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TEEN VULNERABILITY:
DRUG EXPOSURE DURING ADOLESCENCE HAS LONG-LASTING CONSEQUENCES
Teen brain responds differently to drugs than adult

SAN DIEGO — New research released today shows teenagers respond differently to drugs than adults and explores the long-lasting effects of drug use on brain development. One study shows people who start using drugs at a young age have greater cognitive shortfalls, including mental flexibility. Animal studies also suggest adolescents are more susceptible to lower doses of cocaine, are willing to work more for a cocaine "fix" than adults, and are at risk of developing compromised stress responses. The research findings were presented at Neuroscience 2010, the Society for Neuroscience's annual meeting and the world's largest source of emerging news and brain science and health.

Teens' brains are only about 80 percent developed and are not complete until they reach their 20s or 30s. More than 4,300 U.S. teens try an illicit drug for the first time each day. Today's findings provide more clues to the unique effects of drug use at this time of life, and the potential impacts on brain chemistry into adulthood.

Research released today shows that:

- People who start using marijuana at a young age have greater cognitive shortfalls. Researchers also found that the more marijuana a person used corresponded to greater difficulties in focus and attention (Staci Ann Gruber, PhD, abstract 165.9, see attached summary).
- Amphetamine abuse during adolescence permanently alters brain cells involved in memory and decision-making. This animal finding suggests abnormal brain responses in adults may result from drug abuse at a time when the brain is still developing (Joshua Gulley, PhD, abstract 576.6, see attached summary).
- Binge drinking during adolescence alters the stress response in rats as adults. Problems regulating stress are associated with behavioral and mood disorders (Toni Pak, PhD, abstract 792.20, see attached summary).
- Animal research shows adolescents are more susceptible to lower doses of cocaine and work harder for it than adults (Michela Marinelli, PhD, abstract 574.18, see attached summary).

"As parents and neuroscientists, we desperately need to better understand how drug exposure during teen years influences brain development. With the help of further research, scientists and clinicians can lay a foundation for education, intervention, and treatment," said press conference moderator Frances Jensen, MD, of the Children's Hospital in Boston, and an expert on brain developmental stages and injury.

This research was supported by national funding agencies, such as the National Institutes of Health, as well as private and philanthropic organizations.

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Abstract 165.9 Summary

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Human Study Shows Greater Cognitive Deficits in Marijuana Users Who Start Young

Difficulty with focus and attention also increased with greater amount of marijuana used

New research shows that people who start using marijuana at a young age and those who use the greatest amount of marijuana may be the most cognitively impaired. The research was presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Marijuana users show deficits in the ability to switch behavioral responses according to the context of a situation, also known as cognitive flexibility. The new study, directed by Staci Gruber, PhD, at McLean Hospital and Harvard Medical School, compared people's performance on the Wisconsin Card Sorting Task, a test of cognitive flexibility. During the task, people are shown four shown cards that differ in color, symbol, and value. Based on the rules they glean from these displayed cards, they must then sort a deck of cards. The participants are not told what the rules are — only whether their sorting attempt is correct or incorrect. During the test, the researchers change the rules without warning, and participants must adjust accordingly. How a participant responds is a strong indicator of cognitive flexibility.

The researchers found that habitual marijuana users made repeated errors despite feedback that they were wrong. Marijuana users also had more difficulty maintaining a set of rules, suggesting an inability to maintain focus. Those participants who began using marijuana before the age of 16 and those who used the most marijuana showed the greatest impairment.

"Our results provide further evidence that marijuana use has a direct effect on executive function, and that both age of onset and magnitude of marijuana use can significantly influence cognitive processing," said Gruber. "Given the prevalence of marijuana use in the United States, these findings underscore the importance of establishing effective strategies to decrease marijuana use, especially in younger populations," she said.

Research was supported by the National Institute on Drug Abuse.

Scientific Presentation: Sunday, Nov. 14, 8–9 a.m., Halls B–H

165.9, Marijuana use and age of onset impacts performance on the Wisconsin Card Sorting Task
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TECHNICAL ABSTRACT: Marijuana (MJ) is the most commonly used illegal drug in the U.S. with 25.8 million Americans ages 12 and older reporting at least one instance of abuse in 2008. Several studies examining the impact of age of onset of MJ use have indicated that earlier onset of MJ use can lead to increased impairment on several cognitive domains, including verbal IQ, verbal memory, and time to complete visual scanning tasks. We hypothesized that MJ smokers would exhibit impaired performance on tasks of executive function relative to non-smoking control subjects, and that earlier age of onset of MJ use would be associated with higher levels of impairment. A battery of standard neurocognitive tests assessing executive function was administered to a group of 33 chronic, heavy MJ smoking subjects and a group of 26 healthy control subjects. As hypothesized, results indicated that control subjects performed better on several measures of executive function as compared to MJ smokers, specifically on the Wisconsin Card Sorting Task (WCST), an executive measure of cognitive flexibility during changing reinforcement schedules. On the WCST, the MJ smokers made significantly more perseverative errors on deck 1 (7.69 vs 3.55; p=.01) and during the entire task (10.97 vs 6.00; p=.02) relative to control subjects. The MJ smokers also had more losses of set in deck 2 (0.38 vs 0.16; p=.05) as compared to controls, suggestive of an inability to maintain cognitive set. In order to help clarify the impact of early vs later MJ use on executive function, the MJ group was separated into those who began smoking MJ prior to age 16 (n=19) and those who began MJ use at the age of 16 or older (n=14). As expected, early onset smokers achieved fewer categories on deck 1 of the WCST (3.50 vs 4.39; p=.05), and made more perseverative errors on both deck 1 (10.44 vs 4.31; p=.01) and during the entire task (14.69 vs 6.39; p=.01) relative to late onset smokers. In addition, the total number of categories achieved was positively correlated with age of MJ use onset (r=.364, p=.03) and negatively associated with grams of MJ used per week (r=-.316, p=.05) suggesting that MJ use has a direct effect on executive function. Results from this study indicate that MJ use affects executive processing, and that both age of onset and magnitude of MJ use can significantly influence these cognitive processes.

Abstract 576.6 Summary

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Teenage Amphetamine Abuse Affects Adult Brain Cell Function

Animal study may explain memory deficits in adults exposed to amphetamines in youth

Amphetamine abuse during adolescence permanently changes brain cells, according to new animal research. The study shows drug exposure during adolescence, but not young adulthood, altered electrical properties of brain cells in the cortex. The findings were presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Many children and teens with attention deficit hyperactivity disorder benefit from taking amphetamines, such as Adderall®, when closely supervised by parents and physicians. However, these drugs are also highly abused by healthy individuals, particularly adolescents between the ages of 12 and 17, a period when the brain continues to develop and mature.

To test the effects of amphetamine abuse on adult brain cell function, researchers at the University of Illinois, Urbana-Champaign repeatedly treated adolescent and young adult rats with the drug. When the rats reached adulthood, the researchers examined brain cells in the prefrontal cortex, a region important in memory, decision-making, and impulse control.

Brain cells from rats exposed to amphetamine abuse in adolescence, but not young adulthood, showed abnormal responses to electrical stimulation and insensitivity to the brain chemical dopamine. Because brain cells communicate using both electrical and chemical signals, these findings may indicate drug-induced disruptions in brain function.

Previous research showed deficits in working memory in adult rats exposed to amphetamines in adolescence. "Our new findings reveal that this change in cognitive behavior may be due in part to long-lasting changes in the function of neurons in the prefrontal cortex," said the study's senior author, Joshua Gulley, PhD. "We hypothesize that this is due to amphetamine disrupting the normal processes of brain development," he said.

Research was supported by the National Eye Institute.

Scientific Presentation: Tuesday, Nov. 16, 9–10 a.m., Halls B–H

576.6, Lasting alterations in synaptic transmission and intrinsic properties of rat prefrontal cortical neurons following adolescent exposure to amphetamines
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TECHNICAL ABSTRACT: Repeated exposure to amphetamine (AMPH) during adolescence has been shown to produce alterations in cognitive function that persist into adulthood. In order to understand the cellular underpinnings of this, we have examined the intrinsic and synaptic properties of medial prefrontal cortical neurons in rats exposed to saline or 3 mg/kg AMPH (10 i.p. injections) during adolescence (PND 27-45) or adulthood (PND 85-103). Whole-cell electrophysiological recordings were obtained from layer V pyramidal neurons in cortical brain slices taken from these rats at >PND 125. Therefore, recordings were obtained from adolescent- and adult-exposed rats following at least 12 or 3 weeks of withdrawal, respectively. In rats exposed to AMPH during adolescence, we found significant differences in action potential properties (including peak amplitude, time to peak, half-width, maximum rise, and decay slopes) compared to saline- injected controls ($P<0.05$, n(AMPH)=12 neurons, n(saline)=16). Furthermore, excitatory postsynaptic currents (EPSCs) evoked by white matter stimulation also differed in the AMPH-exposed animals. While the peak amplitude and rising slope of the EPSC were unaltered, the decay slope of the EPSC was significantly greater in neurons from AMPH-treated animals (saline: 6.5±1.1 pA/ms, n=9; AMPH: 12.7±2.1 pA/ms, n=7; $P<0.05$). Consistent with this change in decay, EPSC half-width was also significantly reduced in neurons from the AMPH-exposed animals. In the adult-exposed group, EPSC properties (amplitude, rise and decay slope, half-width) and action potential properties did not differ between neurons from AMPH- and saline-exposed rats ($P>0.05$, n(AMPH)=21, n(saline)=15). Our results suggest that adolescent AMPH exposure can lead to a lasting attenuation in excitatory synaptic transmission as well as changes in action potential properties. The dampened EPSC is consistent with a decrease in an NMDA receptor- mediated component. Such alterations could lead to decreased temporal summation of afferent activity and/or an alteration in NMDA receptor- dependent plasticity, such as LTP.

Abstract 792.20 Summary

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Binge Drinking in Adolescence Changes Stress Response in Adulthood

Animal study suggests teen drinking may set the stage for anxiety and depression later in life

Alcohol exposure during adolescence alters the body's ability to respond to stress in adulthood, according to new research in rats presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. Because problems regulating stress are associated with behavioral and mood disorders, the findings may indicate that binge drinking in adolescence leads to increased risk of anxiety or depression in adulthood.

Binge drinking, defined as more than four or five drinks in a single session, typically begins around age 13 and peaks between ages 18 and 22. According to the Substance Abuse and Mental Health Services Administration, 36 percent of teens aged 18 to 20 reported at least one binge-drinking episode in the previous 30 days.

The researchers, directed by Toni Pak, PhD, at Loyola University Stritch School of Medicine, found that rats exposed to a binge pattern of alcohol consumption around the time of puberty had lower circulating levels of the stress hormone corticosterone — akin to the human hormone cortisol — in adulthood. However, in response to the physical stress of alcohol exposure, these same rats showed a greater spike in corticosterone than rats that had not previously been exposed to alcohol.

"Our findings suggest that alcohol exposure during puberty permanently alters the system by which the brain triggers the body to produce stress hormones," said Pak. "This indicates that exposing young people to alcohol could permanently disrupt connections in the brain that are normally formed during puberty and are necessary to ensure healthy adult brain function," she said.

Research was supported by the National Institute on Alcohol Abuse and Alcoholism.

Scientific Presentation: Wednesday, Nov. 17, 11–12 p.m., Halls B–H

792.20, Peripubertal binge-pattern ethanol exposure has long-term effects on HPA axis reactivity in adulthood
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TECHNICAL ABSTRACT: Alcohol abuse among teenagers is a fundamental health concern. Neuronal damage resulting from excessive alcohol consumption during puberty can have permanent effects on adult behavior. Previously, we showed that binge alcohol exposure during puberty increased the expression of two critical central regulators of stress and anxiety behavior, corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) in the paraventricular nucleus (PVN) of the hypothalamus. In this study, we focused on identifying long-term effects of binge alcohol exposure during puberty on these same genes. We hypothesized that the increase in the CRH and AVP mRNA in the PVN observed after binge alcohol exposure during puberty persists into adulthood, thereby altering the responsiveness of the HPA axis to subsequent alcohol exposures. Peripubertal (37 days) male Wistar rats were treated with saline only or binge-pattern ethanol exposure (3 days of ip ethanol injection (3g/kg) followed by 2 days of saline and 3 days of ethanol injections) for a period of 8 days. One month later (67 days), these same animals were subdivided into 3 groups (within each pubertal treatment): 1) saline only, 2) single ethanol injection, or 3) binge-pattern ethanol injections. Body weights were measured daily during the treatments and the dose of ethanol adjusted accordingly. Animals were sacrificed by decapitation one hour after the last injection, trunk blood was collected, and brains were removed and rapidly frozen. Plasma was used to measure blood alcohol and circulating corticosterone (CORT) levels. Brains were sectioned at 200 μm on a freezing microtome and the PVN was microdissected using a 0.75 mm Palkovit's brainpunch tool (Stoelting Co.). Total RNA was isolated from the PVN and quantitative real time RT-PCR was performed to measure CRH and AVP mRNA. Average blood alcohol levels were 216 ± 14 mg/dl and did not differ among groups. Adult treatment with a single, or binge-pattern, ethanol injection significantly increased plasma CORT levels. However, in animals that had received prior ethanol exposure during puberty, plasma CORT levels were significantly higher than those with no prior ethanol exposure. Interestingly, basal CORT levels were lower in animals previously exposed to ethanol, suggesting that the HPA axis had a blunted response to general stressors. Together, these results demonstrate that binge alcohol exposure during puberty permanently alters the function of the adult HPA axis and also, alters its response to subsequent ethanol exposure. Overall, this permanent dysregulation of the HPA axis during pubertal development might lead to behavioral and/or mood disorders in adulthood.

Abstract 574.18 Summary

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Adolescent Rats More Vulnerable to Drug Addiction than Adults

Younger animals consumed more cocaine and worked harder for it than did adults

Adolescent rats take cocaine more readily than adults, are sensitive to lower doses, and work harder for access to the drug, according to new research presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The findings suggest that adolescence is a period of increased vulnerability to drug abuse and addiction.

Earlier use of cocaine is associated with more severe addiction; however, it has been unclear whether this was due to more opportunities for drug exposure or increased sensitivity to addiction in young people.

To answer this question, researchers directed by Michela Marinelli, PhD, at Rosalind Franklin University of Medicine and Science trained adolescent and adult rats to poke their noses into a small hole to obtain cocaine intravenously. Over a wide range of doses, adolescent rats learned how to get cocaine more readily than did the adults, and they also took more cocaine overall. In addition, when the researchers made cocaine harder to get, the adolescent rats worked two to three times harder than the adults to obtain the drug.

"Our study shows, for the first time, that adolescents are more sensitive to lower doses of cocaine, and they will work harder to obtain it," Marinelli said. "Our research is the first to offer scientific evidence that when all opportunities to take drugs are equal, biology alone makes adolescents more likely to use cocaine compared to adults," she said.

Research was supported by the National Institute on Drug Abuse and the American Recovery and Reinvestment Act.

Scientific Presentation: Tuesday, Nov. 16, 9–10 a.m., Halls B–H

574.18, Sensitivity and motivation for cocaine self-administration in adolescent rats relative to adults
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TECHNICAL ABSTRACT: Adolescence is a period of heightened propensity to develop cocaine addiction in humans. We have previously shown that midbrain dopamine neurons are more active in adolescent rats compared with adults. Given that elevated activity of dopamine neurons is associated with elevated propensity to self-administer cocaine in rats, we tested whether the period of adolescence is associated with higher liability to self-administer cocaine relative to adulthood. Adolescent (postnatal day 42 at the onset of self-administration) and adult (~postnatal day 88 at the onset of self-administration) rats were compared for their sensitivity to, and motivation for, cocaine using self-administration. To this end, different cohorts of rats were tested either (1) for acquisition of saline or very low to moderate doses of cocaine (75, 150, 600 µg/kg), (2) on a within-session dose-response paradigm (18.75-1200 µg/kg), or (3) on a between-session progressive ratio paradigm (600 µg/kg) in which the ratio was increased every other day (1, 3, 6, 12, 24, 48). In the acquisition tests, adolescents showed higher intake of cocaine than adults at low to moderate doses (150 µg/kg and 600 µg/kg), but did not differ in intake of a very low dose of cocaine (75 µg/kg) or saline. Adolescents and adults did not differ in the within-session dose-response paradigm. In the between-session progressive ratio test, adolescents worked more to obtain cocaine than adults, suggesting that adolescents have greater motivation to self-administer cocaine than adults. In conclusion, we show that adolescent rats are more likely to acquire self-administration of cocaine than adults at low to moderate doses of cocaine, and show greater motivation to self-administer this drug. These experiments could help explain the greater addiction liability observed in human adolescents relative to adults.