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Studies Explore Brain Changes That Can Cultivate or Curb Common Addictions

Research suggests novel treatment approaches, such as learning to dislike cigarettes during sleep

WASHINGTON, DC — Research released today reveals new information on the mechanisms and brain regions involved in some of the most prevalent addictions — including alcohol, nicotine, and cannabis — and suggests new approaches to treating these major public health problems. The findings were presented at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

An estimated 3.3 million people worldwide die each year from the harmful effects of alcohol abuse. An additional 6 million people die as a result of tobacco use. Marijuana, used by 147 million people, is the world's most prevalent recreational drug and has been shown to increase risk for the development of neuropsychiatric disorders such as depression and schizophrenia.

Today's new findings show that:

- Pairing exposure to the scent of cigarettes with unpleasant smells, known as "aversive conditioning," while people sleep may curb smoking (Anat Arzi, abstract 678.07, see attached summary).
- The menthol added to many cigarettes affects the way brain responds to nicotine, which may explain why menthol smokers are less likely to quit smoking than non-menthol smokers (Brandon Henderson, PhD, 231.30, see attached summary).
- Activation of a specific brain circuit appears to dampen the drive to drink alcohol in rats (Zayra Millan, PhD, 756.01, see attached summary).
- An animal study suggests that cannabis use during adolescence alters brain signaling into adulthood and builds on previous research seeking to explain the link between cannabis abuse and disorders such as schizophrenia (Ed Korzus, PhD, 656.18, see attached summary).

"Many of the most powerful drugs of abuse are legal, yet their effects on individual and public health are profound," said moderator Marina Picciotto, PhD, an expert in the molecular basis of behavior at Yale University in New Haven, Conn. "The findings reported today demonstrate the span of approaches, both molecular and behavioral, that are being used to fully understand the mechanisms underlying addiction and its treatment."

This research was supported by national funding agencies such as the National Institutes of Health as well as other private and philanthropic organizations. Find out more about addiction at *BrainFacts.org*.

Related Neuroscience 2014 Presentations:

Special Lecture: Affective Neuroscience of Reward: Limbic Modules for Liking and Wanting
Wednesday, Nov. 19, 1–2:10 p.m., Hall D, WCC

Minisymposium: Bath Salts, Spice, and Related Designer Drugs: The Science Behind the Headlines
Tuesday, Nov. 18. 1:30–4 p.m., Ballroom B, WCC

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Abstract 678.07 Summary

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Learning to Dislike Nicotine Addiction During Sleep

Pairing unpleasant smells with that of cigarettes during sleep can curb the desire to smoke

A new study suggests that addictive behavior may be treated through subliminal learning during sleep. In the study, sleeping smokers who were exposed to the smell of cigarettes along with an unpleasant odor (either rotten fish or rotten eggs) reduced their smoking for days after exposure to the paired smells, revealing a potential new tool in the fight against addiction. The findings were presented at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"We know that behavioral approaches can help treat nicotine addiction, but none have been remarkably successful," said co-author Anat Arzi of the Weizmann Institute of Science in Rehovot, Israel. "Therefore, we decided to try an indirect approach by reconditioning smoking behavior during sleep."

Cigarette smoking is the single largest preventable risk for death and disease in developed countries. It is also one of the hardest addictions to break, as it results from a complex interplay of neurochemistry, behavioral conditioning, personality, and social environment.

Researchers had previously investigated the use of aversive conditioning, a technique that pairs a noxious stimulus with the behavior one wishes to change, while smokers were awake. Experiments have combined exposure to cigarettes with electric shock, noise, and bad tastes.

The new research paired cigarettes with an unpleasant smell during two different phases of sleep: Stage 2 sleep, which transitions to the deeper sleep of Stage 3, and rapid eye movement (REM) sleep, the time of dreams. The 76 study participants completed a daily smoking diary for seven days before and seven days after a one-night or day experiment.

When aversive conditioning was conducted during Stage 2 sleep, smoking was reduced by 34 percent; when conducted during REM sleep, smoking was reduced by 12 percent. When the experiment was conducted while smokers were awake, there was no significant impact. Repeating the aversive conditioning over the course of several nights may lead to a more dramatic reduction in smoking.

Research was supported with funds from I-CORE: The Center of Research Excellence in the Cognitive Sciences.

Scientific Presentation: Wednesday, Nov. 19, 8–10:30 a.m., Room 150B

678.07, Using olfactory aversive conditioning during human sleep to treat addiction
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TECHNICAL ABSTRACT: Cigarette smoking is an addictive behavior associated with significant morbidity and mortality. Efforts to treat addiction using aversive conditioning have seen only limited success. The effectiveness of conditioning may be greater when it is implicit rather than explicit. One implicit path is conditioning during sleep. Therefore, we set out to test the hypothesis that olfactory aversive conditioning during sleep can reduce smoking. A daily smoking diary detailing the number of smoked cigarettes was completed by 76 smokers wanting to quit (mean age = 28.7 ±5.2 years, 26 F) during seven days before and seven days after a one night or day experiment. The experiment consisted of olfactory aversive partial trace conditioning between cigarette odor and profoundly unpleasant odors. The conditioned (cigarette odor) and non-conditioned (unpleasant odors) stimuli were partially reinforced at a ratio of 2:1. On reinforced trials, a 5-s cigarette odor was paired with a 3-s unpleasant odor (either Ammonium Sulfide (AmSu) or Rotten Fish (RF)). On non-reinforced trials, cigarette odor was generated without an ensuing unpleasant odorant (cigarette odor alone). Stimuli were generated in blocks of 30 trials (10 trials reinforced with AmSu, 10 reinforced with RF, and 10 non-reinforced with cigarette odor only, randomized across the block). An initial experiment limited to either Stage 2 sleep or wake revealed that olfactory aversive conditioning during Stage 2 sleep significantly reduced smoking by 47.9% ± 38.6%, and that the reduction lasted several days (all

$t(10) > 2.3$, $p <$ FDR α). Conditioning during wake did not reduce smoking (all $t(9) < 1.45$, $p >$ FDR α). To test whether the reduction in smoking stemmed from the conditioning between cigarette odor and unpleasant odors, or merely from the presentation of either unpleasant odors or cigarette odor we conducted two control experiments: 1) the same experimental procedure without cigarette odor 2) Cigarette and aversive odors randomly interspersed. There was no significant change in smoking following these control experiments (all $t(10) < 2.6$,$p >$ FDR α). To conclude, a single night of olfactory aversive conditioning between cigarette odor and unpleasant odors during sleep can reduce smoking.

Abstract 231.30 Summary

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Why Smokers of Menthol Cigarettes May Find It Harder to Quit

Menthol's interaction with certain brain receptors may affect nicotine addiction

Menthol, the minty flavor added to many cigarettes, can act on the same brain receptors targeted by nicotine and may increase nicotine reward and addiction, according to new findings presented at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Our research shows that menthol changes brain chemistry in ways that are complementary to nicotine and clearly exerts long-term effects on the brain's nicotine sensors," said lead author Brandon Henderson, PhD, of the California Institute of Technology in Pasadena. "This finding may help explain why menthol smokers are less likely to quit smoking than those who smoke non-menthol cigarettes."

Tobacco addiction is a leading cause of disease and death worldwide. In the United States, an estimated 43.8 million people, or 19 percent of all adults, smoke cigarettes, and tobacco use costs the country more than $190 billion annually in health care expenditures and lost productivity. Cigarettes labeled as menthol are used by a third of all smokers, 84 percent of African-American smokers, and a disproportionately large numbers of adolescent, adult female, and low-income smokers.

Addiction to nicotine occurs as its continued use changes the amount and makeup of certain proteins in the brain, called nicotinic receptors. Using both cells grown in the laboratory and mice, the researchers found that menthol alone changed the levels of the most prominent nicotinic receptor. Moreover, these changes were greater when menthol was combined with nicotine. Menthol also interacted with a rarer nicotinic receptor subtype that is associated with the release of the brain chemical dopamine, a "feel good" chemical that encourages rewarding — as well as addictive — behaviors.

Research was supported with funds from the National Institute on Drug Abuse.

Scientific Presentation: Sunday, November 16, 2–3 p.m., Halls A-C.

231.30, Menthol alone alters the number and assembly of α4β2 and α6β2* nAChRs
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TECHNICAL ABSTRACT: We report the first observation that chronic exposure to presumed smoking-relevant levels of menthol affects the properties and numbers of neuronal nicotinic acetylcholine receptors (nAChRs) in vivo and in vitro, even in the absence of nicotine. Using mice expressing fluorescent α4 and α6 nAChR subunits, we show that menthol increases the numbers of α4* and α6* nAChRs in midbrain neurons. The α6* nAChRs on dopaminergic neurons of the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) become more abundant during chronic treatment with menthol. We also found that chronic menthol increased numbers of α4* nAChRs in both VTA and SNc dopaminergic neurons, but α4* nAChRs in GABAergic neurons of the substantia nigra pars reticulata (SNr) did not change. To investigate effects of chronic menthol treatment in more detail, we studied cultured cells transiently expressing α4β2 or α6β2β3 nAChRs. In cells expressing α4β2 nAChRs, chronic treatment with menthol increases α4β2 nAChRs, but does not affect peak current amplitudes or desensitization kinetics of ACh-induced currents. We also found that chronic menthol treatment shifts the α4β2 nAChR stoichiometry from the usual mixed population (higher and lower sensitivity) toward the lower sensitivity using two metrics: 1) analysis of concentration-response curves and 2) the use of Förster resonance energy transfer (FRET). In cells expressing α6β2β3 nAChRs, chronic menthol treatment increased the population of α6β2β3 nAChRs, but decreased peak ACh-induced currents. This decrease in peak current amplitude presumably resulted from menthol-induced stabilization of α6β2 (non-β3) nAChRs. Chronic menthol treatment reduced the FRET efficiency between fluorescent protein-labeled α6 and β3 nAChR subunits. This suggests that chronic menthol treatment does not favor (or destabilizes) assembled nAChRs pentamers containing the β3 subunit. Together, these data suggest that menthol, even in the absence of nicotine, increases nAChR numbers and preferentially stabilizes lower sensitivity assemblies of α4* and α6* nAChRs. These effects of chronic menthol on two populations of high-sensitivity nAChRs differ in detail from the effects of chronic nicotine. Support: DA017279; DA019375; DA033721.

Abstract 756.01 Summary

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Scientists Identify Brain Circuit That May Dampen the Drive to Drink

Animal study suggests that activation of brain circuit may help addicts resist cues to imbibe

Scientists have identified a brain circuit that can suppress the desire to seek alcohol in rats, even in the face of strong environmental cues signaling its availability, according to research presented at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The finding has potential implications for treating alcohol and drug addiction, which are commonly characterized by a significant loss of control over one's behaviors.

"We looked at behavior driven by environments and sensory experiences associated with drinking alcohol, such as seeing your favorite pub with beer on tap and being drawn toward it," said study lead author Zayra Millan, PhD, of the Johns Hopkins University in Baltimore. "We asked what brain mechanism might lead an animal to ignore such a cue and found the answer in a surprising place: the nucleus accumbens, a region of the brain largely recognized for its role in positively reinforcing behaviors such as drinking."

Millan and her associates examined a microcircuit that begins in the amygdala, a part of the brain involved in sensing motivationally important environmental cues, and ends in the brain's primary reward center. Just as human drinkers associate specific cues with alcohol, rats are also able to recognize environmental cues connected with alcohol. Cue-triggered drinking was modeled in rats by repeatedly pairing a noise stimulus with alcohol delivered at a drinking port. The rats approached the drinking port each time they heard the associated sound. The researchers found that when they stimulated specific areas within the microcircuit with a cutting-edge technique called optogenetics, the environmental cue failed to trigger alcohol seeking.

The research suggests that activation of the amygdala-nucleus accumbens pathway may be sufficient to inhibit cues from triggering alcohol-reinforced behavior and provides insight into further research that may help addicts maintain control in the face of environmental cues.

Research was supported with funds from the National Institute on Alcohol Abuse and Alcoholism.

Scientific Presentation: Wednesday, Nov. 19, 8–9 a.m., Halls A-C.

756.01, Optical stimulation of nucleus accumbens shell-projecting basolateral amygdala neurons suppresses Pavlovian cue-conditioned alcohol seeking and unconditioned homecage alcohol drinking
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TECHNICAL ABSTRACT: The nucleus accumbens shell (AcbSh) strongly inhibits feeding during satiety, reward seeking in the presence of an unrewarded cue, and drug seeking following its extinction. Understanding the mechanisms that promote suppressive control over motivated behavior has important implications for pathologies such as drug addiction, which is characterized by a significant loss of control over drug use. Here we used an optogenetic approach to examine basolateral amygdala (BLA) projections that target AcbSh and to test whether stimulation of these AcbSh-projecting BLA terminals might be sufficient to suppress conditioned alcohol-seeking in the presence of an EtOH-predictive cue. Rats received intermittent homecage access to EtOH (15%v/v) and subsequently were trained to acquire Pavlovian-conditioned alcohol seeking given repeated trials of a 10 second auditory cue (CS) paired with EtOH (15% v/v) delivery. On test, rats were assessed for cue-triggered alcohol seeking (port entries) in the presence of both non-reinforced and reinforced presentations of the CS. We found that 5 second stimulation of BLA terminals in AcbSh at the time of CS onset abolished conditioned port entries under non-reinforced extinction conditions. On subsequent CS-reinforced tests, optical stimulation of BLA terminals in AcbSh reduced cue-triggered alcohol seeking when all events -- stimulation, EtOH delivery and CS onset -- co-occurred. Conversely, when alcohol was delivered during the latter portion of the CS interval, coinciding with the offset of the optical stimulation, rats maintained their ability to port entry within the interval of the cue, although at a delayed latency to respond. This latter finding suggests that the impact of stimulation on conditioned port entries is well-timed to the duration of stimulation. Finally, we examined whether the inhibitory effect of BLA terminal stimulation in AcbSh was specific to cue-conditioned behavior or whether it extended to unconditioned EtOH drinking under brief homecage access conditions. Rats were placed on a 15-minute homecage access regime prior to stimulation test. We found that stimulation prevented unconditioned EtOH drinking under a two-bottle choice test. Together, these findings suggest that recruitment of a BLA-AcbSh pathway is sufficient to inhibit alcohol-reinforced conditioned and unconditioned behavior, and may be involved in maintaining control over alcohol-motivated behavior.

Abstract 656.18 Summary

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Animal Study Shows Adolescent Marijuana Abuse May Cause Long-Term Damage to Brain Signaling System

Changes persists in adults, may be linked to increased risk for schizophrenia, depression

A new study in mice suggests that adolescent abuse of cannabis may have long-lasting detrimental effects on brain function. The findings were presented at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The alterations appear in the brain's decision-making center, the prefrontal cortex, and may explain suggested links between adolescent cannabis abuse and heightened risk for disorders such as depression, anxiety, and schizophrenia.

"Cannabis abuse is considered to be a serious environmental risk for neuropsychiatric disorders," said lead author Ed Korzus, PhD, of the University of California, Riverside. "Our study examines the mechanism behind why that may be the case and points the way for developing new treatment strategies."

To understand the effects of cannabis abuse during adolescence, researchers working with a mouse model focused on the brain's natural endocannabinoid system. This system is composed of cannabis-like molecules and their corresponding receptors. In the prefrontal cortex, these receptors affect the neuron-to-neuron communication that underpins the ability to make memories, plans, and decisions.

Cannabis exerts its psychological effects by binding to these receptors, disrupting the function of the brain's endocannabinoid system. The researchers found that such disruption during adolescence leads to long-lasting alterations in endocannabinoid-dependent signaling in mice. The researchers also found that they could use a particular molecule (inhibitor JZL184) to help the adult mouse brain maintain normal endocannabinoid signaling, even after alterations caused by cannabis use in adolescence.

"The use of JZL184 doesn't undo the damage to the endocannabinoid system, but it can help reduce the effects of the damage in the prefrontal cortex," Korzus said. "We don't know how using JZL184 for this purpose could affect the rest of the brain, but it points us in the direction of how we might one day help restore balance in the endocannabinoid system."

Research was supported with funds from the University of California, Riverside and the National Institute of Mental Health.

Scientific Presentation: Tuesday, Nov. 18, 2–3 p.m., Halls A-C

656.18, Animal model of adolescent cannabis abuse exhibits permanent deficit in the endocannabinoid system signaling
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TECHNICAL ABSTRACT: Whereas current data link adolescence cannabis abuse to increased risk for dependence on other drugs, depression, anxiety disorders and psychosis, the mechanism underlying these adverse effects remains controversial. Here we show that a mouse model of adolescent cannabis abuse shows deficits in an endocannabinoid (eCB)-mediated signaling and plasticity at adult central glutamatergic synapses in the prefrontal cortex. Blockade of the monoacylglycerol lipase, the primary enzyme responsible for degrading the endocannabinoid 2-arachidonoylglycerol, with the specific inhibitor JZL184 ameliorates these deficits. The observed deficit in cortical eCB-dependent signaling may represent a neural maladaptation underlying network instability and abnormal cognitive functioning.