RESEARCH NEWS AND TRENDS FROM THE NATIONAL INSTITUTE ON DRUG ABUSE

NIDA Notes

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Behavioral Response to Novelty Foreshadows Neurological Response to Cocaine

Young rats' engagement with novel objects correlates with cocaine-induced dopamine release, shedding light on the mechanisms of drug abuse vulnerability.

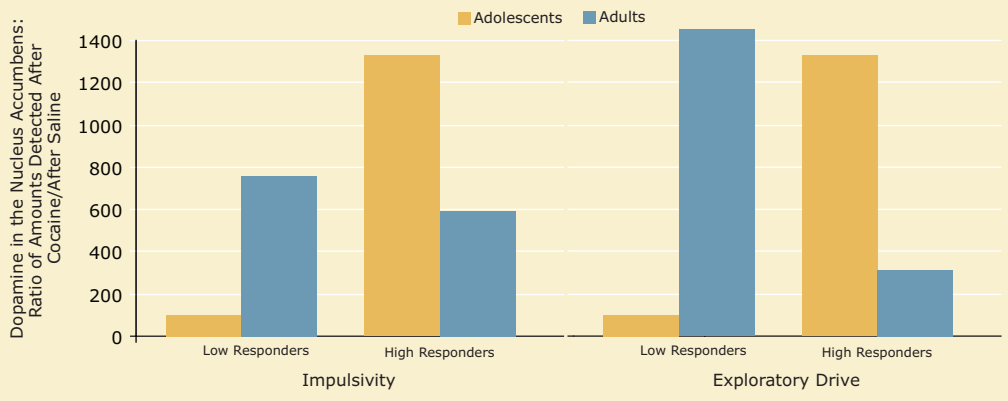
BY LORI WHITTEN,
NIDA Notes Staff Writer

NIDA-supported researchers Dr. Cheryl Kirstein and Ms. Kirstie Stansfield at the University of South Florida have found that higher scores on tests of impulsivity and some behavioral responses to novelty correlate with a heightened biological response to cocaine in adolescent, but not adult, rats. The findings accord well with scientists' widely shared view that developmental differences in brain systems that use the neurotransmitter dopamine underlie age differences in susceptibility to drug abuse.

Dr. Kirstein and Ms. Stansfield conducted a series of behavioral assays to rate rats' relative responsiveness to novelty, then compared these results with measures of dopamine release in the reward pathway after an injection of cocaine. First, they put adolescent rats (34 days old, which is roughly equivalent to adolescence in people) and fully mature rats (59 days old, equivalent to

[*Continued on page 6*]

COCAINE-INDUCED DOPAMINE RELEASE VARIES WITH AGE AND RESPONSE TO NOVELTY
Among adolescents, high responders—rats that demonstrated above-the-mean scores on impulsivity and exploratory drive in tests of response to novelty—released more dopamine after an injection of cocaine than low responders. Adult rats showed no clear relationship with impulsivity and cocaine-induced dopamine response, and those with high exploratory drives released less dopamine after an injection of cocaine than age mates who were low responders.



ALSO IN THIS ISSUE

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

Addiction and Co-Occurring Mental Disorders

As many as 6 in 10 substance abusers also have at least one other mental disorder. Research increasingly supports the benefit of studying and treating co-occurring disorders together, with both medication and behavioral therapies.

Tobacco smoking patterns highlight the striking relationship between addiction and mental illness. Mentally ill individuals are about twice as likely to smoke as others; although they comprise an estimated 28 percent of the population, they consume about 44 percent of all cigarettes smoked, according to a recent U.S. study. Smoking rates are particularly high—75 to 95 percent—among people with schizophrenia. Combining bupropion for nicotine addiction with tailored behavioral smoking cessation treatment can curb smoking by patients with schizophrenia, and controlling symptoms of schizophrenia helps reduce smoking intensity and nicotine addiction.

The reasons why addiction and other mental disorders coincide so frequently are not fully understood. Epidemiological research suggests that each can contribute to the development of the other. Children and adolescents with psychiatric conditions—including conduct disorders, attention deficit hyperactivity disorder (ADHD), and learning disabilities—are at higher risk of abusing drugs than other youth. There is evidence that drug abuse early in life may increase the risk of psychiatric disorders or accelerate their course. NIDA-supported investigators are using neuroimaging, genotyping, statistical modeling, and other tools to parse the interplay of risk factors in the development of such disorders.

Research has yielded some practical help and promises more. Several studies demonstrate that early diagnosis and treatment of ADHD cuts the risk for substance abuse in adolescence, and NIDA is funding research to determine whether early treatment of other psychiatric disorders can have similar benefits. Addressing substance abuse early can prevent the onset or improve the outcome of psychiatric disorders as well. Tailored versions of proven behavioral treatments—for example, cognitive-behavioral and motivational enhancement therapy—are available for clinicians who work with substance abusers with psychiatric conditions.

NIDA's Clinical Trials Network has begun recruiting patients in a large study to test whether treating ADHD can improve substance abuse outcomes in adults and adolescents with both conditions. We are also supporting studies on integrated treatments for addiction and post-traumatic stress disorder (PTSD) and on the relationship between stress-related conditions and drug abuse.

Effective, research-based interventions are available for patients with addiction, depression, and certain other co-occurring disorders. Studies on the root causes of these disorders, common risk factors, and potential interventions will enable us to better serve the large population for whom substance abuse is only part of the problem. ■

NIDA Notes

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Studies Focus on Acculturation and Hispanic Youth

U.S.-Born Hispanic Women Have More Drug Problems Than Immigrants: Among 19- to 21-year-old Hispanic women in South Florida, those born in the United States face a higher risk of drug addiction than immigrants, according to a recent study by Dr. R. Jay Turner and colleagues. The U.S.-born women reported more acculturation, measured as preference for English over Spanish, and greater exposure to stressful events, both of which were associated with increased risk for addiction. The gap in acculturation between the two groups accounted for 40 percent of the risk difference; a high score on either acculturation or stress exposure was associated with a nearly three-fold increase in the odds of addiction, compared with low scores on those measures (evaluated at one standard deviation above and below average). The investigators speculate that cultural influences help protect foreign-born Hispanic young women from stress. Native-born and immigrant young men reported similar levels of stress exposure and had similar rates of addiction.

> Drug and Alcohol Dependence 83(1):79-89, 2006.

Latino Parent Training: Men and women who completed a parent-training program adapted for Latino culture reported improvements in effective parenting practices and their children's (aged 13 years, on average) behavior compared with those who did not receive the intervention. Children whose parents received the program also reported that they were less likely to abuse tobacco, marijuana, and other drugs in the future. The parents also said their children's behavior improved.

Drs. Charles R. Martinez and J. Mark Eddy of the Oregon Social Learning Center randomly assigned 73 Spanish-speaking Latino parents (90 percent were of Mexican heritage) to participate in *Nuestras Familias: Andando Entre Culturas* (Our Families: Moving Between Cultures) or to receive no intervention. During each of 12 weekly 2.5-hour sessions, participants in the intervention group discussed developing effective family communication, bridging cultures, being positive, and encouraging success using appropriate discipline and limit setting, and practiced parenting techniques in role-play.

> Journal of Consulting and Clinical Psychology 73(5):841-851, 2005.

Medical Care During Addiction Treatment Reduces Hospital Use

On-site delivery of primary care reduces emergency department (ED) visits and inpatient hospital stays over the next 12 months among adult patients in methadone maintenance or in long-term residential treatment in programs, according to a recent article by Dr. Peter D. Friedmann and colleagues. Their longitudinal analysis showed that offsite referrals reduced hospitalizations, but not ED visits, among those in long-term residential programs. Neither on-site care nor offsite referral curbed health service use by outpatients in nonmethadone treatment programs. In all three types of programs, health care use declined after substance abuse treatment. Overall, ED visits decreased from 47 percent to 23 percent, and hospitalizations from 42 percent to 13 percent; the greatest reductions were observed among patients with the longest stays in treatment. The National Treatment Improvement Evaluation Study included six methadone maintenance programs, 14 long-term residential programs, and 24 outpatient nonmethadone programs with over 2,000 patients. The investigators advocate future studies of the cost-effectiveness of integrating primary care into addiction treatment.

> Medical Care 44(1):8-15, 2006.

Brain Changes Accompany Cocaine Withdrawal

Rats repeatedly exposed to cocaine and then withdrawn from it exhibit neural changes in the lateral amygdala, a part of the brain involved in responding to pleasurable and aversive stimuli. Such changes may mediate the negative emotional effects that accompany drug withdrawal, say the researchers who documented the effect in a recent study. Dr. Vadim Bolshakov and colleagues at Harvard Medical School have shown that long-term potentiation (LTP), a process underlying learning and memory, occurs in the lateral amygdala when cocaine-exposed rats no longer have access to the drug. They found a clear link between LTP and enhanced levels of the neurotransmitter glutamate in the lateral amygdala and signs of withdrawal in the rats. The findings suggest that amygdala circuits might contribute to drug modulation of motivational states and influence addictive behaviors.

> European Journal of Neuroscience 23(1):239-250, 2006.

NIDA's Division of Basic Neuroscience and Behavioral Research

How Drug Abuse Affects the Brain and Alters Behavior Are Key Questions Driving Division's Work

BY DEBRA P. DAVIS,
NIDA Notes Staff Writer

A compound that appears promising for treating cocaine relapse is wending its way along a chain of discovery and trial that links NIDA's various Divisions. Its discovery occurred under a grant from the Division of Basic Neuroscience and Behavioral Research (DBNBR), NIDA's locus for studies into the fundamental brain mechanisms underlying drug abuse and addiction.

Dr. David Shurtleff, director of the Division, sees his unit as the base of a pyramid upon which other NIDA Divisions and the scientific community at large build. "Much NIDA-supported research hinges on a basic understanding of the important biological components of drug abuse and addiction and how we can modify them to treat this disease," says Dr. Shurtleff. "Our research in DBNBR, which probes the genetic, molecular, neurobiological, and behavioral levels, is fed to all other Divisions at NIDA for further studies and for development of medications and new behavioral treatments."

With an eye toward developing a new medication for treating cocaine relapse, DBNBR "handed over" the JDTic compound, a potent and selective kappa-opioid antagonist that has been shown to significantly reduce stress-induced cocaine relapse in rodents, to the Division of Pharmacotherapies and Medical Consequences of Drug Abuse for further tests in animals and—if warranted—in people. Ultimately, the compound may undergo large-scale clinical trials sponsored by NIDA's Clinical Trials Network.

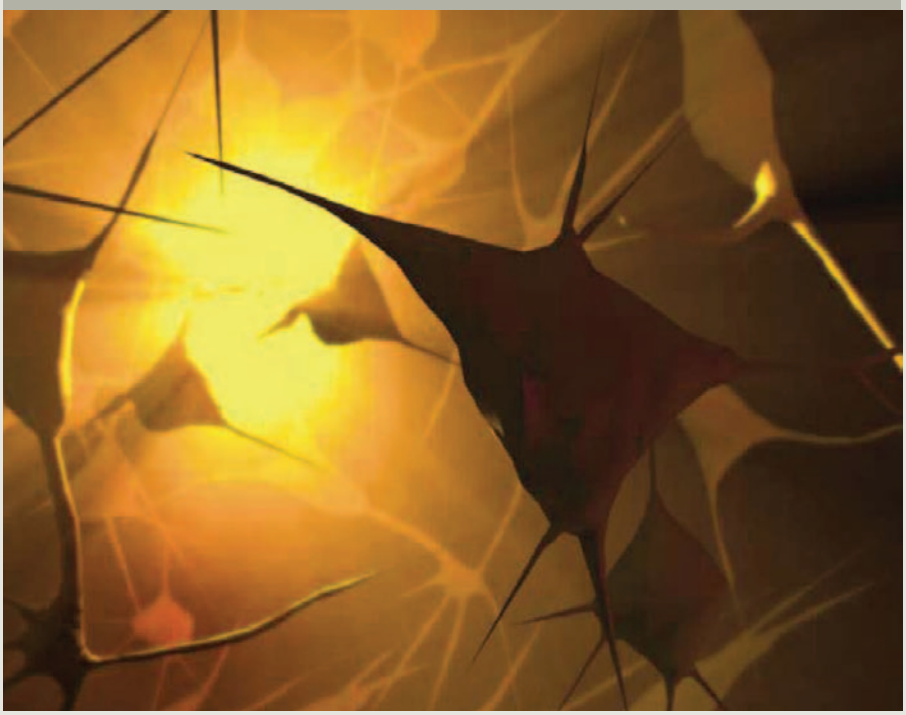
The flow of research is two-way: As DBNBR feeds the findings of its grantees to other Divisions, it also relies on them for information that drives the development of its own research portfolio. For example, says Dr. Shurtleff, "The Division of Epidemiology, Services and Prevention Research tells DBNBR what the trends in drug abuse are and who is affected."

KEY RESEARCH COMPONENTS

DBNBR's research portfolio is divided among four Branches: Genetics and Molecular Neurobiology, headed by Dr. Jonathan Pollock; Behavioral and Cognitive Science, under Dr. Minda Lynch; Chemistry and Physiological Systems, under Dr. Rao Rapaka; and Functional Neuroscience, run by Dr. Nancy Pilotte. Investigations fall into the following categories:

- Genetic, which seeks to pinpoint genetic variations that make some individuals more susceptible to addiction;

SEA OF NEURONS This image appears on the Division's NIDA publications and posters.



- Developmental, which examines, primarily in animal models, the effects of drugs on prenatal development as well as on the still developing brains of children and adolescents;
- Behavioral, which looks at the consequences of drug abuse on behavior and cognition, providing important information for the design of treatment and prevention interventions; and
- Neurobiological, which delves into the processes and mechanisms in the brain and nervous system underlying addiction.

The research projects touch on a broad range of drugs, health problems, populations, and scientific disciplines. For example, teams of scientists specializing in virology, immunology, neuroscience, and other disciplines are trying to determine how and why some individuals with HIV/AIDS develop a type of dementia called neuroAIDS and how exposure to neurotoxic drugs such as methamphetamine exacerbates this condition. Another study, by NIDA-supported scientists using technology developed by the California-based pharmacogenetics company Perlegen, Inc., is probing how genes affect tobacco addiction. The goal is to lay the groundwork for developing antismoking medications tailored to individuals who are genetically predisposed to nicotine addiction. Other nicotine studies focus on the effects of this drug on adolescents. Research by Dr. James Belluzzi and others shows that adolescent rats are more sensitive than adult rats to nicotine and that a combination of nicotine and acetaldehyde, another ingredient of cigarettes, is particularly addictive to the adolescents (see "Study Points to Acetaldehyde-Nicotine Combination in Adolescent Addiction," *NIDA Notes*, Vol. 20, No. 3).

A number of studies are examining how drug abuse changes the brain's structure. They include research by Dr. Eric Nestler and colleagues looking at short- and long-term changes that cocaine engenders in the brain's limbic system and studies by Drs. Terry Robinson and Bryan Kolb indicating that repeated exposure to amphetamine and cocaine alters neuronal structures called dendrites, which, in turn, increases sensitivity to the drugs.

"Thanks to advances in neuroscience and genetics, we're finding answers to longstanding questions," Dr. Shurtleff notes. "Now we're able to view the human brain in action and understand how drug abuse affects the molecular mechanisms of cell signaling. As a result, we can develop new medications to stave off or reverse those effects. Information provided by the mapping of the mouse and human genomes is also helping us to answer longstanding questions about the etiology of drug addiction." ■

[*Continued from page 1*]

human young adulthood) through four behavioral protocols. The tests measured activity in a new environment (how much the rat moved around when put into a new cage); impulsivity (how quickly it approached a new object placed into its cage); exploratory drive in response to a new object (how many times it approached the object in a given period of time); and attraction to new objects (what percentage of a given time interval was spent close to the object).

The researchers then injected the animals with saline and then, 2 hours later, with cocaine 20 mg/kg. Every 10 minutes, starting immediately after the saline injection and continuing until 2 hours after administering the cocaine, they measured the concentrations of the neurotransmitter dopamine and its major metabolite in the rats' nucleus accumbens (NAc). The measurements were made using the technique of *in vivo* microdialysis. By the time of the last measurement, the drug had cleared the animal's system.

ON MOST TESTS, AGE MATTERS

In their analysis, the researchers compared cocaine-induced dopamine release in animals that had responded above the mean level on each test (high responders, HR) to those who had scored below the mean (low responders, LR). The results revealed that among both the adult and adolescent rats, those that exhibited greater activity in a new environment also demonstrated enhanced dopamine release following a cocaine injection. This was the only test, however, in which age did not influence cocaine-induced dopamine release. The other behavioral assays revealed interactions between age and the response to novelty on cocaine-induced dopamine release in the NAc:

- Impulsivity—Adolescent rats with above-the-mean impulsivity scores released more dopamine in response to cocaine than their age mates who were LR. Mature rats exhibited no clear relationship between impulsivity and cocaine-induced dopamine response.
- Exploration of a new object—Adolescent rats with above-the-mean scores on this measure released more dopamine in response to cocaine than their age mates who were LR. Adult rats showed the opposite pattern: Animals with above-the-mean scores showed attenuated cocaine-induced dopamine release compared with age mates who were LR.
- Attraction to a new object—Adolescent rats exhibited no clear relationship between reactivity on this assay and cocaine-induced dopamine release. Mature rats with above-the-mean scores released less dopamine in response to cocaine compared with their age mates who were LR.

Dr. Kirstein's finding that for all the animals, greater activity in a new environment corresponded with increased sensitivity to stimulants is consistent with earlier research. Her team's mixed findings on the impulsivity and other novelty response tests indicates, she says, that those behaviors arise from different physiological mechanisms than does locomotor activity. "My colleagues and I think locomotor activity may reflect primarily dopamine activity in a brain circuit involved with generating and controlling movement. Novelty may instead differentially stimulate mesolimbic dopamine—a pathway implicated in attention as well as reward and motivation," says Dr. Kirstein.

In Vivo Microdialysis

The investigators used in vivo microdialysis to measure dopamine each animal released from its nucleus accumbens (NAc) in response to cocaine. They implanted a probe into the shell area of the NAc. The probe is a fine tube, about the size of a sewing needle, connected to a mini-pump that continuously perfuses it with artificial cerebrospinal fluid. The membrane tip of the probe captures dopamine and its metabolites. The samples collected by the needle are then analyzed using techniques, such as chromatography, that are able to isolate dopamine and its metabolites from other molecules.

INHIBITION DEVELOPS LATER

The findings on the three tests where age affected the relationship between behavior and cocaine-induced dopamine release may reflect maturation of the brain's reward circuit. When rats are adolescents, dopamine-producing and releasing cells in this circuit may be particularly sensitive both to novelty and to pharmacological stimulation. As part of normal neurological development, areas of the brain that dampen the activity of this circuit come "online" later, explaining the age-related differences observed in Dr. Kirstein's study. "The mesolimbic pathway and the cortical areas that inhibit it to regulate dopamine release are not yet fully matured in the adolescent, and this may explain why the adolescent brain responds to drugs differently than the adult brain," says Dr. Kirstein.

"The results of Dr. Kirstein's study, along with other animal research on the interaction of drugs and developmental stage, indicate that the adolescent brain is more responsive to drugs than the adult brain—both neurochemically and behaviorally," says Dr. Nancy Pilotte of NIDA's Division of Basic Neuroscience and Behavioral Research. Studies that identify the physiological and behavioral processes underlying age-related susceptibility to addiction complement epidemiological work on the individual and social factors contributing to adolescent vulnerability to substance abuse. ■

SOURCE

Stansfield, K.H., and Kirstein, C.L. Neurochemical effects of cocaine in adolescence compared to adulthood. *Developmental Brain Research* 159(2):119-125, 2005.

Cocaine Abusers' Pretreatment Cue Responses Predict Recovery Success

In the future, patients' brain scans may help clinicians tailor addiction treatment to improve therapeutic outcomes.

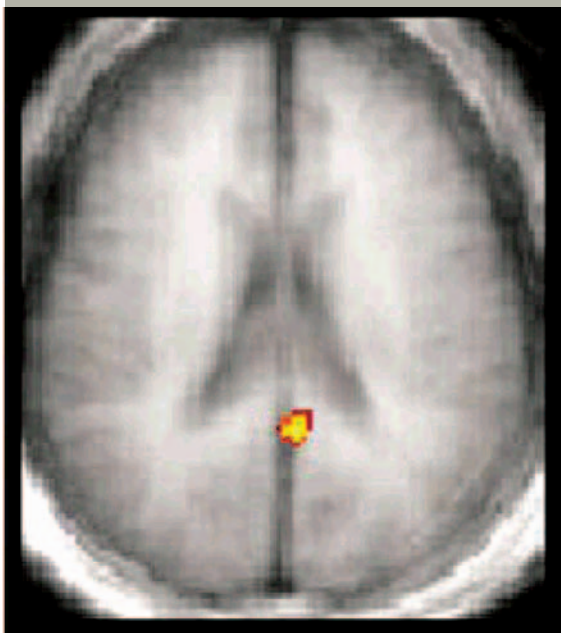
BY LORI WHITTEN,
NIDA Notes Staff Writer

A recent NIDA study strengthens prospects that brain imaging may one day help clinicians assign individual patients to treatment models that maximize their personal chances of a successful outcome. The study, conducted by Dr. Thomas Kosten and colleagues at Yale University School of Medicine, the University of Arkansas for Medical Sciences, and the Massachusetts Institute of Technology, correlated cocaine-addicted patients' regional brain responses to drug cues with their outcomes in subsequent treatment. The patients whose brain scans revealed rapid and strong activation in sensory, motor, and cognition- and emotion-processing brain areas were more likely to drop out of treatment and fail to achieve stable abstinence.

"A test that predicts treatment outcomes, especially vulnerability to relapse, could help guide individualized treatment. For example, a clinician might recommend an extended stay in residential treatment or more intense behavioral intervention for patients with a propensity for relapse," says Dr. Kosten, now at Baylor College of Medicine.

Dr. Kosten and colleagues pursued the implications of an intriguing finding made in a prior study of cocaine cue responses: In some patients, strong, rapid activation of brain areas associated with emotion and sensing preceded the onset of craving. Although craving itself does not generally predict relapse, Dr. Kosten's team speculated that cue-induced brain activation that occurs quickly and reflexively, below awareness, might do so. They hypothesized that patients who showed such responses during the first 30 seconds of cue exposure would also demonstrate poorer treatment outcomes.

fMRI TRACKS CUE-INDUCED BRAIN ACTIVITY
When cocaine-addicted patients watched a drug-related videotape, activation of the posterior cingulate cortex (highlighted in the brain image) occurred more quickly in those who subsequently relapsed.



To test their hypothesis, the investigators recruited 17 men and women who were participating in a trial of an antidepressant—sertraline—that is being evaluated as a possible treatment for cocaine addiction. The participants reported abusing cocaine 20 days, on average, during the month before the study. All met standard clinical criteria for cocaine addiction and had abused the drug for 6 years, on average. Most were new to treatment.

After being cocaine-free for 5 days, on average, each participant underwent functional magnetic resonance imaging (fMRI) while watching two 4-minute videotapes. The first minute of each tape reported on vegetable prices, and the participants' brain activity while hearing this emotionally neutral information served as a baseline for comparison. During the last 3 minutes, an actor pretended to smoke cocaine and experience a "rush." Immediately after viewing the tapes, each participant rated peak cocaine craving intensity on a scale from 0 to 10. After the imaging session, participants began taking either sertraline or a placebo daily and completed 2 weeks of residential treatment. During the 10-week outpatient phase of the trial, they were to continue their medication regimen, receive weekly individual cognitive-behavioral therapy, and submit urine samples three times a week.

INTERPLAY WITHIN CINGULATE CORTEX?

Nine of the 17 participants relapsed, defined by the investigators as submitting fewer than 15 of a possible 30 cocaine-free samples during the study and not completing outpatient treatment. Participants

taking sertraline were just as likely as those taking the placebo to relapse. Relapsers and nonrelapsers reported cue-induced cravings of comparable intensity. The two groups differed, however, on brain activation during the first 30 seconds of the cocaine-cue videotapes. Relapsers showed greater cue-induced activation than nonrelapsers in several areas of the cortex: the left precentral (movement control), right superior temporal (auditory processing), right lingual and right inferior occipital (visual processing), and the left posterior cingulate cortices. The cingulate cortex is integral to attention, response inhibition, emotional regulation, and decisionmaking (see chart).

The relapsers' greater activation of the posterior cingulate cortex (PCC) was the most notable of the findings. Also significant was the lack of any difference between the outcome groups in activation of the neighboring anterior cingulate cortex (ACC). This contrasts with findings from previous studies, in which ACC activation and craving were associated in patients who had longer abstinence (average 14-28 days) and were imaged for periods longer than 30 seconds after being shown cues.

"If researchers can determine changes in brain activity that predict responses to particular treatments, then clinicians could match therapy with individuals' scan results or even monitor progress in therapy."

Taken together Dr. Kosten says, these results suggest that an interplay occurs between the PCC and ACC following exposure to cocaine cues and changes with increasing stability of abstinence. In patients highly vulnerable to cues, intense PCC activation occurs within 30 seconds of cue exposure and is positively associated with risk for relapse. In less vulnerable patients, early PCC activation is less intense, and these patients are able to activate the ACC to counter the association with relapse risk.

Dr. Kosten's findings highlight the promise of imaging linked to behavioral assessments as a tool for guiding the treatment of addictions and other psychiatric disorders. They parallel a previous NIDA-funded study in which brain activity patterns during a decisionmaking task predicted treatment outcomes among patients addicted to methamphetamine (see "Brain Activity Patterns Signal Risk of Relapse to Methamphetamine," *NIDA Notes*, Vol. 20, No. 5).

"If researchers can determine changes in brain activity that predict responses to particular treatments, then clinicians could match therapy with individuals' scan results or even monitor progress in therapy," says Dr. Kosten. More generally, studies that examine biological and behavioral predictors of treatment response elucidate the physiology underlying addiction—particularly the neural circuitry integrating stress, craving, and the propensity to relapse. New tools—for example, scanners that highlight brain areas that are working together—are expected to reveal more about these physiological processes. "With such functional connectivity imaging, one could examine how the anterior and posterior cingulate 'talk' to each other during a drug cue or other experience," says Dr. Rajita Sinha, an investigator in the Kosten study.

"Eventually, researchers will integrate the findings of such studies into a complete picture that will specify therapeutic pathways or help in the development of targeted medications to reduce relapse probability," adds Dr. Harold Gordon of NIDA's Division of Clinical Neuroscience and Behavioral Research. ■

WHAT RESEARCHERS KNOW ABOUT THE CINGULATE CORTEX AND BEHAVIOR

The cingulate cortex connects to both the limbic systems (emotion and motivation) and the prefrontal cortex (planning and control of behavior) and seems to integrate emotion and cognition. The anterior and posterior regions of the cingulate are connected to different brain areas and differ functionally.

Anterior Cingulate Cortex (ACC)	Posterior Cingulate Cortex (PCC)
Paying attention—The ACC monitors inputs from the senses (competing options) and selects what we attend to.	Responding reflexively—The PCC integrates sensory and movement information with established behavior patterns and acts "below awareness." The PCC responds to reward and positive feedback.
Making decisions—Influenced by past experience, the ACC assesses risk, reward, and conflict. It works with areas of the frontal cortex to select a response.	Reacting emotionally—The PCC processes emotion-related autobiographical memories and the emotional perspective of self and others. Its activity correlates with internal physiological responses (heart rate, anxiety, and arousal level).
Inhibiting responses—The ACC integrates input from the prefrontal cortex and detects and corrects errors in behavior.	
Detecting and controlling emotions—The ACC monitors what is going on inside (feelings, pain, and bodily arousal) and controls voluntary suppression of these sensations.	

SOURCE

Kosten, T.R., et al. Cue-induced brain activity changes and relapse in cocaine-dependent patients. *Neuropsychopharmacology* 31(3):644-650, 2006.

Stress Cues Also Signal Relapse Risk

Exposing patients to stress cues at the beginning of cocaine addiction treatment triggers craving and measurable biological responses that may predict drug abuse outcomes during early recovery. NIDA-funded researchers found that stress-induced craving was associated with a shortened interval to relapse following inpatient treatment, while hormonal responses to stress predicted the amount of cocaine the patients consumed during relapse.

The findings were reported in a followup to prior research conducted by Dr. Rajita Sinha and colleagues at Yale University School of Medicine. In the previous study, patients who listened to tapes reminding them of a stressful experience and a drug-related experience demonstrated an elevated biological stress response and increased cocaine craving compared with their response to tapes of relaxing experiences (see "Cocaine-Related Environmental Cues Elicit Physiological Stress Responses," *NIDA Notes*, Vol. 20, No. 1).

Dr. Sinha and colleagues followed up with 49 of the 54 patients 3 months after completion of inpatient behavioral treatment. They found that patients who had experienced more intense cocaine craving while revisiting their stressful experiences via audiotape tended to relapse sooner. The probability of relapse 3 months after treatment was 56 percent among patients who reported no craving. Each unit increase on a craving intensity scale of 0 to 10 was associated with a 31 percent rise in the likelihood of relapse during the followup period.

Participants who released high levels of the stress hormones adrenocorticotropic hormone (ACTH) and cortisol in response to the stressful tapes consumed more cocaine than low-level responders during the followup. Three months after treatment, high-level responders had consumed about 8 g of cocaine cumulatively over their cocaine abuse periods, while low-level responders consumed about 3 g.

The findings of the study suggest that different components of the stress response are associated with various aspects of relapse: craving with reinitiating abuse and hormonal responses with the ability to control intake after reinitiating abuse. "Greater hormonal release during stress may 'prime' higher cocaine consumption or bingeing after return to abuse, perhaps by altering the rewarding effects of the drug," Dr. Sinha says.

Dr. Sinha and colleagues did not find a link between drug cue-induced craving and relapse outcomes, a result that is consistent with previous studies. However, because the drug cue imagery produced physiological reactions similar to those triggered by the stress cues, the researchers speculated that studies using a larger sample or exposure to actual drug cues, rather than just images of them, may show such an association.

Prior studies that did not find a link between cue-induced craving and relapse generally assessed only one or two dimensions of craving, Dr. Sinha points out. Studies that address multiple components—wanting the drug, feelings about the drug and about wanting it, drug-seeking behaviors, coping reactions, physiological arousal, and stress hormone levels—may better indicate vulnerability to relapse, she says.

"For people who are not addicted, knowing that you want a particular thing probably defines craving. Our findings suggest that for addicted people, craving is a 'state'—a multidimensional experience—comprised, in part, of stress-like arousal. In this state, desire becomes pathological, and people cannot delay gratification or divert their attention," says Dr. Sinha.

The results of Dr. Sinha's study suggest that stress-induced drug craving and physiological responses may be used as a diagnostic indicator of relapse propensity and might one day help clinicians tailor their interventions toward regulating stress and coping with stress-induced craving. "Research on each component and the role that it plays in continued drug abuse is just beginning, but such studies ultimately may improve our ability to help people attain long-term recovery," she says. ■

SOURCE

Sinha, R., et al. Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. *Archives of General Psychiatry* 63(3):324-331, 2006.

Nicotine Alters the Developing Rat Brain

Exposure to the drug during gestation or adolescence may cause lasting alterations in reward and motivation circuits.

BY CARL SHERMAN,
NIDA Notes Contributing Writer

Most people who become chronic smokers start in adolescence, and the risk of addiction at this time is even greater among those whose mothers smoked while pregnant. NIDA-funded animal studies recently identified two neurobiological effects of nicotine that could underlie these vulnerabilities. Investigators at the University of Tennessee, led by Dr. Burt Sharp, found that prenatal nicotine exposure reduces the availability during adolescence of a receptor that mediates the drug's impact on cells in the brain's reward system. At the University of Wisconsin, Dr. Charles Landry and his research team found that nicotine stimulates a set of genes involved in synapse formation to a higher level of activity in adolescent than in adult rats.

NICOTINE'S IMPACT ON RECEPTORS

The University of Tennessee researchers pursued a clue from previous work in which they examined the effects of prenatal nicotine exposure on the mesolimbic reward pathway. Nicotine and other drugs of abuse stimulate neurons in the brain area where this pathway originates, the ventral tegmental area (VTA), to release the neurotransmitter dopamine in the nucleus accumbens (NAc) and prefrontal cortex (PFC). The dopamine influx into the NAc produces the feelings of reward and pleasure that are primary motivators of continued drug-taking. Dr. Sharp and colleagues found, however, that exposing rats prenatally to nicotine reduced the amount of dopamine released in the NAc when the animals were given the drug again as adolescents.

"We asked ourselves, 'What causes this?'" Dr. Sharp says. "We decided to look at nicotine's impact on the expression of nicotinic cholinergic receptors—the principal sites where nicotine molecules interact with brain cells to exert their stimulating effects." The researchers hypothesized that exposure to nicotine during gestation would reduce the number of such receptors present on dopamine-producing cells in the VTA in adolescence.

They gave nicotine to pregnant rats via an implanted pump at the rate of 2 mg/kg/day (the equivalent of a human smoking a pack a day) throughout gestation. At birth they increased the nicotine infusions to 6 mg/kg/day and continued them for 2 more weeks, while the rat pups nursed. Because rat pups are born at an earlier stage of development than humans, the weeks of continued exposure were necessary to give them cumulative nicotine exposure equivalent to a smoking mother's baby at full-term. A control group of rats received the nicotine delivery solution without the drug.

The researchers took brain sections from the rat pups when they were 35 days old, developmentally equivalent to mid-adolescence in humans, and assayed them for nicotinic cholinergic receptors. In confirmation of their hypothesis, the results showed significantly fewer receptors in the VTA, NAc, and PFC of the adolescent rats that had been exposed to nicotine *in utero*. Messenger RNA (mRNA) for the receptors declined only in the VTA, suggesting that gestational nicotine had primarily affected dopaminergic neurons that originate in that area. The total number of VTA neurons also dropped in the brains of nicotine-exposed rats.

These findings "show how gestational exposure to nicotine may alter maturation, literally changing the brain," Dr. Sharp says. Although it is not clear how such changes could enhance the likelihood of dependence, "one hypothesis might be that prena-

LOWER BINDING CAPACITY SUGGESTS LOWER NICOTINE REWARD The capacity to bind epibatidine is a marker for the concentration of nicotinic cholinergic receptors in a tissue sample. In the brain regions tested, this capacity was significantly lower in adolescent rats that had been exposed to nicotine during gestation. This suggests that prenatal exposure reduces later nicotine sensitivity in a brain circuit believed central to the drug's rewarding effect.

	Male		Female	
	Control	Nicotine	Control	Nicotine
Binding capacity (fmol / mg protein)				
NAc	38.2	30.2	37.7	27.1
PFC	55.1	45.6	55.7	41.9
VTA	59.5	43.3	45.9	39.3

tally exposed adolescents, having fewer nicotinic receptors, must take more puffs to release a rewarding amount of dopamine into the NAc, and this leads to stronger conditioning," he says.

Dr. Allison Chausmer of NIDA's Division of Basic Neuroscience and Behavioral Research says, "The findings confirm the long-term effect of smoking during pregnancy and underscore the importance of smoking cessation at this time."

NICOTINE AFFECTS SYNAPSE DEVELOPMENT

The University of Wisconsin team studied the impact of nicotine on genes that contribute to neural plasticity. This process—the formation of new synaptic connections between neurons and pruning of old ones—wires the brain during development and reaches a crescendo during adolescence. The researchers specifically focused on the genes—including *arc*, *c-fos*, and *NGFI-B*—that produce a set of neurochemicals involved in building synapses. Using rats as subjects, they compared the expression—roughly, the production rate—of these genes following exposure to nicotine in adolescents (average age 30 days) and adults (average age 70 days).

The investigators injected the rats with nicotine at a dose large enough (0.4 mg/kg) to cause a behavioral response—increased motor activity—or with saline. An hour later, they examined slices of the rats' brains, with particular attention to areas that play central roles in learning and motivation: the medial PFC, ventral and lateral orbital cortex (VLO), cingulate cortex, somatosensory cortex, ventral striatum, and dorsal striatum. They assessed the expression of plasticity-related genes by measuring the amount of their corresponding mRNA.

Throughout the brain, they found higher amounts of mRNA for *arc* and *c-fos* in the adolescent than the adult brains, an indication of more synaptic plasticity overall, Dr. Terri Schochet suggests. In both age groups, *arc* and *c-fos* mRNA jumped after injection of nicotine, compared with saline, indicating that the drug "switched on" these genes. In certain prefrontal regions, the nicotine-evoked increase in *arc* mRNA was significantly greater in adolescent animals. In the VLO, for example, *arc* expression increased by 182 percent in adolescents after nicotine injection, compared with 98 percent in adults.

"These findings show that at the basic biochemical level, the adolescent brain responds differently to a single dose of nicotine," says Dr. Landry, principal investigator for this study. "The enhanced expression of *arc*, a gene involved in dendrite formation, in adolescent forebrains following acute nicotine reflects a very dynamic synaptic milieu. It's difficult to speculate further, but my suspicion is that the adolescent brain responds to the drug with a greater increase in synaptogenesis and pruning."

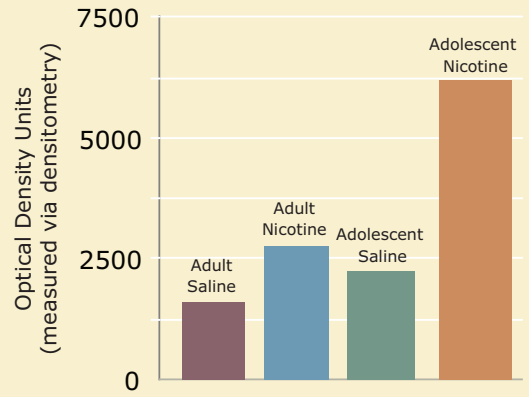
"The adolescents' greater changes in molecular systems involved in learning may indicate that this age group is more susceptible to developing the nicotine habit," Dr. Schochet suggests. The striking effect of a single dose of nicotine could have implications for treatment, she adds: "It's really important to intervene as early as possible to prevent adolescents from trying nicotine in the first place."

Research that explores and compares adult and adolescent behavior and neurobiology is a particular interest of NIDA's, says Dr. Susan Volman of the Institute's Division of Basic Neuroscience and Behavioral Research. This study was valuable because it "looks at both what's different in general between the maturing and adult brain and how that difference interacts with nicotine."

Dr. Volman notes that the adult/adolescent disparity in response to nicotine was greatest in the ventrolateral PFC. "Neural adaptations here could have to do with altering motivation and the value placed on particular rewards," she says. Smoking might be equally pleasurable to adults and adolescents, that is, but the experience would be more highly valued by the adolescent—a difference with potential implications for tailoring behavioral treatments to this age group. ■

arc EXPRESSION INCREASES WITH NICOTINE

The height of the bars represents the expression of *arc*, a gene involved in neural plasticity. Administration of nicotine increases *arc* in the ventral and lateral cortex of both adolescent and adult rats, but significantly more in adolescents. This suggests that nicotine triggers synaptic development—a key process in learning—in a region important in motivation and goal-directed activity. Because the effect is greater in adolescents, they may more readily "learn" the nicotine habit.



SOURCES

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Schochet, T.L., Kelley, A.E., and Landry, C.F. Differential expression of *arc* mRNA and other plasticity-related genes induced by nicotine in adolescent rat forebrain. *Neuroscience* 135(1):285-297, 2005.

Cocaine Craving Activates Brain Reward Structures; Cocaine "High" Dampens Them

A study documented changing emotional and neurobiological responses to cocaine with successive doses during a single session of drug taking.

BY LORI WHITTEN,
NIDA Notes Staff Writer

NIDA-funded researchers mapped the dynamic of drug-induced brain activity and emotional responses that occur during a cocaine abuser's typical binge-like pattern of self-administration. Dr. Robert Risinger and colleagues at the Medical College of Wisconsin found that craving corresponds with increased activity in key brain areas underlying reward and motivation, while the cocaine-induced "high" is linked with decreased activity in these same regions. "Our results suggest that, as one takes multiple 'hits' of cocaine, pleasure accumulates with each successive dose, but lasts for a shorter time—a pattern that would compel people to keep abusing," he says.

"My colleagues and I wanted to know what cocaine does to the brain to compel drug-seeking behavior in addicted people—particularly, why taking a small amount of the drug can lead to a binge. Understanding this could help identify interventions to stop such abuse," says Dr. Risinger.

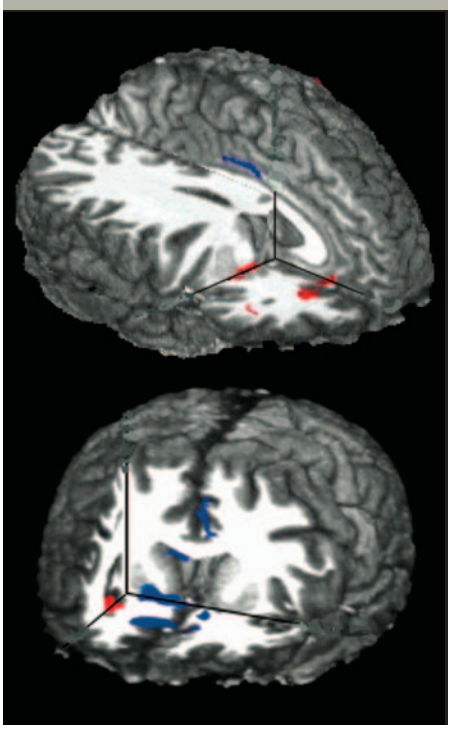
Dr. Risinger's team recruited six cocaine-addicted men who were not seeking treatment. The men, aged 23 to 41, had abused crack cocaine for 11 years, on average. They completed a medical examination, received counseling on the health consequences of cocaine abuse, and were offered (but all declined) addiction treatment before the study.

Each man participated in two 1-hour sessions of cocaine self-administration. At the beginning of the first session, he learned how to press a joystick button to receive infusions of cocaine through an intravenous catheter. After a 5-minute baseline period, he saw a computer-displayed signal that the joystick was activated, and for the next 55 minutes he pressed the button at will. Each press delivered a 20 mg/70 kg of body weight dose of the drug—except that, for safety reasons, doses could not be repeated at intervals of less than 5 minutes, and total doses over the course of the hour were limited to six. Meanwhile, in response to prompts on a computer display, the volunteer used a joystick to rate his cocaine craving, high feelings, and other sensations once per minute. During the second session, the researchers used functional magnetic resonance imaging (fMRI) to obtain brain scans synchronized with the subjective reports. After each session, each man underwent a brief physical examination and left the facility once his vital signs returned to baseline levels and he no longer showed drug effects or reported craving.

BEHAVIORAL RESULTS

Participants administered 4.5 injections a session, on average, spacing the doses about 7.4 minutes apart. Only two administered the maximum six doses. "For many patients, the amount of cocaine consumed during a self-administration session was less than they typically abused," says Dr. Risinger.

COCAINE CRAVING AND "HIGH" CORRESPOND WITH OPPOSITE PATTERNS OF BRAIN ACTIVATION
Cocaine craving was linked with activation (red areas, top panel), and euphoria with deactivation (blue areas, bottom panel) of the same brain regions according to an fMRI study in which cocaine-addicted participants reported subjective responses during a 1-hour self-administration session. The brain regions affected by craving and high are involved in reward anticipation, emotional response, and control over actions. The insula—a brain structure that seems to translate bodily sensations into emotions—was activated during cocaine-induced euphoria (red area, bottom panel).



As anticipated, the men's feelings of being high decreased before and increased after cocaine administration. From the first

through the fourth injection, the intensity of each successive high was greater, and its duration shorter. Craving peaked about 1 minute before each injection and decreased to a low point about 2 minutes after cocaine administration, before rising again during minutes 3 to 4. Absolute levels of craving decreased with each successive injection, but the preadministration increase in craving rose more sharply.

Dr. Risinger says the participants' reports match other abusers' accounts of their feelings during binges: "People often talk about 'chasing the high.' They abuse the drug several times in an episode, feel increasingly high with the first few hits, and experience a rapid dropoff in the duration of pleasure with repeated use—which may explain consuming larger amounts and more frequently over a session. Consuming cocaine satisfies craving only briefly, and then the feeling increases again before another administration, which may also contribute to the binge pattern."

"It is not clear whether the subjective feeling of craving was directly responsible for driving the participants to self-administer, or whether some other process, perhaps response-outcome learning, was responsible for initiation of self-administration," says Dr. Steven Grant of NIDA's Division of Clinical Neuroscience and Behavioral Research.

IMAGING FINDINGS

Cocaine-induced craving was associated with increased neural activity in brain areas involved in reward anticipation, emotional response, and control over actions: the nucleus accumbens (NAc), the orbitofrontal cortex, and the anterior cingulate cortex. The findings accord well with those of cue-induced craving studies, which generally indicate that the anticipation of a reward is accompanied by activation of the dopamine-rich mesolimbic pathway—a neural circuit involved in reward, motivation, and directing attention to stimuli. Such a neural response is thought to "set up" the brain to experience reward and to drive goal-directed behavior.

The researchers also found that cocaine-induced euphoria depressed activity in the areas activated by craving (see figure, page 12). In prior studies, Dr. Risinger's team has observed NAc suppression in participants who reported experiencing a cocaine-induced high. Although researchers do not yet fully understand the neurobiological mechanisms underlying the high, some have speculated that suppression of NAc firing may be an important component, perhaps reflecting altered receptor sensitivity or weakened stimulation from other brain structures. Another research team found that participants who reported feeling high after receiving a single researcher-controlled dose of cocaine exhibited increased activity in the NAc. The different findings may reflect the teams' divergent experimental methods.

The study represents an important step in correlating drug-induced craving and high with neural activity in specific regions of the human brain. "It provides insight into the neurobiology involved in drug-taking binges, a very common and dangerous behavior associated with the disease of addiction," says Dr. Risinger.

"Dr. Risinger's study is a good example of translational research, which applies a well-established technique in animal research to people. Although the results need replication in a larger number of participants, the findings are provocative because they raise good questions about the relationship between the various neurobiological responses—the fMRI signal and dopamine release, for example. We currently do not have a complete picture of how neurochemical responses and neural activation patterns exactly relate to the entire drug-taking experience, but this issue can be addressed in reverse translational research—animal imaging studies of self-administration and passive cocaine delivery," says Dr. Grant. NIDA-funded investigators are developing such techniques, he adds. ■

The study represents an important step in correlating drug-induced craving and high with neural activity in specific regions of the human brain.

SOURCE

Risinger, R.C., et al. Neural correlates of high and craving during cocaine self-administration using BOLD fMRI. *NeuroImage* 26(4):1097-1108, 2005.

Videos Help Treat Deaf People

Two new training videos portray various scenarios involving dialectical behavior therapy for deaf people. In one scene, deaf clinicians—one experienced in DBT, the other a novice—discuss the treatment while watching a video lecture by the therapy's originator.

A new training DVD designed to improve deaf people's access to behavioral health care is now available to clients, and a second is on the way. NIDA-funded researchers Dr. Linda Dimeff and colleagues at Behavioral Tech Research, Inc. in Seattle produced the DVD in collaboration with Dr. Robert Pollard and colleagues at the Deaf Wellness Center (DWC) at the University of Rochester School of Medicine. The DVDs, especially adapted for deaf viewers, train clients in the skills developed in an empirically supported behavioral treatment. Researchers estimate that only about 2 percent of the deaf population needing mental health treatment receive it.

The DVDs present dialectical behavior therapy (DBT) skills being taught by deaf clinicians to deaf consumers. Originally developed by Dr. Marsha M. Linehan for chronically suicidal people with borderline personality disorder (BPD), DBT has been adapted for other difficult to treat populations, including people with co-occurring BPD and substance abuse and patients with eating disorders and, now, by the DWC for the deaf population. The DVDs, which require no prior knowledge of DBT concepts and methods, address the same learning points as the original Linehan films but feature a highly interactive script involving a number of deaf characters communicating in sign language. "In addition to using the videos with clients, many clinicians may find them useful as a means of training other colleagues in DBT skills," says Dr. Dimeff. Both DVDs have English soundtracks and subtitles.

The first recording, *Opposite Action: An Adaptation From the Deaf Perspective*, tells a story about the appropriate channeling of anger. It refers to the efforts of deaf people to gain passage of the Americans with Disabilities Act as an example of using anger in a positive way. The second film, *Radical Acceptance: An Adaptation From the Deaf Perspective*, scheduled for release in 2007, focuses on helping patients overcome and let go of negative life experiences, says Dr. Pollard.

As part of its efforts to improve access to mental health care among deaf people, the DWC led the adaptation of DBT materials and methods for this community. Such work goes beyond translation from English to American Sign Language (ASL) and "immerses" the treatment in deaf culture by making the learning points, analogies, and examples used during therapy relevant and appropriate to deaf people. However, the scope of their efforts did not include adapting the DBT skills training films for deaf audiences, which is where NIDA-funded researchers picked up the ball. "These products are an example of NIDA's efforts to improve treatment accessibility for people of other cultures, especially those who do not speak English, and to address drug abuse among people with disabilities," says Dr. Cecelia McNamara Spitznas of the Division of Clinical Neuroscience and Behavioral Research. The DVDs are available for purchase at *www.behavioraltech.org*.

Journal Highlights Opportunities in Hispanic Drug Abuse Research

"Scientific Opportunities in Hispanic Drug Abuse Research," a NIDA-funded supplemental issue of *Drug and Alcohol Dependence* published in September 2006, compiles information on drug abuse among this fast-growing and diverse population. Nine peer-reviewed articles cover topics ranging from neuroscience to prevention and treatment to the blending of research and practice.

Drs. Hortensia Amaro and Martin Y. Iguchi, editors of the issue, noted the many scientific opportunities in Hispanic drug abuse research—especially in improving culturally specific prevention and treatment interventions, identifying potential racial differences in biological factors and behavioral processes, and developing and refining methods to study the effects of ethnicity on drug abuse and its prevention and treatment.

"The cultural richness and genetic diversity of the Hispanic community pose many challenges in optimizing relevant prevention and treatment strategies for substance abuse and addiction. Awareness is a positive step toward this end," says NIDA Director Dr. Nora Volkow. In publishing the supplement, NIDA's goal is to guide ongoing research, stimulate new studies, and attract the next generation of investigators to the field.

The National Hispanic Science Network on Drug Abuse, based at the University of Miami School of Medicine, contributed to the project by collecting information on drug abuse among Latinos and disseminating it to researchers and clinicians. The Robert Wood Johnson Foundation collaborated with NIDA to publish the results.

Report Calls for Sweeping Changes in Health Care for Mental and Substance Abuse Problems

Each year, more than 33 million Americans seek treatment for mental and substance use (M/SU) disorders, but deficiencies in health care quality and access prevent many of them from receiving the treatment they need, the National Academy of Science's Institute of Medicine says in a recent 600-page report. *Improving the Quality of Health Care for Mental and Substance-Use Conditions: Quality Chasm Series* discusses the personal and national consequences of these deficiencies and proposes strategies for improvement. NIDA is one of eight cosponsors of the report, the second in a series that examines the quality of health care in the United States.

Numerous studies have documented a discrepancy between care that is known to be effective and care that is actually delivered, the report says. A review of studies published from 1992 through 2000 assessing the quality of care for M/SU conditions—which include alcohol withdrawal, bipolar disorder, depression, panic disorder, psychosis, schizophrenia, and substance abuse—found that only 27 percent reported adequate rates of adherence to established clinical practice guidelines. Less than a quarter of patients treated for depression received care that meets minimum standards, according to a 2003 study.

"The data suggest that people with M/SU disorders don't get the care they need. This is especially true in the general medical sector, where most patients are initially seen or treated for psychiatric and substance abuse disorders. Referrals that could be made at this point in treatment often are not made," says Dr. Paul Appelbaum, director of the Division of Psychiatry, Law and Ethics at Columbia University College of Physicians and Surgeons and a member of the committee that wrote the report.

These deficiencies have serious consequences. Together, major depression and drug and alcohol abuse and dependence are the leading causes of disability for American women and the second highest for men, behind heart disease. Moreover, M/SU disorders co-occur with a substantial number of illnesses, such as heart disease and cancer, and adversely affect the results of treatment. About one-fifth of patients hospitalized for heart attack, for example, suffer from major depression, and post-heart attack depression roughly triples one's risk of dying from a future attack or other heart condition. Mental and substance use disorders are also major risk factors for suicide.

"The report encourages coordination and complete integration of care so that patients who receive substance abuse treatment don't have to go to the other side of the city for general medical care," Dr. Appelbaum adds.

STRATEGIES FOR IMPROVING CARE

The report recommends that the U.S. Department of Health and Human Services establish a high-level office to take the lead in coordinating M/SU reforms. Other recommendations include:

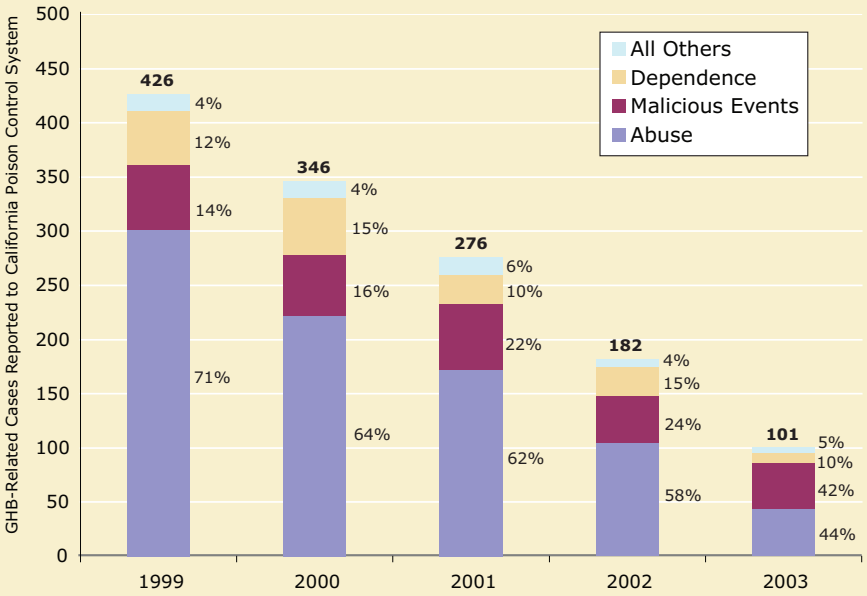
- Establishment of a stronger infrastructure for M/SU care by improving the synthesis and dissemination of effective, evidence-based treatments.
- Enhanced collaboration between M/SU services and general health care, as well as between providers of mental health services and their counterparts in the substance abuse field.
- Development of national standards for credentialing and licensing M/SU providers.
- Use of quality measures by government and private purchasers of health care.
- More widespread use of information technology to maintain and distribute medical records, information about quality care, and clinical support systems.

"Technology can facilitate attainment of all the other recommendations in our report," Dr. Appelbaum observes. "It would give all stakeholders access to common medical records, with appropriate protections for patient privacy, and give purchasers a way to judge the quality of the services for which they are paying."

The report is available online at *www.iom.edu/report.asp?id=30836*. ■

WHAT THE NUMBERS SAY

GHB Intoxication Reports Decline in California



SOURCE: Anderson, I.B., et al. Trends in gamma-hydroxybutyrate (GHB) and related drug intoxication: 1999 to 2003. *Annals of Emergency Medicine* 47(2):177-183, 2006.

Gamma-hydroxybutyrate (GHB)—abused for its euphoric, sedative, and body-building effects—can induce coma and seizures. Because the drug is colorless, tasteless, and odorless, assailants can also use it for malicious purposes. Cases of intoxication related to GHB, its precursors, and related chemicals reported to the California Poison Control System fell 76 percent from 1999 to 2003—a trend that paralleled recent national data from the American Association of Poison Control Centers (2001 to 2003). The decrease in the number of reports occurred across all case types: abuse, malicious events, and dependence. The proportion of reported cases related to abuse fell while that of malicious events, including GHB-facilitated related to sexual assault, increased.

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