Methamphetamine Increases, and HIV Decreases, Brain Volumes

HIV infection and methamphetamine addiction produce distinct, partly overlapping effects on brain structures.

By John S. DeMott, NIDA NOTES Contributing Writer

In a study that confirmed the association between HIV infection and loss of brain volume, NIDA-funded investigators also found an association between methamphetamine addiction and increased regional brain volume. Each type of volume change was associated with neurocognitive impairments, but it was unclear whether the two together caused any cognitive effects beyond the sum of what each produced individually.

Using structural magnetic resonance imaging (MRI), Drs. Terry L. Jernigan, Anthony C. Gamst, and colleagues at the University of California, San Diego (UCSD) mapped the major gray-matter brain structures of 103 people in four age and education-matched groups: HIV-infected; methamphetamine-addicted; having both conditions; and having neither. The methamphetamine-addicted individuals were in recovery at UCSD’s HIV Neurobehavioral Research Center.

After accounting for normal age-related reductions in brain volume, the participants with HIV had smaller volumes of cortical, limbic, and striatal structures, with the associations being most pronounced in the frontal and temporal lobes. Methamphetamine addiction was linked with increased volume in the parietal cortex and in all three segments of the basal ganglia—caudate nucleus, lenticular nucleus, and nucleus accumbens (NAc). In the caudate, volume reductions related to HIV and increases related to methamphetamine overlapped, producing a net volume approximating normal.
A further analysis of the volume data may reinforce existing evidence that drug abuse is especially damaging during adolescence and young adulthood, when the brain is still developing. The results showed that addicted individuals who were younger had greater NAc volume differentials compared with their non-drug-abusing age mates than did older addicted individuals. One possible explanation for this is that the drug interfered with the pruning of some NAc connecting fibers that normally occurs in the transition to adulthood, producing a small but measurable reduction in NAc volume. "While we can't be certain of the explanation, this finding highlights the concern that exposure during adolescence may alter the course of ongoing brain maturation," says Dr. Jernigan (see chart).
The fact that brain alterations in methamphetamine dependence and HIV infection are distinct from each other is a clue that may help us to sort out the origins of different kinds of mental problems in these individuals.

Although the study results provided little information about specific drug mechanisms, the investigators note that animal studies have shown methamphetamine can incite inflammatory responses and abnormal growth of nerve fibers, each of which can increase tissue volume. “These findings emphasize that the brain’s response to stimulant exposure, and indeed to HIV as well, is probably quite dynamic, characterized by overlapping responses in different glial, as well as neuronal, cell populations,” says Dr. Jernigan. “The findings raise interesting questions for multiple-modality imaging studies, and underscore the degree of neural plasticity, and thus the potential for targeted intervention.” Dr. Jernigan says a finding of extensive change in the parietal cortex of methamphetamine abusers “helps to confirm the importance of parietal lobe involvement and may help correct a tendency in the field to neglect this region.”

**IMPLICATIONS FOR BRAIN FUNCTION**

The researchers looked for correlations between the brain volume abnormalities and ratings of neuropsychological impairment. At the outset of the study, all other groups were significantly impaired relative to the HIV-negative and methamphetamine-negative group, which had a rating of 2.9 compared with 4.7 for those with both conditions, 4.2 for methamphetamine-addicted participants and 4.1 for HIV-positive individuals. Brain impairment was most pronounced in the HIV-positive participants with the most extensive loss of cortical volume and in the methamphetamine-addicted participants with the highest increase in cortical volume. The investigators found only one significant correlation between brain volumes and impairment in addicted individuals with HIV, a finding they believe probably reflects confounding by the opposed volume impacts of the two pathologies. The correlation
was between hippocampal volume—a structure that both factors may damage—and severity of cognitive impairment in the dually diagnosed group.

"The fact that brain alterations in methamphetamine dependence and HIV infection are distinct from each other is a clue that may help us to sort out the origins of different kinds of mental problems in these individuals," Dr. Jernigan says. "This is very exciting, because our results raise a number of specific questions that may not have been posed without these findings."

Dr. Ro Nemeth-Coslett, a NIDA psychologist, agrees. "As often happens in research, these results raise more questions than they answer. Dr. Jernigan's findings of structural inconsistencies in pathology are unaccounted for. Now we need mechanistic studies to provide a clearer understanding of what aspects of microscopic cellular organization actually drive the MRI measures."

**SOURCE**


[Abstract]
Behavioral therapy can help gay and bisexual men (GBM) reduce methamphetamine abuse and risky sexual behaviors and sustain these gains for 1 year, NIDA-funded researchers report. By the end of a 16-week trial of four different behavioral therapies, study participants’ stimulant-positive urine samples fell 31 percent, and their number of past-month sexual partners fell more than 50 percent—outcomes that regressed little at the followup visits. Symptoms of depression also improved.

Benefits of Behavioral Therapy Persist Up to One Year

![Graph showing the percentage of stimulant-positive urine samples over time for different therapies.]

Although all interventions were effective, participants who received contingency management (CM), cognitive-behavioral therapy (CBT) and CM, or culturally tailored Gay CBT (GCBT) submitted fewer stimulant-positive urine samples during treatment, compared with those in standard CBT.

Dr. Steven Shoptaw and colleagues at the University of California, Los Angeles and the Friends Research Institute recruited 263 methamphetamine-addicted GBM throughout Los Angeles County, particularly in Hollywood, where HIV prevalence is especially high. Of these, 162 completed the requirements for entering the treatment phase of the study, which were to attend six assessments and participate in at least two of four group sessions on abstinence skills during a 2-week "baseline period." Men who met the requirements reported less severity and shorter duration of methamphetamine abuse than those who did not, despite having abused methamphetamine for 5 years and having spent $293 on the drug in the past month, on average. Half had engaged in unprotected anal intercourse (UAI) with someone other than their primary partner in the past month, and 84 percent of these men linked the behavior to methamphetamine abuse. Most participants (73 percent) reported symptoms of depression, with about 30 percent describing these as moderate to severe.
The researchers randomly assigned each patient to one of four behavioral therapies: cognitive-behavioral therapy (CBT), contingency management (CM), CBT+CM, or Gay CBT (GCBT). In CBT, participants analyzed situations and emotions linked with relapse, practiced ways to manage craving and thoughts about drug abuse, and discussed healthy behaviors in group sessions. In CM, participants received vouchers redeemable for groceries, transportation, and clothing if they submitted stimulant-negative urine samples. GCBT addressed standard CBT issues—including relapse, craving, and healthy behaviors—using specific examples from gay cultural events and environments. For example, they compared the experience of owning up to a drug problem with the experience of acknowledging sexual orientation by “coming out.” All four interventions were offered three times a week for 4 months.

Multiple, Lasting Benefits

Participants reduced methamphetamine abuse and risky sexual behaviors and experienced fewer depression symptoms in the last month of treatment compared with the month before therapy, regardless of the therapeutic approach. Overall, they decreased methamphetamine abuse from 9.6 to 2.4 days a month and reduced the number of past-month sexual partners from 9.8 to 4.3, on average. The percentage who reported unprotected insertive anal intercourse—a risk factor for HIV-infected individuals to transmit the virus to partners—fell from 36.9 percent to 16.7 percent by the end of treatment. Beck Depression Inventory (BDI) scores improved from 14.3 (in the “mild to moderate” range) at baseline to 5.4 (“minimal”) in the last week of treatment.

Although all therapies benefited participants, response to the treatments differed. During the treatment period, participants in GCBT and the combined treatments attended more weeks of therapy and submitted fewer stimulant-positive urine samples than those who received standard CBT during treatment. Participants receiving GCBT showed a faster decrease in unprotected receptive anal intercourse— a risk factor for acquiring the virus from a partner—compared with those in standard CBT. Most participants (80 percent) took part in the 1-year followup. Generally, they sustained the lower levels of methamphetamine abuse, risky sexual behaviors, and depression observed at the end of treatment (see “Benefits of Behavioral Therapy Persist Up to One Year”).

“It is encouraging that several types of behavioral treatment reduced both drug abuse and risky sexual behaviors among gay and bisexual men at high risk for contracting or transmitting HIV,” says Ms. Debra Grossman of NIDA’s Division of Neuroscience and Behavioral Research. However, more studies are needed to determine the components of treatment that affect risky sexual behaviors and the link between methamphetamine abuse and such behaviors in other populations, she adds.

All Four Therapies Reduced Depression Symptoms

![Graph showing the reduction in Beck Depression Inventory (BDI) scores over time for each therapy group.](http://archives.drugabuse.gov/NIDA_notes/NNvol20N4/Treatment.html)

Participants demonstrated improvement in Beck Depression Inventory scores, which dropped sharply the first week of treatment and leveled off at week 4.

Methamphetamine Treatment as HIV Prevention
For about a decade in California, the drug most tightly linked with HIV infection in GBM has been methamphetamine. The drug conveys a sense of heightened sexuality in the short term and is associated with risky sexual behaviors and extremely high rates of HIV infection in those seeking treatment. Sixty percent of the participants in Dr. Shoptaw’s study reported HIV-positive status, a prevalence much higher than his group has observed among GBM seeking treatment for cocaine (30 percent), alcohol (15 percent), or heroin (5 percent) abuse.

"The reductions in risky sexual behavior in this study exceeded those observed in HIV prevention trials among GBM. We conclude that treatment for meth abuse fits into a comprehensive HIV prevention strategy," says Dr. Shoptaw. The findings have already made an impact: These data helped policymakers at the California Office of AIDS decide to allocate $3 million for programs that address methamphetamine abuse among GBM.

**Methamphetamine and the Blues**

The researchers were not surprised by the high percentage of their study participants who reported depression symptoms at the beginning of the study. GBM are three times as likely as heterosexual men to have clinical depression.

Methamphetamine abusers often say they take the drug to kick the blues, but results from the current study suggest that continuing abuse may serve to relieve low moods related to stimulant withdrawal rather than alleviate underlying chronic depression.

When they analyzed the temporal link between methamphetamine abuse and depression, Dr. Shoptaw and his colleagues found that a urine sample indicating abuse of the drug within the past 5 days strongly predicted high BDI scores and abstinence strongly predicted low scores. In contrast, BDI scores did not predict episodes of future methamphetamine abuse, which is what would be expected if the men were abusing the drug to alleviate depression. "Meth abusers probably remember feeling better after taking the drug, but this perception may not match the physiology of long-term stimulant abuse," says Dr. James Peck, a member of the research team who led the analysis of the depression data.

**Sources**

Long-Term Abstinence Brings Partial Recovery From Methamphetamine Damage

By Patrick Zickler, NIDA NOTES Staff Writer

Methamphetamine abusers who remain abstinent for 9 months or longer show modest improvement in performance on some tests of motor skill and memory. They also appear to recover from some of the drug’s damaging effects on metabolism in the thalamus, a brain region involved in relaying and filtering sensory, motor, and emotional signals between the cerebral cortex and other brain structures. Drug-related deficits appear to persist longer, however, in another brain region, the striatum, which plays a role in reward-linked motivation, planning, and impulse control.

Some Methamphetamine-Related Deficits Recover After Protracted Abstinence

Relative metabolic activity (regional metabolic rate compared with rate for entire brain) was reduced in the striatum and thalamus of five methamphetamine abusers, compared with nonusers, after short abstinence. After protracted (more than 9 months) abstinence, thalamic metabolism returned to normal levels (blue line indicates median level for healthy comparison subjects). Striatal metabolism showed no recovery after abstinence.

Dr. Gene-Jack Wang and colleagues at the Brookhaven National Laboratory in Upton, New York, evaluated metabolism and neuropsychological function in a small group of methamphetamine abusers (three women and two men; average age, 29) who entered treatment as part of a California drug court rehabilitation program. In tests...
following an abstinence of 2 months or less, the methamphetamine abusers scored lower than nonabusers, though within normal ranges, on tests of gross motor function (timed while walking in a straight line for a defined distance), fine motor coordination (inserting pegs into small angled holes), memory (learning and recalling lists of unrelated words immediately, after a delay, and after a distraction), and attention (identifying numbers previously associated with symbols). When tested again after an additional 9 months of abstinence (average total abstinence was 17 months), these methamphetamine abusers had improved performance on three of five neuropsychological measures: the timed gait test, symbol-digit association, and delayed word recall. The changes in test scores correlated with improvement in thalamic metabolism.

The researchers used positron emission tomography (PET) to evaluate methamphetamine's effect on metabolism in the thalamus and striatum. This technique involves injection of a radioactively labeled form of glucose, the body's basic metabolic fuel. Differences in activity among brain regions are reflected by different rates of glucose consumption. PET imaging captures the signals emitted by the radioactive glucose molecules; the strength of the signal indicates the intensity of metabolic activity. The methamphetamine abusers had lower metabolism in the thalamus than did nonabusers when evaluated after the short abstinence. However, the abusers' thalamic metabolism was not significantly different from the nonabusers' after the longer drug-free period, suggesting that drug damage in this brain region is reversed with abstinence. "The correlation between increased thalamic metabolism and the tendency to better scores on some tasks suggests that the thalamic changes are functionally significant," Dr. Wang says.

After a short abstinence, metabolism in another brain region, the striatum, also was lower in methamphetamine abusers than in participants who had never used the drug. In contrast to the findings with thalamic metabolism, however, abusers did not show recovery of striatal metabolism after the longer abstinence.

The emerging pattern of these studies offers encouraging evidence that some of the destructive effects of methamphetamine abuse may be reversible. The brain may respond to damage by rerouting some connections. Earlier work made it clear that methamphetamine causes damage to brain circuits that rely on the neurotransmitter dopamine. "Recovery of thalamic metabolism could indicate in part a compensatory adaptation to the loss of these dopamine cells by increased activity in other brain cells that extend from the striatum into the thalamus," says Dr. Joseph Frascella of NIDA's Division of Clinical Neuroscience, Development, and Behavioral Treatments. "But there is a troubling indication that some of the drug's damage is longer lasting. The persistent reduction in striatal metabolism seems to reflect the drug's toxicity to dopamine terminals in that region."

This lasting deficit in striatal metabolism may hold a clue to the cause of other methamphetamine-related effects. In some followup studies, methamphetamine abusers report lack of motivation and anhedonia—an absence of pleasure in response to acts that had previously been pleasurable—as long as 2 years after their last use of methamphetamine. Motivation and pleasurable response are both governed in part by activities in one specific region of the striatum, the nucleus accumbens, Dr. Wang explains.

"The anhedonia and decreased motivation reported by some abstinent abusers may be the result of reduced activity—indicated in this study by reduced metabolism—in the nucleus accumbens, which has a high density of dopamine cells," says Dr. Wang.

Source


[Abstract]