

Ethnic Groups Have Contrasting Genetic Risks for Nicotine Addiction

Differences and similarities show up in genetic profiles of African-Americans and European-Americans who are heavy smokers.

BY LORI WHITTEN,
NIDA Notes Staff Writer

African-American smokers, on average, consume fewer cigarettes daily, inhale more deeply, and break down nicotine more slowly than European-American smokers. Such contrasts suggest that some of the biochemical processes underlying nicotine addiction differ between the two ethnic groups and may reflect genetic differences. Two NIDA-funded large-scale studies have linked some regions of the

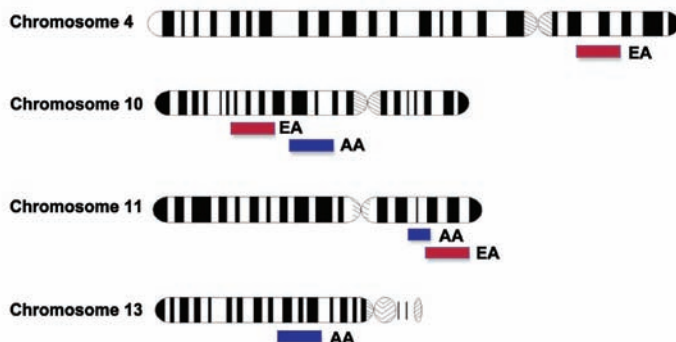
genome to the risk for nicotine dependence in African-Americans, other regions to risk in European-Americans, and still others to risk in both groups. The findings raise the possibility that specialized medications to treat smoking addiction in groups with different genetic backgrounds may eventually be developed.

“Environmental factors, such as whether family and friends smoke, strongly affect how and when a young person tries cigarettes. Studies suggest, however, that once that first cigarette is smoked, genetic makeup accounts for up to 50 percent of the likelihood that the

individual will become nicotine dependent,” says lead researcher Dr. Ming D. Li of the University of Virginia. “Identifying the genes that set addicted smokers apart, as well as those that increase the risk of the disorder in particular groups, ultimately will help determine the best brain proteins to target with medications. Future treatments may vary depending on a person’s genes.”

DIFFERENT CHROMOSOME AREAS INFLUENCE CIGARETTE

SMOKING Some of the chromosome regions that have been linked with smoking behavior are illustrated below. The genetic differences on chromosomes 4, 10, and 13 were identified among either European-American (EA) or African-American (AA) families. But a portion of chromosome 11 appears to link with smoking in both groups. (The linked regions are not drawn to scale on the chromosomes.)



ALSO IN THIS ISSUE

Research Findings

- 4** Intervention for Disruptive Children Shows Long-Term Benefits
- 9** Manic Mice Show Heightened Sensitivity to Rewards
- 11** Abstinent Smokers' Nicotinic Receptors Take More Than a Month to Normalize
- 12** Program Reduces Girls' Delinquent Behavior
- 15** Receptor Complexes Link Dopamine to Long-Term Neuronal Effects

Director's Perspective

- 2** Suiting Treatment to the Nature of the Disease

Research in Brief

- 3**
 - Combined Treatments Improve Dual Abstinence
 - Drug Cues Outside Awareness Rapidly Trigger Brain's Emotion Centers
 - Sensory Aspects of Smoking May Counter Bad Mood, Craving
 - Methamphetamine Abuse Alters Responses to Facial Cues

Bulletin Board

- 17**
 - NIDA Reprises Online Chat Day
 - Three Scientists Receive Grants for Innovative AIDS Research
 - Conferees Discuss Ways to Eliminate Disparities in Health Care

Tearoff

- 19** Smoking and Drinking Continue to Decline, But Marijuana Stalls in Latest MTF Survey

- 20** What the Numbers Say

[Continued on page 7]



Suiting Treatment to the Nature of the Disease

Addiction is a chronic disease. Epidemiological evidence clearly shows that while science-based treatments are effective, many patients achieve long-lasting recovery only after years of therapy, often including multiple treatment episodes. Neurobiological research on drugs' effects reinforces the message of chronicity: It shows that repeated drug use causes long-term changes in the way the brain processes information and emotions.

As a chronic disease, addiction responds best to treatment approaches already applied to other chronic conditions, such as hypertension and diabetes. These incorporate patient education and self-care, long-term monitoring with attention to complications, and prompt escalation to higher levels of care when symptoms intensify. Continuity of care is key. Without it, patients are less likely to accumulate the sequential gains that ultimately result in long-term, stable control over their condition.

Accordingly, NIDA is sponsoring a wide range of research to understand and respond to substance abuser's needs at each point of care, from the initial presentation for treatment through all stages of recovery. Our ultimate aim is to develop and promote a full-spectrum system of care with powerful initial treatments, long-term followup and support, interventions to stave off relapses, and rapid return to treatment when relapse occurs. Further, we are designing these programs for use by community treatment providers so that they can be implemented there as soon as they become available.

Some established interventions, such as methadone and buprenorphine maintenance, are inherently suited to the chronic nature of addiction. NIDA investigators have recently demonstrated positive results from several new approaches that build on patients' achievements in initial treatment, including monthly cognitive behavioral therapy booster sessions and telephone-based continuing care. NIDA researchers are also seeking to facilitate the efficient implementation of new treatment protocols and practices and invite feedback from staff implementing these protocols in therapeutic settings.

Many questions must still be answered before we can fully understand and respond to all the implications of addiction over its long, perhaps lifelong, course. Recognizing that addiction is a chronic illness enables us to ask the most important questions and translate the answers into new and improved treatment approaches and interventions. ■

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Combined Treatments Improve Dual Abstinence

Two anti-addiction medications are better than one for people who abuse both cocaine and alcohol, according to a new NIDA-funded study. Researchers randomly assigned 208 men and women to one of four protocols for an 11-week trial: disulfiram and naltrexone; disulfiram with placebo; naltrexone with placebo; or a double placebo. Among the dual-medication participants, 35 percent attained 3 consecutive weeks of abstinence from both cocaine and alcohol, compared with 17 percent of those taking either naltrexone or disulfiram and 15 percent of those receiving the double placebo, report Drs. Helen Pettinati, Kyle Kampman, Charles O'Brien, and colleagues at the University of Pennsylvania.

The patients who attained 3 weeks of abstinence during treatment had double the rates of abstinence at a 6-month follow-up than those who did not attain that standard. The combination treatment may meet a widespread need; an estimated 50 percent of cocaine abusers are also addicted to alcohol.

> *Addictive Behaviors* 33(5):651-667, 2008.

Drug Cues Outside Awareness Rapidly Trigger Brain's Emotion Centers

Even when a cocaine abuser is not aware of briefly seeing a drug-related image, such a picture can instantaneously activate the emotion and reward circuits in the brain.



Quick views of sexual images also activate many of the same brain areas. That pattern of activity may be “the brain’s primordial signature for desire,” according to Drs. Anna Rose Childress and Charles O'Brien and colleagues at the University of Pennsylvania.

In a study with 22 men seeking treatment for cocaine abuse, the researchers demonstrated that the participants’ brains responded to images outside their conscious awareness. The researchers used a technique in which a target picture, which featured either sexual or drug-related imagery, was flashed for 33 milliseconds, followed by a gray screen and then a 467-millisecond presentation of a neutral picture.

Participants reported remembering the neutral pictures, but not the target pictures. Nevertheless, activity in their neural circuits increased in response to the target images.

The researchers did not determine whether participants felt a surge in craving after viewing the subliminal pictures. Cocaine abusers’ rapid neural response to reward cues outside awareness may signify vulnerability

to relapse, the researchers suggest.

> *JPLoS ONE* 30;3(1):e1506, 2008.

Sensory Aspects of Smoking May Counter Bad Mood, Craving

The act of smoking—apart from actual or expected nicotine delivery—may soothe a smoker’s negative mood. Dr. Kenneth A. Perkins and colleagues at the University of Pittsburgh showed 200 smokers combinations of images and music, some pleasant and others disturbing, to induce a good or bad mood. The study participants began smoking sooner and smoked more after the disturbing presentations than after the pleasant ones.

The participants reported that smoking alleviated their negative feelings, offset symptoms of nicotine withdrawal, and relieved cigarette craving. As in past research, their responses were similar whether they were given regular nicotine cigarettes or cigarettes with only trace amounts of nicotine. Strikingly, however, their responses were also similar when they recognized that the cigarettes contained almost no nicotine.

The team repeated the procedure with 20 smokers, this time giving them unlit cigarettes to handle and pretend to puff. These smokers reported no alleviation of their negative moods or craving.

Taken together, the two studies suggest that the sensory experience of smoke inhalation, but not nicotine, is critical to the acute emotional

benefits of smoking experienced by chronic smokers and that these benefits accrue even when the smokers know they are getting almost no nicotine.

> *Journal of Abnormal Psychology* 117(1):79-93, 2008.

Methamphetamine Abuse Alters Response to Facial Cues

Methamphetamine abusers may have more difficulty than nonabusers in responding with empathy and self-control to people who are experiencing intense emotions, according to Dr. Edythe London and colleagues at the University of California, Los Angeles. Using functional magnetic resonance imaging, the researchers compared the brain patterns of 12 recently abstinent methamphetamine abusers and 12 nonabusers while they viewed images of fearful or angry faces. Compared with the nonabusers, the abusers showed less activity in brain areas related to important socioemotional processes such as interpreting facial expressions, controlling aggressive impulses, and building a concept of another person. The abusers showed greater activity than the others, however, in a region involved in pain processing and social distress. The deficit in socioemotional processing combined with the heightened signaling of negative feelings may contribute to socially inappropriate behaviors among methamphetamine abusers, the researchers say.

> *Drug and Alcohol Dependence* 93(1-2):93-102, 2008.

Intervention for Disruptive Children Shows Long-Term Benefits

Teaching aggressive youngsters social coping skills reduces their chances of becoming substance abusers.

BY LORI WHITTEN,
NIDA Notes Staff Writer

An intervention that teaches children to think before they act out can help them avoid substance abuse in adolescence. In a recent clinical trial, the Utrecht Coping Power Program (UCPP) offset the added vulnerability to cigarettes and marijuana that typically attaches to children's aggressive and disruptive behavioral disorders. Five years after completing the program, 30 teens whose problem behaviors at ages 8 to 13 had been severe enough to warrant professional attention reported no more experience with those substances than a group of peers who had not shown such problems.

The UCPP is a version of the Coping Power Program (CPP), which has improved children's school adjustment in two sizeable trials in the United States. The new study, conducted in the Netherlands, shows that the model can succeed in a European cultural context as well.

FROM CPP TO UCPP

Dr. John Lochman of the University of Alabama and Dr. Karen Wells of Duke University developed CPP in 1994 to help children whose behaviors cause problems in school and family and predict later delinquency and substance abuse. The program trains children to relax, rethink, and generate nonaggressive solutions to situations and social cues that they interpret—often mistakenly—as hostile or threatening.

CHILDREN GAIN COPING POWER Children use puppets to try out nonaggressive ways to solve a conflict during a session of the Coping Power Program.



Clinicians administering CPP use the motto “stop and think” together with a variety of techniques and exercises to enable children to:

- revise negative interpretations of others' actions;
- manage anger using such techniques as relaxation, distraction, and self-chosen slogans (e.g., “I’ll keep my cool and not be a fool.”);
- shift expectations that aggression will solve problems;
- develop nonaggressive ways to handle distressing situations; and
- think about short- and long-term consequences.

During 34 group sessions, children practice these skills extensively in role-playing exercises based on their interactions with peers, teachers, siblings, and

parents. In 16 separate group sessions, parents learn to control anger, manage stress, reward their children's good behaviors with attention and small treats, and respond more effectively to misbehavior. Parents and counselors often discuss the lessons conveyed to the children and sometimes watch video from those sessions.

For the Dutch study, Dr. Lochman collaborated with Dr. Walter Matthys of the Rudolf Magnus Institute of Neuroscience in Utrecht to adapt and refine the program. UCPP is more compact than the original version, consisting of 23 child and 15 adult sessions, and UCPP sessions take place in an outpatient mental health clinic rather than a school. Another difference is UCPP's greater emphasis on learning through activities such as role

playing and games, which are considered especially appropriate for children with mental health problems. UCPP parents receive briefings on their children’s session so that they can reinforce the lessons at home.

In a particularly engaging component of both CPP and UCPP, children create a videotape describing frustrating and provocative situations and several solutions to these problems—for example, being verbally assertive rather than physically aggressive—and play them out with others in the group. “Children enjoy making the videos and enthusiastically show them to parents, peers, and teachers,” says Dr. Lochman. “The videos give them a chance to show off their new skills and see how the different solutions work out.”

BENEFITS SOONER AND LATER

Dr. Matthys and colleagues recruited 77 children, mostly boys, from psychiatric

UTRECHT COPING POWER PROGRAM DEMONSTRATES LONG-TERM BENEFITS
 Five years after participating in the Utrecht Coping Power Program (UCPP), adolescents with histories of childhood aggressive disorders reported cigarette and marijuana use rates similar to those of adolescents without such histories and scored no higher on a formal delinquency assessment.

Problem/Treatment	Cigarette Smoking (past month)	Marijuana Use (lifetime)	Delinquency Scale*
Aggression disorder/ Standard treatment	42 percent	35 percent	1.5
Aggression disorder/ UCPP treatment	17 percent	13 percent	1.2
No aggression disorder/ No treatment	20 percent	13 percent	1.2

*Calculated from the National Youth Survey questionnaire and based on 43 delinquency acts, ranging from minor to major offenses.

outpatient clinics and mental health centers. Clinic staff psychiatrists diagnosed the children as having various conditions, including oppositional defiant disorder, conduct disorder, and attention deficit hyperactivity disorder. Each child was randomly assigned to attend either UCPP

or a conventional therapy, such as family, behavioral, or other group therapy, for 9 months.

Five years later, 61 trial participants (now aged 14, on average) filled out followup surveys. Their responses indicated that UCPP, but not the conventional therapies, eliminated the extra increment of substance involvement that is normally anticipated among children with histories of disruptive disorders.

Of the 30 respondents who had completed UCPP, 13 percent acknowledged having abused marijuana at least once in their lifetime and 17 percent reported smoking cigarettes in the past month. These rates almost exactly matched those reported by a comparison group of 61 mentally healthy teens of approximately the same age and educational attainment. In contrast, the prevalence of marijuana abuse and smoking were 35 percent and 42 percent, respectively, among 31 teens who had received behavioral or family therapy in the trial.

All of the therapies—UCPP as well as conventional—reduced disruptive behaviors and delinquency equally well. As assessed by the parents immediately after the close of the trial, UCPP had a much greater effect on the children’s problem

Expanding the Program’s Reach

In a U.S. study, Dr. Lochman’s team has explored how counselor training influences CPP. Examining 57 elementary schools, the researchers found that the program can succeed—and be valued by school staff, parents, and children—in a wide range of settings, but it requires intensive counselor training.

The team next plans to implement CPP in disadvantaged, rural areas of south Alabama. Four international groups, in Puerto Rico, Spain, Ireland, and Italy, are already providing the intervention to small groups of children. Dr. Lochman and colleagues are currently training school counselors from around the world to provide CPP in their home countries.

To further extend use of the program, the investigators have teamed with colleagues at The Johns Hopkins University to generate CPP tailored for middle-school children who live in Baltimore’s inner city. The researchers and colleagues at the University of Illinois at Chicago are also developing a CPP program for first-graders that has a more extensive family component.

behaviors than behavioral treatment and marginally more than family therapy. At the 5-year followup, the teens who had either received UCPP or one of the other therapies reported rates of antisocial

the children resist drug use and avoid other trouble 5 years later.” She notes that these results are consistent with other NIDA-funded research showing long-term effects of prevention interventions

other cultures,” says Dr. Steven Gust, director of NIDA’s International Program.

Manuals for CCP are available for purchase from Oxford University Press, www.oup.com. ■

“The children and their parents appeared to learn skills in the program that helped the children resist drug use and avoid other trouble 5 years later.”

—Dr. Eve Reider

activities—including stealing, destroying property, fighting, and cheating on tests—similar to those of their healthy peers.

“Children who show aggression are an important and difficult group to work with, and it is impressive that UCPP produced lasting benefits,” says Dr. Eve Reider of NIDA’s Division of Epidemiology, Services and Prevention Research. “The children and their parents appeared to learn skills in the program that helped

for youth who are at risk for drug use and other problem behaviors.

NIDA’s International Program supported the UCPP evaluation under an ongoing collaboration between NIDA researchers and the Dutch Addiction Program. “This study is a good example of collaborations between NIDA-funded investigators in the United States and international researchers that focus on adapting and testing interventions in

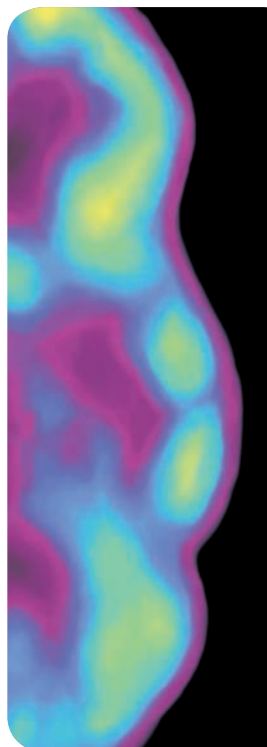
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NIDA previously distributed its educational materials via the Substance Abuse and Mental Health Services Administration National Clearinghouse for Alcohol and Drug Information. That clearinghouse is now forwarding requests for NIDA publications to the new distribution center.



ETHNIC GROUPS
[Continued from page 1]

SMOKE AND MARKERS

Dr. Li and colleagues at the University of Virginia and five other universities conducted the studies, which together included 402 African-American families and 200 European-American families. Most of the 1,890 participants were from Tennessee, Mississippi, and Arkansas. One or more members of each family had smoked for at least 5 years and had smoked a pack or more a day for the past year. Most families had two or more smokers; 80 percent of all the study participants smoked. The researchers assessed each individual’s smoking dependence by three different measures: the number of cigarettes smoked daily, the Heavy Smoking Index (HSI), and the Fagerstrom Test for Nicotine Dependence (FTND). The last two measures rate addiction severity based on the number of cigarettes smoked plus other behavioral indicators such as how soon after waking the first cigarette is smoked and how much difficulty the person has in refraining from smoking.

Each participant submitted a blood sample for DNA scanning. The research team genotyped hundreds of genetic markers—segments of DNA at known locations on a chromosome. If the marker showed up in most participants with high scores on one or more of the three smoking measures but not in most of the nonsmokers, researchers concluded that genes linked with the risk of nicotine addiction were likely to be situated nearby.

ETHNICITY AND RISK

The strongest correlation observed in the two studies, and the only one meeting the statistical standard for being “highly significant,” linked a region on chromosome 10 to the number of cigarettes smoked by African-Americans (see table).

GENETIC LINKS WITH SMOKING IN TWO ETHNIC GROUPS Genetic markers on various chromosomes were linked with smoking and nicotine dependence, according to a study that compared these connections in African-Americans (AA), European-Americans (EA), and the two groups combined. An additional test, called a convergence analysis, corroborated and extended the findings.

Chromosome Number	African-Americans	European-Americans	Combined Sample	Convergence Analysis
2		Suggestive		EA
4*		Suggestive		EA
9 (region 1)*		Suggestive	Suggestive	AA and EA
9 (region 2)*	Suggestive		Suggestive	AA and EA
10 (region 1)*	Highly significant		Suggestive	AA
10 (region 2)		Suggestive		EA
11	Suggestive	Suggestive	Suggestive	AA and EA
12		Suggestive	Suggestive	EA
13	Suggestive		Suggestive	AA
17		Suggestive		EA
18		Suggestive	Suggestive	AA and EA

* The region was linked with more than one measure of smoking.

Among African-Americans, statistically “suggestive” relationships tied this same region to HSI and FTND scores. “Because the same area on chromosome 10 linked with all three measures of smoking, we have confidence that the area is truly connected with nicotine addiction in African-Americans,” says Dr. Li. The researchers did not see an association between this area and smoking behavior among European-Americans. Similarly, regions on chromosome 13 were associated with the number of cigarettes African-Americans smoked daily, but not with any dependence measure among European-Americans. “Further study of sites unique to African-Americans may elucidate the particular genes that increase vulnerability to nicotine addiction in this population,” says Dr. Li.

In their study with European-American families, the researchers found suggestive relationships between eight chromosomal regions and risk for nicotine dependence. Regions on chromosomes 4 and 9 produced the strongest links. The region on chromosome 4 was associated with all three nicotine dependence measures, and the region on chromosome 9 was linked to two of them.

All the other linked regions—on chromosomes 2, 10, 11, 12, 17, and 18—appeared to affect only one of the three measures.

Except for one region on chromosome 12, all of the regions linked with smoking among European-Americans in Dr. Li’s study had been detected in prior research. “Replication of the results in different populations gives one additional confidence of a connection with nicotine dependence. The converging evidence suggests that these chromosomal regions should receive top priority in the search for genes that increase susceptibility to nicotine dependence,” says Dr. Li.

Comparison of the data from the separate studies showed that four regions on three chromosomes—9, 11, and 18—influenced risk in both the African-American and European-American families.

REFINING THE ANALYSES

Analyses of the combined data from the two studies affirm the importance of focusing on risk genes within ethnic groups rather than solely on ethnically mixed populations. Although many of the linkages seen in the two separate analyses

were also observed in the analysis of data from the combined group of African-Americans and European-Americans, the regions on chromosomes 2, 4, 10, and 17 that affected vulnerability to nicotine addiction in the study of just European-Americans did not appear in the analysis of the mixed group. Dr. Li notes that if the research team had conducted a study only with the combined group, they would not have detected the risks associated with these regions.

Finally, the researchers conducted a further examination, called a convergence analysis, on their combined samples. In this study, the chromosomal regions linked with all three of the nicotine dependence measures among only African-Americans or only European-Americans showed an association with smoking in both groups. The convergence analysis implicated four regions in risks for both ethnic groups and

seven regions in risks for one group or the other.

NEXT STEPS

The chromosomal regions associated with vulnerability to nicotine dependence by Dr. Li and colleagues typically harbor hundreds of genes. Fortunately, geneticists already know the identity of many of those genes. They can point to several whose proteins have biochemical properties that make them likely to play a role in smoking addiction. The next step in this line of research is to choose the most promising of these genes and examine their effects on nicotine biochemistry. Animal studies are usually best for this type of investigation. Once genetic researchers pinpoint culpable genes and trace their effects, developers of medications can begin to create and test compounds to alter the genes' effects.

“Scientists have much work to do before they determine how gene variations affect the neurobiology underlying addiction, but these next steps will lead ultimately to improved smoking cessation treatment,” says Dr. Joni Rutter of NIDA’s Division of Basic Neuroscience and Behavioral Research. “Dr. Li’s work suggests that future treatment options may differ according to the genome of the affected individual.” ■

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Manic Mice Show Heightened Sensitivity to Rewards

Manipulation of a gene produces mice with behaviors characteristic of bipolar disorder and signs of drug abuse vulnerability.

BY LORI WHITTEN,
NIDA Notes Staff Writer

During episodes of mania, people with bipolar disorder become avid seekers of new experiences, and some binge on psychostimulants such as cocaine and amphetamine. A NIDA-funded animal study suggests that mania promotes these and other extreme behaviors by enhancing sensitivity to rewards, both natural and drug-related. Mutant mice that exhibit behaviors resembling mania seemed to get a bigger kick than normal mice from sugar water, cocaine, and electrical stimulation of the brain’s reward center. The finding implicates the manipulated gene, which is called *Clock*, in the mood disorder, vulnerability to substance abuse, and perhaps their co-occurrence.

PLEASURE GOES A LONG WAY

Dr. Colleen McClung and colleagues at the University of Texas Southwestern Medical Center and other institutions created a strain of mutant mice for use in studies to understand the neurobiology of circadian rhythms. They initiated the current study after observing that these mice exhibit behaviors often associated with heightened reward sensitivity and vulnerability to stimulant addiction. For example, compared with normal mice, the mutants explore novel environments more vigorously and spend significantly more time in an environment they associate with cocaine.

OF MICE AND MANIA Mice with a disrupted *Clock* gene show behaviors that resemble those of bipolar patients experiencing a manic episode.

Bipolar patients	<i>Clock</i> mutant mice
Hyperactivity	Hyperactivity
Decreased need for sleep	Sleep less than wild-type mice
Feelings of euphoria	Exhibit fewer depression-like behaviors than wild-type mice
Excessive involvement in activities that have a high potential for adverse consequences	Increased risky behavior in behavioral models
Propensity toward drug use and abuse	Greater sensitivity to the rewarding effects of cocaine, sucrose, and brain stimulation

Dr. McClung and colleagues tested the responses of these mice to three types of rewards. In each instance, genetically engineered mice demonstrated more sensitivity to rewards than normal animals. For example:

- Given the opportunity to turn a wheel that sent electrical impulses to the pleasure pathway of their brains, the genetically engineered mice turned the wheel more often and responded to a lower current than normal mice, indicating that they found brain stimulation more rewarding.
- After a dose of cocaine, both normal and mutant animals pushed the wheel less often—a sign that they were feeling pleasure from the cocaine. But the genetically engineered mice reduced their wheel-turning responses more, indicating that they received more pleasure from the drug.
- Given a choice between water and a sugar solution, which mice find rewarding, the genetically engineered animals consumed more

of the sweet drink than the normal animals.

In their heightened responsiveness to rewards, the genetically engineered animals resemble a subset of normal animals—those that show special interest in exploring novel environments. Compared with less active peers, novelty-seeking animals show greater sensitivity to drugs in behavioral protocols that mimic the early stages of addiction. High responsiveness to novelty predicts drug-related behavior so reliably that animal researchers often use it as a test for vulnerability to initiating drug abuse.

BUILDING A MODEL MOUSE

To produce the mice that have characteristics resembling bipolar patients’ manic symptoms, Dr. McClung’s colleagues at Northwestern University disrupted a gene called *Clock*. The gene is a critical regulator of daily rhythms—including sleep and wakefulness, body temperature, hormone levels, blood pressure, and heart activity. Particular variants

of this gene have been linked with bipolar disorder in clinical research.

Dr. McClung's mutant mice mimic key symptoms experienced by bipolar patients in the manic phase of the disease. For example, the animals' hypersensitivity to rewards parallels the extreme euphoria seen in mania. In addition, the mice become hyperactive, have disrupted circadian rhythms, and sleep less than the wild-type mice. In a situation that provokes nervous behavior from normal rodents, the mutant mice show reduced anxiety—a trait that mimics bipolar patients' increased risk-taking during a manic phase. Like bipolar patients, the mice respond to mood-stabilizing drugs with reduced mood- and anxiety-related behaviors.

“My colleagues and I suspected that the animals might to some extent resemble patients with mood disorders, but we were surprised to find that they had such a complete profile of manic-like behaviors,” says Dr. McClung.

In the long term, Dr. McClung is interested in determining the genetic roots of bipolar disorder, which is highly heritable: An estimated 80 to 90 percent of affected individuals have a relative with a mood disorder.

RHYTHMS AND REWARD: A DOPAMINE CONNECTION?

Dr. McClung and colleagues plan to use the *Clock* mutant mice to elucidate the neurobiology underlying bipolar patients' proclivity to risky behaviors, particularly drug abuse, during manic episodes. Clinicians observe that both depression and manic episodes increase substance abuse: People tend to abuse stimulant drugs during a manic phase and alcohol during a depressive period. The lifetime rate of substance abuse is 38 percent for people with bipolar disorder, as compared with

10 percent for those without a psychiatric illness, according to a 2006 analysis by the National Epidemiologic Survey on Alcohol and Related Conditions. When bipolar patients abuse drugs, their risks for hospitalization and suicide increase—a fact that adds urgency to the task of devis-

“My colleagues and I suspected that the animals might to some extent resemble patients with mood disorders, but we were surprised to find that they had such a complete profile of manic-like behaviors.”

—Dr. Colleen McClung

ing means to prevent drug abuse among people with the disorder.

The *Clock* mutant mice differ from normal rodents not only in behavior but also in their neurobiology. Neurons in their ventral tegmental area (VTA)—the starting point for brain dopamine pathways, including the reward circuit—fire more frequently and strongly than in normal animals, resulting in greater dopamine release. Extra dopamine in the reward pathway is a critical factor in addiction and may influence vulnerability to both drug abuse and manic symptoms. In ongoing studies, Dr. McClung's team is examining whether restoration of the *Clock* gene normalizes dopamine release in the reward circuitry and behavioral sensitivity to reward. To date, this work has demonstrated that insertion of a normal *Clock* gene in the VTA of the genetically engineered animals eliminated their manic-like hyperactivity.

The researchers also plan to identify the mechanism by which a disrupted *Clock* gene leads to augmented dopamine in the reward pathway. Dr. McClung's team has found that *Clock* regulates some genes that affect neurochemical processes

related to dopamine. One of these genes, for example, influences an enzyme that controls dopamine production.

When researchers learn how the *Clock* gene influences dopamine levels, they may be able to explain the frequent co-occurrence of drug abuse and bipolar

disorder. The findings may also provide clues to new treatments for both bipolar disorder and drug abuse. Dr. McClung's team is already using *Clock* mutants to screen potential new medications.

A variety of human genes appear to increase the risk of bipolar disorder, says Dr. Minda Lynch of NIDA's Division of Basic Neuroscience and Behavioral Research. Dopamine may emerge as a common factor among the actions of such genes, some of which may also influence addiction vulnerability.

“Dr. McClung's research is relevant to co-occurring psychiatric and addiction disorders,” says Dr. Lynch. “NIDA is trying to stimulate the development of such animal models because researchers might use them to elucidate the neurobiological underpinnings of co-occurring substance abuse and psychiatric disorders.” ■

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Abstinent Smokers' Nicotinic Receptors Take More Than a Month to Normalize

Prolonged increase in brain receptors after smokers quit may explain the struggle to kick cigarettes and high risk for relapse during early abstinence.

BY LORI WHITTEN,
NIDA Notes Staff Writer

For up to 6 weeks after smokers quit, their brain cells have more nicotine-binding receptors than nonsmokers' cells do, according to a recent NIDA-funded study. Scientists speculate that the brain develops extra receptors to accommodate the large doses of nicotine from tobacco and that the resulting expanded receptor pool contributes to craving and other discomforts of smoking withdrawal.

"In smokers who quit cold turkey, the brain has a big adjustment to make—excess receptors and little nicotine to fill them," says investigator Dr. Julie K. Staley of Yale University School of Medicine. "The brain is used to having nicotine stimulate all those receptors, and when they are not stimulated, it needs time to adapt to the loss of nicotine. Withdrawal symptoms occur until the brain has had sufficient time to make the neurochemical adaptations necessary for a person to feel normal without nicotine."

In the study by Dr. Staley, Dr. Kelly Cosgrove, and colleagues, 19 nicotine-dependent people, who had smoked about a pack a day for an average of 21 years,

The editors and writers of NIDA Notes offer their condolences to the family, colleagues, and friends of Dr. Julie Staley (Gottschalk), who died on July 25, 2009.

SMOKERS DEMONSTRATE EXCESS NICOTINIC RECEPTORS DURING FIRST MONTH OF ABSTINENCE The predominance of green rather than blue in these brain scans of abstinent smokers indicates higher than normal levels of β_2^* -nACh receptors. Smokers continue to show elevated amounts of the receptors through 4 weeks of abstinence, but levels normalize by 6 to 12 weeks.



underwent imaging by single-photon emission computed tomography (SPECT) at various times after they quit. The technique measured β_2^* nicotinic acetylcholine (β_2^* -nACh) receptors, which are the most prevalent nicotinic receptor subtype and contribute to the rewarding aspects of nicotine.

During the first month of abstinence, images of the former smokers showed higher levels of β_2^* -nACh receptors in several brain areas than did images of nonsmokers who were matched for age, gender, and race. The former smokers had, on average, 21 to 29 percent more of the receptors in the cerebral cortex, the brain area responsible for thinking; 24 percent more, on average, in the cerebellum, which regulates sensation and movement; and 22 percent more in the striatum, which produces feelings of reward. After 6 to 12 weeks of abstinence, the former smokers' brain receptor levels tended to match those of nonsmokers, although

there was significant variation among individuals.

The temporarily elevated pool of β_2^* -nACh receptors may explain why the first months of smoking cessation are difficult for many people. The researchers surmise that smokers' larger complement of β_2^* -nACh receptors indicate that their brains have adapted to nicotine, so normal operation requires high levels of stimulation. When a smoker quits and nicotine no longer floods the brain, the reduced stimulation might disrupt the receptors' regulation of dopamine and other neurochemicals involved in the reinforcing effects of smoking. Dopamine depletion in the reward system has been linked to lethargy, moodiness, and other symptoms seen in smoking cessation. Also, research by Dr. Arthur Brody at the University of California, Los Angeles has associated the $\alpha_4\beta_2^*$ -nACh receptor—a subset of the β_2^* -nACh receptors measured by Dr. Staley's team—with craving ("Imaging Studies

[Continued on page 14]

Program Reduces Girls' Delinquent Behavior

The power of the family and a focus on homework were keys to success.

BY NIDA NOTES STAFF

Adolescent girls can be treated for delinquent behaviors more effectively in a well-supervised family setting than in residential treatment programs. That is the conclusion of NIDA-funded researchers studying Multidimensional Treatment Foster Care (MTFC). During 6 months of treatment and 18 months of followup, girls in MTFC had fewer incidents of delinquency than a comparison cohort who were treated in group residences. The girls in foster care also attended school more regularly and spent more time on homework.

MTFC was previously shown effective in reducing delinquency among teenage boys. The protocols used in the new study, which was co-funded by the National Institute for Mental Health, enhanced the standard MTFC program to address mood and social problems that are common among delinquent girls. The need for such interventions is clear: A 2001 American Bar Association report described girls under 18 as the fastest growing segment of the U.S. juvenile justice population, citing an 83 percent increase in their rate of delinquency between 1988 and 1997.

“The study demonstrates that even severely delinquent girls can be treated in the community and that placement in family homes with caretakers who are well-trained and supervised can produce results that are superior to those of group care,” says Dr. Patricia Chamberlain, who

conducted the study with colleague Dr. Leslie Leve. Both are affiliated with the Oregon Social Learning Center in Eugene, Oregon.

FOSTERING BETTER BEHAVIOR

Girls in MTFC live with foster families and attend local public schools. The program trains the foster parents to provide positive reinforcement and encouragement to the girls while mentoring their academic and living skills. The foster parents closely supervise the girls' whereabouts and provide a daily structure of clear expectations and limits, such as getting to class on time, doing homework, and complying with curfews. They also administer well-specified consequences—for example, loss of privileges for negative behaviors and gift cards for positive behaviors.

Dr. Chamberlain's team tailored the standard MTFC program to the needs of delinquent girls. For many of them, prior exposure to trauma and abuse had contributed to anxiety and mood problems, poor interpersonal relationships, and social aggression. The foster parents and therapists taught the girls how to reduce aggression in social situations and personal relationships. They also provided strategies enabling the girls to recognize and deal with emotional distress, generate options to solve problems, and make long-range plans.

The girls who participated in the study had been court-mandated to care away from their original homes because



of chronic delinquency. On average, they had been arrested 12 times, often for drug abuse. Three-quarters of the girls were of European descent, and all were between the ages of 13 and 17. Following an initial assessment, they were randomly placed in either MTFC or group care (GC). The GC girls lived in one of 19 group residences and attended school onsite. Their treatment programs varied. At the end of their time in MTFC or GC, which averaged 6 months, 56 percent of the girls returned to their biological or another family, and 23 percent began living independently. Others were detained for subsequent criminal offenses or remained in a treatment setting.

Both groups exhibited less delinquent behavior during and after treatment than they had before. The MTFC girls' average number of days spent in locked settings fell from 75 in the year prior to the initial assessment to 22 in the year following, while the GC group's average dropped from 89 days to 56 days. During the same period, scores on a delinquency measure that combined the number of criminal referrals, days locked up, and self-reports

of delinquent behaviors dropped by about half among the MTFC girls and roughly a third among the GC girls. The MTFC girls' advantages on both measures widened as behavioral improvement continued during the next year.

The researchers linked MTFC's superior outcomes to the program's greater emphasis on homework. "Homework completion was an important factor in reducing the time girls spent in locked settings, and MTFC was better than GC at promoting homework completion," Dr. Leve explains. An analysis of the data found that time spent studying accounted for about 8 percent of both groups' reductions of time in locked settings in the first 12 months. The MTFC girls were given incentives to study at least 50 minutes per day in a quiet setting where adults could monitor and confirm their performance.

ONE-YEAR COMPARISONS Girls in the Multidimensional Treatment Foster Care (MTFC) program did better than those receiving group care when assessed 1 year after study enrollment.

Characteristic (mean value)	MTFC	Group Care
School attendance	5.5*	4.9*
Days per week during which girls spent at least 30 minutes of homework	3.5	2.0
Days in locked settings**	22	56
Number of arrests	0.76	1.3
Caregiver reports of delinquency***	65	70

*Rated on a scale of 1-6, where 5 represents attending regularly and 6 represents attending 100 percent of the time.
 **Includes juvenile detention or correctional facilities, jail, and prison.
 ***Score on the Child Behavior Checklist delinquency subscale.

The number of days per week during which they spent at least 30 minutes on homework increased from an average of 2 days to 3.5 days. The GC girls, without such incentives, slightly decreased their

engagement with homework over the same period.

According to the researchers, completing homework was important for several reasons: It got the girls into a nightly routine of working on a task that would help them prepare for the next day, it required that they spend more of their time engaged in supervised activities at home rather than unsupervised activities outside the home, and the repeated exposure and practice made them feel more comfortable performing academic tasks.

POWER OF THE FAMILY

In designing the MTFC intervention, Dr. Chamberlain hypothesized that life lessons learned in a family setting would be more directly applicable post-treatment than lessons learned in institutional environments. "The inter-

Intervention Lowers Risk of Pregnancy

Adolescent girls who participated in Multidimensional Treatment Foster Care (MTFC), an intervention designed for young people with histories of arrest for illicit drug use and other crimes, were half as likely as their peers in standard residential treatment to get pregnant within 2 years of enrollment. This is the finding of a new study, funded by NIDA and the National Institute of Mental Health, by Dr. Patricia Chamberlain and Dr. Leslie Leve of the Oregon Social Learning Center.

Drs. Chamberlain and Leve had previously shown that the well-supervised foster care provided by MTFC reduced arrest and lockup rates and increased homework completion and school attendance among chronically delinquent 13- to 17-year-old girls (see article page 12). In their new study, with colleague Dr. David Kerr, the researchers randomly assigned 81 girls to MTFC and another 85 girls to group residences. At the 2-year followup, 27 percent of the MTFC girls had reported a pregnancy since enrollment, compared with 47 percent of the girls in group care.

The study was designed principally to compare the two interventions, but researchers also wanted to explore whether MTFC

would produce better outcomes if it included a component that targeted risky sexual behaviors. Hence, half of the MTFC girls received counseling in how to avoid risky sexual behaviors and practice responsible dating, while the other half received no such counseling. Both of those MTFC groups had similar pregnancy results, which "suggests that the general approach of increasing supervision and reducing delinquent peer associations might be just as effective as programs that specifically focus on preventing sexual risk taking," says Dr. Leve.

"Delinquency prevention programs, such as MTFC, that aim to increase supervision through positive relationships with caring adults and to reduce the amount of time that adolescents spend with delinquent peers may have an unexpected benefit of simultaneously reducing other risk behaviors, such as unplanned pregnancies," Dr. Leve adds.

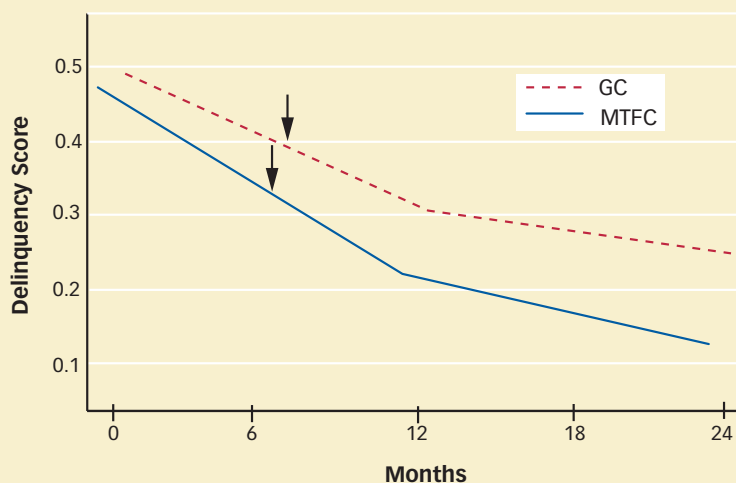
Source: Kerr, D.C.R.; Leve, L.D.; and Chamberlain, P. Pregnancy rates among juvenile justice girls in two randomized controlled trials of Multidimensional Treatment Foster Care. *Journal of Consulting and Clinical Psychology* 77(3):558-593, 2009.

vention also capitalizes on the power of the family environment,” says Dr. Leve. Both the foster parents with whom the girls live during MTFC and the adult with whom they will live after treatment receive training in well-tested techniques to encourage and reinforce acceptable behavior. The foster parents also receive daily support via telephone from project staff.

MTFC may also confer another major advantage: cost savings. Even though the current study did not analyze expenses, other research has shown that MTFC costs, depending on location, are one-half to two-thirds those of group care. MTFC for boys has saved about \$22,000 to \$88,000 per child in long-term costs. These costs were estimated by the Washington State Institute on Public Policy and included savings to taxpayers for victim and crime costs (see www.wsipp.wa.gov).

The MTFC model is now being implemented in more than 75 sites in the United States and Europe, including Latino and African-American communities in these areas. According to Dr. Eve Reider of NIDA’s Division of

DOING BETTER SOONER Girls in Multidimensional Treatment Foster Care (MTFC) scored significantly lower on indicators of delinquency—number of criminal referrals, days locked up, and self-reports of delinquent behaviors—than girls in group care (GC) at their 1-year and 2-year assessments. Arrows indicate end of average intervention.



Epidemiology, Services and Prevention Research, these studies address a growing need for research-based interventions that are effective for delinquent girls. “The next steps for this area of research can include examining more ethnically diverse juvenile justice populations and performing effectiveness trials,” Dr. Reider says. ■

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■ ABSTINENT SMOKERS’

[Continued from page 11]

Elucidate Neurobiology of Cigarette Craving,” *NIDA Notes*, Volume 22, Number 2).

FOCUS ON SMOKERS WITH MENTAL DISORDERS

The neurochemicals influenced by stimulation of the β_2^* -nACh receptors are also implicated in many psychiatric illnesses—including anxiety disorders, depression, and schizophrenia. People with these disorders are more likely to smoke than those who do not have mental

health problems. Accordingly, Dr. Staley and colleagues are beginning to explore neurobiological underpinnings that may connect smoking and mental illnesses, and they are targeting the β_2^* -nACh receptor. In a recent study, they found that high β_2^* -nACh receptor levels in the thalamus, a structure that acts as a switchboard for signals traveling between brain regions, are associated with recurring symptoms of anxiety among nonsmokers with posttraumatic stress disorder. The researchers also are tracking changes in the receptors after smoking cessation among people with schizophrenia and depression.

“Dr. Staley’s results reveal the impact of smoking on nicotinic receptors in the brain and establish a baseline that future researchers can use to assess the effects of different treatments on receptor normalization,” says Dr. Ro Nemeth of NIDA’s Division of Clinical Neuroscience and Behavioral Research. ■

SOURCE

Cosgrove, K.P., et al. β_2 -nicotinic acetylcholine receptor availability during acute and prolonged abstinence from tobacco smoking. *Archives of General Psychiatry* 66(6): 666-676, 2009.

Receptor Complexes Link Dopamine to Long-Term Neuronal Effects

Discovery may open a new window on substance abuse and potential therapies.

BY LORI WHITTEN,

NIDA Notes Staff Writer

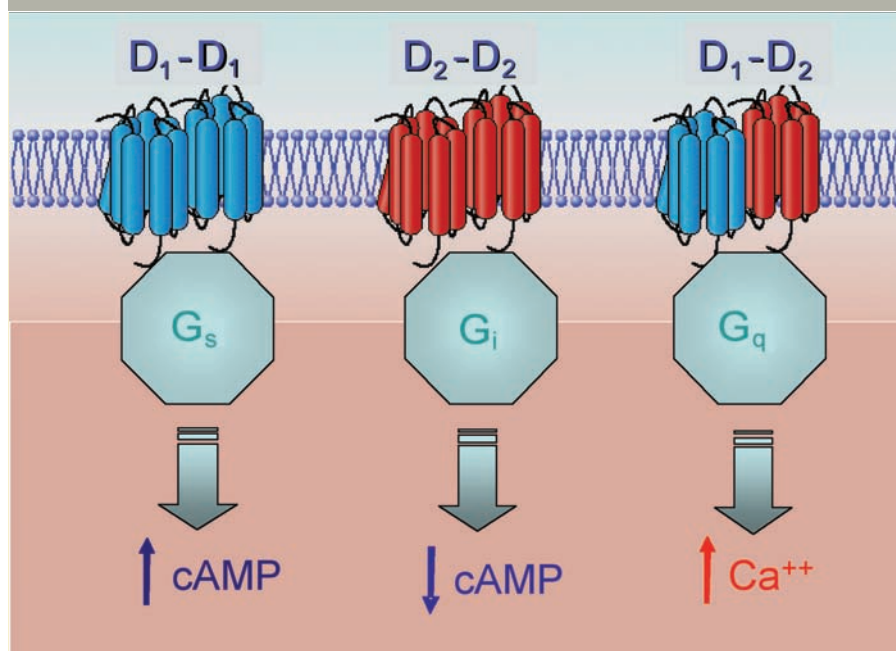
Drugs of abuse trigger abrupt, massive increases in levels of the neurotransmitter dopamine that give rise to intense feelings of reward and reinforcement—the drug high—by temporarily altering the activity levels of dopamine-responsive neurons. These dopamine surges are transient, but NIDA-funded researchers recently identified a mechanism whereby they may promote long-lasting or permanent changes in behavior and cognition.

Dr. Susan George and colleagues at the University of Toronto identified a set of previously unrecognized dopamine receptors in a brain area called the striatum. When stimulated by the neurotransmitter, these receptors set in motion a cascade of events leading to a burst of calcium from stores within nerve cells. Because the cells use calcium to build and strengthen synaptic connections to other neurons, such bursts, when repeated in the setting of chronic drug abuse, can potentially rewire neural pathways that affect learning, memory, emotions, and other responses. The consequences could include the persistent symptoms and adverse effects of addiction, such as craving and reduced responsiveness to natural rewards.

RECEPTOR COMPLEXES MODIFY CELLULAR RESPONSES

Although scientists had established prior to Dr. George's work that dopamine receptors can initiate calcium signaling

DOPAMINE RECEPTOR COMPLEXES TRIGGER DIFFERENT CELLULAR CASCADES Stimulation of the D_1 - D_2 receptor complex (on right) spurs a burst of calcium within the cell—activating the neuron, making the cell more prone to firing again, and ultimately forging new neural connections. Stimulation of the two other complexes influences slower acting biological cascades involving cyclic AMP (cAMP).



within the brain, none of the five known dopamine receptors (D_1 to D_5) had been shown to do so. After searching in vain for a sixth receptor, Dr. George's team began studies that eventually led to the discovery of a set of receptors that consist of conjoined D_1 and D_2 receptors (see box). The researchers had previously identified other dopamine receptor complexes, including D_1 - D_1 , D_2 - D_2 , and D_5 - D_2 .

When a D_1 or D_2 receptor is stimulated singly, it incites a train of intracellular biochemical reactions that scientists have mapped. When both parts of a

D_1 - D_2 receptor complex are stimulated, however—something that is likely when dopamine levels surge as a result of exposure to a drug of abuse—the receptor set initiates a modified cascade that releases calcium within the cell.

Simultaneous stimulation of the two receptors in a complex results in the activation of a specialized protein, called a transducer, in the cell. The transducer acts as a molecular switch to initiate further biochemical changes. The specific transducer, called G_q , that ties activation of the D_1 - D_2 receptor complex to the

calcium cascade effects changes in gene expression, protein production, enzyme levels, the cell's firing rate, and its sensitivity to dopamine. Although scientists had already been aware of G_q, Dr. George and colleagues are the first to link it to dopamine receptors.

"The direct link my colleagues and I observed between dopamine and the calcium signaling cascade suggests that drugs of abuse can rapidly and directly cause long-term changes in brain cells that respond to dopamine," says Dr. George. "The cellular mechanisms underlying these changes may provide a new window for viewing drug abuse." She adds that the D₁-D₂ receptor complex may also figure in schizophrenia, a disease that is thought to involve abnormal interactions between dopamine receptors and dysfunctional calcium signaling.

"To understand the full importance of the complex, researchers need to identify the specific types of neurons that express the D₁-D₂ complex, analyze its physiological functions, and determine how repeated

"The connection that Dr. George's team made between the D₁-D₂ complex and calcium signaling expands the range of therapeutic targets for dopamine-related neurological conditions."

—Dr. David Shurtleff

activation influences the process of addiction," Dr. George says. "With such knowledge, scientists might develop compounds that selectively target the D₁-D₂ complex to reverse or prevent addiction or affect schizophrenia."

This work has already begun. Dr. George and her team are currently investigating the consequences for cellular form and function due to calcium signaling

triggered by the D₁-D₂ receptor complex. Other scientists are attempting to identify compounds that selectively activate the complex. Such compounds would

enable researchers to fashion radiolabeled tracers and use brain imaging to assess the quantity and distribution of the receptor complex and determine whether drugs change them. If repeated activation by drugs alters the levels or function of the complex, those changes could serve as useful markers for diagnosing drug abuse and monitoring the effects of treatment.

Complexes Expand Dopamine's Repertoire

In addition to the D₁-D₂ dopamine receptors, Dr. Susan George and her team at the University of Toronto have found three additional dopamine receptor complexes. Two of these consist of pairs of receptors of the same type—D₁-D₁ and D₂-D₂. Dopamine binding simultaneously to both receptors in either of these complexes activates a transducer, G_s or G_i, respectively, that ultimately stimulates or blocks synthesis of cyclic AMP, an intracellular regulatory protein (see diagram, page 15). The other dopamine receptor complex, D₅-D₂, triggers a calcium burst inside the cell, like the D₁-D₂ but does so via a different series of biochemical interactions. D₅-D₂ is less likely than the D₁-D₂ to contribute significantly to addiction because it is not abundant in addiction-related brain areas such as the striatum.

"The connection that Dr. George's team made between the D₁-D₂ complex and calcium signaling expands the range of therapeutic targets for dopamine-related neurological conditions," says Dr. David Shurtleff of NIDA's Division of Basic Neuroscience and Behavioral Research. "The emergence of D₁-D₂ receptor complexes over the lifespan and how they affect the progression of addiction and other neurological diseases are important areas for future research." ■

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NIDA Reprises Online Chat Day

NIDA staffers responded to 1,300 questions about drug abuse and addiction during the Institute's second annual Chat Day. Students and teachers from 100 schools in 23 states sent 11,000



Q & A NIDA Director Dr. Nora D. Volkow answers student questions on Drug Facts Chat Day.

queries from classroom computers. Nearly 40 NIDA scientists and science communicators responded to the queries during the day-long program. Although the sheer number of inquiries prevented personal replies to every questioner, the NIDA team's answers covered the issues that students asked about most often.

"Reaching people in their teen years with accurate information is one of the most important addiction-prevention efforts we can make," says NIDA Director Dr. Nora D. Volkow, who was one of the scientists responding to questions. "The unexpectedly high volume of questions underscores how much teens—and their teachers—want to learn real facts about drug use."

The queries covered a wide range of substances, including alcohol, cigarettes, marijuana, methamphetamine, cocaine, prescription medications, inhalants, steroids, heroin, LSD, over-the-counter medications, and lesser known substances like hallucinogenic mushrooms and salvia, a psychoactive herb.

Some sample exchanges:

Q: What makes drugs addictive?

A: Drugs are addictive because they affect parts of the brain that are involved in feelings of pleasure (drugs increase the chemical dopamine in the reward system). When something activates the reward system it makes you want to do it again and again. But there's a catch—when you take drugs repeatedly, the brain changes. The reward system becomes less sensitive so you need more of a drug to feel good, and those things in your life that used to feel good—like eating an ice cream sundae, listening to music, hanging out with friends—lose their ability to give you pleasure. Ultimately, it all backfires, and drugs become the main motivating force in your life in an attempt to try and feel normal.

Q: What is the strongest/most dangerous drug?

A: Opiates such as heroin or prescription painkillers can cause a person to stop breathing. Cocaine can cause seizures, mental problems like anxiety and psychosis (losing touch with reality), and problems with your heart. Drugs can

even cause your heart to stop beating. Methamphetamine can cause strokes, heart disease, and problems with thinking. PCP can cause people to stop breathing and can cause psychosis.

Q: My boyfriend tells me if I do weed, then he won't leave me. I love him, but I don't want to do it. I guess you can say that if he wants me to do that, then he's not being a good boyfriend.

A: You'll have to decide for yourself whether your boyfriend is good for you or not. But ... good for you for knowing that marijuana, besides being illegal, is a health hazard. There are many negative effects of smoking marijuana. It can cause loss of coordination and affect memory, judgment, and perception. Under the influence of marijuana, you could fail to remember things you just learned, watch your grade-point average drop, or crash a car. Some people may suffer sudden feelings of anxiety and have paranoid thoughts, which is more likely to happen when higher doses are used or when it is taken orally. It's difficult to tell what the effects of marijuana will be because they vary based on the person, their drug history, how much marijuana is taken, and its strength.

Many students asked about the effects of using drugs or alcohol during pregnancy, how they could get help for a friend or family member, and whether addiction could be inherited. To read the Chat Day transcript and find answers to frequently asked questions, see www.nida.nih.gov/chat/.

Three Scientists Receive Grants for Innovative AIDS Research

NIDA announced the first three recipients of its new Avant-Garde Award, which supports groundbreaking research to prevent and treat HIV/AIDS in drug abusers. The awardees will each receive \$500,000 per year for 5 years.



Julio Montaner, M.D., head of the Division of AIDS at the University of British Columbia and director of the British Columbia Centre for Excellence in HIV/AIDS in Vancouver, will study HIV/AIDS treatment and prevention outcomes in injection drug users (IDUs). Current evidence indirectly suggests that expanded use of the therapy known as highly active antiretroviral treatment (HAART) will not only decrease sickness, hospitalization, and death among IDUs infected with HIV but also decrease the rate of new HIV infections. Dr. Montaner's project will provide HAART to IDUs in the Vancouver neigh-

[Continued on page 18]

■ BULLETIN BOARD

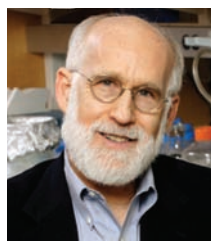
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borhood considered British Columbia's epicenter of both HIV and drug use. The work will test innovative strategies for monitoring HIV in this hard-to-reach population, evaluate novel approaches to providing care and enhancing adherence to the treatment, and track the sources of new infections using social and sexual networks and HIV gene sequencing. Dr. Montaner says that unless society finds a way to deal with HIV among IDUs in a compassionate and supportive fashion, we will not succeed in controlling the broader HIV epidemic.



Ileana Cristea, Ph.D., an assistant professor in the Department of Molecular Biology at Princeton University, Princeton, New Jersey, will investigate how HIV usurps a person's cellular machinery for its own purposes and how the human cell responds. She recently developed a technique that visualizes proteins in live cells and identifies their interactions. In her project, her research team will use the technique to characterize the interactions of 11 enzymes that play a role in a process called chromatin remodeling, which HIV uses to conceal itself within host cells. The team also plans to search for mechanisms that regulate the fate of a cell after HIV infection. Dr. Cristea says that the work may provide new therapies for purging latent viruses from their cellular reservoirs.

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Jerome Groopman, M.D., professor of medicine at Harvard Medical School and chief of the Division of Experimental Medicine at the Beth Israel Deaconess Medical Center in Boston, Massachusetts, plans to develop agents to block the spread of HIV within the body. To inhibit HIV passage between cells and through lymphatic channels, Dr. Groopman and his team will exploit a newly discovered ligand-receptor system. The project's goal is to contain the virus at the site of the initial infection, where it can be targeted with a combination of antiviral treatments. Dr. Groopman says that the work may lead to a paradigm shift in HIV therapy.

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Conferees Discuss Ways to Eliminate Disparities in Care

Many African-American and Latino drug abusers with HIV and hepatitis C (HCV) avoid screening and treatment for their infection because they distrust the health care system and fear discrimination on the part of providers, according to NIDA-funded researcher Dr. Carmen Masson and colleagues at the

University of California, San Francisco.

This and other barriers to care faced by minorities and the poor were discussed at the National Institutes of Health Summit on the Science of Eliminating Health Disparities, held December 16-18, 2008, in National Harbor, Maryland. The summit brought together more than 4,000 scientists, clinicians, policymakers, educators, and health advocates from the United States and abroad, including a dozen NIDA officials and 15 NIDA-funded researchers. "The summit presented the collective contribution of NIH and NIH-funded researchers to new knowledge related to eliminating health disparities," says Dr. LeShawndra Price, a member of the NIH Planning Committee and the Health Disparities Workgroup in NIDA's Division of Epidemiology, Services and Prevention Research. "The meeting highlighted the progress of research aimed at improving prevention, diagnosis, treatment, and services and considered strategies to maximize the research's public health impact."

Dr. Masson reported on a study of 100 men and women infected with either HIV or HCV who took part in syringe exchange and methadone maintenance programs in New York and San Francisco. Dr. Masson and colleagues found that, in addition to distrusting the health care system and expecting to be stigmatized, these patients had misconceptions about HCV transmission, received inadequate HIV post-test counseling, and lacked followup on treatments.

The following NIDA-funded studies were also presented:

- "Always Be Straight With Me": Black Patients' Experiences in Racially Discordant Mental Health Encounters, by Dr. Margarita Alegria, Harvard Medical School and Center for Multicultural Mental Health Research;
- Developing and Sustaining a University-based Research Infrastructure Serving Latinos with Substance Abuse and HIV/AIDS, by Dr. Mario De La Rosa, Florida International University;
- Environmental Strategies for Mental Health Promotion, by Dr. Debra Furr-Holden, Johns Hopkins Bloomberg School of Public Health; and
- Reducing Substance Use and HIV Health Disparities Among Hispanic Youth: The Familias Unidas Program of Research, by Dr. Guillermo Prado, University of Miami.

Along with the research reports, the meeting showcased best practices, highlighted achievements in minority health care and health disparities research, and provided a forum for networking and future dialogue. The National Center on Minority Health and Health Disparities planned the meeting in collaboration with other NIH agencies and several private and nonprofit partners. ■

Smoking and Drinking Continue to Decline, But Marijuana Stalls in Latest MTF Survey

In the latest Monitoring the Future survey of teenage substance abuse, cigarette smoking and alcohol use have declined to the lowest levels in 2 decades, but marijuana abuse—which had dropped steadily since the mid-1990s—appears to have stopped falling.

About 15 percent of students in the 8th, 10th, and 12th grades had abused one or more illicit drugs in the month prior to answering the 2008 edition of the annual survey. The rate is similar to that of 2007, but 25 percent lower than in 2001. In all cases, the higher the grade, the greater the prevalence of illicit drug abuse.

The past-month cigarette smoking rate in all three grades combined was 12.6 percent, a 7 percent decline since 2007. Past-month alcohol use also dropped by 7 percent. Smoking and drinking rates are substantially lower than in 2001. NIDA officials credited prevention efforts for the drop in smoking and drinking.

Marijuana abuse, in contrast, was essentially unchanged from 2007. Slight increases in the 8th and 12th grades were counterbalanced by a slight decrease in the 10th grade.

Most of the good news in the 2008 survey came from 10th-graders, who reported substantial declines in all measures of drinking and drunkenness (past-month, past-month daily, past-year, and lifetime) since 2007. Their improved rates were largely responsible for driving down the overall rate across the three grades.

The 10th-graders also reported significant declines in cigarette smoking and abuse of amphetamines, methamphetamine, and tranquilizers. Twelfth-graders reported less use of stimulants such as amphetamines, crystal meth, and crack cocaine.

TROUBLE AHEAD?

“While the long-term general decline is encouraging, especially for cigarettes and alcohol, some of our other findings this year amplify our concerns for potential problems in the future—especially the nonmedical use of prescription drugs,” says NIDA Director Dr. Nora D. Volkow. Abuse rates for prescription drugs, particularly narcotic pain relievers, have held steady or risen in recent years.

In the most recent survey, 15.4 percent of high school seniors said they had abused prescription drugs in the past year. Six of the top 10 drugs abused by high school seniors were prescription

or over-the-counter medications, including the opioid painkillers Vicodin (abused by about 10 percent) and OxyContin (abused by about 5 percent).

Another area of concern is an apparent softening of teenagers’ perceptions of the risks of certain substances. Such views often presage an increase in abuse. For example, the percentage of high school seniors who said LSD was harmful declined between 2007 and 2008, and over the same period, those who reported abusing this hallucinogen went up from 0.6 percent to 1.1 percent.

Similarly, the perceived risk of regular marijuana abuse has fallen for the past 2 years among 12th-graders and in the past year among 8th-graders, and the 2008 survey documented a slight increase in marijuana abuse by 8th- and 12th-graders. Dr. Lloyd Johnston of the University of Michigan, the study’s principal investigator, is also concerned that the proportion of students in all three grades who see ecstasy (MDMA) as very risky has declined, although its abuse rate remains low.

The 2008 survey included 46,348 students in 386 public and private schools across the United States. Further information and the full text of the survey are available at www.drugabuse.gov/drugpages/MTF.html and at www.monitoringthefuture.org.

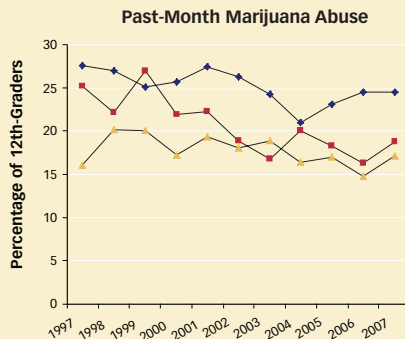
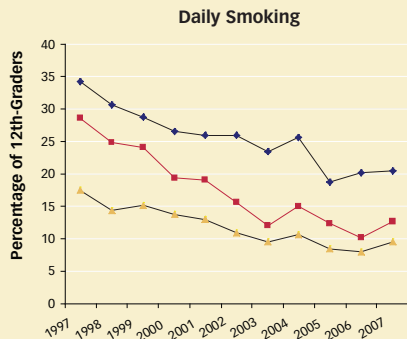
PERCENTAGE OF STUDENTS REPORTING PAST-MONTH SUBSTANCE ABUSE

	2001	2007	2008
Any illicit drug			
All grades	19.4	14.8	14.6
8th grade	11.7	7.4	7.6
10th grade	22.7	16.9	15.8
12th grade	25.7	21.9	22.3
Cigarettes			
All grades	20.2	13.6	12.6
8th grade	12.2	7.1	6.8
10th grade	21.3	14.0	12.3
12th grade	29.5	21.6	20.4
Marijuana			
All grades	16.6	12.4	12.5
8th grade	9.2	5.7	5.8
10th grade	19.8	14.2	13.8
12th grade	22.4	18.8	19.4
Alcohol			
All grades	35.5	30.1	28.1
8th grade	21.5	15.9	15.9
10th grade	39.0	33.4	28.8
12th grade	49.8	44.4	43.1

Lower Rates of Cigarette and Marijuana Smoking Among Exercising Teens

Frequency of Exercising Vigorously

◆ Seldom/Never ■ Sometimes/Most Days ▲ Nearly every day/Every day



Teens who exercise regularly are less likely than less active peers to have smoked cigarettes daily or to have abused marijuana during the past month. This pattern has persisted over the past decade, according to an annual survey of the nation's high school students.

Source: An analysis of repeated cross-sectional data from the Monitoring the Future Survey, by Dr. Lloyd Johnston, University of Michigan.

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