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INNOVATIONS Special Issue

Resting Brain Studies Shed New Light on Vulnerabilities

Brain circuits that remain active when individuals are resting provide clues to what goes awry in addiction and other mental disorders.

BY LORI WHITTEN,
NIDA Notes Staff Writer

Findings from a recent NIDA-funded study represent early fruits of research on a recently recognized network of brain circuits. Dr. Elliott Hong and colleagues

at the University of Maryland School of Medicine and collaborators at the NIDA Intramural Research Program showed that the strength of one of these “resting-state” circuits correlates with individuals’ vulnerability to nicotine dependence. Moreover, this circuit appears to mediate the increases in dependence associated with an important genetic risk factor.

Dr. Marcus E. Raichle and colleagues at the Washington University School of Medicine in St. Louis opened the door to the study of resting-state circuits about 10 years ago when they noted that some brain regions synchronize their activity when individuals are awake and alert but are not performing any specific task. The researchers suggested that these inter-regional interactions provide an

intrinsic functional organization of the brain. In addition to Dr. Hong’s recent research, other studies have borne out this idea, for example by identifying what appear to be resting-state neural signatures for different types of mental illness.

The initial observations of resting-state circuits were made with functional magnetic resonance imaging (fMRI) data obtained while individuals were idle between cognitive tasks. Such data are routinely produced in fMRI studies but had generally been regarded as simply byproducts of studies that focused on the brain’s activity during task performance. Today, however, many research teams are conducting studies specifically to generate resting-state data. NIDA and other agencies within the National Institutes of Health are supporting this work for the light it may shed on questions related to their respective missions. Research on resting-state circuits promises to yield insights into how the brain works at a hitherto unexplored basic level.

CIRCUIT RESPONSES TO NICOTINE

Dr. Hong and colleagues set out to

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HEAD SHOT In this diffusion spectrum image, fiber bundles are color coded according to their directions of impulse transmission. The Human Connectome Project uses diffusion spectrum and other cutting-edge neuroimaging techniques to map fiber pathways in the normal human brain. (For more images, see <http://www.humanconnectomeproject.org/gallery/>.)



Courtesy of the Laboratory of Neuro Imaging at UCLA and Martinos Center for Biomedical Imaging at MGH, Consortium of the Human Connectome Project.



NIDA's Drug Abuse Research Advances Science as a Whole

Drug abuse and addiction disrupt brain processes that govern fundamental capacities of motivation, memory, and learning. It is no wonder, then, that scientists seeking answers to addiction make discoveries that have broad implications for human development and health. As in the first *NIDA Notes* Innovations issue (www.drugabuse.gov/NIDA_Notes/NNVol22N1/Index.html), this second in the series draws attention to some of the most original and far-reaching recent findings of NIDA-supported scientists. Among them:

- MicroRNAs, snippets of RNA that have recently been implicated in a wide range of biological processes, regulate genes linked to drug addiction (see “New Class of Regulators for Addiction Genes,” page 11). The finding opens potential avenues for new therapeutic interventions not only for addiction, but for other neuropsychiatric disorders as well.
- Short-term memories acquire long-term traction partly because the same process that originally registers experiences in the hippocampus repeats in the frontal cortex (see “Molecular Alterations of DNA Contribute to Persistence of Memory,” page 8). This work provides a new perspective on the drug-related memories that commonly trigger relapse, and it may pave the way for the development of therapies for age-related memory loss.
- Drugs of abuse can diminish new neuron formation in the adult brain (see “Disruption of Neuron Production in Adult Rats Increases Cocaine Taking,” page 5). By illuminating the determinants and consequences of the sparse but apparently critical process of adult neurogenesis, this discovery may have wide implications.
- Recently discovered “resting-state” brain circuits exert considerable influence over responses to nicotine and vulnerability to addiction (see “Resting Brain Studies Shed New Light on Vulnerabilities,” page 1). NIDA-supported scientists are spearheading two large-scale projects that will map and analyze the brain’s entire complement of hitherto unappreciated resting-state circuits, which appear to shape an extensive set of individual traits and capacities, potentially including vulnerabilities to many neuropsychiatric illnesses.
- Scientists have successfully pilot tested the core components of a device for delivering transdermal medications in programmable, dynamic, finely calibrated doses over days or weeks (see “Nanotechnology Powers Smart Skin Patch,” page 3). When fully developed, the device, no bigger than a wrist watch but containing billions of carbon nanotubes, should enable physicians to ensure consistently safe and effective doses of pain and anti-addiction medications, even when patients’ needs fluctuate and motivation wavers.

The findings reported here provide a glimpse of the many ways in which NIDA-supported researchers are working at the frontiers of scientific discovery. While concentrated on the goal of reducing addiction and its consequences, their insights and solutions resonate for many other contexts of living and healing. ■

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Nanotechnology Powers Smart Skin Patch

Programmable device will feature adjustable dosing for personalized therapy.

BY LORI WHITTEN,
NIDA Notes Staff Writer

NIDA-funded researchers have conducted a successful *in vitro* demonstration of a prototype programmable medication skin patch. As envisioned by developers Drs. Bruce Hinds and Audra Stinchcomb of the University of Kentucky, the smart patch will enable physicians to schedule transdermal medication doses that vary dynamically to match patients' fluctuating needs. Doctors in the addiction field will tailor personalized nicotine replacement and other relapse-prevention therapies—for example, to program dose increases when stress, metabolic cycles, or environmental exposures may increase cravings.

Dr. Hinds, a chemist, and Dr. Stinchcomb, a research pharmacologist, developed the innovation that makes the patch possible: a membrane containing billions of carbon nanotubes, each 10,000 times thinner than a human hair. The unusual fluid flow within the carbon nanotubes allows for extremely efficient pumping; the nanotubes are voltage-gated so that they open and close to allow fluid to flow through them at rates proportional to applied electrical current. In the prototype test, the researchers steadily delivered a nicotine solution to human skin at two therapeutic dose levels.

PROOF OF CONCEPT

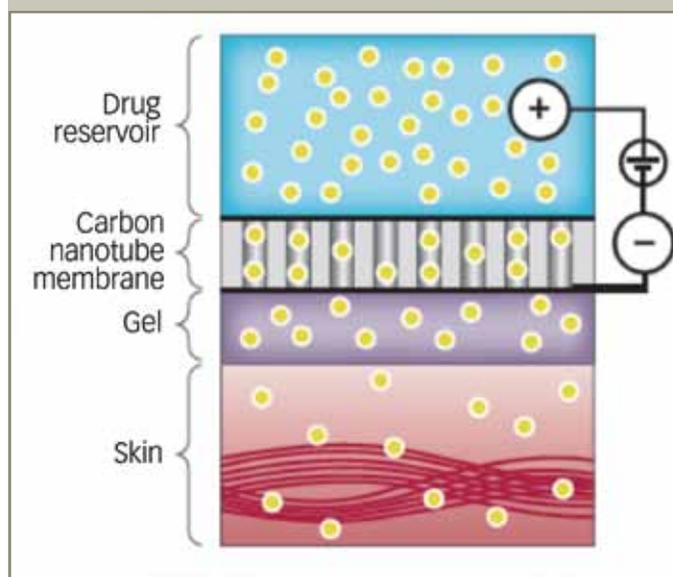
The smart patch comprises three layers: a medication reservoir on top; the nanotube membrane in the middle; and

a gel that attaches the membrane to the skin and diffuses the medication into the skin (see illustration, right). A watch battery that can power the pump continuously for 10 days and electronic controls complete the device, which will resemble a digital watch when fully developed.

In their recent demonstration, Dr. Hinds and colleagues filled the prototype reservoir with nicotine solution and applied a steady, low electrical current to the two sides of the central membrane. The gel held the device against a thin slice of human skin removed from a patient who had undergone plastic surgery for abdominal firming.

In response to the current, the membrane pumped a steady flow of nicotine through the skin into a saline bath underneath. The device delivered nicotine at two rates, both of which were consistent with therapeutic levels currently used to support smoking cessation. When the researchers shut off the power, the flow of nicotine dropped to a residual amount. No irritation of the skin was observed. “Although there are concerns about inserting carbon nanotubes into the body,

MEMBRANE PUMPS NICOTINE THROUGH SKIN When power was applied to a carbon nanotube membrane placed on a slice of gel-coated skin, the device delivered nicotine solution through the skin and into a saline bath below (not shown).



Reprinted by permission from Macmillan Publishers Ltd. Nature Materials 9(8):605, 2010.

our membrane is applied externally and the nanotubes are embedded in a polymer, so it is very safe,” says Dr. Hinds.

The Kentucky team is now performing animal tests to lay the foundation for clinical studies. The results will show whether a smart patch powered by a watch battery can deliver therapeutic levels of nicotine into the bloodstream of guinea pigs. Dr. Hinds says that additional animal studies will help refine the delivery devices, ensuring that they can provide nicotine at the necessary rates, are safe on active creatures, and can function for long periods.

If the animal tests are successful, the next major step will be to develop a prototype smart patch for people. For this, the team plans to use a standard watch

battery and, as the reservoir component, the nicotine patch already in medical use. The researchers have also created a working prototype that is controlled by Bluetooth technology and run by a smart phone program.

WIDE APPLICATIONS FORESEEN

Transdermal patches are currently available for about 20 different medications, including addiction therapeutics, replacement hormones, pain killers, and medications for motion sickness. In these treatments, the small size and other chemical properties of the active molecules enable them to move passively across the skin. For some other medications, which do not penetrate skin, adding an array of microneedles can facilitate delivery (see “Naltrexone via Skin Patch Proves Effectiveness of New Technology,” *NIDA Notes*, Volume 22, Number 5, page 13). However, with current transdermal patches or microneedle devices there is no control over the timing of medication delivery.

Individualized treatment is important in the care of chronic health problems that require close monitoring of a patient’s

Individualized treatment is important in the care of chronic health problems that require close monitoring of a patient’s condition.

condition. For example, combined with a feedback sensor for blood glucose levels, a device containing a carbon nanotube membrane could fine-tune insulin delivery to people with diabetes more effectively than today’s continually active insulin pump. As with other transdermal applications, medications delivered by the new technique bypass potential breakdown in the gastrointestinal tract and avoid causing some liver problems.

Dr. Hinds points to nicotine replacement as an example of an anti-addiction

Modeling Nanotubes on Natural Membranes

Smart patches are just one of many applications under development for carbon nanotubes, which were first pioneered in the early 1990s. The tiny tubes are rolled from sheets of specialized carbon molecules. Strong and flexible, they offer improvement over current materials in the making of many different products, from bicycle parts to clothes to scaffolding that can support bone formation. They are excellent conductors of heat and electricity, so engineers are also using them to improve transistors, memory circuits, batteries, and other electronic components.

Dr. Bruce Hinds and colleagues at the University of Kentucky are using carbon nanotubes to create membranes that are selectively permeable to different molecules and efficient as filters and pumps. The researchers stack billions of nanotubes in the same orientation and fill the spaces between the nanotubes with a polymer. When they apply an electrical current, the tubes open and close quickly, pumping specific molecules across the membrane, just as protein channels do in living cells. The membranes can not only deliver drugs but also act as filters, fuel cells, and biological sensors.

therapy that the smart patch will enhance. “There is such a large population in need of treatment that the numerous visits to a health care provider that are required

design will cap the maximum rate of drug flow and incorporate an anti-tampering feature.

Dr. Thomas Aigner of NIDA’s Division of Basic Neuroscience and Behavioral Research foresees multiple ways in which the smart patch could aid efforts to reduce addiction. “High-tech control of medication release would be very useful for avoiding addiction to opioid painkillers because it would ensure that patients stay within the prescribed dose and not have access to additional amounts of the drug that might be misused,” says Dr. Aigner. “In addition, individualized, finely calibrated dosing of the medications used to treat opioid withdrawal could provide optimally effective alleviation of withdrawal symptoms.” ■

SOURCE

Wu, J., et al. Programmable transdermal drug delivery of nicotine using carbon nanotube membranes. *Proceedings of the National Academy of Sciences* 107(26):11698–11702, 2010.

Disruption of Neuron Production in Adult Rats Increases Cocaine Taking

Interference with the birth of brain cells may also raise drug-relapse vulnerability.

BY LORI WHITTEN,
NIDA Notes Staff Writer

Although most brain regions stop producing new neurons once the organ reaches full maturity, neurogenesis continues throughout life in the hippocampus, a structure crucial to learning and memory. Recent NIDA-funded work suggests that drugs of abuse may diminish production of new hippocampal neurons and thereby increase vulnerability to drug addiction.

Dr. Amelia J. Eisch and colleagues at the University of Texas Southwestern (UTS) Medical Center have shown that suppressing the production of new neurons in the hippocampus of adult rats increases cocaine self-administration and the persistence of cocaine-seeking behavior during withdrawal. Their results suggest that enhancing neurogenesis might be an effective strategy for treating drug abuse and preventing relapse.

A NEXUS OF NEUROGENESIS AND ADDICTION

Dr. Eisch and collaborators hypothesized that disrupting neurogenesis in the hippocampus of laboratory rats would exacerbate the animals' drug-related behaviors. The UTS team had previously shown that cocaine and most other addictive drugs reduce adult neurogenesis (see box, page 6). Other groups had demonstrated that exercise, environmental enrichment, antidepressant medication, and some other factors that protect against drug abuse enhance



neurogenesis and also that stress, a common trigger for drug abuse and relapse, depresses neurogenesis.

To test their hypothesis, Dr. Eisch and colleagues exposed rats to cranial irradiation, an experimental procedure that disrupts production of new neurons without causing illness or otherwise affecting brain function. Five weeks later, the researchers observed that the irradiated animals had only 30 percent as many new hippocampal cells as a group that was not irradiated.

A behavioral trial with the animals linked suppressed neurogenesis with increased sensitivity to the reinforcing properties of cocaine. The team placed irradiated and control rats in a chamber with a lever that the animals could press to self-administer cocaine for 4 hours daily. On the first and second days, the irradiated rats pressed the lever approximately 60 percent more often than the controls, and their frequency of self-administration

remained consistently higher throughout 15 days of testing. In subsequent trials, the researchers observed similar increases in irradiated rats' self-administration of four doses of cocaine. In another experiment, rats with suppressed neurogenesis pressed the lever many more times than the control animals to obtain a single infusion of cocaine.

Before concluding that inhibited neurogenesis was the cause of the irradiated animals' increased motivation to seek cocaine, Dr. Eisch and colleagues performed cross-checks to rule out more general explanations. These experiments showed that the irradiated rats' behavior did not reflect:

- heightened sensitivity to rewards of all sorts, because animals in both groups self-administered a similar number of sucrose pellets, or;
- locomotor stimulation, because rats in the two groups had similar activity levels.

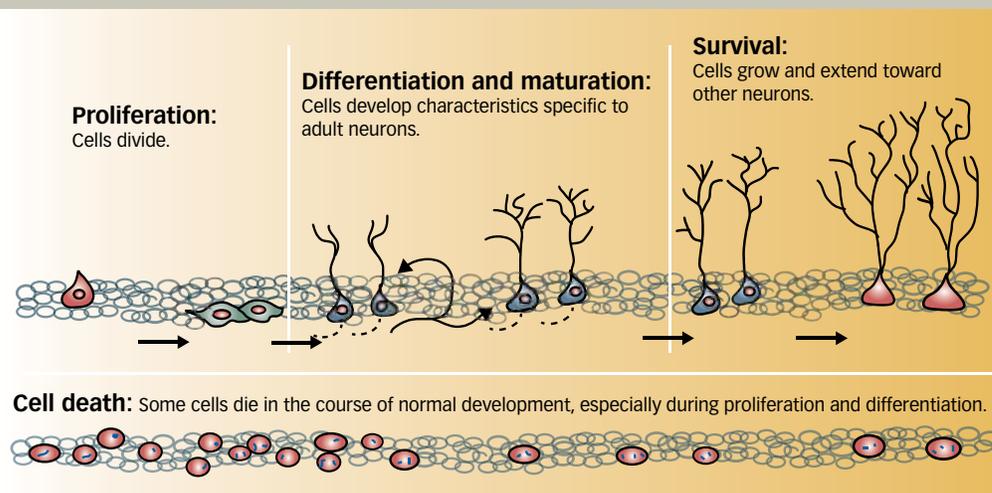
Drug-Induced Disruption in Adult Neurogenesis

In studies with rats, Dr. Amelia J. Eisch and colleagues at the University of Texas Southwestern Medical Center determined the nature of the drug-induced disturbances in adult hippocampal neurogenesis and the developmental stages at which they occurred:

- Self-administered cocaine and methamphetamine inhibit adult neurogenesis at the earliest and most studied stage, called proliferation, during which cells actively divide.
- Cocaine self-administration also interferes with cell maturation, increasing the number of immature neurons in the hippocampus. After cocaine was no longer available, rats that had previously self-administered the drug showed signs of enhanced maturity in new neurons, suggesting that abstinence may promote a compensatory response following drug-induced disruption of neurogenesis.

The team's findings accord well with those of prior research, which indicated that a wide range of drugs—stimulants, nicotine, alcohol, opiates, cannabinoids—depress adult hippocampal neurogenesis. "It is striking that one sees similar

LIVES OF NEURONS Newly generated neurons in the adult hippocampus go through several stages of development. Drug use can affect this process during proliferation and maturation.



results among drugs with different chemical structures, behavioral effects, and neurobiological impacts," says Dr. Eisch. "This suggests that drugs influence neurogenesis by a general mechanism—perhaps by decreasing production of proteins that promote neuron growth—rather than by acting on particular receptors or transporters."

SOURCES

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RELAPSE AFFECTED, TOO

To test whether adult hippocampal neurogenesis influences vulnerability to relapse, Dr. Eisch and colleagues trained rats to self-administer cocaine, then returned the animals to their home cages with no access to the drug. After a month of withdrawal—the equivalent of an extended abstinence for a drug abuser—the rats were returned to the self-administration cages. The researchers measured how long the animals took to quit press-

ing the lever that had previously delivered cocaine but no longer did so. Persistence in futile drug seeking suggests vulnerability to relapse.

To the researchers' surprise, the animals' responses depended upon when hippocampal neurogenesis had been suppressed. As expected, rats irradiated at the start of the experiment pressed the lever more often during the initial self-administration period.

However, following 4 weeks without cocaine, these irradiated rats quit pressing the deactivated lever just as quickly as control rats, suggesting that they were not more vulnerable to relapse. The researchers speculated that the irradiated animals' brains compensated for disrupted neurogenesis during the 12 weeks between irradiation and relapse testing.

In contrast, rats that were irradiated *after* cocaine self-administration showed

more vulnerability to relapse than controls, taking longer to desist from pressing the lever that no longer delivered cocaine. The researchers say that this finding fits with other observations that loss of neurogenesis disrupts animals' ability to quit behaviors that no longer serve a purpose.

"Our results identify reduced adult hippocampal neurogenesis as a novel risk factor for addiction," says Dr. Eisch. "Moreover, our findings suggest that therapies that enhance adult neurogenesis may help prevent initial addiction as well as future relapse." While the team forges ahead with laboratory research to examine possible connections between

reduced adult hippocampal neurogenesis and other drug-induced neurobiological changes, Dr. Eisch is interested in collaborating with clinicians to explore the potential of neuron production as an addiction treatment strategy.

"Although a great deal of research is needed in this area, regenerative medicine is not as far away as one might think," says Dr. Eisch. "In ongoing clinical trials, scientists are testing drugs that enhance neurogenesis as potential treatments for depression, and addiction researchers might learn valuable lessons from the results."

"If scientists can determine how adult

neurogenesis is regulated and the specific function of the new cells, then they may be on the verge of developing a new type of medication to treat addiction—therapies that help the brain renew itself in a location that is compromised by drug abuse," says Dr. Nancy Pilotte of NIDA's Division of Basic Neuroscience and Behavioral Research. "The potential of this frontier area to lay a foundation for regenerative medicine is very exciting—and Dr. Eisch's research is in the vanguard." ■

SOURCE

Noonan, M.A., et al. Reduction of adult hippocampal neurogenesis confers vulnerability to cocaine addiction. *Journal of Neuroscience* 30(1):304–315, 2010.

GOOD-BYE, PAPER

NIDA Notes Is Going All-Web

Starting in early 2012, after 25 years in print, *NIDA Notes* will become exclusively a Web publication. In its dynamic new format, *NIDA Notes* will continue to provide the same highly readable and authoritative coverage of NIDA-supported research that you enjoy now,

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Molecular Alterations of DNA Contribute to Persistence of Memory

Some epigenetic changes may promote vulnerability to drug relapse.

BY CARL SHERMAN,
NIDA Notes Contributing Writer

Addiction is tenacious: People who are in recovery remain vulnerable to relapse even after years of abstinence. Often, it is memory that reawakens the craving. The dormant desire can return with a vengeance when cued by people, places, or situations once associated with drug use. For this reason, memory has become an important area of study for addiction researchers.

Neuroscientists over the last two decades have made important advances in tracing the molecular events that occur in the brain as memories are formed and preserved. In recent experiments, NIDA-supported researchers Drs. Courtney A. Miller, J. David Sweatt, and colleagues at the University of Alabama at Birmingham and The Scripps Research Institute in Jupiter, Florida, delineated what appears to be a key pathway in this process: Reversible changes in DNA regulate the production of proteins that give memories their staying power. The new findings may spur breakthroughs in the study of drug relapse, as well as in a broad range of neurological problems, including age-related memory loss and neurodevelopmental disorders.

THE NEURAL BASIS OF MEMORY FORMATION

Someone enters a restaurant and recalls the taste of its veal scallopini; a man arrives at a shore and thinks of his father, with whom he fished there as a child; a

person in recovery passes a certain corner and recalls the high from the drugs he purchased there. This is remembering: Something in our present experience brings to mind something that was linked with a similar experience in our past. What brain activity makes this happen?

The emerging neuroscientific understanding of memory posits that the world’s various features—for example, the interior of a restaurant or the taste of veal scallopini—each evokes particular patterns of neuron firing in the brain. The brain registers these patterns for future reference by strengthening the synapses between neurons that fire simultaneously. Stronger synapses make neurons more sensitive to each other, so that the subsequent firing of some readily stimulates the others to fire as well. Now, when the restaurant interior reactivates some of the same neurons that it did before, they in turn stimulate the neurons previously excited by the veal taste—even though no veal is actually present.

The brain is constantly registering, storing, and reaccessing neural patterns

in this way. The resulting memory associations can powerfully drive emotions and behavior: The person passing the restaurant suddenly feels famished; the man at the shore feels an urge to call his parents; the person in recovery begins to crave the drug he used long ago.

METHYLATION AND MEMORY FORMATION

Neuroscientists have found that the process of forging the new synaptic links between neurons involves a host of proteins. Drs. Miller and Sweatt reasoned that the process might be strongly influenced by epigenetic factors, which act upon genes to control the rate of production and availability of their proteins. Applying a hypothesis first suggested by Dr. Francis Crick in the 1980s, the researchers focused on one epigenetic process, DNA methylation, which prevents the first step in protein production (see box, page 9).

In an initial experiment, Drs. Miller and Sweatt established that DNA methylation is essential for memory formation. They first placed rats in a special cage and

METHYLATION SUPPORTS FEAR MEMORY FORMATION Normal rats remembered a foot shock a day later, but rats treated with a compound that suppresses methylation did not. Methylation supports memory formation by inhibiting transcription of the gene for calcineurin into messenger RNA. When methylation of the gene is suppressed, more calcineurin is produced and its negative impact on memory formation increases.

Methylation Suppressor Administered Before Foot Shocks	Methyl Groups Attach to Calcineurin Gene	Messenger RNA Produced	Calcineurin Produced	Fear Memory Formed
No	Yes	No	No	Yes
Yes	No	Yes	Yes	No

administered mild electric shocks to the animals' feet. Normal rats remembered the unpleasant experience, and most froze with fear when put back into the cage 24 hours later. But rats that before being shocked were treated with a compound that prevents methylation did not appear to remember the shocks when they were returned to the special cage the next day. They behaved as if nothing untoward had happened to them there.

Drs. Miller and Sweatt next demonstrated that the changes in methylation that occur during memory formation favor synaptic strengthening between neurons in the hippocampus, the brain area known to initially register certain memory associations. Once again, the investigators administered mild shocks to rats, and the animals' behavior the next day showed that they remembered being shocked. This time, the researchers compared hippocampal tissue from these rats and from control groups that were not trained to associate the cage with shocks. The rats with the fear memories showed two changes related to strengthened memory.

- Increased methylation of the gene for protein phosphatase 1 (PP1), an enzyme that inhibits memory formation by interfering with synaptic strengthening;
- Decreased methylation of the gene for reelin, a protein that promotes memory formation by assisting in synaptic strengthening.

Drs. Miller and Sweatt confirmed that these changes resulted in less abundant PP1 and more abundant reelin. They concluded that methylation plays a dual role in memory formation, both increasing the availability of a memory-promoting protein and reducing the presence of the memory-suppressing protein.

The methylation associated with the shock memories proved to be transient, disappearing within an additional 24 hours. The researchers noted that this

Methylation Blocks Protein Production

Protein production begins with transcription, the transfer of information contained in a gene's DNA to a messenger RNA (mRNA) molecule. The mRNA molecule provides the template for assembling amino acids into protein.

Methylation regulates protein production by blocking transcription. Methylation occurs when a methyl group—a cluster of a carbon and three hydrogen atoms—attaches to DNA. Like other epigenetic processes, methylation is reversible—methyl groups attach, detach, and reattach to DNA. By doing so, they vary the rate of protein production to suit the brain's needs in changing situations.

fits with a well-established role of the hippocampus: As the locus of initial memory formation, it provides short-term storage only. If a memory is to last, it must move to another part of the brain. Where this might be, and how the memory might be preserved, were the questions the researchers tackled next.

FROM A WEEK AGO TO YESTERYEAR

Previous research had indicated that within a week of memory formation, the chemical and metabolic activities that support memory storage shift from the hippocampus to the dorsomedial prefrontal cortex (dmPFC). Drs. Miller and Sweatt and collaborators focused their attention on this region.

On the basis of their work on memory formation, Drs. Miller and Sweatt posited that methylation might also be key to the consolidation and preservation of long-term memory. However, they suspected that methylation of the gene for the enzyme calcineurin, rather than PP1 and reelin, might be important in establishing and sustaining memories in the dmPFC.

"There is a lot of published work showing that calcineurin suppresses memory and that memories are more easily formed and last longer if you block calcineurin," Dr. Miller says. Methylation

of the calcineurin gene, by reducing the amount of calcineurin produced, might remove a barrier to the transfer into the dmPFC of memories first formed in the hippocampus.

The researchers returned to the animal lab and repeated the foot-shock procedure with a new set of rats. After they confirmed fear memory, the team assayed dmPFC brain tissue from groups of animals at different times after the procedure: 1 hour, 1 day, 7 days, and 30 days. The results bore out their hypothesis. The calcineurin gene did not exhibit increased methylation after 1 hour, but it did after 1 day and remained highly methylated 7 and 30 days later.

To solidify the link between memory and methylation of the calcineurin gene, the researchers infused the hippocampus of rats with a compound that prevents fear learning. When the animals were then given the foot-shock procedure, as expected, they did not demonstrate the fear response—and 7 days later there was no extra methylation of the calcineurin gene in the prefrontal cortex.

One crucial question remained: Is methylation necessary to maintain a memory after it has been consolidated in the prefrontal cortex? To test this, the researchers infused methylation-blocking molecules into the prefrontal cortex of rats 30 days

after the foot-shock procedure. With methylation suppressed, the animals ceased to display fear when reexposed to the shock-associated cage. Without ongoing methylation, the researchers speculate, a memory effectively disappears.

WIDER APPLICATIONS OF METHYLATION

Although the latter study focused on the calcineurin gene, the complexities of memory formation and maintenance in the prefrontal cortex surely also entail DNA methylation in other genes, Dr. Miller says. Her team plans to identify these genes in future research.

Reducing methylation might, in theory, provide a means to weaken the memories that drive relapse to addiction, Dr. Miller says. But the difficulty of targeting specific memories without inducing a more general amnesia makes this approach a distant prospect at best.

Understanding the molecular basis for the persistence of memory, however, could have more immediate relevance to other problems, such as age-related memory loss. Dr. Miller says, “If we can boost the mechanisms involved in maintaining memory, we might help individuals suffering from cognitive decline.”

What makes the recent findings particularly interesting, says Dr. John S. Satterlee of NIDA’s Division of Basic Neuroscience and Behavioral Research, is the demonstration that methylation activity follows the path of memory from the hippocampus to the prefrontal cortex. “The molecules themselves aren’t moving, of course, but something happens that shifts the process to the right place,” he notes.

The duration of these processes is also intriguing, Dr. Satterlee says. “I wouldn’t go so far as to conclude that DNA methylation is a way of encoding memory, but the fact that molecular changes in this brain

region can last as long as 30 days is very intriguing,” he comments.

While Dr. Satterlee agrees that issues of targeting and potential toxicity pose significant obstacles to methylation-based drug abuse interventions, he suggests that a deeper understanding of the process could have general implications for addiction research. “We know that epigenetic changes occur when the brain responds to drugs of abuse, but scientists haven’t yet looked deeply at methylation in this regard,” he says.

Dr. Satterlee notes that defects in a protein that can bind to methylated DNA have been identified in Rett syndrome (see reference, page 13). He suggests that studies like Dr. Miller’s could help to advance our understanding of neurodevelopmental disorders. ■

SOURCE

Miller, C.A., et al. Cortical DNA methylation maintains remote memory. *Nature Neuroscience* 13(6):664–666, 2010.

NIDAMED

NIDAMED: Resources for Patient Care

NIDAMED is a NIDA initiative designed to provide the medical community with drug abuse resources to enhance patient care.

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New Class of Regulators for Addiction Genes

Some microRNAs promote vulnerability to addiction; others protect against it.

BY NIDA NOTES STAFF

MicroRNAs, snippets of RNA that were first recognized only 2 decades ago, are turning out to be important players in a wide variety of biological processes. They have been implicated, for example, in embryogenesis, cholesterol metabolism, learning and memory, and cancer. Now, two studies by NIDA-funded scientists present evidence that microRNAs also regulate genes involved in drug addiction. Their findings offer a new direction for the development of anti-addiction therapies.

“We have been thinking for a long time that microRNAs might be involved in drug addiction because addiction is such a complex disorder and microRNAs are known to influence multiple circuits in the brain,” says Dr. Paul Kenny of The Scripps Research Institute in Jupiter, Florida. “We have spent quite a few years trying to figure out what they might do.”

In one recent study, Dr. Kenny and colleagues found that rats that generate high levels of one particular microRNA in the brain following extended cocaine exposure are less likely to exhibit addiction-like behaviors. The researchers also traced some of the molecular pathways through which this microRNA exerts its effects.

MASTER REGULATORS OF GENE EXPRESSION

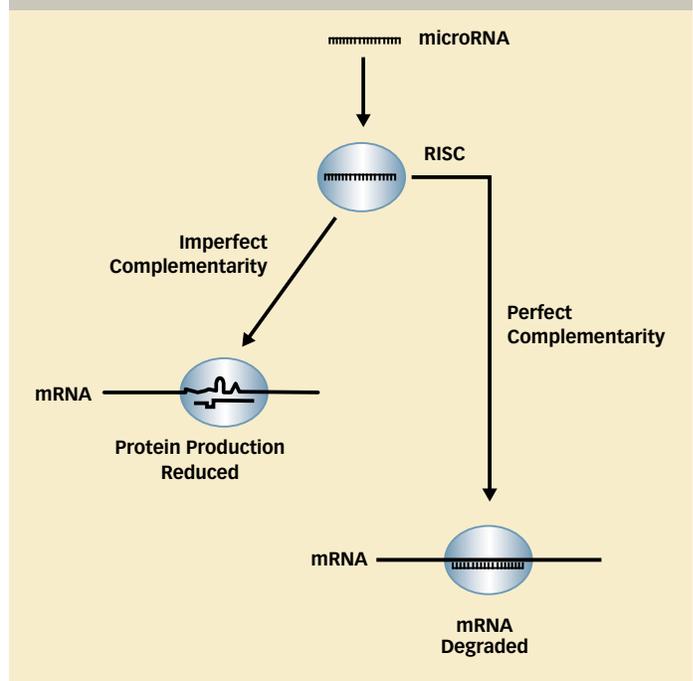
MicroRNAs, like the better known messenger RNAs, are strings of nucleotides arranged in specific sequences.

As their name suggests, microRNAs are far shorter than messenger RNAs, averaging only about 22 nucleotides as opposed to hundreds or thousands.

Functionally, microRNAs interact with messenger RNAs to regulate protein production. The interaction is push-pull in nature: Messenger RNAs execute an essential production step by conveying protein-building instructions from genes to the protein-synthesizing machinery of cells, and microRNAs prevent them from doing so. The relative abundance of the two types of RNAs thus determines the amount of protein produced.

There are approximately 1,000 different microRNAs in human cells, and each attaches to a complementary RNA segment—its “ID code”—present in a messenger RNA (see illustration, above). The microRNA binds to the messenger RNA as part of a complex with several proteins, called an RNA-induced silencing complex (RISC), that either destroys the mes-

REPRESS OR DESTROY Single-stranded mature microRNA becomes part of an RNA-induced silencing complex (RISC), which carries it to a target messenger RNA. The degree of complementarity between the nucleotide sequences of the microRNA and the target portion of the messenger RNA (mRNA) determines whether the mRNA continues to promote production, albeit in reduced amounts, or undergoes cleavage and degradation.



senger RNA or prevents it from making protein.

Because many different messenger RNAs may contain the same ID code, each microRNA may affect the expression of many genes. Researchers suspect that each microRNA can bind to hundreds or thousands of messenger RNA targets, while each messenger RNA can have binding sites for dozens or even hundreds of different microRNAs.

Dr. Kenny’s new work is the first demonstrating a possible role for microRNAs in regulating genes involved

in drug addiction. Researchers have shown that addictive drugs affect the expression of many genes in the brain and have implicated some of these alterations in addictive behaviors such as drug craving and compulsive drug use.

PROTECTION AGAINST ADDICTION

In initial experiments with rats, Dr. Kenny and colleagues identified microRNAs that increase in abundance in the brain's dorsal striatum following extensive exposure to cocaine. One of these, miR-212, appeared to inhibit avid drug-seeking in rodents.

The researchers compared microRNA levels in brain tissue from two groups of rats. One group had freely self-administered cocaine for a week in daily 6-hour sessions; the other, in daily 1-hour sessions. Previous research has shown that rats exhibit addiction-like behaviors—in particular, accelerated, uncontrolled cocaine intake—following the 6-hour regimen but not the 1-hour regimen. Although both groups showed the effects of cocaine exposure per se on brain chemistry, only the 6-hour animals showed changes specifically related to the addictive process. Among the differences, the researchers found twice as much miR-212 in dorsal striatum of the 6-hour animals as compared with that in 1-hour animals (see figure, right). Another microRNA, miR-132, showed a similar pattern of expression, but its role in regulating drug addiction has yet to be analyzed.

In further work, Dr. Kenny and colleagues investigated how increases in miR-212 affect the addictive process. Surprisingly, they found that such increases actually mitigate addictive behaviors.

In this experiment, the researchers introduced a benign virus containing extra copies of the miR-212 gene into the dorsal striatum of rats. This maneuver exaggerated the cocaine-induced increase in miR-212 and demonstrated its behav-

ioral impact. Whereas normal rats steadily increased their cocaine intake throughout a week on the 6-hour regimen, the gene-enhanced animals reduced their intake. In addition, normal animals exhibit another behavioral signature of addiction, a marked preference for higher doses of the drug, but animals with extra miR-212 did not. Conversely, when the researchers blocked miR-212 function, the extended-access animals consumed the drug in increasing amounts and preferred higher doses to lower ones.

The researchers concluded that the brain's increased production of miR-212 following prolonged cocaine exposure may represent a self-protective response against drug-induced changes that underlie addiction. "Individuals who cannot mount a response to cocaine exposure by producing more miR-212 are probably more vulnerable to addiction," says Dr. Kenny.

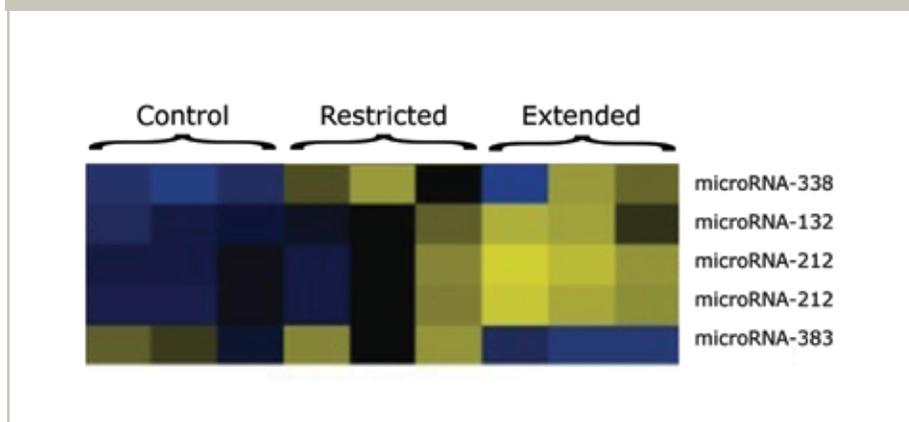
PATHWAYS

Dr. Kenny and colleagues uncovered three mechanisms by which miR-212 preserves animals' control over drug intake. The microRNA weakens animals' motivation to self-administer the drug by:

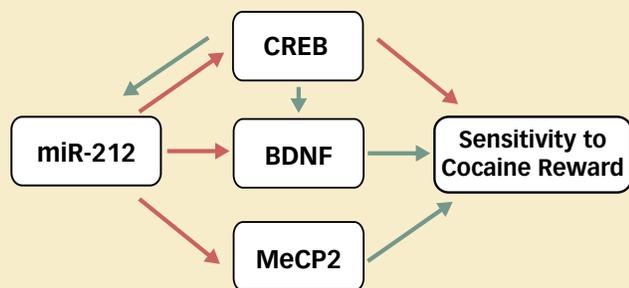
- Promoting increased activity of a transcription factor called CREB (cAMP response element binding protein) that dampens sensitivity to cocaine's rewarding effects;
- Inhibiting production of a molecule called BDNF (brain-derived neurotrophic factor) that enhances sensitivity to cocaine's rewarding effects;
- Inhibiting production of a molecule called methyl CpG binding protein 2 (MeCP2) that is closely linked to BDNF and also intensifies sensitivity to cocaine reward.

Further work by the Scripps team placed miR-212 within a delicately balanced network of epigenetic feedback and feed-forward loops in the dorsal striatum. CREB is pivotal in the network because its effects are bidirectional. Overall, it reduces sensitivity to cocaine reward, but it also promotes production of BDNF, which has the opposite effect. CREB tempers this second effect, however, by also promoting miR-212, which reduces production of BDNF and competes with MeCP2. Ultimately, the sum of the direct and indirect, reciprocal and opposed relationships among all of these molecules shapes

SPOT THE DIFFERENCE Researchers examined the expression of microRNAs in the dorsal striatum of rats with different amounts of cocaine exposure. In the microgram below, the color blue indicates low levels; black, higher levels; and yellow, the highest levels. Thus, miR-132 and miR-212 (the three middle rows) are present in low amounts in samples from control rats (with no access to cocaine) and animals with restricted (1-hour-daily) access, but in large amounts in those with extended (6-hour-daily) access.



DELICATELY BALANCED NETWORK MicroRNA-212 participates in a complex web of interactions in the dorsal striatum that affect animals' motivation to self-administer cocaine. CREB (cAMP response element binding protein) decreases rats' sensitivity to cocaine reward, while brain-derived neurotrophic factor (BDNF) and methyl CpG binding protein 2 (MeCP2) increase sensitivity. Green arrows indicate a positive influence, and red arrows indicate a negative influence.



an individual's vulnerability to cocaine's motivational effects.

Dr. Kenny calls particular attention to MeCP2 in this network. Mutations in this protein have been implicated by other researchers in Rett syndrome, a neuro-

implicated in uncontrolled drug-taking, provides support for an idea that had been suggested but never confirmed: that addiction and neurodevelopmental processes may sometimes share pathways.

developmental disorder that occurs mainly in girls and is related to autism. Like addicted individuals, people with Rett syndrome have abnormal function in the dorsal striatum and behave compulsively.

The Scripps researchers' finding, that MeCP2 is

OPENING THE DOOR TO NEW THERAPIES

A model of addiction is emerging from these two studies by Dr. Kenny and colleagues. It suggests that miR-212 serves as a key regulator of CREB and BDNF and other molecules in the striatum, thus affecting cocaine intake. Other microRNAs may play similar roles, resulting in intricate networks of regulation of the brain's reward pathways.

Dr. Kenny and colleagues have already discovered that levels of other microRNAs, such as miR-132 (see figure, page 12), also increase in the dorsal striatum of rats given extended access to cocaine. However, some of these other microRNAs, unlike miR-212, may promote addiction rather than protect against it (see box, below).

"These studies provide the first strong evidence that microRNAs play a role in

More MicroRNAs Linked to Addiction

Mice whose neurons lack a protein essential for the generation or function of certain microRNAs consume less cocaine than normal mice, according to a study by the team of Dr. Paul Kenny of The Scripps Research Institute in Jupiter, Florida, in collaboration with NIDA-supported investigator Dr. Paul Greengard of The Rockefeller University. The results suggest that some microRNAs may stimulate brain mechanisms that contribute to drug addiction.

The investigators blocked the expression of the gene *Argonaute 2*, which produces the protein (Ago2) that is essential for many microRNAs to function. The Ago2-deficient mice showed reduced motivation to self-administer cocaine.

The researchers examined a group of brain neurons that express dopamine 2 receptors (D₂Rs). These neurons are of particular interest because the neurotransmitter dopamine is implicated in drug abuse and addiction, and animals with fewer available D₂Rs have been shown to be especially responsive to cocaine's reinforcing effects.

In their experiment, the researchers identified 23 microRNAs that have reduced abundance or function in D₂R-expressing neurons of the Ago2-deficient animals. From the nucleotide sequences, the researchers predict that those microRNAs will affect the activity or production of several compounds, including CREB and BDNF, which are already known to play roles in cocaine addiction. Future studies may identify the contribution of each of the microRNAs to various facets of addictive behavior.

This study suggests that unlike miR-212, which tends to reduce an animal's cocaine intake, some microRNAs promote cocaine intake. "There is likely to be tremendous interplay between all the microRNAs in the brain," Dr. Kenny says. "Together, they coordinate responses to cocaine and vulnerability to addiction."

SOURCE

Schaefer, A., et al. Argonaute 2 in dopamine 2 receptor-expressing neurons regulates cocaine addiction. *Journal of Experimental Medicine* 207(9):1843-1851, 2010.

drug abuse,” says Dr. John Satterlee of NIDA’s Division of Basic Neuroscience and Behavioral Research.

One exciting aspect of this work is that

“If we tweak these therapies in just the right way, they might be very beneficial for treating drug addiction.”

– Dr. Paul Kenny

it may be possible to develop treatments for drug addiction or other disorders by replicating the actions of a particular microRNA. Therapies based on microRNAs are already being tested in cancer, with some currently in randomized controlled multicenter trials on large patient groups. “If we tweak these therapies in just the right way, they might be very ben-

eficial for treating drug addiction,” says Dr. Kenny, adding that he is cautiously optimistic about the prospects.

There are, however, many challenges

to developing microRNA therapies that treat addiction. Any therapy targeted to the brain, for example, has to make its way across the barrier of tightly fitting endothelial cells that line blood vessels, preventing many substances from passing from the blood into the brain. This barrier evolved to protect the brain from poisons, but it also keeps many medications out.

In addition, because one microRNA may regulate thousands of genes, harmful side effects might result from turning on or off the production of a microRNA.

Despite these caveats, Dr. Kenny’s work opens the door to a new therapeutic approach, according to Dr. Satterlee. “MicroRNAs and the pathways they regulate provide a huge number of potential drug targets that we did not know about,” he says. ■

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■ RESTING BRAIN

[Continued from page 1]

identify resting-state circuits related to nicotine dependence and to assess the impact of nicotine replacement therapy on those circuits. They focused on circuits that include the cingulate cortex because activity in that brain region appears to be disrupted in addiction (see “Methamphetamine Abusers Show Increased Distractibility,” *NIDA Notes* Volume 22, Number 3, page 9).

The researchers recruited 19 healthy smokers, ages 18 to 50, who were not trying to quit. Each participant underwent fMRI brain imaging in two sessions spaced roughly a week apart. The brain images were obtained while participants rested after performing cognitive tasks for an hour. The participants wore a nicotine patch during one of the imaging sessions and a placebo patch during the other.

The results revealed that the cingulate forms resting-state circuits with 56 of the many brain areas to which it connects anatomically. Several of these circuits were sensitive to nicotine: Their strength—the degree of synchronization between their component areas—markedly increased when participants wore the nicotine patch.

“The enhanced communication of cingulate–frontal cortex circuits after nicotine administration may underlie the well-documented transient cognitive boost from nicotine.”

– Dr. Elliott Hong

Most of the nicotine-sensitive circuits connect the cingulate with cortical areas that influence thinking, attention, and memory. A few of the nicotine-boosted pathways connect the cingulate with the postcentral gyrus, a cortical region that processes sensory information.

“The enhanced communication of cingulate–frontal cortex circuits after nicotine administration may underlie the

well-documented transient cognitive boost from nicotine,” says Dr. Hong.

A CIRCUIT FOR SEVERITY

The Maryland team found that the severity of nicotine addiction was associated with a circuit that connects the dorsal portion of the anterior cingulate cortex (dACC) to the ventral striatum. Participants with weaker communication in this circuit scored higher on the Fagerström Test for Nicotine Dependence (see graph, right).

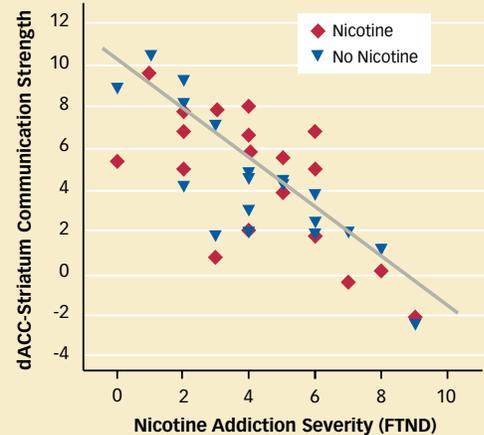
The dACC supports impulse and emotional control, which are impaired in addiction. The striatum processes rewards including the pleasure derived from smoking. “Communication strength within the circuit, rather than the activity of the individual areas, seems to relate to the severity of nicotine dependence among smokers,” Dr. Hong says.

Unlike the cingulate cortex circuits, communication in the dACC–striatum circuit was similar whether the participants wore the nicotine patch or placebo patch. Dr. Hong and colleagues suggest that this

observation may shed light on a clinical conundrum: If people smoke primarily to obtain the effects of nicotine and avoid withdrawal, why is it that some 85 percent of people who try the patch keep on smoking?

“Our finding that the circuit linked with severity of dependence was unresponsive to a nicotine replacement dose is quite provocative,” says Dr. Hong. “It may

NICOTINE ADDICTION LINKED WITH WEAK COMMUNICATION IN CIRCUIT Smokers with greater dependence on nicotine, as evidenced by higher scores on the Fagerström Test for Nicotine Dependence (FTND), demonstrated weaker communication in a brain circuit connecting the dorsal anterior cingulate cortex (dACC) and the striatum. Communication strength was similar with and without a nicotine patch, suggesting that this circuit is unresponsive to the medication.



be one reason why nicotine replacement therapies do not have overwhelming success at helping people quit.”

A PATHWAY FOR RISK

In a second study, the Maryland team produced evidence that a gene variant that increases the risk for smoking dependence does so, in part, by weakening the dACC–striatum resting-state circuit. The researchers also implicated the circuit in the increased susceptibility to smoking addiction seen among individuals with certain mental illnesses.

The 184 adult participants who underwent fMRI in this study included smokers, nonsmokers, and ex-smokers. The researchers determined each participant’s genotype for the $\alpha 5$ subunit of the nicotinic acetylcholine receptor (nAChR). The $\alpha 5$ subunit is abundant in the cingulate, ventral striatum, and extended amygdala areas, and one of its variants—designated rs16969968—increases the risk for smoking dependence.

The $\alpha 5$ risk variant was associated

SEEING THE CONNECTIONS: 20 RESTING-STATE CIRCUITS REVEALED Resting-state functional magnetic resonance imaging (R-fMRI) shows brain circuits that can be identified when people are alert but not doing any particular task. Analyses of scans from more than 1,000 healthy adults revealed 20 resting-state brain networks. Each one is shown here in coronal, sagittal, and transverse views. The colors in these composite images show the statistical robustness of these patterns in each brain region, with yellow indicating the greatest statistical significance; orange, an intermediate level; and red, the least. From the supplement to *Proceedings of the National Academy of Sciences* 107(10): 4734-4739, 2010.



with decreased strength in the dACC-striatum circuit among both smokers and nonsmokers. Among smokers, the circuit influenced vulnerability to smoking dependence more strongly than the gene variant. “Decreased strength in the dACC-striatum brain circuit explained approximately 10 to 12 percent of the differences in nicotine dependence among smokers,” Dr. Hong says. “In contrast, genotype alone accounted for only 1 to 4 percent.” These results suggest that the $\alpha 5$ risk variant interacts with other genes or environmental factors to weaken the circuit and increase vulnerability.

Among the participants in this study were 76 individuals with mental disorders including schizophrenia, substance dependence, and anxiety and depressive

disorders. This group had weaker dACC-striatum circuit strength and higher smoking rates than participants without mental disorders. They were not more likely to have the high-risk $\alpha 5$ gene variant, however, suggesting that other genes or other factors underlie the relative weakness in their circuitry. One possibility is that as-yet-unidentified gene variants may simultaneously predispose certain individuals to mental illness and disrupt the circuit.

“These findings are important because they change the way scientists think about nicotine’s influence on the brain and provoke many new hypotheses for future imaging research,” says Dr. Steven Grant of NIDA’s Division of Clinical Neuroscience and Behavioral

Research. For example, he says, researchers might test whether behavioral therapy or other smoking cessation treatments strengthen the connection and whether the strength of the circuit increases over time with abstinence.

MAPPING THE BRAIN’S FUNCTIONAL CIRCUITS

In addition to investigating the involvement of specific brain pathways in disorders, scientists are striving to achieve an overall understanding of brain circuitry and its functioning. Two projects exemplify different approaches to accumulating and organizing the extensive data needed to develop brain maps and test hypotheses. One, the 1000 Functional Connectomes Project (FCP),

applies a community-wide data-sharing effort among neuroscientists that took its inspiration from the 1000 Genomes Project that helped map the human genome. The other, the Human Connectome Project (HCP), is a prospective in-depth investigation of 1,200 individuals that will also be widely shared with the scientific community.

“The 1000 FCP takes a discovery-science approach, capturing many neural networks that researchers examine in specialized studies. The HCP drills down to provide the rigorous details of brain circuitry,” says Dr. Grant. “Brain science will benefit from both types of projects.”

The 1000 Functional Connectomes Project

In the 1000 FCP, scientists from around the world deposited previously collected resting-state brain scan data into an open-access database (http://fcon_1000.projects.nitrc.org). In what is, at times, a competitive research environment, these investigators agreed to make their data freely available because they recognized the value that a large-scale repository offers to the neuroscience community. The project has accumulated resting-state brain scan data from more than 1,400 study participants scanned at 35 neuroimaging centers.

Any investigator can download data from the ever-expanding collection and use it to search for resting-state pathways or test hypotheses about how the brain works. To date, researchers have downloaded data from the project’s Web site more than 38,000 times.

In an initial paper announcing the 1000 FCP, contributing researchers described 20 functional networks that were identified by analyzing brain scans of 1,093 individuals at 24 imaging centers. The group included NIDA-funded researcher and 1000 FCP project advisor Dr. F. Xavier Castellanos of New York University (NYU) and project

co-founders Drs. Michael P. Milham of NYU and Bharat B. Biswal of New Jersey Medical School.

“The full number of functional networks remains to be seen—estimates range up to several hundred, depending upon the criteria and approaches used to define them,” says Dr. Milham. The 20 circuits identified by the team (see graphic, page 16) were consistently present in both males and females regardless of age, but some varied in strength depending on gender and age. Other researchers have

also noted variations in the strength of certain circuits, which may be clues to differences in behaviors.

“The team’s observation of distinct functional networks indicates that there is a fundamental organizational principle to the brain that all humans share,” says Dr. Grant.

Dr. Castellanos says that neuroscientists participating in the 1000 FCP also plan to build brain scan repositories for two critical populations—youths and people with psychiatric disorders. Drs. Mil-

BRAIN MAPPING ACROSS THE DECADES

Since the mid-to-late 1970s, neuroscientists have used structural magnetic resonance imaging (MRI) and other techniques to map the brain’s anatomical structures. But anatomy does not provide a complete picture of how the brain works.

The early 1990s saw the advent of functional MRI (fMRI), which maps changes in brain activity rather than anatomy. In a typical fMRI experiment, scientists scan the brain while a study participant experiences particular stimuli or performs assigned mental tasks. Such studies have identified brain circuits that underlie specific behaviors and has provided pieces of the functional map, also known as the functional connectome.

Before 2001, most scientists doing fMRI experiments ignored so-called deactivations—the tendency for some brain regions to become less active when participants switch from rest to performing a task. However, Dr. Marcus E. Raichle and colleagues at the Washington University School of Medicine in St. Louis noted that a pattern of consistent deactivations could be identified during almost any task and that the brain consumes a great deal of energy whether or not individuals are performing specific tasks. Using a technique called resting-state functional MRI, Dr. Raichle and other neuroscientists discovered that when the brain is at rest, its activity patterns are not random. Analysis of its synchronized activity patterns has begun to reveal the brain’s overall functional organization.

SOURCE

Raichle, M.E. A paradigm shift in functional brain imaging. *Journal of Neuroscience* 29(41):12729–12734, 2009.

ham and Castellanos and their colleagues at the Nathan Kline Institute for Psychiatric Research have also provided an open dataset of 207 individuals. It includes a range of brain imaging measures and an extensive set of behavioral information—including psychiatric interviews, exercise fitness, metabolic measures, and the amount of food eaten in a controlled meal. These data, from individuals aged 6 to 85, most of whom are free of psychiatric diagnoses, are available to scientists at http://fcon_1000.projects.nitrc.org/indi/pro/nki.html.

“The 1000 FCP has achieved a huge normative brain imaging dataset at a relatively low cost because scientists volunteered to share data and work together,” says Dr. James Bjork of NIDA’s Division of Clinical Neuroscience and Behavioral Research. “If this spirit of collaboration takes hold in sub-areas of neuroimaging—among the many research groups studying depression, for example—many discoveries will be possible.”

The Human Connectome Project

The National Institutes of Health Blueprint for Neuroscience Research is sponsoring the HCP, which will map the neural circuitry of the normal adult brain using a battery of cutting-edge and traditional techniques. According to the HCP Web site, the project’s goal is an unparalleled compilation of neural data and an interface to “navigate the brain in a way that was never

before possible; fly through major brain pathways, compare essential circuits, zoom into a region to explore the cells that comprise it and the functions that depend on it.”

Starting in 2012, HCP scientists will perform high-resolution resting-state fMRI and diffusion imaging on 1,200 healthy adults. To make possible studies of the heritability of brain circuits and their associated traits, the study population will include 300 twin pairs and their siblings. Some study participants will also undergo traditional fMRI, which documents brain changes during the performance of tasks, and magneto/electroencephalography. The images obtained will be made freely available to researchers, along with the study participants’ genotypes and results on tests of sensory, motor, and cognitive function. A supercomputer and a user-friendly toolbox of advanced computer programs will be available for researchers who wish to use the resulting vast datasets to answer questions about brain structure and function.

The foundational work for the HCP is being conducted by consortiums between the University of California, Los Angeles, and Massachusetts General Hospital, and between Washington University, St. Louis, and the University of Minnesota, Twin Cities. Information on the current status and future plans can be found at <http://www.humanconnectomeproject.org/> and <http://humanconnectome.org>.

FUTURE CLINICAL TOOLS

“The brain maps that ultimately will

arise from repositories that combine imaging and behavioral information will be very useful to clinicians,” says Dr. Castellanos. As a pediatric psychiatrist, he anticipates someday using maps of typical brain development, just as clinicians use physical growth charts, to assess children’s progress and catch problems early.

Dr. Castellanos predicts that psychiatrists may eventually use brain scans in diagnosing mental disorders, just as cardiologists use electrocardiograms in diagnosing heart disease. “Current psychiatric diagnosis is based on symptoms, but different causes and underlying circuits can produce the same or similar symptoms. Brain maps can greatly advance the identification of particular mechanisms underlying neuropsychiatric disorders,” Dr. Castellanos says. Brain maps could also provide a basis for tracking the effects of interventions, thereby speeding the development of evidence-based preventive measures and treatments targeting drug addiction and other mental illnesses. ■

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NIDA Research Report on Marijuana Abuse

This updated NIDA report contains scientific information on the scope, effects, and consequences of marijuana abuse.

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NIDA Recognizes Developer of a New Business Model for Science



Dr. Redonna K. Chandler, recipient of NIDA's 2011 Innovator Award.

Dr. Redonna K. Chandler, chief of NIDA's Services Research Branch in the Division of Epidemiology, Services and Prevention Research, is the recipient of the Institute's 2011 Innovator Award. Dr. Chandler recognized that

independent research projects within the Seek, Test, and Treat in Criminal Justice Populations initiative focused on HIV would yield more information if their findings could be examined as a whole. She envisioned an integrated dataset and developed a collaborative method with NIDA-funded researchers to achieve such a resource. The Institute is now replicating the process with an international research initiative on the Seek, Test, and Treat approach to prevent HIV among vulnerable populations.

With an integrated dataset, information is comparable across independent projects so that "the whole is greater than the

sum of its parts," according to Dr. Chandler. For example, an integrated dataset allows analyses of outcomes from subpopulations, whereas each separate study would not have enough participants to provide robust findings. Researchers can also determine whether results are similar across different studies, potentially quickening the pace of replication of findings and contributing valuable information on the best ways to prevent HIV.

To develop such a resource, the projects must use similar data collection methods. The researchers had already designed their studies when they applied for funding and had not anticipated aggregating their data. After agreeing to participate in harmonization activities, the investigators were brought together for a meeting. "At these meetings, Dr. Chandler showed tremendous skill in helping the group reach consensus around data strategies," says Dr. Wilson Compton, who nominated Dr. Chandler for the award. "The result is that the separate grants have a degree of coordination and collaboration that is rarely seen. The resulting data will be much better for full-scale modeling of HIV-transmission and HIV-prevention studies."

"I enjoy working with people who are at the top of the field and facilitating collaboration and creativity among them," says Dr. Chandler. "The scientists involved in this effort saw that working together will greatly advance HIV research, as did the many NIDA colleagues who also worked to achieve this method of coordinating data." ■

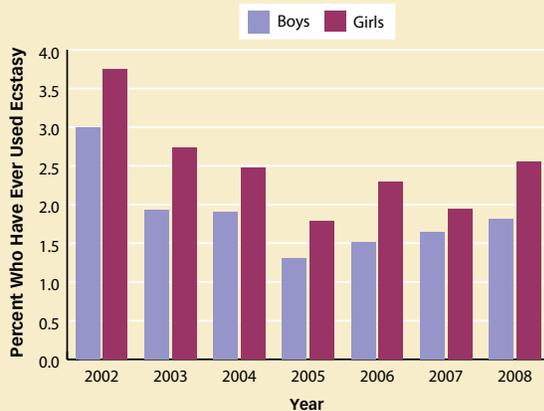
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Girls More Likely Than Boys to Use Ecstasy



From 2002 through 2008, among adolescents aged 12 to 17, girls' rates of lifetime ecstasy use were higher than boys'. This pattern contrasts with that for marijuana, which boys used in higher percentages than girls during this period. The higher prevalence of ecstasy use among girls persisted when the researchers separated out the effects of household income, ethnicity, and population density of youths' areas of residence. The researchers analyzed annual data from the National Survey on Drug Use and Health. The number of adolescents who participated varied by year and ranged from 17,429 to 19,430.

Source: Wu, P., et al. Ecstasy use among U.S. adolescents from 1999 to 2008. *Drug and Alcohol Dependence* 112(1-2):33-38, 2010.

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