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ON DRUG ABUSE

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News Scan
NIDA ADDICTION RESEARCH NEWS

NEWS UPDATE

Research News

Imaging Study Correlates Areas of Brain Activity with Sensation Seeking

Sensation seeking is a personality trait that includes the tendency to pursue thrill and adventure, the willingness to take risks, and easy susceptibility to boredom. People classified as high sensation seekers (HSSs) are more likely to abuse drugs and engage in other risky behaviors than low sensation seekers (LSSs). The specific brain systems responsible for sensation seeking are not well understood. In a study funded by NIDA, researchers used functional magnetic resonance imaging (fMRI) to measure brain activity during emotional arousal in 20 HSSs and 20 LSSs between 18 to 25 years old. While undergoing fMRI, participants viewed one hundred images containing 'high arousal' stimuli (e.g., nudity and violence) that could trigger either positive or negative emotions, and 100 containing 'low-arousal' stimuli (e.g., food). The HSSs showed more activity in brain regions associated with arousal and reinforcement (such as the insula) in response to high-arousal stimuli compared to LSSs. In contrast, LSSs showed earlier and stronger activity in regions of the brain involved in emotional regulation, behavioral monitoring, and decision making (such as the anterior cingulate) when viewing high-arousal images compared to HSSs. HSS subjects were also less sensitive to whether an image was positive or negative, and were more likely to show brain activity indicative of arousal than LSSs even when responding to negative stimuli. "Individuals high in sensation seeking not only are strongly activated by exciting, thrilling, and potentially dangerous activities, but also may be less likely than other people to inhibit or appropriately regulate their activation," explain the authors. These results may help scientists understand the neural processes by which sensation seeking leads to negative behaviors.

Joseph JE, Liu X, Jiang Y, Lynam D, Kelly TH. Neural correlates of emotional reactivity in sensation seeking. *Psychol Sci*. 2009 Feb;20(2):215-23.

Suppressing Glial Cell Activity Reduces Rewarding Effects of Morphine and Withdrawal in Rats

Glial cells are non-neuronal cells that make up the supportive tissue and participate in signal transmission in the nervous system. Glial cells have recently been shown to help mediate the effects of opioid drugs such as morphine, including analgesia (pain suppression), tolerance, and dependence—effects that were previously thought to be controlled by neurons alone. To better understand the role glial cells play in morphine's effects in the brain, researchers funded by NIDA gave rats either twice-daily doses of a drug called ibudilast, which inhibits the activity of glial cells, or a control injection. On the third day, the rats began receiving morphine in increasing doses. After 5 days of morphine exposure, the rats received a dose of the opioid inhibitor naloxone to induce withdrawal. In contrast to control rats that showed dramatic increases in levels of the chemical dopamine in the nucleus accumbens (NAc) region of the brain in response to morphine injection, rats who had received the ibudilast showed smaller increases. Moreover, the rats who received ibudilast also showed significantly fewer physical signs of withdrawal after naloxone injection. They also noted that, after naloxone administration, as dopamine levels decreased so did the physical signs of withdrawal. These results show that inhibiting glial cells with ibudilast can reduce dopamine levels in the NAc, which are considered indicators of morphine reward and may also be associated with withdrawal. Therefore, targeting glial cell activity with drug therapies such as ibudilast may be a promising approach for treating opioid addiction.

Bland ST, Hutchinson MR, Maier SF, Watkins LR, Johnson KW. The Glial Activation Inhibitor AV411 Reduces Morphine-Induced Nucleus Accumbens Dopamine Release. *Brain Behav Immun.* 2009 Feb 2. [Epub ahead of print]

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Imaging Study Shows Awareness Deficit in Marijuana Abusers

A new study funded by NIDA has used brain-imaging technology to show that during a decision game, chronic marijuana users show less activity in an error-processing part of their brains than peers who do not use marijuana. These results provide preliminary evidence in the debate on whether substance abusers willfully ignore their problem or whether cognitive deficits prevent them from fully understanding their addiction and its potential consequences. Functional magnetic resonance imaging (fMRI) of 16 heavy marijuana users and 16 non-drug-using peers provided real-time pictures of brain activity during the decision game. The marijuana abusers in the study did not make more mistakes during the game than participants who did not use the drug, but they were significantly less likely to recognize that they had made the mistakes. Non-marijuana-using participants were aware of 91 percent of their mistakes during the game, and marijuana abusers were aware of only 77 percent of their mistakes. fMRI revealed that when they made errors that they did not consciously recognize, the marijuana abusers showed less activity than the other participants in an area of the brain called the anterior cingulate cortex (ACC). The authors caution that marijuana withdrawal may have played some role in the lack of error awareness, as higher scores in several categories on a marijuana craving questionnaire were associated with poorer error awareness. However, if drug abusers cannot monitor their behavior accurately, this deficit in awareness may contribute to their continued use of a drug despite the consequences or to their continued associations with situations that make them liable to relapse.

Hester R, Nestor L, Garavan H. Impaired Error Awareness and Anterior Cingulate Cortex Hypoactivity in Chronic Cannabis Users. *Neuropsychopharmacology*. 2009 Jun 24. [Epub ahead of print]

Ibudilast and Minocycline Reduce Symptoms of Withdrawal from Two Different Opioid Drugs

The antibiotic minocycline has previously been shown to improve the efficacy of morphine and reduce reward responses to the drug in an animal model of pain. These effects are thought to be at least partially due to minocycline's ability to suppress the activity of glial cells—cells that release inflammation-inducing proteins that interfere with the ability of morphine to reduce pain—in the spinal cord. Researchers funded by NIDA tested two different drugs that block glial cell activity, ibudilast and minocycline, in a rat model of opioid addiction in an effort to determine whether blocking glial cell activity can also reduce the severity of opioid withdrawal. In one set of experiments, rats received either ibudilast, minocycline, or an inactive control for several days, and then underwent morphine exposure for 5 days. After the last dose of morphine, rats were given an injection of naloxone to induce withdrawal. The rats receiving either ibudilast or minocycline exhibited significantly fewer withdrawal-related behaviors than rats that received the inactive control. Analyses of the rat brains showed that both ibudilast and minocycline given before morphine administration reduced the expression of proteins associated with glial cell activity and inflammation in areas of the brain associated with opioid withdrawal compared to the control. In a follow-up experiment, rats were exposed to either morphine or oxycodone over a 12-day period and then treated with 7 days of ibudilast, to determine whether ibudilast would be effective after opioid dependence has occurred. Ibudilast administration significantly reduced morphine and oxycodone withdrawal-induced weight loss as well as morphine withdrawal-induced hyperactivity. Ibudilast was also able to prolong the pain-killing effects of both morphine and oxycodone. Since both ibudilast and minocycline have also been shown to reduce morphine-induced reward, the authors suggest that clinical studies of these or other drugs that target glial cells may be warranted.

Hutchinson MR, Lewis SS, Coats BD, Skyba DA, Crysdale NY, Berkelhammer DL, Brzeski A, Northcutt A, Vietz CM, Judd CM, Maier SF, Watkins LR, Johnson KW. Reduction of opioid withdrawal and potentiation of acute opioid analgesia by systemic AV411 (ibudilast). *Brain Behav Immun.* 2009 Feb;23(2):240-50.

Salvinorin A Causes Rapid, Short-Lasting Sedation in Non-Human Primates

Salvinorin A is the main biologically active compound in the hallucinogenic plant Salvia divinorum. While it's believed that salvinorin A exerts its effects on the brain by activating kappa opioid (κ-opioid) receptors, the behavioral effects of salvinorin A in people have not been well characterized. To better understand these behavioral effects, researchers funded by NIDA administered intravenous doses of salvinorin A to rhesus monkeys, whose brains are similar to those of humans. Intravenous injections of salvinorin A induced sedation in a dose-dependent manner, with the largest dose of the compound inducing the greatest sedation. Extent of sedation was measured by changes in reactions to stimuli, posture, facial relaxation, and ptosis (eyelid drooping). Sedation happened rapidly (observed within 5 minutes) and

was short-lived (the effects began to decline by 15 to 30 minutes after injection and were gone by 60 minutes after injection). Salvinorin was detected in the CSF immediately after injection, peaked in concentration 2 minutes after injection, and then declined gradually up to 30 minutes after injection. Nalmefene, an opioid antagonist that can block κ-opioid receptors, blocked the sedative effects of salvinorin A when given either before or after salvinorin A injection. However, injection of an antagonist that blocks 5HT2 receptors (a type of receptor in the brain targeted by many other hallucinogens) did not block the sedative effects of salvinorin A. These antagonist experiments confirmed that the powerful sedative effects of salvinorin A are initiated and maintained by κ-opioid receptors.

Butelman ER, Prisinzano TE, Deng H, Rus S, Kreek MJ. Unconditioned behavioral effects of the powerful kappa-opioid hallucinogen salvinorin A in nonhuman primates: fast onset and entry into cerebrospinal fluid. *J Pharmacol Exp Ther.* 2009 Feb;328(2):588-97.

Traumatic Brain Injury is an Understudied Risk Factor for Drug Abuse

A large body of research has established that drug and alcohol use are risk factors for traumatic brain injury (TBI). In contrast, whether TBI increases the risk of substance abuse in people who were not abusing drugs before experiencing a TBI is unclear. With the number of TBI survivors in the United States increasing dramatically due to the wars in Afghanistan and Iraq, more research in this field is urgently needed, explain investigators from NIDA's Intramural Research Program in a recent review article. Many challenges to studying the link between TBI and substance abuse exist, including the fact that a diagnosis of TBI includes a wide range of injury types, many of which are difficult to detect even with modern imaging techniques. Some preliminary studies have indicated that TBI may increase drug or alcohol use in people without a history of substance use or dependence. For example, in a study of about two million military personnel, those with a mild TBI were more than two and a half times likely to be discharged from the military due to alcoholism or drug use. Individuals with a moderate TBI were over five times as likely. Animal studies suggest that TBI may disrupt brain dopamine pathways (these pathways mediate the effects of all drugs of abuse), however experiments directly examining drug-related behavior after TBI have not been performed. The authors state that both laboratory and clinical studies are needed to understand whether TBI alone can increase the risk of drug abuse in the absence of other risk factors, and to measure the extent to which TBI increases drug abuse or triggers relapse in people with a history of substance abuse.

Bjork JM, Grant SJ. Does traumatic brain injury increase risk for substance abuse? *J Neurotrauma*. 2009 Feb 9. [Epub ahead of print]

Marijuana Use Associated with a Subtype of Testicular Cancer

Testicular germ cell tumors (TGCTs) are the most common type of cancer in American men between the ages of 15 and 34. For the last 50 years, the incidence of TGCTs has increased yearly in the United States and many other Western countries. A corresponding increase in marijuana abuse during this time period has been suggested as a potential causative factor. Chronic marijuana use is known to affect the body's hormone and reproductive systems, disruption of which can potentially lead to cancer development. To test this hypothesis, researchers funded by NIDA interviewed 371 men aged 18 to 44 in Seattle and Puget Sound, Washington who had been treated for an invasive TGCT between 1999 and 2006, and 979 men from the same area who had not had testicular cancer. The researchers asked all participants about their lifetime marijuana and hashish use, as well as cigarette, alcohol, and other recreational drug use. They also collected data on other suspected risk factors for TGCT, including cryptorchidism (an undescended testicle) and a family history of TGCT. The researchers found that current marijuana use was associated with a 70 percent increased risk of nonseminoma TGCTs, but was not associated with risk of seminoma. (Seminoma and nonseminoma are the two subtypes of TGCT.) For nonseminoma tumors, the risk increased more for frequent (at least weekly) marijuana use and for use beginning in adolescence. This increased risk was independent of any other measured risk factor. The authors conclude that additional studies are needed to confirm these results, and to understand the biological processes that may link marijuana use to an increase in risk for nonseminoma TGCTs.

Daling JR, Doody DR, Sun X, Trabert BL, Weiss NS, Chen C, Biggs ML, Starr JR, Dey SK, Schwartz SM. Association of marijuana use and the incidence of testicular germ cell tumors. *Cancer*. 2009 Mar 15;115(6):1215-23.

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CREB Protein Activity in the Nucleus Accumbens Shell Mediates Environmental Cues Associated with Nicotine

Environmental cues are thought to contribute to continued tobacco use—for example, a smoker is likely to crave a cigarette when entering a place in which he or she most often smoked. The nucleus accumbens (NAc) shell is an area of the brain in which dopamine release is thought to be activated by nicotine and by environmental cues associated with smoking. A molecule called CREB is thought to play a role in environmental associations with smoking, but its exact function has not been clear. To understand whether CREB is required for environmental associations with smoking, researchers funded by NIDA performed a series of conditioned place preference (CPP) experiments using mice. CPP occurs when an animal is exposed to a pleasurable drug in a specific environment, and learns to prefer that environment over others when given a choice. The researchers exposed mice to either nicotine or a control injection for three days and immediately placed the mice in one of two visually distinct environments, to allow a CPP to develop. Mice that received nicotine injections and developed a CPP showed increased CREB activity in the NAc shell when placed their preferred environment, even without exposure to nicotine. Mice who had received the control injections did not show an increase in CREB activity in the same test. When CREB activity in the NAc shell was blocked using gene transfer of a modified version of CREB, mice did not develop a CPP after nicotine exposure. "The current study shows that nicotine CPP cannot occur without CREB activity in the NAc shell," explained the authors. Drugs that decrease or block CREB activation may hold promise as smoking cessation aids.

Brunzell DH, Mineur YS, Neve RL, Picciotto MR. Nucleus accumbens CREB activity is necessary for nicotine conditioned place preference. *Neuropsychopharmacology*. 2009 Jul;34(8):1993-2001.

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