RESEARCH NEWS AND TRENDS FROM THE NATIONAL INSTITUTE ON DRUG ABUSE

NIDA Notes

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Cocaine Locks Rats Into Unrewarding Behaviors

Brain circuits that guide behavior by registering consequences become less flexible after drug exposure.

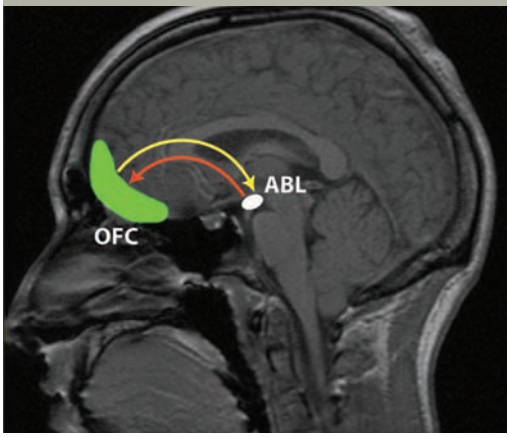
BY NIDA NOTES STAFF

People initially take cocaine for pleasure, but for most chronic abusers, the high becomes progressively shorter and weaker, and negative social and economic consequences grow increasingly dire. Relationships hit the rocks, financial problems mount, and legal trouble follows, but the cocaine abuser often fails to adapt his or her behavior to avoid the accumulating personal disasters and instead remains stuck in self-damaging patterns.

New NIDA-funded research with rats indicates that cocaine may contribute to this inflexibility by impeding abusers' ability to associate warning signs with outcomes. The research links successful sign reading to two connected brain structures—the orbitofrontal cortex (OFC), located directly above the eye sockets, and the basolateral amygdala (ABL), deep in the brain. Cocaine appears to weaken neural signaling in these structures.

"Our findings may explain why cocaine abusers and cocaine-exposed animals have difficulty adapting their behavior to avoid negative outcomes," says Dr. Geoffrey Schoenbaum, who led the University of Maryland School of Medicine studies. "Cocaine seems to disrupt the information-processing ability of neurons in a learning circuit that helps animals and people accommodate their behavior when the environment changes."

CRITICAL INFORMATION PROCESSING
Research indicates that cocaine weakens neural signaling in a learning circuit between the orbitofrontal cortex (OFC) and the basolateral amygdala (ABL).



LEARNING TO USE CUES

To test cocaine's impact on learning and adaptation, Dr. Schoenbaum and colleagues used a protocol called the two-odor go/no-go discrimination task (see box, page 6). The protocol consists of two parts. The first tests an animal's ability to link cues to desired and aversive outcomes. It challenges the animal to perform a task analogous to that of a person learning that right-hand faucets deliver cold water and left-hand ones, hot. In Dr. Schoenbaum's protocol, the counterparts to the faucets are odors. The researchers give a rat a whiff of one odor immediately before filling a well in the cage with a delectable sucrose-flavored drink, and they provide

[*Continued on page 6*]

ALSO IN THIS ISSUE

By NORA D. VOLKOW, M.D., *NIDA Director*

Stimulus Money Will Fund a Surge in Knowledge

The American Recovery and Reinvestment Act of 2009, signed into law by President Obama on February 17, aims to restore the Nation to economic health. To establish conditions for lasting prosperity, the stimulus package will invest in research to protect and improve the physical and mental health of our citizens. The National Institutes of Health is receiving a one-time stimulus infusion of $10.4 billion to support groundbreaking studies, modernize the research infrastructure, and engage more people in scientific endeavors. All the projects must create and preserve jobs and be completed within 2 years.

To fund programs that will yield the greatest payoff in improved public health, NIDA has set two overarching priorities. Its first is to make progress toward eradication of smoking addiction. Smoking causes an estimated 400,000 premature deaths in the United States annually and costs the economy hundreds of billions of dollars in medical care and lost work. NIDA's second priority is to elucidate the ways that genes affect brain development and structure. Such knowledge will advance our ability to treat addiction and many other conditions.

NIDA plans to apply stimulus funds to advance several strategic approaches to yield powerful therapeutic interventions. These include (1) conducting safety and efficacy studies of new medications to treat addiction and prevent relapse; (2) accelerating followup studies on anti-addiction vaccines and augmenting immunotherapy development; (3) developing biomarkers—screens for drug exposure and addiction vulnerability—that practitioners can use to target anti-addiction efforts; (4) identifying new targets for treatment by discovering genetic variations that affect behavioral hallmarks of addiction; (5) determining how chronic drug exposure and other environmental factors activate or silence genes; and (6) learning to use genetic profiles to tailor therapy to individual patients.

Stimulus package resources will allow NIDA to support many skilled scientists, including some in small laboratories, whom it would otherwise not have the resources to fund. The new funding will also enable science teachers and students to participate in summer projects in NIDA-funded labs.

NIDA plans to allocate its stimulus funding to applications previously reviewed as well as to new proposals submitted under three grant programs:

- The Research and Research Infrastructure Grand Opportunities (GO) program (*www.nida.nih.gov/Recovery/gograntshtml*) will fund large-scale research projects to accelerate breakthroughs, support early and applied research on cutting-edge technologies, and develop approaches to improve interactions among multidisciplinary research teams.
- Challenge Grants in Health and Scientific Research (*www.nida.nih.gov/Recovery/NIDAChallenge.html*) are designed to yield quick advances by filling knowledge gaps, spurring new technologies, and strengthening methodology.
- Core Center Grants (*www.nida.nih.gov/Recovery/p30corecenters.html*) are for faculty recruitment to enhance research resources through the multidisciplinary biomedical research core centers.

NIDA Notes

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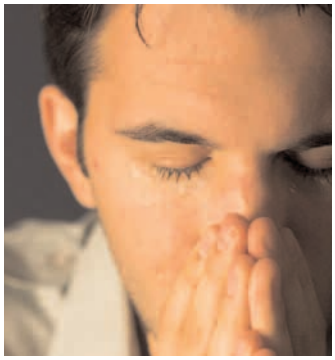


Court Mandates Help Men With Antisocial Personality Disorders Stay in Treatment

Men with co-occurring substance abuse and antisocial personality disorders may particularly benefit from judicially mandated addiction treatment. Such legal pressure has been shown to exert a positive effect on treatment retention in a general population of drug abusers (see What the Numbers Say, page 20).

Dr. Stacey B. Daughters and colleagues at the University of Maryland recently studied 236 men who began therapy for substance abuse problems. Ninety-three of the men met standard criteria for antisocial personality disorder (ASPD), a condition characterized by chronic behavior problems, deceitfulness, and lack of conscience and regard for others.

Among men without ASPD, 85 percent remained in therapy whether the treatment was voluntary or mandated. However, the investigators found that among men with ASPD, about 94 percent of those who were legally required to participate in residential substance abuse treatment remained for a month, compared with just 63 percent of those who had volunteered to enter treatment.

Although ASPD is rare in the general population, researchers estimate that 40 to 50 percent of people in drug treatment programs have the disorder. Moreover, prior research suggests that ASPD increases the risk for addiction treatment dropout, relapse, and, among those with jail sentences, a return to criminal behavior.

The Maryland team's findings have two important implications for substance abusers with ASPD: Judicial mandates offer a way to keep them in addiction treatment programs, and voluntary participants may require special interventions to keep them actively engaged in therapy.

> Journal of Substance Abuse Treatment 34(2):157-164, 2008.

New Tracer for Nicotinic Receptors Promises Improved Specificity

Researchers at NIDA's Intramural Research Program have developed a radiolabeled compound for animal studies of nicotinic acetylcholine receptors in the brain. Tests in monkeys indicate that the new tracer readily enters the animals' brains and binds primarily to the nicotinic receptor subtype called α4β2*. These receptors play a role in nicotine addiction and have been implicated in other neurological conditions, including dementia, epilepsy, depression, and anxiety.

In brain regions containing these receptors, the new radiotracer's accumulation is greater than that of 2FA, the tracer currently used in human imaging studies. As a result, the new tracer produces sharper and more detailed positron emission tomography images and may be especially useful for studying α4β2* nicotinic receptors in brain areas where they are sparsely distributed. The specificity of the new radiotracer accumulation for the regions with these receptors is three- to four-fold that of 2FA, and tests in mice indicate that the new compound is equally safe, says Dr. Alexey G. Mukhin, now at Duke University in Durham, North Carolina.

If further animal and human imaging research confirms these results, the tracer could advance the study of the relationships between α4β2* receptors and specific aspects of nicotine addiction and promote the development of medications for a wide variety of disorders. The chemical name for the new tracer is 6-chloro-3-((2-(S)-azetidinyl)methoxy)-5-(2-fluoropyridin-4-yl)pyridine ([18F]NIDA522131).

>Journal of Neurochemistry 104(2):306-315, 2008.

Adolescent Rats Self-Administer More Nicotine Than Adults

Studies comparing adolescent and adult rats have added to the evidence that the adolescent brain is particularly vulnerable to nicotine addiction. Dr. Edward D. Levin and colleagues at the Duke University Medical Center allowed male rats not previously exposed to nicotine to self-administer the drug for 4

weeks. During the first 2 weeks, the 13 adolescent rats took more than three times as much nicotine as the 13 adults. Nicotine consumption decreased as the adolescents matured, and it reached adult-like levels by the end of week 4.

In a prior study with female rats, the researchers found that adolescents self-administered twice as much nicotine as adults. Unlike the male rats in the current study, however, as the adolescent female rats matured, they continued to self-administer more nicotine than adults. Taken together, the team's results suggest that adolescent male rats may initially be more sensitive than females to nicotine, but females may experience a more persistent vulnerability.

> Neurotoxicology and Teratology 29(4):458-465, 2007.

Criminal Justice-Drug Abuse Treatment Studies Project

Research Addresses Needs of Criminal Justice Staff and Offenders

BY LORI WHITTEN,
NIDA Notes Staff Writer

NIDA established the Criminal Justice–Drug Abuse Treatment Studies (CJ-DATS) project in 2002 to reduce substance abuse and recidivism among offenders following their release from jail or prison. CJ-DATS investigators in nine research centers collaborate with criminal justice partners to fashion and test science-based, practical tools for integrating drug abuse treatment in the Nation's prisons and probation and parole programs.

Dr. Bennett Fletcher serves as CJ-DATS program scientist and provides NIDA input to the network's planning and decisionmaking. According to Dr. Fletcher, "As many as half of the individuals serving sentences in the Nation's jails and prisons have drug problems. The transition from detention or incarceration is a period of high risk for relapse to drug use, acquisition and transmission of infectious diseases, and drug-related recidivism. In its first 5 years, CJ-DATS identified a range of effective practices to reduce these risks. The project is now beginning a new phase of research to determine how correctional and community agencies can most efficiently and effectively implement and sustain these practices."

IDENTIFYING EFFECTIVE PRACTICES

The first phase of CJ-DATS encompassed 13 studies in three areas:

Brief Screening and Assessment Instruments—These studies give criminal justice staff user-friendly tools to identify an offender's need for treatment and criminal justice services and to monitor his or her treatment progress. The researchers have designed a variety of instruments to help providers determine whether a prisoner is responding to therapy, requires referral to a mental health provider, or will need intensive treatment after release. Studies show that these instruments have good reliability, validity, sensitivity, and specificity.

Strategies to Promote Successful Community Re-entry—Many individuals need help to stay engaged in addiction treatment as they re-enter communities following release from prison. Many also require assistance with housing, employment, family relationships, health issues, and building a social support network. CJ-DATS researchers and their criminal justice partners together developed interventions (see box, page 5) to reduce re-entering adults' and adolescents' criminal activity, substance abuse relapse, and sexual behaviors that carry high risk of HIV/AIDS and other sexually transmitted diseases. Investigators have now tested interventions in seven randomized controlled trials, with 3- and 9-month followups. Several appear promising.

Surveys of Treatment Services for Offenders—A team led by the CJ-DATS Research Center at Virginia Commonwealth University and the University of Maryland conducted a National Criminal Justice Treatment Practices Survey to inventory treatments available in correctional facilities, community supervision programs, and drug treatment programs with offender clientele. The data included information on treatment providers, frequency and duration of treatment, and

Effective Treatment Is Not Widely Available

Less than 10 percent of adults and about 20 percent of adolescents with substance abuse problems in the Nation's jails, prisons, and probation programs can receive treatment on a given day, according to the National Criminal Justice Treatment Practices Survey (NCJTPS). Although 65 percent of adult facilities report that they offer substance abuse treatment, the number of people who can participate in these programs is often severely limited.

These findings further reveal the scope of the problem highlighted by previous research indicating that the most frequently provided services for adults and adolescents—substance abuse education and low-intensity group therapy (less than 4 hours a week)—are not likely to help offenders change their behavior. The survey also disclosed that only 40 percent of adult facilities and 29 percent of juvenile facilities reported having full-time personnel to provide drug abuse therapy. For more information, see the *Journal of Substance Abuse* 32 (3), April 2007; this special issue of the journal was dedicated to NCJTPS.

the number of offender clients. The results indicate that there is a significant shortage of treatment opportunities for this population (see box, page 4).

Another survey, by investigators at the National Development and Research Institutes Rocky Mountain Research Center, focuses on services for offenders who have both substance abuse and other mental disorders—a large and growing percentage of the U.S. criminal justice population. This survey is using the specially developed CJ-DATS Co-occurring Disorders Screening Instrument (CODSI) to identify patients with dual disorders. The findings will provide a foundation for efforts to improve treatment services for these offenders.

In a third practice-monitoring project, CJ-DATS investigators are developing a Web-based system to inventory drug court processes and treatment services for the drug court participants. The researchers have pilot-tested a drug court management information system based on the Center for Substance Abuse Treatment's Web Infrastructure for Treatment Services (WITS) system.

NEW DIRECTIONS

Over the next 5 years, CJ-DATS investigators will shift their focus to issues of implementation. NIDA program officer Dr. Akiva Liberman says, "The new studies will identify efficient and effective ways to implement screening and assessment tools, a continuum of HIV care, and behavioral or medications interventions. They will provide criminal justice organizations with science-based information on how staffing, infrastructure, policies, practices, and incentive systems may be adjusted to facilitate new evidence-based practices." Dr. Liberman will monitor these studies.

Dr. Redonna K. Chandler, chief of NIDA's Services Research Branch in the Division of Epidemiology, Services and Prevention Research, says, "Federal, state, and community criminal justice facilities are overwhelmed by the number of offenders with drug problems, and many administrators and staff want to incorporate addiction treatment into their programs. CJ-DATS will offer them evidence-based therapies and information to guide decisionmakers as they integrate treatment into their services."

To date, reports of CJ-DATS research have appeared in several publications and in five special issues: *The Prison Journal*, March 2007; the *Journal of Substance Abuse Treatment*, April 2007; *Criminal Justice and Behavior*, September 2007; *Behavioral Sciences and the Law*, July/August 2008, and the *Journal of Psychoactive Drugs*, December 2008. For more information about ongoing research from the CJ-DATS treatment studies, see *www.cjdats.org*. ■

RESEARCH NETWORK TESTS INTERVENTIONS TO PROMOTE SUCCESSFUL COMMUNITY RE-ENTRY Investigators in the Criminal Justice–Drug Abuse Treatment Studies project are comparing standard supervised release from prison with approaches that integrate drug abuse treatment.

Study	Treatment	Lead Center
Targeted Interventions for Corrections	Six brief, flexible interventions address problems faced by adult offenders re-entering the community: motivation to change behavior, anger management, healthier thinking patterns, communication in relationships, social support, and skills and knowledge to reduce risk of sexually transmitted infections.	Southwest Research Center, Texas Christian University
Step'n Out	In this approach, criminal justice staff monitor specific behaviors (e.g., abstinence, employment searches, and counseling attendance) and reward clients who meet agreed-upon goals with social acknowledgement (e.g., congratulatory letter from parole supervisor) and small material incentives (e.g., partial payment for clothes for job interviews).	Rhode Island Research Center, Brown University and Lifespan Hospitals
Two Re-entry Strategies for Drug-Abusing Juvenile Offenders	Juvenile probation officers trained in cognitive restructuring intervene to change adolescents' belief structures underlying criminal activity and drug abuse. This intervention yielded good results for adult offenders but has not previously been tested in adolescents.	Midwest Research Center, National Development and Research Institutes
Facilitating Adolescent Offenders' Reintegration From Juvenile Detention to Community Life	Multidimensional Family Therapy—an evidence-based treatment for adolescent substance abuse—blends individual and family therapy. The intervention also includes family-based HIV/STI prevention. The results of this component of the study may have implications for adolescent substance abuse treatment beyond the criminal justice system.	Florida Research Center, University of Miami
Transitional Case Management	This team case management intervention focuses on adult offenders' post-release goals, social support, accomplishments, and skills.	Pacific Coast Research Center, University of California, Los Angeles
Restructuring Risky Relationships–HIV	This intervention helps women change problematic thinking patterns about relationships and reduce their HIV risk.	Central States Research Center, University of Kentucky
HIV/Hepatitis C Prevention for Drug-Involved Offenders During Re-entry	This study compared three interventions for men and women: (1) education only; (2) state-of-the-art HIV prevention; and (3) a peer-based, interactive multimedia intervention tailored for gender and ethnicity.	Mid-Atlantic Research Center, University of Delaware

COCAINE LOCKS

[*Continued from page 1*]

another odor when the well is about to be filled with a repugnant, quinine-flavored concoction. The rats have to learn to use both cues to obtain the sweet drink and shun the nasty one.

The second part of the go/no-go protocol tests rats' ability to adjust when cues change their meanings. The odor that formerly indicated the sweet drink now signals the bitter one, and vice versa. This put the animals into a situation analogous to that of a person whose inattentive plumber crossed the pipes leading to a sink's faucets. A person in this predicament must quickly learn to change expectations or risk repeated scaldings.

Dr. Schoenbaum's team ran two groups of rats through the go/no-go protocol. One group had been exposed to cocaine daily for 2 weeks one month prior to the protocol, and the other was drug-free. In the first part of the protocol, both groups readily learned to discriminate between the odor cues. After a dozen trials, both groups consistently—though not unerringly—went to the well following the cue for sweet and shunned it following the cue for bitter.

One observation during the first part of the protocol suggested that, despite their similar learning curves, the cocaine-exposed rats had reduced sensitivity to cues predicting negative experiences. The behavior of the rats in the two groups differed in those occasional instances where rats mistakenly went to the well following the cue for the bitter drink. The drug-naïve animals hesitated before setting off, suggesting that they had some inkling that the consequences might not be desirable. The drug-exposed animals, in contrast, rushed right to the well.

In the second part of the protocol, cocaine markedly reduced some rats' ability to adapt to the switched odor-drink pairings. The drug-naïve rats and half of the drug-exposed rats learned to reverse their responses to the cues after an average of 28 trials. The other half of the drug-exposed rats, however, required 35 trials.

NEURON FLEXIBILITY

The cocaine-exposed rats' poorer performance in the go/no-go protocols suggested that the drug impairs neurons in a brain circuit that links cues to the expectation of satisfaction or dissatisfaction. When a person or an animal responds to a cue—whether it be the position of a faucet or an odor—these neurons encode whether the experience that follows feels good or bad. In subsequent encounters with the cue, some neurons increase their firing rate if past responses led to a satisfying experience; others increase their firing rate if past responses caused aversive or disappointing outcomes.

"The firing of these neurons represents the linking of the cue to an expectation of an outcome, based on previous experience," says Dr. Schoenbaum. "We believe that at the time an animal has to decide whether or how to respond, these expectations influence its decision."

To test the hypothesis that cocaine exposure affects these outcome-expectant neurons, the research teams ran rats through go/no-go protocols while monitoring the animals' neuronal activity in two brain areas: the OFC and ABL. The OFC is part of the brain's decisionmaking circuit; its neuronal activity has been associated with stimulant addiction and craving. The ABL is part of the brain's emotional circuit. In previous studies, people with a damaged OFC or ABL were slow to change response

TASKS TEST MENTAL FLEXIBILITY

Task 1—Go/no-go discrimination

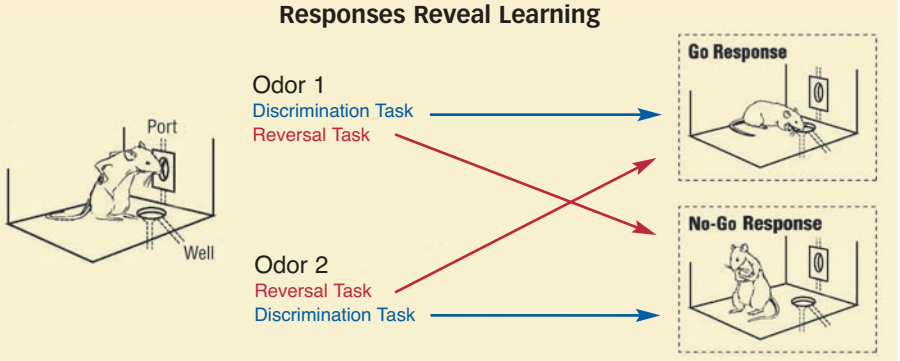
Illuminated lights indicate an odor will be forthcoming when the rat pokes its nose in the port. The odor signals which liquid, either sucrose or quinine, will appear in the well after 3 seconds. Odor 1 predicts sucrose; odor 2 predicts quinine. The rat repeatedly experiences the association between each odor cue and its taste outcome.

Interpreting the Response:
As rats learn to discriminate between the odors and use each odor's predictive significance to obtain desirable taste outcomes, they will begin to consistently head for the well when the port contains odor 1 and avoid it when the port contains odor 2.

Task 2—Reversal

Everything is the same as before, with a critical exception: The odors predict the opposite outcomes. Now, odor 1 predicts quinine; odor 2 predicts sucrose. The rat again repeatedly experiences the association between each odor cue and its taste outcome.

Interpreting the Response:
As rats learn to reverse their expectations in line with the switched predictive significance of the two odors, they will increasingly head for the well when the port contains odor 2 and avoid it when the port contains odor 1.



Brain Activity Differs in Cocaine Abusers According to Gender

Cocaine abusers have reduced neural activity in the orbitofrontal cortex (OFC), a brain region that mediates decisionmaking. NIDA-funded researchers have discovered that gender determines where in the OFC the dampening occurs.

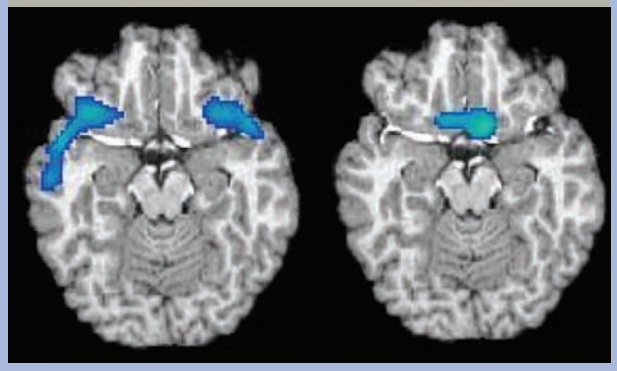
Dr. Bryon Adinoff and colleagues at the University of Texas Southwestern Medical Center and the Veterans Affairs North Texas Health Care System measured OFC neural activity, as indicated by blood flow, of 35 people who had used cocaine for 12 years, on average, but had been abstinent for 2 to 4 weeks. They compared the results with measurements from 37 people who had never used the drug. The researchers found that the OFC contributed a smaller portion of total brain activity in cocaine abusers than in nonabusers. However, the relative deficit was in the lateral OFC in men and in the medial OFC in women.

"One can hypothesize that sex differences in regional blood flow may give rise to contrasting behavioral responses," says Dr. Adinoff. Such differences might arise because the areas most affected in each gender support different behaviors. For example, brain scans of people who do not use drugs have suggested that the lateral OFC is active when people refrain from doing something that they anticipate will have a bad outcome. In contrast, the medial OFC engages when people take action to try to achieve a desired result.

The depressed neural activity in the lateral OFC among men who abuse cocaine may lead to problems putting the brakes on behaviors with bad outcomes and so hinder their ability to abstain, says Dr. Adinoff. The less active medial area in women may reflect a blunted drug reward, he adds.

While his findings are likely to be relevant for individuals in early abstinence, Dr. Adinoff notes that they may not apply to individuals in later stages of recovery. "The participants in our study had only been abstinent 2 to 4 weeks," he says. "Scientists need to examine whether the depressed neural activity we observed among cocaine abusers recovers with long-term abstinence."

LOCAL LULLS Abstinent cocaine abusers show gender-specific reduction of blood flow (blue) in the OFC. Below, differences between a male brain (left) and a female brain (right).



"Future research might examine whether regional differences influence treatment strategies and recovery success," notes Dr. Harold Gordon of NIDA's Division of Clinical Neuroscience and Behavioral Research.

Dr. Adinoff concurs, suggesting that through understanding these differences, treatment providers may eventually be able to tailor gender-specific therapies that promote abstinence.

Source: Adinoff, B., et al. Sex differences in medial and lateral orbitofrontal cortex hypoperfusion in cocaine-dependent men and women. *Gender Medicine* 3(3):206-222, 2006.

patterns after consequences had changed from rewarding to adverse. This behavior resembles that of chronic cocaine abusers—and also some of the cocaine-exposed rats in the team's earlier experiment.

In both cocaine-exposed and unexposed rats, electrode recordings taken during the first part of the protocol showed that about 19 percent of the neurons monitored in the OFC and 26 percent of those in the ABL developed outcome-expectant firing patterns. This finding is consistent with the observation that the two groups of animals learned equally well to use the initial cues to guide their drinking.

Nevertheless, the two groups' neuronal responses may help explain why, on those

COCAINE EXPOSURE REDUCED THE ABILITY OF ABL NEURONS TO CHANGE RESPONSE DURING A REVERSAL TASK Researchers recorded effect on individual ABL neurons during the two-odor, go/no-go discrimination and reversal tasks.

	Changed Response	Failed to Change Response	Became Nonselective
Cocaine-exposed Rats	15%	27%	58%
Unexposed Rats	48%	3%	48%

occasions when the rats mistakenly responded to the quinine cue, the cocaine-exposed rats went directly to the well while the unexposed rats hesitated. The recordings revealed that the exposed rats' OFC quinine-predicting neurons failed to activate in response to the odor.

In the second part of the go/no-go protocol, the cocaine-exposed animals' slower adaptation correlated with reduced flexibility of outcome-expectant neurons. When the researchers reversed the odor cues, neurons predicting sweet and bitter must switch their responses to continue to support decisions leading to happy drinking experiences.

Yet approximately 27 percent of those neurons in the ABL of the drug-exposed rats failed to make the switch—compared with only approximately 3 percent in the drug-free rats. The ABL neurons of the drug-exposed rats that initially signaled favorable expectations proved more inflexible than those that signaled unfavorable expectations.

A MODEL FOR DECISIONMAKING

Dr. Schoenbaum's results led him to propose a model to explain how the ABL and OFC interact in cue response decisions. In this schema, when an individual encounters a familiar cue, ABL outcome-expectant neurons send the OFC a "good/go" or "bad/don't-go" message, or no message at all. The OFC combines this message with information arriving from other brain areas to form a comprehensive picture of the likely consequences of acting.

This picture becomes the basis for a decision to respond to the cue or refrain. If the individual does respond, the OFC then compares the resulting consequences with the picture and notifies the ABL whether the latest data confirm or contradict the expectation. Completing the cycle, the ABL outcome-expectant neurons use this feedback to adjust their future responses to the cue.

The key to cocaine abusers' persistent self-defeating behaviors is the drug's interference with the last step in this cycle, Dr. Schoenbaum says. Feedback from the OFC is weakened by drug exposure; consequently, ABL outcome-expectant neurons fail to change their responses. Instead, they persist in established firing patterns, continuing to signal outdated information to the OFC, and become a hindrance rather than a help to good decisionmaking.

"Cocaine renders the OFC and other frontal cortex areas' messages about likely outcomes less effective. Such signals both guide behavior and facilitate learning when things don't go as expected. By weakening the responses of these frontal cortex areas, chronic cocaine use may make people more prone to relapse and compulsive drug-seeking," says Dr. Schoenbaum.

"A person in drug abuse treatment is trying to change his or her behavior, yet these animal findings suggest that cocaine exposure ossifies a neural circuit likely involved in these changes," says Dr. Susan Volman of NIDA's Division of Basic Neuroscience and Behavioral Research. "Scientists may someday develop medications that enhance neural flexibility and facilitate reengagement of cognitive circuits, which would help behavioral therapy lessons sink in."

"By weakening the responses of these frontal cortex areas, chronic cocaine use may make people more prone to relapse and compulsive drug-seeking."

—Dr. Geoffrey Schoenbaum

Dr. Elliot Stein of NIDA's Intramural Research Program, who is performing brain imaging of cocaine abusers as they do reversal learning tasks, agrees: "If the drug-exposed brain lacks plasticity for new learning, then restoring the functional integrity of the circuit may increase the effectiveness of behavioral interventions." ■

SOURCES

Stalnaker, T.A., et al. Abnormal associative encoding in orbitofrontal neurons in cocaine-experienced rats during decision-making. *European Journal of Neuroscience* 24(9):2643-2653, 2006.

Stalnaker, T.A., et al. Cocaine-induced decisionmaking deficits are mediated by miscoding in basolateral amygdala. *Nature Neuroscience* 10(8):949-951, 2007.

Methamphetamine Abusers Show Increased Distractibility

Reduced ability to choose between conflicting stimuli corresponds to neural damage.

BY LORI WHITTEN,
NIDA Notes Staff Writer

Long-term methamphetamine abuse appears to induce lasting impairment to brain cells whose activity underpins a person's ability to attend to significant stimuli and screen out distractions.

In a recent NIDA-funded study, brain images of former methamphetamine abusers showed evidence of impairment in the anterior cingulate cortex (ACC), an area of the brain that is known to influence cognition and emotion and help regulate behavior and decision-making. These individuals also received lower scores, compared with individuals who never abused the drug, on a psychological test that measures the ability to stay on task. According to the NIDA-funded research team that documented the damage, one consequence might be to heighten former abusers' vulnerability to relapse.

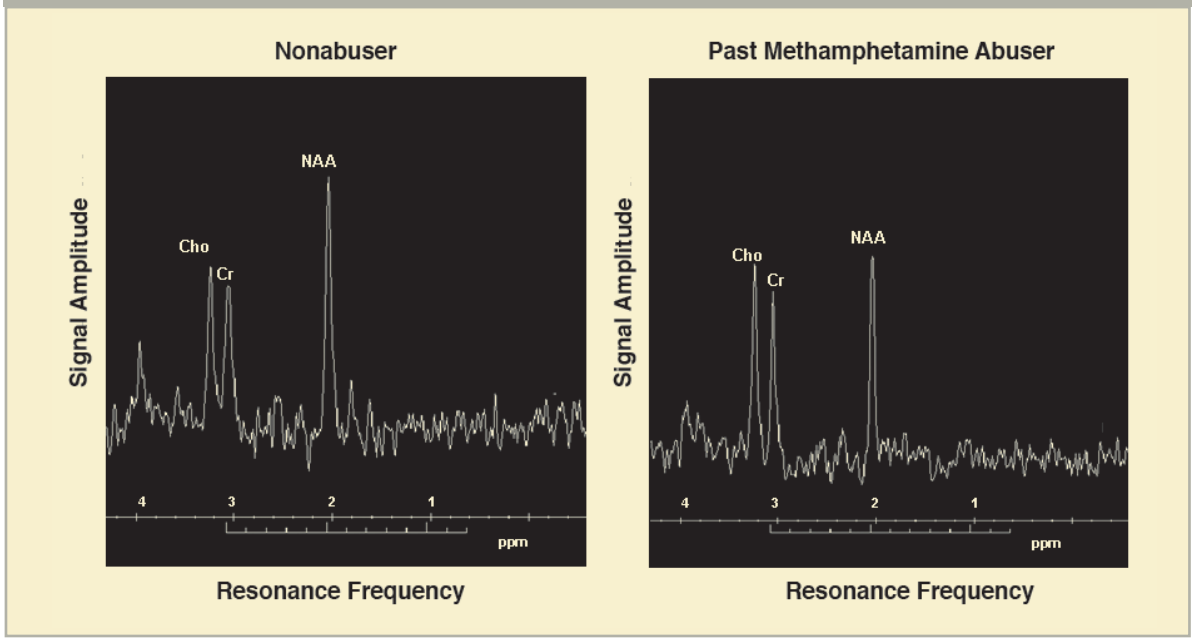
"The cognitive process that is measured by the laboratory test we gave participants is most relevant to everyday life," says Dr. Ruth Salo of the University of California, Davis, whose team collaborated in the study with investigators from California Pacific Medical Center in San Francisco and Kaiser Chemical Dependence Recovery Program in Sacramento. "The former methamphetamine abusers' poorer performance on the test suggests that the neurochemical compromise we observed may give rise to problems in choosing between healthy and unhealthy behaviors."

DROP IN NEURONAL WELL-BEING

Dr. Salo and colleagues used proton magnetic resonance spectroscopy (MRS) to visualize a chemical marker of neuronal health in 52 men and women aged 18 to 55. Although abstinent at the time of the study, 36 of the participants had regularly abused methamphetamine, reporting that it had been their primary drug for 12 years, on average. The other 16 participants had not abused illegal drugs or alcohol during the past 5 years and had never experienced methamphetamine dependence.

When researchers examined the MRS scans of the ACC in the former

NEUROCHEMICAL MARKER OF DAMAGE TURNS UP IN METHAMPHETAMINE ABUSERS These graphs show a set of three neurochemical signals from magnetic resonance spectroscopy of the anterior cingulate cortex brain region in two representative study participants, a nonabuser (left) and a past long-term methamphetamine abuser (right). In the abuser, the N-acetyl aspartate (NAA) peak is lower relative to the peaks of two control chemicals—choline (Cho) and creatine + phosphocreatine (Cr)—a result that suggests neural damage.



methamphetamine abusers, they observed a pattern that suggests neural injury (see figure, page 9). The images revealed a diminished signal for N-acetyl aspartate (NAA), a byproduct of cellular energy production that is considered a sign of neuronal well-being. The investigators standardized their data by computing ratios of NAA and another brain chemical, creatine, which did not differ between groups in any brain region in the current study.

The ACC appeared to be a focal area for methamphetamine neurotoxicity. A comparison brain region—the primary visual cortex—showed no difference in neurochemical patterns between past methamphetamine abusers and participants who had not abused drugs.

The neurochemical result correlated with the trial participants' performance on the Stroop test, which measures a person's ability to screen out distractions, focus on the information that matters, and make choices in the face of conflicting inclinations. In the test, which was administered on the same day as the MRS session, the participants watched a computer screen on which sets of letters flashed. The participant's task was to announce, as quickly as possible, the color of letters used to display a word or a set of letters that does not represent a word. The task is easy when the meaning of the word and its color match (e.g., **RED**) or when the letters don't make up a word. In such instances, all participants answered quickly and erred only 1 to 2 percent of the time.

When the word and color do not match, however (e.g., **RED**), the need to suppress the habitual tendency to read the word and focus instead on the color of the letters slowed the response and led to more errors. The methamphetamine abusers found these adjustments more challenging than the nonabusers. They required 155 milliseconds longer, on average, to respond to nonmatched than to matched examples, while the nonabusers required only an additional 125 milliseconds. Both groups had an average error rate of 13 percent.

The associations between methamphetamine exposure, diminished NAA, and slower performance on the Stroop test held even when researchers made allowance for differences in other characteristics linked with brain health—for example, years of drug abuse, months of abstinence, and age. In earlier studies, the research team had demonstrated similar patterns of neural damage and attention problems in recently abstinent methamphetamine abusers, but without linking the two.

Prior research had also suggested that ACC function can affect recovery from methamphetamine abuse. In that study, led by Dr. Martin Paulus of the University of California, San Diego, high activity in a former user's ACC during a decisionmaking task predicted success in avoiding relapse during the next year ("Brain Activity Patterns Signal Risk of Relapse to Methamphetamine," *NIDA Notes*, Volume 20, Number 5).

The ACC appeared to be a focal area for methamphetamine neurotoxicity.

The attention problems observed by Dr. Salo's team in past methamphetamine abusers in the recent study are similar to those observed by other researchers in people who had abused cocaine. The similarity is not surprising: Both stimulants increase activity of dopamine neurons. Methamphetamine, however, may be particularly harmful because it has a longer duration of action (8 to 13 hours) than most other stimulants and is a powerful neurotoxin.

A CRITICAL LINK

"The findings of Dr. Salo's team, along with the results of other studies, suggest that long-term meth abuse causes damage to the ACC that impairs former abusers' ability to perform the Stroop task," says Dr. Steven Grant of NIDA's Division of Clinical Neuroscience and Behavioral Research. "The connection to a behavior with functional relevance is often missing in MRS studies, but this study makes that critical link."

According to Dr. Salo, awareness of abusers' specific cognitive deficits could also enable development of more effective relapse-prevention therapies. "The Stroop test taps into something people do in everyday life: make a choice in the face of conflicting impulses and inhibit a strong but detrimental tendency," Dr. Salo says.

"A person recovering from addiction may face a conflict on payday—for example, he or she must inhibit a strong impulse to buy drugs instead of paying rent and purchasing food. The neurobiological changes following long-term methamphetamine abuse appear to compromise this cognitive control. Our findings point to a specific addiction-related cognitive impairment and reinforce the importance of helping patients during therapy to develop key skills: making healthy choices and thinking about future consequences," Dr. Salo says. ■

SOURCE

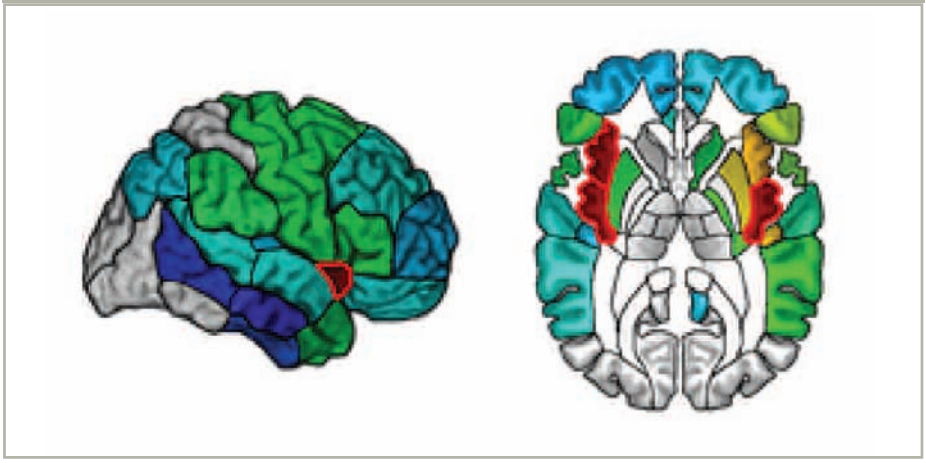
Salo, R., et al. Attentional control and brain metabolite levels in methamphetamine abusers. *Biological Psychiatry* 61(11):1272-1280, 2007.

Damage to Brain Area May Immediately Halt Cigarette Addiction

Patients with injury to the insula lost the urge to smoke.

BY LORI WHITTEN,
NIDA Notes Staff Writer

BRAIN REGION LINKED TO SUDDEN CESSATION OF SMOKING In these two views of the brain, red indicates regions where damage was associated with the sudden disruption of cigarette addiction in 12 of 19 patients. The regions identified are the right and left insula, which other studies have linked to emotional feelings and cue-induced drug urges.



"My body forgot the urge to smoke." That's how one patient with damage to the insula, an area of the brain within the cerebral cortex, described the aftereffects of his stroke on his smoking habit. He is not alone. NIDA-funded investigators repeatedly heard of similar experiences while interviewing people who had sustained brain injuries.

Many people who have suffered a stroke or other brain injury try to quit smoking out of concern for their health, says Dr. Antoine Bechara of the University of Southern California and the University of Iowa. Most have difficulty. "In some brain injury patients, however, the urge to smoke seemed to be switched off, while other desires, such as for food, were not disrupted," says Dr. Bechara. He and his colleagues found that the experience of quitting cigarettes immediately, easily, and without relapse was much more common among people with damage to the insula than those with injuries elsewhere in the brain. If Dr. Bechara's preliminary findings are validated, the insula is likely to become an important target for future addiction research.

DIFFERENT EXPERIENCES OF SMOKING CESSATION

Scientists suspect that in chronic abusers, drugs or drug-associated cues produce bodily sensations that the insula relays to other brain areas as urgent needs. To explore the insula's role in addictive behavior, Dr. Bechara's team contacted men and women who had suffered brain damage and were listed in the Patient Registry of the Division of Behavioral Neurology and Cognitive Neuroscience at the University of Iowa.

Before suffering brain damage, mostly from stroke, all the participants had been long-term, heavy cigarette smokers; on average, they had smoked a pack and a half a day for 27 years.

The patients' brains had been injured 8 years before the study, on average, and 32 of the 69 patients had quit smoking immediately following their injury or some time thereafter. The researchers used brain imaging to verify injury locations: 19 patients had insula lesions, and 50 showed damage to other regions. Patients with damage in the insula and those with damage to other regions were matched for the number of cigarettes smoked and duration of smoking before the injury.

Patients with insula and noninsula damage were equally likely to have quit smoking cigarettes after their brain injury. To identify those whose smoking addiction had ceased suddenly, the researchers settled on four criteria: quitting cigarettes less than a day after lesion damage; reporting no relapse after quitting; rating the difficulty of quitting as less than 3 on a scale of 1 (very easy) to 7 (very difficult); and reporting no urges to smoke since quitting.

Of the 32 patients who quit smoking, 16 met all four criteria and were designated as having "disrupted smoking addiction." They

included 12 of the 13 patients with lesions in the insula who quit smoking, but just 4 of the 19 quitters with lesions only in other areas. "The much higher likelihood of disrupted smoking among patients with insula damage was striking and suggests that the area is a prime candidate in drug-taking urges," notes Dr. Bechara.

"For patients with insula damage, it seems that smoking quit them—they lost the desire to smoke—which is a provocative and unexpected finding," says Dr. Steven Grant of NIDA's Division of Clinical Neuroscience and Behavioral Research. "Dr. Bechara's results have cast a searchlight onto a relatively new area of interest among addiction researchers."

NEW FOCUS FOR DRUG ABUSE RESEARCH

Current interest in the role of the insula in drug abuse was sparked a few years ago by research that linked activity in that brain area with abstinence in methamphetamine abusers ("Brain Activity Patterns Signal Risk of Relapse to Methamphetamine," *NIDA Notes*, Volume 20, Number 5). Recent studies have also tied insula activation to cravings and drug administration among substance abusers. According to Dr. Bechara, his team's next step is to examine urges for and abuse of substances—cigarettes, alcohol, and illicit drugs—in a larger number of patients who have recently suffered damage to the insula and other parts of the brain.

"Our findings so far suggest that the insula maby be a structure to target in the development of new smoking cessation medications," Dr. Bechara says. "Obviously, damaging the insula is not a therapeutic option." But scientists could determine the types of receptors present in the insula, for example, and then test whether blocking them blunts nicotine reward.

Drs. Bechara and Grant agree that with animal protocols that mimic different aspects of addiction—reward, craving, and relapse—scientists may learn what specific role the insula plays in drug abuse. ■

SOURCE

Naqvi, N.H., et al. Damage to the insula disrupts addiction to cigarette smoking. *Science* 315(5811): 531-534, 2007.

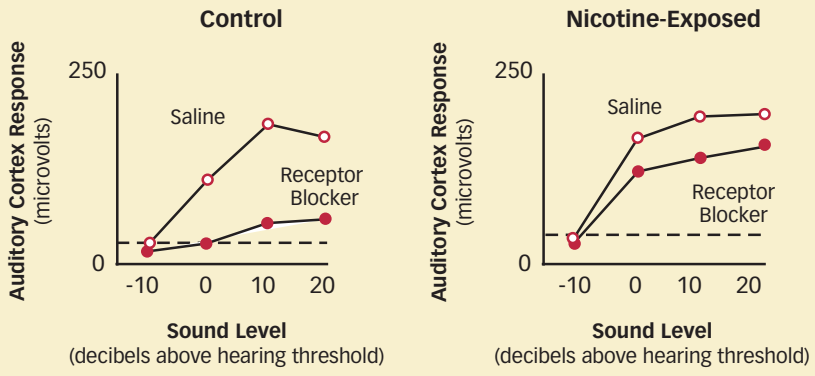
Prenatal Nicotine Exposure May Damage Receptors That Influence Auditory Processing

Tests correlate biochemical abnormality with deficits in rats' responses to sounds.

BY NIDA NOTES STAFF

Some children of women who smoked during pregnancy experience subtle difficulties processing auditory information; for example, they may have more than average problems recognizing slightly garbled words or understanding speech in a noisy environment. A recent series of animal experiments indicates that the cause of the problem is not in the ear but in the brain: Nicotine exposure during development damages a set of receptors in the brain's auditory processing center.

NICOTINE EXPOSURE DURING DEVELOPMENT ALTERS AUDITORY RESPONSE
Normal rats rely on nicotinic acetylcholine receptors in the auditory cortex to process auditory information. Rats exposed to nicotine shortly after birth have damaged nicotinic acetylcholine receptors and develop compensatory sound-processing mechanisms. As a result, blocking the receptors with mecamylamine reduces auditory cortex responsiveness dramatically in normal rats, but only slightly in rats exposed to the drug as pups.



HEARING VERSUS HEEDING

The NIDA-funded experiments first demonstrated a deficit in sound processing in rats that had been exposed to nicotine at a developmental stage corresponding to that of a human fetus in the third trimester of gestation. Dr. Raju Metherate and colleagues at the University of California, Irvine, began by injecting rat pups with nicotine twice daily for 5 days (postnatal days 8 to 12). The injections produced nicotine blood levels approximating those of smokers, and presumably of pregnant smokers' fetuses. A group of same-aged control rats received injections of saline.

When the rats were 2 months old, a researcher trained them to escape an electrical shock by crossing from one chamber of an experimental box to another. The next day, a 5-second tone preceded each shock. All the animals immediately turned their heads toward the tone, indicating that they had heard it. Over 4 days, the rats had the opportunity to learn that the tone signaled an impending shock.

By the end of the training, all but one of the 12 control animals had learned the lesson well enough to routinely avoid the shock by crossing into the safe chamber during the tone. These animals moved to the safe chamber more rapidly as time went on, and eventually, many went into the safe chamber as soon as the tone began. Just 6 of the 11 rats exposed to nicotine, however, learned to associate the tone with the shock, and they responded more slowly than the control animals. The remaining 5 nicotine-exposed rats moved to the safe chamber only after receiving the shock.

A LESS RESPONSIVE CORTEX

The UC-Irvine researchers' next experiment linked the nicotine-exposed rats' poorer responses to warning tones to a difference in the animals' brains.

The auditory cortex is the brain's primary area for interpreting sounds. Normally, nicotine amplifies the cortex's responsiveness to auditory inputs. Researchers measure

this effect by comparing electrical activity levels in the cortex before and after an injection of the drug.

Using this protocol when their rats were 2 to 3 months of age, Dr. Metherate's team documented smaller increases in cortical activity levels, on average, in the animals with early exposure to nicotine than in the control animals. Among adult rats not exposed to nicotine as pups, a stronger auditory cortex response to nicotine at 2 to 3 months of age correlated with faster and more accurate learning to associate sound with electrical shocks. These observations may provide a hint why rats' early nicotine exposure leads to later difficulty using warning tones.

UNDERDEVELOPED RECEPTORS

The researchers next investigated the underlying mechanism for their nicotine-exposed rats' diminished cortical responsiveness. The findings indicated that nicotine exposure during early development prevents a key receptor in the brain's acetylcholine signaling system from achieving full functionality.

Nicotine binds to the same receptors as acetylcholine, a chemical that neurons in the auditory cortex and elsewhere use to transmit electrical excitation to neighboring neurons. "When nicotine or acetylcholine binds to a receptor on the surface of a nerve cell, the binding process sets off chemical reactions inside the cell that help the cell function properly and fulfill its special physiological role," Dr. Metherate says.

The researchers measured electrical activity in the auditory cortex before and after injecting 2- to 3-month-old rats with mecamylamine, a compound that shuts down the nACh receptors. The injection markedly reduced electrical activity in normal rats but made little difference in the rats that had been exposed to nicotine shortly after birth. This finding indicates that their nACh receptors were ineffective.

New Role for a Neurotransmitter and Its Receptor

Researchers have discovered a novel function of the nicotinic acetylcholine (nACh) receptor: It influences the propagation of signals along an axon.

Previous research had revealed nACh receptors along the myelinated axons that carry signals from the thalamus—a sensory processing center—to the auditory cortex. The new work, by Dr. Raju Metherate and colleagues Drs. Hideki Kawai and Ronit Lazar, at the University of California, Irvine, indicates that both nicotine and normally occurring acetylcholine activate nACh receptors along these axons, thereby increasing the effectiveness of a signal. This influence is distinct from the known mechanisms of acetylcholine activity at synapses.

"The regulation of axon excitability offers a powerful mechanism to control signal propagation," says Dr. Metherate. This action, he notes, might underlie nicotine's effect on the response of the auditory cortex to sound. However, that effect seems to be specialized. The team has recently found evidence that nACh receptors are not present along many other axons in the nervous system.

Source: Kawai, H.; Lazar, R.; and Metherate, R. Nicotinic control of axon excitability regulates thalamocortical transmission. *Nature Neuroscience* 10(9):1168-1175, 2007.

"Somehow, early nicotine exposure disconnects the receptors from the inside of the cell," Dr. Metherate says. "Acetylcholine and nicotine bind to the cell surface, but no chemical reactions take place in the interior."

A CLUE AND A CAUTION

Because human and rat brains process sounds similarly, the UC-Irvine findings may relate to the problems that people prenatally exposed to nicotine have interpreting sounds, and the experimental results may provide a clue to effective treatments as well. "If we can figure out how to reconnect the receptors to the activity inside the cells, we may be able to reverse these auditory-cognitive deficits in children, adolescents, or even adults," Dr. Metherate says.

He adds that nACh receptors also play a role in the development of other parts of the brain, including cortical areas that process vision and touch. So, prenatal nicotine exposure may undermine brain activity in those areas as well.

"Even though Dr. Metherate's rats were exposed to nicotine for only 5 days, the damage to their brains was long-lasting," says Dr. Thomas Aigner of NIDA's Division of Basic Neuroscience and Behavioral Research. "This is important information for women who think that smoking only intermittently during pregnancy is safe for the fetus. If they smoke during a critical period of brain development, in this case a few days into the third trimester, it looks as though the nicotine exposure can produce serious and long-lasting damage." ■

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Liang, K., et al. Nicotinic modulation of tone-evoked responses in auditory cortex reflects the strength of prior auditory learning. *Neurobiology of Learning and Memory* 90(1):138-146, 2008.

Low Dopamine Receptor Availability May Promote Cocaine Addiction

Reduced availability heightens reinforcing effects of cocaine in monkeys, and the drug drives this measure even lower.

BY LORI WHITTEN
NIDA Notes Staff Writer

In a study with rhesus monkeys, Dr. Michael Nader and colleagues at Wake Forest University recently showed that cocaine lowers availability of the dopamine D_2 receptors in the basal ganglia—the brain region that includes key components of the reward system. The consequences may include addiction-promoting alterations in cognitive functioning and decisionmaking.

Dr. Nader's study also confirms previous findings that individual animals with lower D_2 receptor availability are especially responsive to cocaine's reinforcing effects.

In a promising finding for people trying to recover from cocaine addiction, receptor availability levels in some of the monkeys recovered after less than a year of abstaining from drug use.

RECEPTOR AVAILABILITY AND COCAINE EXPOSURE

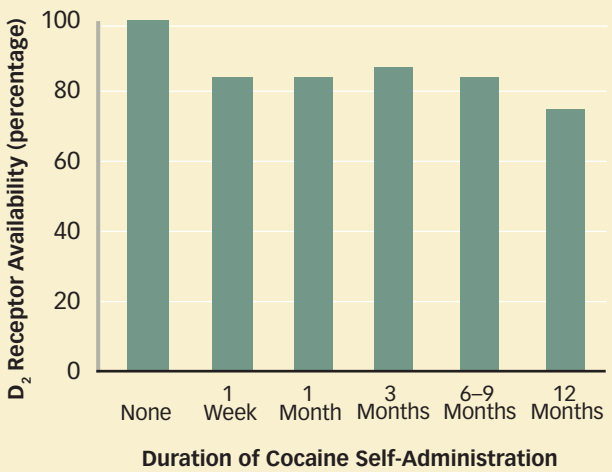
The D_2 receptor resides in the outer membrane of brain cells that shape motivation and emotion, thought, and movement. The receptor protein enables the neurotransmitter dopamine to attach to these cells and affect their activity. At any given time, dopamine molecules occupy some of the D_2 receptors, while the rest of the receptors remain available until a stimulus—such as drug exposure—increases dopamine levels. One hypothesis holds that the proportion of D_2 receptors a person has free affects how strongly he or she responds to the stimulus.

Imaging studies of the human brain have found reduced levels of available D_2 receptors among abusers of cocaine. But that work could not distinguish between pre-existing differences in the proportion of available receptors and changes induced by drug use. The human studies also showed reduced availability of D_2 receptors among abusers of heroin, nicotine, amphetamine, and alcohol. Lower D_2 receptor availability has also been observed in other populations, such as the severely obese. So, findings on D_2 receptor availability may be relevant to a wide range of addictions and conditions.

To measure monkeys' D_2 receptor availability before cocaine exposure, Dr. Nader and colleagues injected each animal with a radiotracer that binds to the receptors. The radiotracer competes with dopamine for the receptor and provides a measure of D_2 function. Over the course of a 3-hour brain imaging study, the scientists used positron emission tomography (PET) to visualize and quantify the bound radiotracer.

Next, the researchers allowed the monkeys to self-administer cocaine. Every day, they placed each monkey in an experimental chamber equipped with two levers—one that delivered banana pellets during the first 20 minutes of the test and another that provided the animal with an infusion of cocaine during the next 60 minutes. Then, the researchers put the animals through this sequence a second time. To describe the neurobiological effects of chronic cocaine exposure, the investigators continued the self-administration experiments and measured D_2 receptor

COCAINE REDUCES AVAILABILITY OF D_2 RECEPTORS



availability for a year.

The monkeys whose PET scans had revealed lower D_2 receptor availability at baseline testing before their initial cocaine exposure self-administered cocaine at higher rates. This finding suggests that lower D_2 receptor availability increases sensitivity to cocaine reward. Similar findings have been reported in studies that compared drug abusers and people who do not abuse drugs. The results also complement those of a prior study by Dr. Nader, which showed that subordinate monkeys, having lower D_2 receptor availability, self-administered more cocaine than dominant monkeys, which have higher D_2 receptor availability.

This finding suggests that lower D_2 receptor availability increases vulnerability to cocaine reward.

"This result, as well as findings of other studies, indicates that low D_2 receptor availability corresponds to increased vulnerability to cocaine abuse," says Dr. Nader. "Perhaps an individual with low availability gets a greater kick from cocaine because the drug-induced dopamine release stimulates a greater percentage of their receptors. Another possibility is that the drug prompts some individuals' brain cells to release dopamine in particularly high quantities that are sufficient to fill the great majority of vacant D_2 receptors, and this augments the high."

VARIABLE RECOVERY

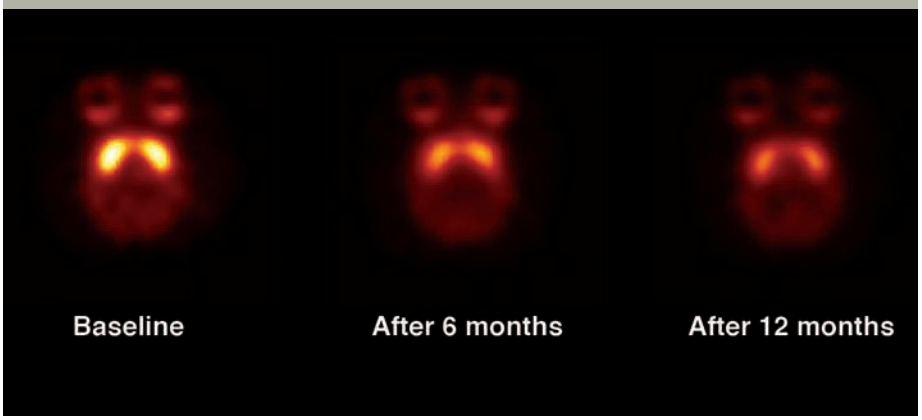
PET scans obtained at intervals throughout the trial revealed a rapid and marked suppressive effect of cocaine on D_2 receptors. After 5 days of self-administration, the monkeys' available receptors had dropped by 15 percent, on average. This effect was reversible: In three monkeys that were allowed to self-administer the drug for 1 week, D_2 receptor availability returned to baseline values by the third week of abstinence.

The picture was more complex, however, in five monkeys that self-administered cocaine for a year. At that time, D_2 receptor availability was down 22 percent (see graph, page 15). When access to cocaine was then stopped, three of the monkeys showed strong recovery—93 percent, on average—of receptor availability a month after cocaine cessation. But two monkeys had recovered only 80 percent and did not recover further over 12 months of abstinence.

FOOD VERSUS DRUG

The researchers parsed the implications of the relationships between cocaine and D_2 receptors by comparing the monkeys' patterns of lever pressing for the drug and for food. In contrast to the cocaine self-administration results, there was no correlation between D_2 receptor availability and how often monkeys pressed the food lever. This suggests that low D_2 receptor availability disposes individuals to seek the cocaine experience specifically, rather than rewarding experiences in general.

BRAIN SCANS Dopamine 2 receptor availability (yellow) in the basal ganglia falls dramatically after 6 and 12 months of cocaine self-administration.



A clue to why recovery is more difficult for some individuals than others may come from the two monkeys whose D_2 receptor availability failed to recover completely following year-long cocaine self-administration. Throughout the year of cocaine self-administration, these animals exhibited a reduced attraction to food, Dr. Nader says. When given the opportunity to press a lever for banana pellets, these animals did so only half as often as the monkeys whose receptors returned to baseline after long-term cocaine self-administration. "Although the findings are preliminary, we believe that these individuals may find rewards other than cocaine devalued," Nader says. "If it is not cocaine, it is just not rewarding to them." That trait may presage an unusually long-lasting influence of the drug.

TOWARD TREATMENT

"Predisposition seems to play a role in addiction, as does the dopamine system's rapid and robust reduction in D_2 receptor availability in response to cocaine," says Dr. Nader.

The team's findings and those of others suggest that therapies that elevate D_2 receptor availability may help prevent and treat cocaine abuse. According to Dr. Nader,

[*Continued on page 18*]

NIDA's National Advisory Council Welcomes New Members

The National Advisory Council on Drug Abuse introduced five new members at its May 2008 meeting at NIDA headquarters in Rockville, Maryland:

Photo Credit: M.H. Cohen

NEW MEMBERS WELCOMED BY NIDA (left to right) NIDA Deputy Director Dr. Tim Condon, new National Advisory Council members Drs. Hazel Szeto, Steven Childers, and Xavier Castellanos, NIDA Director Dr. Nora D. Volkow, additional new Council members Drs. Anita Everett and Thomas Crowley, and NIDA Office of Extramural Affairs Director Dr. Teresa Levitin.

F. Xavier Castellanos, M.D., is director of research at the New York University (NYU) Child Study Center and director of the Phyllis Green and Randolph Cowen Institute for Pediatric Neuroscience. He is also a professor of child and adolescent psychiatry at the NYU School of Medicine. Dr. Castellanos' research focuses on attention deficit hyperactivity disorder and related conditions.

Steven R. Childers, Ph.D., is a professor in the Department of Physiology and Pharmacology at Wake Forest University. His research characterizes how drugs affect neuronal receptors and signaling within cells. Dr. Childers and colleagues study opioids, cannabinoids, and cocaine.

Thomas J. Crowley, M.D., is a member of the Department of Psychiatry, University of Colorado School of Medicine in Denver, where he is a professor and director of the Division of Substance Dependence. His research addresses co-occurring substance dependence and conduct disorder in adolescents and includes genetic and functional imaging techniques.

Anita S. Everett, M.D., is section chief of community and general psychiatry at The Johns Hopkins Bayview Medical Center and a faculty member at The Johns Hopkins School of Medicine and the Bloomberg School of Public Health. Dr. Everett's current research concentrates on the health behavior of individuals with long-term mental illnesses. She is engaged in several international projects, including consultation with the ministries of health in Iraq and Afghanistan on the implementation of mental health services in these countries.

Hazel H. Szeto, M.D., Ph.D., is a professor of pharmacology at Weill Cornell Medical College. Dr. Szeto's team designs and develops peptides that interact with specific opioid, vasopressin, and oxytocin receptors. The research goal is to develop well-tolerated medications for pain, blood pressure, neurodegenerative diseases, and other conditions.

The Council advises NIDA in its efforts to identify, review, and fund scientific research that supports the Institute's mission. The Council is made up of 12 experts in scientific fields, 6 members of the public knowledgeable about research on drug abuse, and ex officio members from other Government entities.

Universities Offer Online Master's Program in Addiction Studies

A consortium of three universities launched a 12-month intensive online program last August that leads to a master's degree in addiction studies. The full-time international program, developed by the University of Adelaide (Australia), King's College London (United Kingdom), and Virginia Commonwealth University in Richmond, prepares participants to assume leadership roles in addiction science and related fields, such as health care, law enforcement, policy, and education.

Courses focus on the scientific basis of addiction, comparative epidemiology, evidence-based interventions (including pharmacological, psychosocial, and public health approaches), research methodology, and addictions policy. Lecturers include leading authorities in these fields. The goal of the International Programme in Addiction Studies is to produce specialists in addiction who will translate research into effective treatment and prevention practices and local, state, national, and international public health policies.

In the program, all online lectures, assignments, and correspondence are conducted in English. For more information about the program, including eligibility requirements, visit *www.adelaide.edu.au/addiction/* or contact program officers Dr. Femke Pijlman, *femke.pijlman@adelaide.edu.au*; Dr. Kim Wolff, *kim.wolff@iop.kcl.ac.uk*; or Dr. Mary Loos, *meloos@vcu.edu*.

[*Continued on page 18*]

BULLETIN BOARD

[*Continued from page 17*]

NIDA Initiates Pediatrics Symposium on Adolescent Health

Adolescence and early adulthood are times of self-definition and increasing autonomy. They are also periods of heightened sensitivity to social influences and vulnerability to the onset of mental problems, including substance use and mood disorders. The physical and mental health of adolescents was the focus of a day-long program, "What's Happening to Me? Inside the Mind and Body of an Adolescent," at the 2008 annual meeting of the American Academy of Pediatrics, held in Boston in October. About 60 pediatricians and scientists who study adolescents attended a symposium, sponsored and organized by NIDA, that described the adolescent brain and cognitive development and considered the impact of drug abuse on young people.

At the symposium, neuroscientists presented findings of imaging studies indicating that the brain continues to mature during adolescence and into young adulthood. They also noted recent findings on the structural and functional changes that occur in the brain as children mature into adolescents; the changing balance between emotional and inhibitory neural circuits that influence an increased tendency toward risk-taking during adolescence; and the negative impact of adolescent marijuana abuse on cognitive abilities, including attention and memory. Researchers also described studies that seek to determine whether individuals exposed prenatally to drugs are more vulnerable to substance abuse and other behavior problems than unexposed peers.

"The primary goal of the session was to update clinicians on the influence of drugs on neurodevelopment from infancy through young adulthood—particularly recent data on adolescent brain development that may shape substance abuse prevention and treatment for teens," said NIDA's Dr. Karen Sirocco, the symposium moderator. ■

LOW DOPAMINE RECEPTOR

[*Continued from page 16*]

the medications that appear most likely to accomplish this without deleterious side effects do so indirectly by altering neurotransmitters other than dopamine—either by increasing serotonin or gamma-aminobutyric acid. Dr. Nader and his colleagues plan to test this strategy in monkeys.

In prior research, Dr. Nader has shown that enriching individuals' environments also can prompt the brain to generate additional D_2 receptors. "My colleagues and I are most intrigued by an environmental enrichment strategy for increasing D_2 receptor levels," Dr. Nader says. "This approach is based on the most profound result that my colleagues and I have ever observed: Adult monkeys that have a high level of control over the social environment show enhanced D_2 receptor availability and markedly diminished response to cocaine's rewarding effects" (see "Social Environment Appears Linked to Biological Changes in Dopamine System, May Influence Vulnerability to Cocaine Addiction," *NIDA Notes*, Volume 17, Number 5).

Other researchers have reported that, in rodents, environmental enrichment reverses the rewarding effects of cocaine. Dr. Nader and his team are preparing to test whether enhancing monkeys' environments—for example, by reducing stress, providing novel objects, and increasing peer interaction—can increase receptor availability and curb cocaine self-administration.

If the enrichment is successful, analogous provisions for people—improved living conditions, broad recreational choices, stress management techniques, and rewarding activities—might reduce vulnerability to cocaine abuse.

"A question for further research is whether animals whose D_2 receptor availability levels remain low during abstinence are more likely to exhibit behaviors akin to relapse, compared with those whose receptors recover," says Dr. Cora Lee Wetherington of NIDA's Division of Basic Neuroscience and Behavioral Research. Dr. Nader says his team plans to adapt its current experimental protocol to explore this question in rhesus monkeys. ■

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High School Seniors Report Alcohol- or Drug-Impaired Driving Experiences

About one in three high school seniors has, in a 2-week period, either driven a vehicle after drinking alcohol or taking illegal drugs or ridden as a passenger with a driver under the influence of those substances, a NIDA-supported study suggests.

Researchers looked at data from six annual Monitoring the Future surveys—2001 to 2006—each of which asked approximately 2,500 high school seniors whether they had, in the 2 weeks prior to the survey, driven after drinking alcohol or using an illicit drug or ridden with a driver who had. Although the prevalence of alcohol- or drug-impaired driving and riding has declined over the 6 years, from 35 percent in 2001 to 30 percent in 2006, the problem remains serious and widespread, the study authors say.

The researchers focused on four categories of substance abuse: use of marijuana; use of any illicit drug other than marijuana; consumption of any amount of alcohol; and heavy drinking, defined as five or more alcoholic drinks in a row. The most prevalent single activity, reported by 21 percent of high school seniors in 2006, was riding with a driver who had used alcohol, closely followed by riding with a driver who had used marijuana (20 percent). Nearly a quarter of the students in the class of 2006 admitted to taking a ride with someone who had either used an illicit drug or had been drinking heavily. Fourteen percent admitted to driving after using alcohol, and 13 percent to doing so after marijuana use.

INFLUENCE OF LIFESTYLE, GENDER, AND RACE

Lifestyle factors and, to a lesser degree, gender and race influenced the students' likelihood of engaging in the risky behaviors. For example, driving after using marijuana was reported more commonly by seniors who reported truancy and those who went out more often in the evenings for recreational activities, worked more hours per week, or drove more miles per week than average. Factors associated with lower-than-average reports of driving after marijuana use included higher grade-point averages and statements indicating religious commitment. Also, Hispanic students were less likely than white students to drive after using marijuana.

Different factors influenced driving after heavy drinking. Boys were more likely than girls to report that behavior. Boys and girls who were not living with at least one parent were more likely than their counterparts to drive after heavy drinking; seniors with the most highly educated parents were less likely to do so. Black seniors were much less likely than white seniors to drive after heavy drinking.

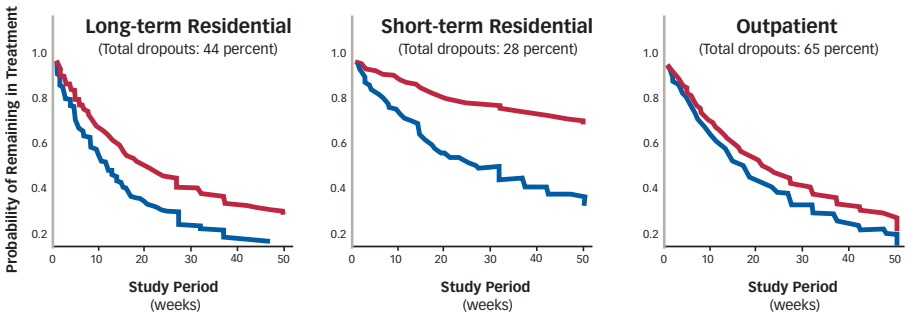
Boys were slightly more likely than girls to drive after using an illicit drug or to ride with a driver who had. Boys and girls reporting average grades of B- or below were much more likely than A students to drive after such illicit drug use or heavy drinking or to ride with a driver who had engaged in such behavior. ■

SOURCE

O'Malley, P.M., and Johnston, L.D. Drugs and driving by American high school seniors, 2001-2006. *Journal of Studies on Alcohol and Drugs* 68(6):834-842, 2007.

WHAT THE NUMBERS SAY

Legal Pressure Increases Treatment Retention



People who participated in substance abuse treatment on the recommendation or requirement of an attorney or criminal justice professional (red lines) were more likely to stay in treatment than were people who voluntarily chose to participate in treatment (blue lines). Legal pressure had the largest effect on treatment retention rates among persons in short-term residential programs, where participants sometimes stayed much longer than the typical 2-month period.

SOURCE: Analyses of data collected during the National Treatment Improvement Evaluation Study, which involved publicly funded, nonmethadone treatment programs including long-term residential (*n* = 757), short-term residential (*n* = 756), and outpatient treatment (*n* = 1,181) reported in: Perron, B.E. and Bright, C.L. The influence of legal coercion on dropout from substance abuse treatment: Results from a national survey. *Drug and Alcohol Dependence* 92(1-3):123-131, 2008.

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