Researchers identify brain network that is uniquely activated through injection vs. oral drug use

November 8 2023

Credit: CC0 Public Domain

Results from a new clinical trial suggest that a group of brain regions known as the "salience network" is activated after a drug is taken intravenously, but not when that same drug is taken orally.

When drugs enter the brain quickly, such as through injection or smoking, they are more addictive than when they enter the brain more slowly, such as when they are taken orally. However, the brain circuits underlying these differences are not well understood. This study offers new information that helps explain what may be causing this difference.

The study was published in *Nature Communications* and led by researchers at the National Institute on Drug Abuse (NIDA) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA), parts of the National Institutes of Health, at the NIH Clinical Center.

"We've known for a long time that the faster a drug enters the brain, the more addictive it is—but we haven't known exactly why. Now, using one of the newest and most sophisticated imaging technologies, we have some insight," said Nora Volkow, MD, NIDA Director, chief of the NIAAA Laboratory of Neuroimaging, and senior author on the study.

"Understanding the brain mechanisms that underlie addiction is crucial for informing prevention interventions, developing new therapies for substance use disorders, and addressing the overdose crisis."

People who smoke or inject drugs—two methods that deliver drugs to the brain quickly—often report doing so to get faster relief from withdrawal or to experience euphoria more quickly. However, drug smoking and injection are associated with developing a substance use disorder more quickly than taking drugs orally or by insufflation (e.g., snorting).

In addition, injecting drugs is also associated with higher rates of infectious diseases and overdose. To better understand how route of drug administration impacts the brain's response to the drug, researchers conducted a double-blind, randomized, counterbalanced clinical trial using simultaneous PET/fMRI imaging.

Twenty healthy adults participated in the trial. Over three separate sessions, participants received either a small dose of a placebo or of the stimulant drug methylphenidate, commonly known as Ritalin, orally or intravenously. Methylphenidate is a safe and effective prescription medication used for the treatment of attention deficit hyperactivity disorder (ADHD). For research purposes, methylphenidate can be a useful model drug to safely study the relationship between how drugs affect the brain and the subjective experience of drug reward.

After participants received the study drug or placebo, researchers then simultaneously looked at differences in dopamine levels (through PET imaging) and brain activity (through fMRI imaging) while people reported their subjective experience of euphoria in response to the drug.

The PET scan gave an estimate of how fast dopamine increased in the brain in response to the different drug administrations. Consistent with previous research, this study showed that when participants received methylphenidate orally, the rate of dopamine increases peaked more than an hour after administration. Comparatively, when participants received an intravenous injection of methylphenidate, the rate of dopamine increases peaked much faster—within 5 to 10 minutes of the administration.

Through the fMRI, researchers observed that one brain region, the ventromedial prefrontal cortex, was less active after both oral and intravenous administration of the study drug. However, two brain regions, the dorsal anterior cingulate cortex and the insula, which are part of the brain's salience network, were activated only after receiving the injection of methylphenidate, the more addictive route of drug administration. These same areas of the brain were not activated after taking methylphenidate orally, the route with lower addiction potential. This finding was consistent among all 20 research participants.

The salience network attributes value to things in our environment and is important for recognizing and translating internal sensations—including the subjective effects of drugs. This research adds to a growing body of evidence documenting the important role that the salience network appears to play in substance use and addiction. For instance, studies have shown that people who experience damage to the insula, part of the brain's salience network, can have a complete remission of their addiction.

In this study, researchers also asked patients to track the real-time, conscious experience of drug reward or euphoria in response to both the oral and intravenous dose of the medication. After receiving the drug intravenously, researchers noticed that the activity and connectivity of the salience network, observed via fMRI imaging, very closely paralleled almost every participant's subjective experience of feeling high.

When the imaging showed increased activity in this part of the brain, participants' reports of feeling high increased. When the imaging showed decreasing activity in the salience network, participants' reports of feeling high decreased. Researchers theorize that the network identified in this study is relevant not just for the chemical action of the drug, but also the conscious experience of drug reward.

The authors note that a key next step for this research will be to study whether inhibiting the salience network when someone takes a drug effectively blocks the feeling of being high, which could further support the salience network as an appropriate target to treat substance use disorders.

"I've been doing imaging research for over a decade now, and I have never seen such consistent and clear fMRI results across all participants in one of our studies. These results add to the evidence that the brain's salience network is a target worthy of investigation for potential new

therapies for addiction," said Peter Manza, Ph.D., research fellow at NIAAA and lead author on the study.

More information: P Manza, et al. Neural circuit selective for fast but not slow dopamine increases in drug reward, *Nature Communications* (2023). DOI: 10.1038/s41467-023-41972-6.
www.nature.com/articles/s41467-023-41972-6

Provided by National Institutes of Health