depletion on focussed attention and attentional search. Psychopharmacology 1995; 121:222–230

83. Soubrie P: Reconciling the role of central serotonin neurons in human and animal behavior. Behav Brain Sci 1986; 9:319–364

84. Park SB, Coull JT, McShane RH, et al: Tryptophan depletion in normal volunteers produces selective impairments in learning and memory. Neuropharmacology 1994; 33:575–588

85. Riedel WJ, Klaases T, Deutz NEP, et al: Tryptophan depletion in normal volunteers produces selective impairment in memory consolidation. Psychopharmacology 1999; 141:362–369

86. Takeuchi S, Jodo E, Suzuki Y, et al: Effects of repeated administration of methamphetamine on P3-like potentials in rats. Int J Psychophysiol 1999; 2:183–192

87. Iwanami A, Suga I, Kato N, et al: Event-related potentials in methamphetamine psychosis during an auditory discrimination task. A preliminary report. Eur Arch Psychiatry Clin Neurosci 1993; 242:203–208

88. Iwanami A, Kuroki N, Iritani S, et al: P3a of event-related potential in chronic methamphetamine dependence. J Nerv Ment Dis 1998; 186:746–751