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WHY CAN'T I FORGET MY LAST FIX? NEW RESEARCH REPORTS ON KEY BIOLOGICAL CHALLENGES TO TREATING ADDICTION

Addictive drugs prey on impulsivity, hijack emotional and cognitive centers of the brain and brain processes like learning and memory

Washington, DC — A new study reported today finds that high levels of innate impulsiveness play a major role in triggering drug addiction relapse in rats, and suggests that current medications used to reduce impulsivity, such as those for hyperactivity disorders, may be useful in preventing drug addiction relapse. The study was released at Neuroscience 2008, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news on brain science and health. It was presented during a discussion of the biological underpinnings of addictive behaviors and the powerful effects of addictive drugs on brain systems involved in emotions, insight, and learning and memory. Advances in understanding the biology of addiction are helping to identify new, more effective treatment options.

New findings show that:

- Innately impulsive rats show increased rates of drug relapse. A nonstimulant drug used to treat attention-deficit hyperactivity disorder in humans reduced relapse behaviors in highly impulsive rats (Daina Economidou, abstract 214.5, see attached summary).

In addition, researchers discussed related findings demonstrating that:

- Addicts' brains react emotionally to drug-related images before such images are recognized by the conscious brain (see attached speaker's summary).
- Drugs hijack brain regions responsible for weighing the salience, incentive, and motivational aspects of reward (see attached speaker's summary).
- Drug addiction, like schizophrenia and other mental disorders, impairs insight. Because drug addicts and patients suffering from these mental illnesses tend to have impairments in similar brain regions, specific brain dysfunction may cause the impaired insight into illness in drug addiction (see attached speaker's summary).
- The addictive drug morphine blocks a new form of synaptic plasticity — the cellular building block of learning and memory — in a region of the brain important in drug addiction. In this way, morphine may upset the balance of communication in reward pathways of the brain, potentially contributing to early stages of addiction (see attached speaker's summary).

"Cells in the brain communicate using both electrical and chemical signals, and drugs of addiction can interfere and alter those channels of communication, producing lasting changes and behavioral problems," said press conference moderator Robert Malenka, MD, PhD, of Stanford University School of Medicine. "Research is helping us gain key insight into potential treatment options for addiction, which is complex because it taps into multiple biological and psychological systems."

Malenka is on advisory boards of Pfizer and Seaside Therapeutics.

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Related Presentations:

Symposium: **Functional Neuroimaging Evidence for a Brain Network Underlying Impaired Insight Into Illness in Drug Addiction**
Sunday, November 16, 8:30–11 a.m., Washington Convention Center, Ballroom B

Special Lecture: **Neural Mechanisms of Cortical Dysfunction in Addiction: Consequence or Cause of Compulsive Behavior**
Monday, November 17, 11:30 a.m.–12:30 p.m., Washington Convention Center, Hall D

Special Lecture: **Synaptic Plasticity: The Control of Inhibitory Circuits**
Tuesday, November 18, 10–11 a.m., Washington Convention Center, Hall D

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Abstract 214.5 Summary

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Cambridge, United Kingdom

Study Links Cocaine Relapse to Impulsive Behavior Trait

Finding suggests a new, more effective strategy for treating cocaine addiction

Cocaine addiction is a notoriously difficult habit to "kick." Relapse is common, in large part because exposure to cocaine-associated people, places, or things can easily trigger overwhelmingly memory-based cravings for the drug, even after a long period of abstinence.

New animal research now suggests that impulsivity, a behavior trait recently found to be associated with the development of cocaine addiction, may play a major role in triggering a relapse as well. The research, carried out by Barry Everitt, PhD, and colleagues of the University of Cambridge also suggests that a medication currently used to reduce impulsive behavior may one day prove useful in preventing drug addiction. The findings were released at Neuroscience 2008, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

For these studies, Everitt and his colleagues selected rats for high- or low-impulsive behavior. (High-impulsive-behavior animals choose small, immediate rewards over large, delayed ones.) The animals were taught to take cocaine and then to cease its use voluntarily. After a period of abstinence, the rats were reintroduced to cocaine-associated environmental cues.

"We found that the high-impulsive animals were significantly more likely to relapse than the low-impulsive ones," said Everitt. The researchers then treated the animals with atomoxetine, a drug that reduces impulsive behavior and that is used to treat attention-deficit hyperactivity disorder (ADHD). Relapses among the treated animals fell significantly.

"These experiments present new potential strategies for preventing drug use and relapse," Everitt said.

The research was supported by the British Medical Research Council.

Scientific Presentation: Sunday, November 16, 2–2:15 p.m., Washington Convention Center, Room 149A

214.5, Relapse to cocaine seeking after extended access is predicted by trait impulsivity
D. ECONOMIDOU, J. W. DALLEY, Y. PELLOUX, T. W. ROBBINS, *B. J. EVERITT; Dept Exp Psychol, Univ. Cambridge, Cambridge CB2-3EB, United Kingdom

TECHNICAL ABSTRACT: Relapse to compulsive drug use after periods of abstinence is both a key feature of drug addiction and a challenge for treatment strategies. Therefore, it is important to develop effective animal models of relapse and identify factors that influence relapse behaviour, in order to provide promising future treatment targets.
Our recent work showed that impulsivity is highly predictive of excessive cocaine taking in rats. In the present study, we evaluated whether rats impulsive in a 5-choice serial reaction time task (5-CSRTT) show a higher propensity to relapse for cocaine seeking after abstinence induced by intermittent punishment of the drug seeking response. Following 5-CSRTT screening, high (HI) and low impulsive (LI) rats were trained to self-administer cocaine (0.25 mg/infusion) under a seeking-taking schedule: pressing the seeking lever (RI-120s) resulted in presentation of the taking lever which, when pressed (FR-1), resulted in delivery of cocaine and 5 s illumination of a cue light. A 10 min timeout period followed completion of each seeking-taking cycle. In addition, as a measure of nonspecific behaviour, throughout each 2 h session animals had free access to 20% sucrose contingent on magazine nose poking. After stable performance was achieved, punishment contingencies were introduced: completion of the seeking link resulted (randomly) in either presentation of the taking lever or a mild foot-shock. During this phase (8 days) animals significantly decreased cocaine seeking. Relapse, was assessed 7 days after the last punishment day in an extinction session in which all stimuli, levers and chains where the same, but there was no delivery of cocaine, shock or sucrose. After a short period of cocaine taking, HI rats tended to relapse at slightly higher rates than LI rats. However, after extended access to cocaine self-administration (6 h/day, 12 days), HI rats showed a significantly increased propensity to relapse compared to LI rats. The results, suggest that relapse to cocaine seeking may depend upon previous negative experiences and that impulsivity may be an important factor influencing this behaviour, especially after extended drug access. In addition, in preliminary experiments we showed that treatment with the selective noradrenaline reuptake inhibitor, atomoxetine, a drug known to reduce impulsivity, may also be beneficial in attenuating relapse to cocaine seeking.

Speaker's Summary

Speaker: Anna Childress, PhD **(215) 222-3200**
University of Pennsylvania School of Medicine **childress_a@mail.trc.upenn.edu**
Philadelphia, Pa.

Struggling Against the "Unseen": Limbic Vulnerability to Drug Reward Cues Outside Awareness
(104.5)
Symposium: Functional Neuroimaging Evidence for a Brain Network Underlying Impaired Insight Into Illness in Drug Addiction
Sunday, November 16, 10:20–10:55 a.m., Washington Convention Center, Ballroom B

Using a brain imaging technology called functional magnetic resonance imaging (fMRI), scientists have discovered that cocaine-related images trigger the emotional centers of the brains of patients addicted to drugs — even when the subjects are unaware they've seen anything. The study, published Jan. 30 in the journal *PLoS One*, was funded by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health (NIH).

A team of researchers at the University of Pennsylvania, led by Dr. Anna Rose Childress and Dr. Charles O'Brien, showed cocaine patients photos of drug-related cues like crack pipes and chunks of cocaine. The images flashed by in just 33 milliseconds — so quickly that the patients were not consciously aware of seeing them. Nonetheless, the unseen images stimulated activity in the limbic system, a brain network involved in emotion and reward, which has been implicated in drug-seeking and craving.

"This is the first evidence that cues outside one's awareness can trigger rapid activation of the circuits driving drug-seeking behavior," said NIDA director Dr. Nora Volkow. "Patients often can't pinpoint when or why they start craving drugs. Understanding how the brain initiates that overwhelming desire for drugs is essential to treating addiction."

To verify that the patterns of brain activity triggered by the subconscious cues reflected the patients' feelings about drugs, Childress and her colleagues gave the patients a different test two days later, allowing them to look longer at the drug images. The patients who demonstrated the strongest brain response to unseen cues in the fMRI experiment also felt the strongest positive association with visible drug cues. Childress notes, "It's striking that the way people feel about these drug-related images is accurately predicted by how strongly their brains respond within just 33 milliseconds."

Childress and her colleagues also found that the regions of the brain activated by drug images overlapped substantially with those activated by sexual images. This finding supports the scientific consensus that addictive drugs usurp brain regions that recognize natural rewards needed for survival, like food and sex. According to Childress, these results could improve drug treatment strategies. "We have a brain hard-wired to appreciate rewards, and cocaine and other drugs of abuse latch onto this system. We are looking at the potential for new medications that reduce the brain's sensitivity to these conditioned drug cues and would give patients a fighting chance to manage their urges."

Speaker's Summary

Speaker: Jane Taylor, PhD **(203) 974-7727**
Yale University School of Medicine **Jane.Taylor@yale.edu**
New Haven, Conn.

Special Lecture: **Neural Mechanisms of Cortical Dysfunction in Addiction: Consequence or Cause of Compulsive Behavior**

Monday, November 17, 11:30 a.m.–12:30 p.m., Washington Convention Center, Hall D

Addiction is a progressive and chronic relapsing disorder where drug craving and relapse to drug-seeking and taking behavior persist even after long periods of abstinence. Substantial evidence now points to widespread dysfunction of brain dopamine function and/or alterations of dopamine-regulated signaling molecules in circuits involved in learning and memory processes. We have found multiple neuroadaptations in regions of the prefrontal cortex that regulate salience, incentive and motivational properties of rewards. Historically recidivism was theorized to be attributable to heightened incentive processing of drugs and/or drug-associated cues, or to avoid dysphoria during abstinence, with a focus on dysfunction of regions such as the basal ganglia (notably the nucleus accumbens) and amygdala. We originally hypothesized that addiction should be viewed as a disorder of cognitive control (i.e., poor decision-making, choice selection and inability to inhibit drug intake), secondary to changes in prefrontal cortical regions, that encompass and regulate learning and memory.

Our data now show that addictive drugs produce long-lasting dysfunction in cortico-limbic-striatal function, resulting in a combination of aberrant enhancements in the limbic-striatal dopamine motivation system and deficits in inhibitory (or impulsive) response control functions that are dependent on prefrontal-executive functions. Together these changes are argued to underlie the development of compulsive behavior. In primates we showed that prior repeated exposure to cocaine produces persistent cognitive and motivational deficits that are dependent on the orbitofrontal region of the prefrontal cortex that are associated with alterations in synaptic protein expression. In particular, several transcription factors that regulate dopamine neurotransmission and a host of plasticity-associated molecules known to be involved in diverse learning and memory processes were found to be changed. Such alterations in cortical regions are important because an inability to modulate changes in reward-motivated behaviors may increase the motivational significance of cues, contributes to relapse and to difficulties in inhibiting drug-associated thoughts and behaviors. Indeed, it was previously known that addicts exhibit both greater cognitive impulsivity and dysfunctions in brain regions associated with impulse control compared to non-addicts. Together, this has led to much evidence in support of the hypothesis that chronic drug use increases impulsivity that promotes further drug use, ultimately resulting in compulsive, and habitual, drug-taking and drug-seeking behavior. Newer evidence suggests that vulnerability factors that relate to inhibitory response control and drug exposure interact to produce an addicted state. We hypothesize the level of function in the orbitofrontal region of the prefrontal cortical prior to cocaine exposures may also predict the extent of cocaine-induced dysfunction in this region. While the interaction between pre-existing neurobiological differences and drug-exposure may be a determining factor in addiction there is the potential to modify prefrontal cortical and regulated circuitry in order to promote abstinence. New evidence suggests that even in animals that meet diagnostic criteria for addiction, manipulating specific mnemonic processes can reduce the ability of drug-associated memories to produce relapse and drug-seeking behavior. Treatments for addiction that include altering motivational systems, enhancing self-control, altering memory consolidation, reconsolidation and extinction processes to promote brain plasticity are currently being studied, and offer exciting future therapeutic approaches for addiction.

Of the many processes implicated in addiction, the impact of learning and memory processes has recently received considerable attention because environmental cues associated with addictive drugs come through learning processes to evoke salient and pervasive memories of drug experiences. These memories can

induce both drug craving and relapse and are thought to be major factors in addiction. Understanding why it is so hard for addicts to “forget their last fix”, will require pairing rapidly evolving technologies with sophisticated behavioral measurements to elucidate the changes that occur in the brains of addicts. Additionally, we need to understand how pre-existing individual differences in cognitive processes, such as self-control, decision-making and executive functions, and their regulation of more basic reward-related biological drives, contribute to altered learning and memory processes that may underlie the development of addiction.

Addiction involves a highly complex interplay between a diverse and interacting array of biological and environmental factors. These include both pre-existing vulnerability factors and the effects of drug-exposure that together cause a pathological subversion of neuronal systems resulting in compulsive drug-seeking and drug-taking behavior. Strategies for the prevention and treatment of addiction may therefore require an integrated approach at a systems level of analysis that spans from the molecular to the social.

Speaker's Summary

Speaker: Rita Goldstein, PhD **(631) 344-2657**
Brookhaven National Laboratory **rgoldstein@bnl.gov**
Upton, N.Y.

Symposium: **Functional Neuroimaging Evidence for a Brain Network Underlying Impaired Insight Into Illness in Drug Addiction** (104)
Sunday, November 16, 8:30–11 a.m., Washington Convention Center, Ballroom B

Drug abusers are often characterized as being in "denial" — not recognizing the severity of their disorder. Although "denial" is often considered to be a form of deception, emerging research suggests that it may be due to a specific brain dysfunction similar to that observed in other neuropsychiatric illnesses.

Scientists from a variety of fields will present relevant research during a symposium on "Impaired Insight into Illness in Drug Addiction" at the Society for Neuroscience annual meeting in Washington, D.C., November 16, 8:30–11 a.m., Washington Convention Center, Ballroom B. Rita Z. Goldstein, a psychologist who leads the neuropsychoimaging group at the U.S. Department of Energy's Brookhaven National Laboratory, will chair this symposium along with Steve Grant of the National Institute on Drug Abuse as co-Chair.

"Patients suffering from mental illnesses such as schizophrenia often have compromised awareness and affective responsiveness to having a mental illness," Goldstein said. This 'insight deficit' appears to originate from impairments in many of the same brain regions (the prefrontal and parietal cortices, insula cortex, and subcortical areas such as the amygdala) that underlie addiction symptoms — such as continued drug use despite catastrophic consequences and even when the drug is no longer pleasurable. "It is therefore possible that these core clinical addiction symptoms (craving, compulsion), and the chronic relapsing nature of addiction, may be a consequence of compromised insight into illness," Goldstein said.

Such impaired insight might account for drug-addicted patients' compromised acceptance/acknowledgment of addiction signs and symptoms and their lack of perceived need for treatment. It could also explain these patients' tendency to not comply fully with treatment regimens — or to relapse.

"Deficits in insight and the interrelated interoception and emotional awareness have largely been ignored in the field of addiction, despite the fact that this disorder is now recognized as a 'disease of the brain,' amenable to intervention and treatment," Goldstein said. "My hope is that this symposium will help bridge this gap and contribute to the design of new diagnostic tools and treatment approaches, pointing us toward more effective intervention strategies to improve prognosis in this illness."

The SfN symposium was organized by Goldstein and Grant to: define insight into illness specifically vis-à-vis drug addiction; review functional neuroimaging and neuropsychological evidence of the extent of impaired self-awareness and insight deficits in addiction; and highlight impaired insight into illness as a hallmark of drug addiction.

In addition to Goldstein and Grant, participants include:
• A. D. (Bud) Craig, Atkinson Research Laboratory, Barrow Neurological Institute, will discuss the role of the insula in insight and interoception in healthy states and in psychopathology.
• Antoine Bechara, The University of Southern California, will discuss the role of the insula and prefrontal cortex in impaired awareness of nicotine craving and concern about the potential long-term consequences in cigarette smoking.

• Hugh Garavan, School of Psychology & Institute of Neuroscience, Trinity College, Dublin, will discuss the role of the anterior cingulate cortex in blunted awareness to errors and compromised behavioral and situational monitoring in cocaine addiction, compromises that could precipitate excessive, unintended use or relapse.
• Anna Rose Childress, Department of Psychiatry, University of Pennsylvania School of Medicine, will discuss the role of subcortical regions (striatum, amygdala) in response to drug-related stimuli that, even when outside of conscious awareness, can predict emotional reactions and behavior in drug addiction.
• Nora D. Volkow, Director, National Institute on Drug Abuse, will serve as a discussant to summarize and draw connections between these research areas.

Speaker's Summary

Speaker: Julie Kauer, PhD **(401) 863-9083**
Brown University **Julie_Kauer@brown.edu**
Providence, R.I.

Special Lecture: **Synaptic Plasticity: The Control of Inhibitory Circuits**
Tuesday, November 18, 10–11 a.m., Washington Convention Center, Hall D

An influential hypothesis is that addiction represents a pathological yet powerful form of learning and memory. Strong evidence supports the idea that during learning, the connections between neurons (synapses) are strengthened or weakened in particular patterns that the brain translates into the storage of a memory. These changes in synapse strength are known as synaptic plasticity, and the two best-studied forms are long-term potentiation (LTP) and long-term depression (LTD). Intriguingly, in parts of the brain that are important for survival drives and reward, drugs of abuse appear to drive similar changes in synaptic strength. In the work to be presented at this meeting, we will show that brief exposure to the addictive opiate drug, morphine, entirely blocks a new form of synaptic plasticity in a region of the brain known to be required for drug addiction. Much of this work was published in the journal, *Nature*. Although the brain circuitry underlying addiction is complex, it is clear that the mesolimbic dopamine system, consisting of the ventral tegmental area (VTA) and nucleus accumbens (NAc) are essential regions for the neural adaptations that underlie addiction. Interactions between addictive drugs and synaptic plasticity in different brain regions are thought to contribute to specific aspects of addiction, including craving, withdrawal and relapse. The brain contains both excitatory and inhibitory synapses, both of which are necessary components of normal brain functioning. Inhibitory synapses, which release the neurotransmitter, GABA, are essential for normal activity in the VTA, as suggested by the fact that blocking inhibitory GABA receptors strongly increases the cell firing rate both in vivo and in brain slices from this area. Thus plasticity of GABAergic synapses could have a profound influence on the function of VTA neurons. The work of others showed previously that when animals were exposed to cocaine (5-7 daily injections) the GABA receptor-mediated inhibitory output onto VTA neurons decreased.

Although excitatory brain synapses are strengthened or weakened in response to specific patterns of synaptic activation (during LTP and LTD, for example), there are few examples of synaptic plasticity of fast GABAergic synapses. Here we report LTP of GABA-mediated synaptic transmission onto dopamine neurons of the VTA, the brain region required for the development of drug addiction and the normal processing of salient environmental stimuli. This novel form of LTPGABA is is entirely absent after either in vitro or in vivo treatment of rats with the opioid drug, morphine, given 24 hours earlier. This neural adaptation far outlasts the presence of morphine in the brain, and thus represents a persistent drug-induced alteration in VTA circuit function. The loss of LTPGABA is due to an opioid receptor-mediated disruption of the coupling between specific signaling molecules in the VTA. Together specific experiments suggest that a single in vivo exposure to morphine either causes a loss of the enzyme, guanylate cyclase, from nerve terminals that release the inhibitory transmitter, GABA, or renders guanylate cyclase insensitive to the signaling molecule, nitric oxide. This loss of LTPGABA is expected to increase the firing rate of VTA neurons (a common feature known to occur following exposure to multiple drugs of abuse). Restoration of guanylate cyclase function may represent an avenue that might be exploited to rescue or prevent loss of normal inhibition after opiate exposure. In summary, LTPGABA represents a novel cellular mechanism capable of balancing the strengthening of excitatory synapses with strengthening of nearby inhibitory synapses, and may be important for maintaining neuronal firing rates within a normal range. Opioid drugs will upset the balance, favoring increased firing rates of dopamine neurons, and potentially contributing to the early stages of addiction.