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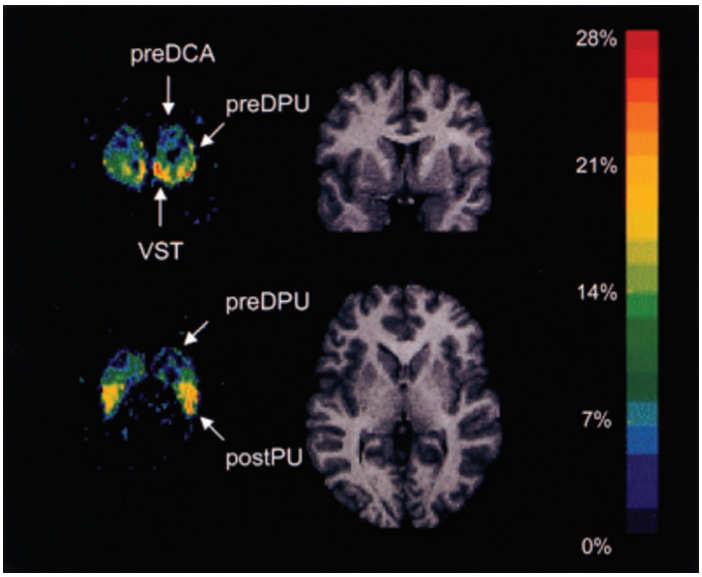
Uncovering the Genetic Roots of Drug Abuse



Above: Genes and brain regions that meditate drug sensitivity in humans all have counterparts in mice.

When it comes to risk factors for drug abuse, we're not all created equal, it seems.

Assistant Professor of Human Genetics Abraham Palmer's work with Psychiatry Professor Harriet de Wit and others has identified a variant of the gene Casein Kinase I Epsilon that is associated with a euphoric reaction to the drug amphetamine. Roughly 50 percent of people are thought to carry the variant (either in one chromosome or both), putting them at heightened risk for abusing the drug. The findings carry special import because of the broad therapeutic use of amphetamines and related drugs, which are prescribed for narcolepsy, attention deficit disorder, to keep military pilots alert on long-range missions, and other legitimate uses, along with their widespread illegal use. Since their publication in 2006, a 2008 study found that the same variant was significantly more common in a sample of heroin addicts versus a control group.

Scientists have long suspected that susceptibility to drug abuse has genetic underpinnings. Studies conducted decades ago found identical twins were more similar in their response to drugs than non-identical twins.

But Palmer and de Wit's research highlights the precision made possible by today's gene analysis techniques, plus the utility of computation in analyzing research results in novel and sophisticated ways. It also opens the door to detecting other genes that produce so-called "main effects" in drug responses. Scientists hope such discoveries will ultimately help them identify the whole networks of genes they suspect are implicated in people's different responses to drugs.

The findings sprang from Palmer's work with mice selectively bred to be highly-sensitive to methamphetamine. He discovered that these animals inherited a more active variant of Casein Kinase I Epsilon. Because the brain circuits governing motivation and reward are common across all mammals, Palmer hypothesized that the gene might hold clues for understanding genetic predisposition to drug abuse in humans.

Enter de Wit, who uses behavioral studies to identify risk factors for drug use. "Where my research fits in with Abraham's is that we're both interested in how people differ in their acute responses to drugs," she explains. Previously, de Wit had looked at gender and personality type—whether people are introverted or extroverted, for example—as factors in drug use. Genetics offered a powerful new tool in the quest to understand how people respond to drugs.

The two joined forces, securing a five-year, $1.25 million grant from the National Institutes of Drug Abuse to conduct studies that would generate a rich dataset on human behavior cross-referenced with genetic information mined by Palmer.

For the behavioral studies, de Wit recruited a cohort of healthy young people without a history of heavy drug use, mental illness, or heart issues. These volunteers received amphetamine or a placebo under controlled circumstances on several occasions. In each session, they were posed a set of standardized, quantitative questions designed to evaluate their subjective experience and assess their ability to perform tasks requiring impulse control and concentration. Palmer then analyzed the volunteers' DNA. They discovered a "remarkable concordance

of findings with what was found in the mice," relates de Wit, with the same variant of Casein Kinase I Epsilon disproportionately present in those who displayed the most pronounced positive reaction to amphetamine.

The research is ongoing and computational analysis will be key to parsing the data in fresh ways and flushing out previously unsuspected trends and relationships between observed behavior and genetic markers. To this end, Palmer is working with statistics faculty and tapping computational resources available under the Initiative in Biomedical Informatics.

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For de Wit, the research is inspiring and humbling. "I'm impressed by how complicated it is. We're selecting individual genes and tiny variations in those genes and somehow they end up resulting in variations in behavior. But behavior is such a complex thing, with so many variables, that it's like putting one drop at a time into a huge pool. The steps are small, but if we didn't take them we wouldn't make progress."

Above: Psychiatry Professor Harriet de Wit and Assistant Professor of Human Genetics Abraham Palmer are bringing behavioral studies and genetic analysis together to advance understanding of the risk factors for drug abuse.

For his part, Palmer is interested in pursuing research into the interrelationship between genes, drugs, and decision-making. "Decision-making is a critical question in drug abuse," he explains. "The problem is the person is seeking current reward at the expense of future consequences."

How genes interact with drugs and the environment, and how these factors together affect decision-making may also hold more general insights, he adds, into "how it is that some people are able to participate in modern society because they can value future rewards whereas others are possibly impaired in some way in doing that and suffer various adverse consequences."