

Research News

PTSD contributes to teen and young adult marijuana abuse and dependence

Post-traumatic stress disorder (PTSD) has been associated with cannabis use disorders (CUD). In fact, adults diagnosed with PTSD are three times more likely to exhibit CUD compared to those without PTSD. However, while the onset of CUD typically occurs during adolescence, limited research has been conducted on the relationship between PTSD and CUD in youth. NIDA-funded researchers recently evaluated the relationship between PTSD and CUD among high-risk adolescents. For this study, researchers recruited children of adult men taking part in the Center for Education and Drug Abuse Research (CEDAR) study, a long-term study examining how substance use disorders develop in families. Study participants, initially recruited at age 10-12, were assigned to groups that either had fathers with a lifetime history of substance use disorder (SUD) or a control group (fathers with no SUD history) and were then assessed for drug and alcohol use, mental disorders and measures of family, social, cognitive and psychological functioning at ages 12-14, 16, 19, 22, and 25 (peak ages of CUD and other SUD initiation). Of the 693 participants, 31 were diagnosed with PTSD (average onset age 15.4), and 161 were diagnosed with a CUD (average onset age 16.7), 11% of whom also met criteria for PTSD. Researchers found that the development of CUD was associated with PTSD, being African-American, and having deviant peers and a father

PTSD was also found to be directly associated with CUD

with a history of SUD. PTSD was also found to be directly associated with CUD (CUD more common in individuals with PTSD than without) and peer deviance. In fact, PTSD was found to mediate the association between peer deviance and CUD. Authors note that among adolescents with SUD, PTSD is often neglected in clinical evaluations among youth, thus future studies are warranted to further

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clarify the etiology, clinical course and optimal treatment of youth with comorbid PTSD and clarify the role of PTSD and other anxiety disorders in the etiology of CUD.

Cornelius JR, Kirisci L, Reynolds M, Clark DB, Hayes J, and Tarter R. PTSD contributes to teen and young adult cannabis use disorders. *Addict Behav.* 2010; Feb;35(2):91-4. Epub 2009 Sep 11.

Identified receptor helps explain how synapses are formed

Synapses—specialized junctions between nerve cells that allow them to pass signals between one another—are the primary means of neuronal communication. NIDA researchers recently discovered that the protein Thrombospondin (TSP) and its receptor alpha2delta-1 ($\alpha 2\delta-1$) play an integral role in the formation of certain types of synapses—called excitatory synapses—in the central nervous system. Previous studies from this laboratory showed that TSPs were necessary to increase synapse number—especially early in development when new synapses are forming—however the exact mechanism was poorly understood. Through a series of studies, researchers showed that when TSP binds directly to specific regions of the $\alpha 2\delta-1$ receptor, it initiates a host of signaling events

that not only leads to the formation of new synapses, but also the conversion of silent synapses into fully active ones. Researchers further showed that neurons engineered to over-express $\alpha 2\delta-1$ produced twice as many synapses following exposure to TSP; however TSP administration was not able to stimulate synaptogenesis in mice lacking the $\alpha 2\delta-1$ receptor. These studies confirm that the initiation of new excitatory synapse formation in the CNS is at least in part mediated by the interaction between TSP and its receptor. In additional studies, researchers showed that gabapentin, a medication commonly used to treat neuropathic pain and epilepsy, blocks new synapse formation by interfering with TSP binding to $\alpha 2\delta-1$. This finding suggests that irregular excitatory synaptogenesis may contribute to the pathophysiology of neuropathic pain and epilepsy and potentially explains gabapentin's therapeutic effects.

Eroglu C, Allen NJ, Susman MW, O'Rourke NA, Chan Young Park, Özkan E, Chakraborty C, Mulinyawe SB, Annis DS, Huberman AD, Green EM, Lawler SB, Dolmetsch R, Christopher Garcia K, Smith SJ, Luo ZD, Rosenthal A, Mosher DF, and Barres BA. The gabapentin receptor $\alpha 2\delta-1$ is the neuronal thrombospondin receptor responsible for excitatory CNS synaptogenesis. *Cell*. 2009;139(2):380-92.



Family-based interventions may help to prevent or reduce substance use and unsafe sexual behavior in Hispanic youth

Substance abuse and unsafe sexual behaviors are two of the leading preventable causes of serious injury and death among adolescents. This is of particular concern for ethnic minorities, including Hispanics, a growing population in the United States, for whom there are few interventions that have been empirically evaluated. Researchers funded by NIDA, recently tested the effectiveness of Familias Unidas, a parent-centered prevention and intervention program focused on increasing family functioning and preventing problem behavior in high-risk Hispanic youth. Researchers identified 210 8th grade students (136 boys and 77 girls) with at least mild behavior problems and randomly assigned them and their primary caregivers to the Familias Unidas intervention or a control group (i.e., referrals to other local agencies). Familias Unidas consists of nine 2-hour group sessions, ten 1-hour family visits, and four 1-hour booster sessions. Each family was given a baseline assessment with follow-up assessments at 6-, 18- and 30-months post-baseline. Results showed that, relative to the control group, children of families participating in Familias Unidas reported less high-risk behavior, including less drug and alcohol use in the past 30 days (i.e., 21% in Familias Unidas group vs. 34% in control group) at the 6-month post-assessment; fewer externalizing behavior problems, including ADHD, conduct and oppositional defiant disorders; and significantly increased levels of condom use during sexual activity from 6-months to 30-months post-baseline assessment. Researchers also found that the effects of Familias Unidas were partially mediated by improvements in family functioning. The findings from this study confirm the importance of family functioning in preventing youth substance use and HIV risk behaviors. Additionally, the study found positive parenting, parent-adolescent communication, and parental monitoring may be important in protecting Hispanic youth from these harmful behaviors.

Pantin H, Guillermo P, Lopez B, Huang S, Tapia MI, Schwartz SJ, Sabillon E, Brown CH, Branchini, J. A Randomized Controlled Trial of Familias Unidas for Hispanic Adolescents With Behavior Problems. *Psychosom Med*. 2009;Oct;71: 987-95.

Identifying TRPV1 agonists may lead to new approach in developing pain relievers

TRPV1 (the transient receptor potential vanilloid receptor) is a member of a family of receptors involved in the regulation of inflammation and pain and the integration of painful stimuli. While TRPV1 receptors and their role have been fairly well characterized in the peripheral nervous system, little is known about how TRPV1 mediates pain in the central nervous system. In order to better understand the role of TRPV1 receptors in the regulation of central pain mechanisms, researchers funded by NIDA isolated and tested a compound called 9-HODE. Researchers found that 9-HODE, a compound originally extracted from male rat spinal cord tissue, selectively activated the expression of TRPV1 in cultured cells. They also found

Better understating of TRPV1 physiology and functioning may eventually lead to the development of new classes of pain relievers

that spinal administration of 9-HODE induced mechanical allodynia, or sensitivity to touch, as tested by exposure to a stimulus that is not usually painful—an effect that was completely prevented by administration of a TRPV1 blocker. Finally, researchers found that peripheral inflammation (from injection of an irritating agent) induced the release of chemicals that increase the amount of TRPV1 in the spinal cord, and lead to TRPV1-mediated mechanical allodynia, an effect that was reversed following an injection of antibodies against 9-HODE. Collectively, these results reveal a mechanism by which 9-HODE, may centrally mediate inflammation and pain and also demonstrate a direct role of TRPV1 and related molecules in triggering different types of pain. Better understating of TRPV1 physiology and functioning may eventually lead to the development of new classes of pain relievers that block the synthesis of TRPV1 compounds in the spinal cord.

Patwardhan AM, Scotland PE, Akopian AM, and Hargreaves KM. Activation of TRPV1 in the spinal cord by oxidized linoleic acid metabolites contributes to inflammatory hyperalgesia. *Proc Natl Acad Sci U S A*. 2009; Nov;106(44):18820-4.

Constructive parenting behaviors improve adjustment, decrease antisocial behavior, and are commonly passed between generations

Research studies have recently confirmed what many parents already know—children learn parenting practices from their parents and use those methods to raise their own children. What may not be as clear, however, is exactly how patterns of parenting and discipline are passed from one generation to the next (i.e., intergenerational transmission). Researchers funded by NIDA examined more than 20 years of prospective data from the Oregon Youth Study, a study examining risk factors for delinquency, in order to better understand how constructive parenting—a composite of parenting behaviors consisting of age-appropriate discipline and increased parental involvement—is transmitted from parent to child and on to successive generations. Study participants—fathers (G1), their sons (G2) and sons of G2 men (G3) were recruited when the G2 males were in the 4th grade. Participants were assessed annually via interviews, surveys, interaction tasks and at-home observations. Results suggest continuity of intergenerational parenting practices; G1 constructive parenting of G2 adolescents predicted the use of constructive parenting by G2 males when they became parents (they also introduced constructive parenting earlier, during early childhood). G1 constructive parenting was also associated with higher levels of positive adjustment and lower levels of antisocial behavior in G2 adolescents. According to the authors, these findings suggest that constructive parenting leads to the development of positive behavior patterns, which in turn impacts constructive parenting in future generations. Authors note that results also provide evidence that the effects of prevention may be wider in scope since changes in parenting may lead to enhanced functioning in adult children and even grandchildren.

Kerr DCR, Capaldi DM, Pears KC, Owen LD. A Prospective Three Generational Study of Fathers' Constructive Parenting: Influences from Family of Origin, Adolescent Adjustment, and Offspring Temperament. *Dev Psychol*. 2009 Sep;45(5):1257-75. Mar;44(3):283-90.

Combining extinction therapy with pharmacotherapy holds promise in treating cocaine addiction

Relapse is one of the most serious barriers to the effective treatment of addiction. Because such strong associations are made between drug use and environmental cues (i.e., people, places and things associated with drug use), extinction therapy—an intervention that seeks to extinguish the association between drug use and its environmental cues—holds promise as an approach to prevent relapse and could possibly be enhanced by the addition of medications. To assess whether combining extinction therapy with pharmacotherapy could alter learned associations between cocaine and a cocaine-paired stimulus (e.g., a brief light flash), NIDA researchers administered varying doses of D-cycloserine (an antibiotic that is also thought enhance learning) to rats and non-human primates trained to self-administer cocaine. Animals then underwent extinction training to help erase any associations between the cocaine and cocaine-paired stimulus. In both species, pretreatment with higher doses of DCS (30mg/kg) before extinction training attenuated reacquisition of cocaine self-administration compared to either extinction training or DCS administration alone. The results show that DCS enhances extinction therapy to deter rats and monkeys from reverting to cocaine self-administration. Authors suggest that this approach may also hold promise in humans, as “DCS combined with exposure therapy may constitute a rational strategy for the clinical management of cocaine relapse.”

Dhonnchadha BA, Szalay JJ, Achat-Mendes C, Platt DM, Otto MW, Spealman RD, and Kantak KM. D-cycloserine Deters Reacquisition of Cocaine Self-administration by Augmenting Extinction Learning. *Neuropsychopharmacology*. 2010 Jan;35(2):357-67.

Genetic variation in zebrafish advances knowledge of nicotine addiction

The role of genetics and genetic variation in human behavior has been debated for decades. One of the obstacles to studying the effects of genes on behaviors such as drug addiction is finding a reliable model system in which genes may be manipulated and then studied.

Much of the work that has been done to understand the genetics of drug addiction has been carried out in mammalian systems, like the rodent. More recently however, researchers have been turning to a new non-mammalian model system, the zebrafish. Researchers funded by NIDA developed a novel nicotine behavioral assay in zebrafish to search for genes that are affected by nicotine exposure. First, researchers assessed zebrafish behavioral responses following exposure to nicotine and found similar behavioral profiles as rodent models—low doses result in increased behavioral activity, while higher doses result in reduced behavioral activity and repeated administration resulted in a phenomenon

researchers assessed zebrafish behavioral responses following exposure to nicotine and found similar behavioral profiles as rodent models

called sensitization (where later nicotine administration can result in a marked increase in behavioral activity). Researchers then induced mutations in particular DNA segments of the zebrafish and looked at changes in the nicotine response profile of mutant carriers compared to their siblings. From these mutations, researchers identified two new genes, which result in altered nicotine responses, and subsequently named them for celebrities that suffered from tobacco-related cancers: *bdav/cct8* (*bette davis*) and *hbog/gabbr1.2* (*humphrey bogart*). This study demonstrates that zebrafish are a viable vertebrate model for the discovery of new genes in conserved behavioral paradigms and also provides new starting points for potential diagnostic and medications development for nicotine addiction.

Petzold AM, Balciunas D, Sivasubbu S, Clark KJ, Bedell VM, Westcot SE, Myers SR, Moulder GL, Thomas MJ, Ekker SC. Nicotine Response Genetics in the Zebrafish. *Proc Natl Acad Sci U S A*. 2009 Nov 3;106(44):18662-7. Epub 2009 Oct 26.

Enhanced contextual memories caused by nicotine use may increase context-induced relapse

Environmental cues are thought to contribute to continued tobacco use and relapse—for example, a smoker is more likely to crave a cigarette when they are in an environment where they often smoked. Although it is well known that smoking can change brain circuits in a manner that influences the formation of drug-related associations, the exact mechanisms by which this process occurs remains unclear. Researchers funded by NIDA recently investigated how nicotine influences learning and long-term memory consolidation, which could play a role in the development of drug-cue associations. In this study, animals were given a dose of nicotine (or saline) and then trained to associate their test environment with an unpleasant sensation (e.g., a mild shock to the feet)—thus animals would exhibit a fearful reaction when they were placed in that environment in the future. Mice that received nicotine injections prior to training exhibited enhanced contextual learning (associating environment with shock) and also exhibited higher levels of JNK1

(a molecule shown to be important in the consolidation of learning and memory) in the hippocampus. Neither nicotine administration alone nor fear training in the absence of nicotine had an effect on JNK1 levels. Researchers also found that mice lacking the gene for a particular nicotine receptor subtype as well as direct injections of a molecule which blocks JNK into the hippocampus of normal mice prevented enhanced nicotine-induced learning and any increases in JNK1. The findings suggest—for the first time—that nicotine and learning interact to affect changes in hippocampal neuron networks that may influence the consolidation of contextual memories in a manner that is specific to JNK1 expression. The findings suggest a new avenue of research for understanding the effects of nicotine on learning and how nicotine receptors may contribute to addiction.

Kenney JW, Florian C, Portugal GS, Abel T, and Gould TJ. Involvement of Hippocampal Jun-N terminal Kinase Pathway in the Enhancement of Learning and Memory by Nicotine. *Neuropsychopharmacology*. 2010;35:483–492. E-pub 2009 Sep 23.

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The National Institute on Drug Abuse is a component of the National Institutes of Health, U.S. Department of Health and Human Services. NIDA supports most of the world's research on the health aspects of drug abuse and addiction. The Institute carries out a large variety of programs to inform policy and improve practice. Fact sheets on the health effects of drugs of abuse and information on NIDA research and other activities can be found on the NIDA home page at www.drugabuse.gov. To order publications in English or Spanish, call NIDA's new DrugPubs research dissemination center at 1-877-NIDA-NIH or 240-645-0228 (TDD) or fax or email requests to 240-645-0227 or drugpubs@nida.nih.gov. Online ordering is available at <http://drugpubs.drugabuse.gov>. NIDA's new media guide can be found at <http://drugabuse.gov/mediaguide>.

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