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Brain Activity Patterns Signal Risk of Relapse to Methamphetamine

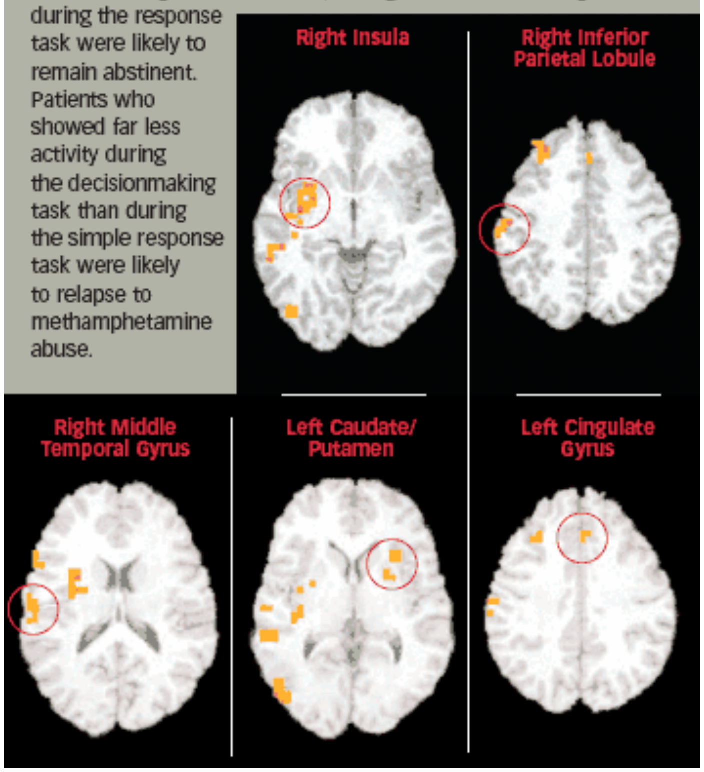
Research Findings
Vol. 20, No. 5 (April 2006)

Methamphetamine abusers who relapse after treatment appear to make decisions using different brain regions than do those who remain abstinent.

By Patrick Zickler, *NIDA NOTES* Contributing Writer

NIDA-supported investigators have found that functional magnetic resonance imaging (fMRI) of the brain, performed during a psychological test, can predict with high accuracy whether an individual will relapse following treatment for methamphetamine abuse. Their study revealed a characteristic pattern of brain activity in methamphetamine-abusing men who relapsed within 1 to 3 years after completing treatment and a different pattern in men who did not.

Dr. Martin Paulus and colleagues at the University of California, San Diego, took the point of departure for their work from previous research that showed methamphetamine abusers and nonabusers activating different brain areas during psychological tests of decisionmaking. These earlier studies showed that poor choices made by drug abusers correlate to distinctive patterns of activity in some areas of the brain. Dr. Paulus's team hypothesized that activity patterns in those regions might also be associated with relapse to drug abuse, which involves similarly destructive decisions.



DRUG ABUSE AND DECISIONMAKING Researchers used functional magnetic resonance imaging (fMRI) to measure patterns of regional brain activity while abstinent methamphetamine abusers performed two tasks, one that required decisionmaking and one that required only a simple response. Participants who showed greater activity in selected brain regions (circled and highlighted in the brain images shown below) during the decisionmaking task than during the response task were likely to remain abstinent. Patients who showed far less activity during the decisionmaking task than during the simple response task were likely to relapse to methamphetamine abuse.

To test their hypothesis, the

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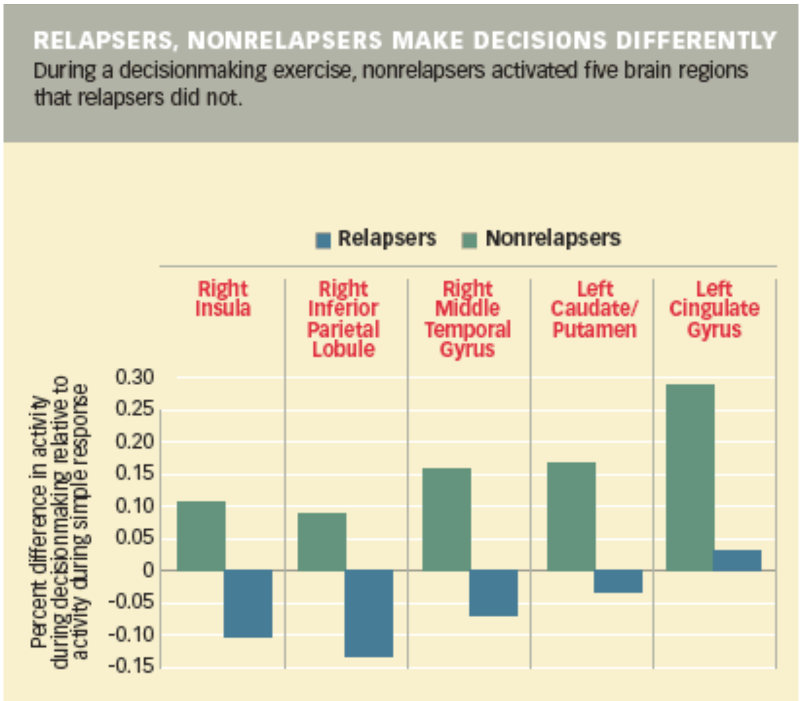
researchers recruited 46 men who had voluntarily entered and completed a 28-day inpatient drug treatment program after abusing methamphetamine for periods ranging from 3 to 34 years. When each man had been abstinent for about 4 weeks, he participated in two psychological tests. During one, he was asked to watch a computer screen and press a button every time a symbol appeared. In the other, he was asked to try to predict whether a flashing symbol would next occur on the left side or right side of the computer screen. The difference between the two tasks was that, in the first, the test-taker needed only to react upon seeing the symbol, while in the second, he needed to decide which side to choose. The researchers recorded the men's brain activity with fMRI throughout the tests.

A year or more (360 to 967 days) after the imaging sessions, Dr. Paulus's team was able to locate and contact 40 of the 46 patients. Of these, 18 had relapsed to methamphetamine abuse (median time to relapse, 279 days; range, 36 to 820 days). Comparing their fMRI results with those of the 22 nonrelapsers, the researchers noted nine regions where the groups' brain activity had differed during decisionmaking. The relapse group showed less activation of the dorsolateral, prefrontal, parietal, and temporal cortices and the insula—regions associated with evaluation and choice among actions that may lead to either beneficial or harmful outcomes. The patterns of brain activation predicted relapse in 17 of the 18 men who had resumed methamphetamine abuse and predicted successful abstinence in 20 of the 22 patients who had not relapsed, Dr. Paulus says.

"The most striking aspect of this result is that the fMRI pattern has 90 percent accuracy in predicting outcome," Dr. Paulus says. "The differences in brain activity are pronounced, with little overlap." Differences in the right insula, right posterior cingulate, and right middle temporal gyrus differentiated relapsers from nonrelapsers. Other brain regions predicted the timing of relapse.

"The most striking aspect of this result is that the fMRI pattern has 90 percent accuracy in predicting outcome. The differences in brain activity are pronounced, with little overlap."

"Some of these predictive areas have not previously been strongly associated with drug abuse," observes Dr. Steven Grant of NIDA's Division of Clinical Neurosciences and Behavioral Research. "For example, while other investigators have reported alterations in the parietal lobe related to drug abuse, this is the first study to show the parietal cortex playing an important role. However, because so many brain regions were related to relapse, we still do not have a full understanding of what specific process might be dysfunctional in the relapse group."



The potential clinical implications of the new finding are promising, but uncertain. For example, no women were included among the participants, who were enrolled from treatment programs. "It's important to confirm the findings in women, for whom social, demographic, and other factors associated with relapse may differ," Dr. Paulus points out. Nonetheless, he says that, in principle, programs treating methamphetamine abuse might use the fMRI protocol to assess patients, then assign those likelier to relapse to higher levels of care. Dr. Paulus believes such an approach might prove cost-effective, even with typical fMRI charges of up to $700 per hour in academic imaging centers. "The human and social costs of relapse are high," Dr. Paulus says. "Using this imaging technique to precisely allocate care to the patients who need it most might well produce enough savings elsewhere to more than offset its expense. An alternative, more practical course of action might be to use these fMRI results as a benchmark for development of other assessments that are less costly, but have the same predictive strength."

Source

Paulus, M.P.; Tapert, S.F.; and Schuckit, M.A. Neural activation patterns of methamphetamine-dependent subjects during decision making predict relapse. *Archives of General Psychiatry* 62(7):761-768, 2005. [Abstract]

Methamphetamine Evokes and Subverts Brain Protective Responses

Research Findings
Vol. 20, No. 6 (July 2006)

Two new studies appear to highlight the role of glial cells—the nervous system's equivalents to the body's immune cells—in methamphetamine abuse.

By Patick Zickler, *NIDA NOTES* Contributing Writer

NIDA-supported researchers have produced brain images demonstrating that structures in an area called the striatum expand in volume during early methamphetamine abuse, then regress toward normal. The investigators believe their findings likely are attributable to neuroprotective cells in the brain mounting an initial attempt to counteract the drug's toxic effects, which continued exposure subsequently overwhelms. In a related result, scientists working with mice have produced evidence that methamphetamine may prompt cells that normally serve neuroprotective functions to instead attack healthy brain cells.

STRUCTURAL FLUCTUATION SUGGESTS GLIAL ACTIVATION

Dr. Linda Chang (now at the University of Hawaii) and colleagues at the University of California, Los Angeles, used magnetic resonance imaging to measure the volumes of striatal brain structures, including the putamen and globus pallidus, in a group of methamphetamine abusers. The studied individuals, 26 women and 24 men (average age 31 years), had abused methamphetamine (average 1.6 g/day on 6.3 days/week) for periods ranging from 4 to 15 years. All had been abstinent for periods ranging from 1 week to 4 years at the time of the study; 44 also took tests of verbal memory and intelligence, gross and fine motor function, mood, executive function, and other capacities likely to be affected by striatal damage.

The researchers expected

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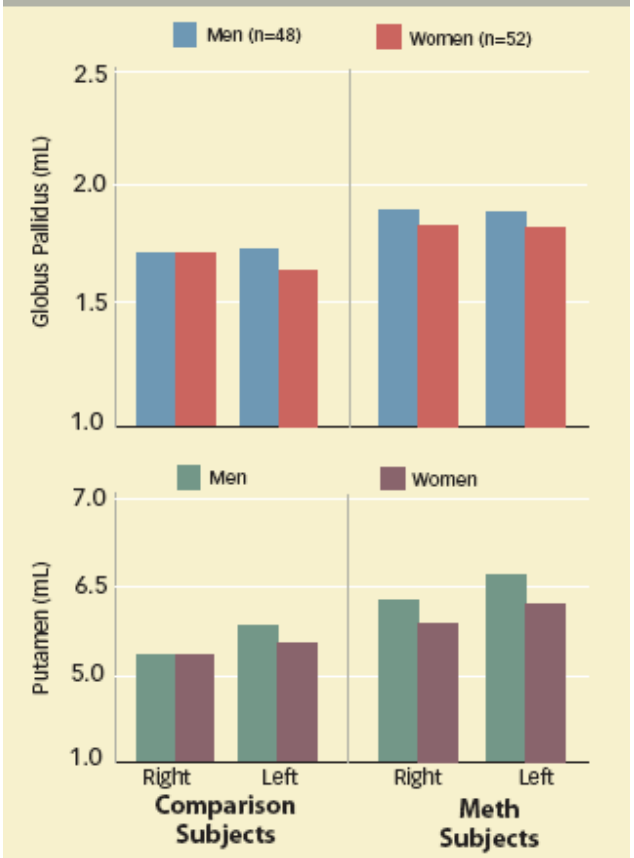
to find that the methamphetamine abusers' striatal regions were smaller than those of a comparison group of age- and gender-matched individuals with no history of methamphetamine abuse. Such a finding would be consistent with previous research showing that methamphetamine reduces the density of striatal dopamine terminals. Instead, says Dr. Chang, "Contrary to our hypothesis, striatal volumes were larger in the methamphetamine abusers as a group." The size difference was greatest among individuals with less cumulative exposure to the drug, and smaller among those with more. Those with the most exposure also performed slightly worse on neuropsychological tests of verbal fluency and visual-motor coordination.

STRUCTURES IN THE BRAIN'S STRIATAL REGION ARE ENLARGED IN METHAMPHETAMINE ABUSERS
Average volumes of the globus pallidus and putamen—structures in the brain's striatal region—are larger in men and women with a history of methamphetamine abuse than in men and women with no exposure to the drug.



Dr. Chang believes the surprising increase in striatal volumes of methamphetamine abusers may reflect the activity of glia—cells that provide protective and reparative functions for the brain's main functional cells, the neurons. When molecules potentially harmful to neurons penetrate the brain, glia mount a response resembling the inflammation and scar tissue formation associated with immune responses in other parts of the body. Possibly, Dr. Chang suggests, methamphetamine provokes glia to react in this way, leading to an increase in regional volume analogous to the swelling seen in bodily immune responses. Subsequently, she speculates, the glial response may taper off as cumulative exposure to the drug—and neuron damage—mount. Continued abuse results in damage that is manifested in decreased cognitive performance.

"This work is consistent with an increasing body of research that shows a relationship between methamphetamine exposure and structural changes in the brain," says Dr. Steven Grant of NIDA's Division of Clinical Neuroscience and Behavioral Research. "It links methamphetamine abuse, structural change, and functional deficits and suggests that the magnitude of these effects is related to the degree of abuse. We don't understand what is happening at deeper levels, but the observations made in this study suggest that the volume changes are related to methamphetamine's direct or indirect effect on glial cells. We still need to understand how structural changes result in functional deficits; how much, if any, of this damage can be reversed; and how methamphetamine acts at the cellular level."

IN MICE, METHAMPHETAMINE MISDIRECTS GLIA TO ATTACK BRAIN CELLS

A study by Drs. Donald Kuhn and David Thomas and colleagues at Wayne State University School of Medicine indicates that methamphetamine's toxic effects may include subverting some glial cells to attack rather than preserve neurons. Specifically, their results indicate that the drug incites a subset of glia called microglia to mount an immune response against dopamine neurons.

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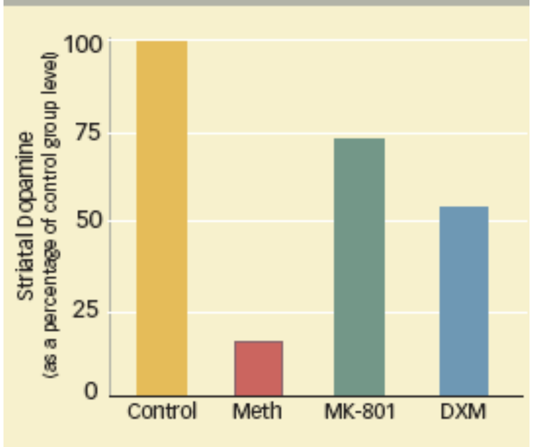
Normally, microglia protect neurons against toxic injury by several mechanisms. They detect and bind to invading molecules, including viruses or bacteria, making them easily accessible to destructive immune system cells such as lymphocytes. As well, they produce compounds, some toxic, to help contain or eliminate the danger. Methamphetamine, the new study suggests, causes dopamine neurons to release a signal that decoys the microglia into turning these normally protective responses against the neurons themselves. When that happens, Dr. Kuhn says, "The microglia aren't reacting to methamphetamine's neural damage. Instead, they are active participants in the drug's neurotoxicity."

To begin their experiments, the researchers reasoned that if microglia contribute to methamphetamine toxicity to dopamine terminals, compounds that protect against such toxicity might do so, at least in part, by inhibiting microglial activation. Their first hypothesis, accordingly, was that the compound MK-801, which is known to be protective, blunts microglial activation. The team showed this to be the case by exposing cell cultures of mouse microglia to two proteins known to precipitate damaging microglial responses: lipopolysaccharide (LPS) and HIV Tat, a derivative of the human immunodeficiency virus. Compared with LPS and HIV Tat exposure without pretreatment, exposure following pretreatment with MK-801 significantly reduced the amount of two protein products of microglial activation, called cyclooxygenase-2 (Cox-2) and tumor necrosis factor-ɑ (TNF-ɑ). Dextromethorphan (DXM), a compound biochemically similar to MK-801, had the same effect.

"These results suggested that both MK-801 and dextromethorphan exert direct action on the microglial cells in culture to block the activation process," Dr. Kuhn says. Having determined that the two compounds block microglial activation *in vitro*, the researchers next hypothesized that they would also do so in living animals.

COMPOUNDS THAT BLOCK THE ACTION OF MICROGLIA COUNTER A TOXIC EFFECT OF METHAMPHETAMINE Striatal regions of mice exposed to methamphetamine contain decreased dopamine content, compared with those of unexposed controls. Treatment with MK-801 or dextromethorphan (DXM) prior to methamphetamine injection reduced the extent of depletion, suggesting that microglia play a role in methamphetamine's toxic effect on the brain's dopamine system.



Drs. Kuhn and Thomas injected mice with either MK-801 or DXM and then methamphetamine (5 mg/kg of body weight) 15 minutes later, repeating this sequence four times at 2-hour intervals. A control group of mice received the same regimen, but with saline substituted for methamphetamine. Forty-eight hours after the last injection, the researchers assayed the brains of the mice for Cox-2 and TNF-ɑ, the indicators of microglia activation, and for striatal dopamine levels, a widely used index of damage to dopamine neurons. Dr. Kuhn says, "We found that both DXM and MK-801 significantly reduced the markers of striatal microglial activation associated with methamphetamine exposure and protected against dopamine nerve terminal damage in the striatum. The close association between the ability of MK-801 and DXM to significantly lower both microglial activation and neuronal damage suggests a causal link between the two. It looks as though the damage associated with methamphetamine abuse is the result of microglial action."

The apparent association of microglia and damage to dopamine neurons has implications beyond what it may reveal about methamphetamine abuse, says Dr. Jerry Frankenheim of NIDA's Division of Basic Neuroscience and Behavioral Research. "Microglia are the primary immune defense cells in the brain. They safeguard neural functions, yet excessive activation can cause microglia to harm neurons. Other research implicates microglial involvement in a wide range of neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and stroke.

Understanding how methamphetamine is able to decoy microglia into a destructive rather than reparative role could also help explain the processes involved in these other disorders."

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