Collaborative Research

Dopamine Across Divides

Harriet de Wit, Professor of Psychiatry and Director of the Human Behavioral Pharmacology Lab at the University of Chicago, explains different approaches to researching dopamine in the context of her work.

Dopamine, a critical neurotransmitter central to physical and mental wellness in both animal and humans, is the subject of a comprehensive research program conducted by Harriet de Wit, Director of the Human Behavioral Pharmacology Lab at the University of Chicago. Looking at dopamine in new ways has yielded a more comprehensive understanding of its role in brain function.

"Dopamine was initially thought of as a cause of hedonia. It was supposed to produce a feeling of well-being or stimulate the pleasure center of the brain. We are finding that this may not be the case, and we are finding new and better ways of studying its effects," explains de Wit.

De Wit studies drugs' effects on behavior, mood, and decision-making with healthy human volunteers. Understanding dopamine is a central component of understanding how drugs impact the brain, why people take drugs, and how different interventions might be structured. Answering these questions requires the use of many different research methods, and fosters critical connections across diverse kinds of research.

Understanding Dopamine

Contrary to earlier conclusions about dopamine's role in generating feelings of well-being, recent research establishes an intricate framework for the role of the neurotransmitter in the brain.

"Recently, people are thinking that dopamine acts on other, more cognitive processes (such as learning processes) and how environmental cues are associated with feeling states or motivational systems. The central question in drug abuse research remains: What is it that dopamine does?" says de Wit.

One study, currently conducted by de Wit and colleagues, attempts to understand this question through the study of MDMA, ±3,4-methylenedioxymethamphetamine, also known as ecstasy. Ecstasy is widely used as a street drug and also used as a pharmacological aid during psychotherapy. This drug is thought to increase feelings of empathy and closeness to others, so-called 'empathogenic' effects on social and emotional processing. Ecstasy acts on neurotransmitter systems, including serotonin and dopamine systems.

De Wit explains, "Traditionally, we have studied the direct mood and behavioral effects of drugs that act on dopamine. These are called agonists or antagonists, drugs that stimulate or suppress the dopamine system. But our ideas of what drugs do, and therefore, what dopamine does, have evolved over time. The alternative is to think, 'Could these drugs be acting on the interface between environmental stimuli and the individual? Could they be changing how a person responds to environmental stimuli?'"

In their proposed study, the de Wit lab and collaborators will look more closely at how the drug ecstasy interacts with the environment and neurotransmitters.

In this study, healthy volunteers, who have used ecstasy in the past, will be tested using MDMA as well as the hormone oxytocin, which is known to affect social bonding. Participants will complete several tasks assessing their recognition of differently valenced emotions,

like fear, anger, and sadness. In a separate part of the study, Megin Wardle, a post-doctoral fellow in the laboratory, will measure subtle facial muscle movements that are indicators of positive and negative emotions. Participants will also be asked if they want to be with other people or if they would rather be alone.

"This project will potentially broaden our perspective on how drugs interact with the social and emotional context in which they are used, and how these interactions influence vulnerability to repeated or compulsive use of these drugs," explains de Wit.

Translational research: Animals and Humans

De Wit's studies facilitate the translation of animal research to human research. Through innovative research methods, de Wit and colleagues connect animal research on drug use to human research and help confirm that the conclusions of animal studies may have relevance in humans.

Animal studies have certain advantages. Studies with nonhuman subjects (such as rats and mice) use procedures that would be unlawful to perform on humans. In these studies, investigators can administer drugs that are not yet FDA approved or that might increase a person's chance to develop drug dependence. Also, nonhuman subjects are often used in genetic studies in which the animals are bred for specific characteristics. From these studies with animals, researchers have gained a great deal of knowledge about how drugs act on neurotransmitter systems and how brain structures are involved in drug addiction.

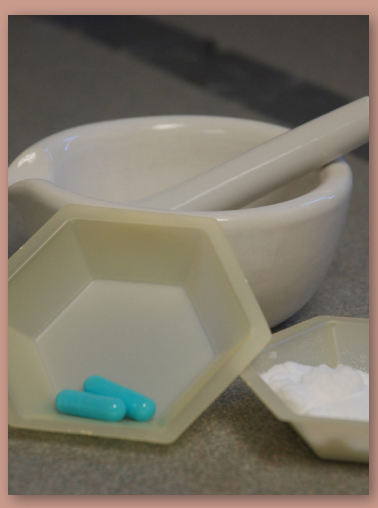
"I see our lab as a bridge between what can be done in animal behavioral studies and what might have applications in the real world of drug abuse. Part of our role is seeing whether the behavioral processes observed in animal studies also occur in studies with humans," says de Wit.

De Wit's lab has developed methods for making this key connection between animal and human studies and building knowledge of drug effects. In animal studies, conditioned place preference is commonly used to determine animals' preference for drugs. In this procedure, animals are placed in one chamber under the influence of a drug, and then in an adjacent chamber under the influence of saline or a placebo. After repeated

THE CENTRAL QUESTION IN DRUG ABUSE RESEARCH REMAINS: WHAT IS IT THAT DOPAMINE DOES?

HARRIET DE WIT

FEATURED PUBLICATION FROM THE DE WIT LAB



Bedi, G., Hyman, D., & de Wit, H. (2010)
Is Ecstasy an "Empathogen"? Effects of +/-3,4-Methylenedioxymethamphetamine on Prosocial Feelings and Identification of Emotional States in Others. *Biological Psychiatry.* Epub ahead of print.

Users of +/-3,4-methylenedioxymethamphetamine (MDMA), "ecstasy," report that the drug produces unusual psychological effects, including increased empathy and prosocial feelings. These "empathogenic" effects are cited as reasons for recreational ecstasy use and also form the basis for the proposed use of MDMA in psychotherapy. However, they have yet to be characterized in controlled studies. Here, we investigate effects of MDMA on an important social cognitive capacity, the identification of emotional expression in others, and on socially relevant mood states. Over four sessions, healthy ecstasy-using volunteers (n = 21) received MDMA (.75, 1.5 mg/kg), methamphetamine (METH) (20 mg), and placebo under double-blind, randomized conditions. They completed self-report ratings of relevant affective states and undertook tasks in which they identified emotions from images of faces, pictures of eyes, and vocal cues.MDMA (1.5 mg/kg) significantly increased ratings of feeling "loving" and "friendly", and MDMA (.75 mg/kg) increased "loneliness". Both MDMA (1.5 mg/kg) and METH increased "playfulness"; only METH increased "sociability". MDMA (1.5 mg/kg) robustly decreased accuracy of facial fear recognition relative to placebo.The drug MDMA increased "empathogenic" feelings but reduced accurate identification of threat-related facial emotional signals in others, findings consistent with increased social approach behavior rather than empathy. This effect of MDMA on social cognition has implications for both recreational and therapeutic use. In recreational users, acute drug effects might alter social risk-taking while intoxicated. Socioemotional processing alterations such as those documented here might underlie possible psychotherapeutic benefits of this drug; further investigation of such mechanisms could inform treatment design to maximize active components of MDMA-assisted psychotherapy.

LINKING ANIMAL AND HUMAN RESEARCH STRENGTHENS THE CONCLUSIONS OF BOTH INQUIRIES, AND PROVIDES A GREATER UNDERSTANDING OF HOW DRUGS WORK IN THE BRAIN.

pairings, the researchers remove the divider between the chambers, and animals have the opportunity to choose which chamber they prefer. Through this type of study, researchers have determined that animals prefer to be in the chamber with the drug. Coupled with an understanding of neurotransmitter levels, researchers are able to draw conclusions about how drugs affect the brain.

With collaborator Emma Childs, Assistant Professor of Psychiatry at the University of Chicago, de Wit has completed this type of study for the first time with humans. In this study, parallel to the animal procedure, two rooms were used. Participants received an amphetamine in one room and a placebo in another room. After several trials, the participants were asked which room they preferred. The researchers found that the participants preferred the room where they had received the amphetamine.

"We also found that, during the pairing trials, participants liked the room better if they liked the feeling of the drug more. It was completely consistent with findings from non humans and assumptions about the procedure. This helps to validate the findings of the researchers doing mouse and rat studies. It also helps the animal researchers to infer that the animals really are choosing the room with the drug because they 'like' the way the drug makes them feel," explains de Wit.

Linking animal and human research strengthens the conclusions of both inquiries, and provides a greater understanding of how drugs work in the brain.

Genetics and Dopamine

In addition to these research projects, de Wit's research on the genetic components of drug use offers another tool in understanding the role dopamine plays in the brain.

De Wit has also conducted recent studies with Abraham Palmer, Assistant Professor in the Department of Human Genetics at the University of Chicago, on the genetic basis of responses to drugs. With post-doctoral fellow, Ajna Hamidovic, the researchers gave a placebo and three different doses of methamphetamine to participants. Physiological measures, cognitive measures, and subjects' perception of the drugs' effects were assessed. In turn, the researchers also determined the individual participant's genotype as related to several different genes involved in dopamine function.

Using these methods, the researchers examined variations in the different genes involved in the effects of amphetamine, including the dopamine transporter system or in COMT (catechol-O-methyl transferase) an enzyme that breaks down dopamine. They also looked for variations in the gene for dopamine receptors (D2 and D4).

"In these genetic studies, we have a strong new tool to look at normal physiological variations in dopamine mechanisms across individuals, to see how those physiological variations influence responses. We can measure the magnitude of drug effect, anxiety, and how much they like the drug and look for genetic variations," explains de Wit.

Future Directions

As the neurocircuits involved in drug abuse and motivated behaviors overlap with those involved in social interactions and social bonding, research on the role of neurotransmitters is critical to our understanding of people's social world. As scientists learn more about these chemical processes new questions arise.

Explains de Wit, "For me, a lot of the questions are still very basic: Why do people take drugs? And what is it that drugs do uniquely in the brain that captivates that person's attention, memory, or feelings or becomes so compelling that use of the drug interferes with his or her life? In the end, we hope to answer those basic questions and improve people's lives." ■

LEFT: The de Wit lab.
BELOW: Harriet de Wit, Professor of Psychiatry at the University of Chicago.

RECENT PUBLICATIONS FROM THE DE WIT LAB

Hamidovic, A. & de Wit, H. (2009). Sleep deprivation increases smoking. *Pharmacology, Biochemistry and Behavior*, 93: 263-269.

Childs, E. & de Wit, H. (2009). Amphetamine-induced place preference in humans. *Biological Psychiatry,* 65: 900-904.

de Wit, H. (2009). Impulsivity as a determinant and consequence of drug use: A review of underlying processes. *Addiction Biology,* 1: 22-31.

Childs, E. & de Wit, H. (2009). Hormonal, cardiovascular and subjective responses to acute stress in smokers. *Psychopharmacology*, 203: 1-12.

Miczek, K.A. & de Wit, H. (2008). Challenges for translational psychopharmacology research: Some basic principles. *Psychopharmacology*, 199: 291-301.

Acheson, A. & de Wit, H. (2008). Bupropion improves attention but does not affect impulsive behavior in healthy men and women. *Journal of Experimental Clinical Psychopharmacology,* 16: 113-123.