Embargoed until Nov. 17, 4:30 p.m. EST
Press Room, Nov. 15-19: (202) 249-4130

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Early-Life Experiences Affect Brain Development Into Adolescence

Effects of maternal and early-life stress, caregiver bonds seen on key brain circuits and receptors

WASHINGTON, DC — Studies released today reveal that maternal and early-life stress impact key brain structures in children, potentially contributing to the development of addictive behaviors, mental health disorders, and emotional problems later in life. Another study shows that the presence of a caregiver helps children to regulate their emotional responses until the brain circuits responsible for this task mature. 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 societal costs associated with addictive behaviors, emotional problems, and mental health disorders are substantial. Understanding the role that early-life experiences play in the subsequent development of these conditions may be a first step toward finding ways to prevent the occurrence of these serious health issues.

Today's new findings show that:

- Early-life stress appears to reduce the number of a key receptor in the brain's reward center; this same receptor is linked to subsequent development of addictive-like behaviors in mice (Scott John Mitchell, MS, presentation 782.13, see attached summary).
- Exposure to abuse or neglect during childhood is associated with differences in the development of circuits in the brain's decision-making center during adolescence, impacting the regulation of emotions and impulses (Elizabeth Cox, PhD, presentation 675.11, see attached summary).
- A caretaker's presence buffers children against emotional reactivity and influences the function of brain circuits regulating emotion. These circuits mature by adolescence, at which time they are no longer influenced by a caretaker's presence (Dylan Gee, MA, presentation 836.02, see attached summary).

Another recent finding discussed shows that:

- The combination of maternal stress during pregnancy and prenatal exposure to air pollution increases anxiety-like behavior in offspring (Jessica Lynn Bolton, BS, presentation 584.01).

"We are gaining new insight into how maternal and childhood stressors and caregiver relationships affect brain development," said moderator Martha Farah, PhD, a cognitive neuroscientist at the University of Pennsylvania in Philadelphia. "Clear correlations between early-life experiences and the function of specific brain circuits and receptors point toward new directions for preventing and treating mental health disorders."

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 the neuroscience of early development at *BrainFacts.org*.

Related Neuroscience 2014 Presentation:
Symposium: Nature, Nurture, and Trajectories to Mental Health
Wednesday, Nov. 19, 8:30–11 a.m., Ballroom A, WCC

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Abstract 782.13 Summary

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Research Identifies Possible Mechanism Linking Early-Life Stress to Addiction

Mice exposed to early-life trauma have reduced number of key receptor in brain's reward system

A new study in mice implicates a subtype of an important chemical receptor in cocaine addiction. The study also found that stress early in life reduces the number of these receptors, potentially influencing the subsequent development of addictive behaviors. 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.

"Early-life stress is known to be a risk factor in predisposing people to drug addiction," said lead author Scott Mitchell of Dundee University in the United Kingdom. "Now we have identified a biological mechanism that may help explain the complex association of childhood trauma with drug misuse, which could pave the way for the future development of new therapeutic strategies."

Addictive behaviors such as gambling and drug abuse have the ability to highjack the function of brain pathways that signal pleasure in response to natural rewards such as food. Within these pathways, a brain region called the nucleus accumbens processes the signals that occur in response to, or in anticipation of, such rewards. This brain region relies substantially on the chemical messenger GABA, which communicates about these rewards by activating the $GABA_A$ receptor ($GABA_AR$). This new research indicates that a subtype of this receptor appears to be significantly affected by early-life stress, providing a possible explanation behind the association of stress and addiction.

Researchers used a mouse model to ascertain how early-life adversity may affect $GABA_AR$ function in the nucleus accumbens and thus influence the development of cocaine addiction. They analyzed three groups of adult mice: a group of normal mice; a group that had been exposed to the stress of fragmented maternal care early in life; and a group of mice genetically engineered to lack the $GABA_AR$ subtype.

All mice were administered a daily dose of cocaine for 10 days, and researchers measured their response immediately after cocaine administration. The normal mice gradually increased their response to the same dose of cocaine over the 10 days — an addictive-like behavior. By contrast, the mice subjected previously to early-life stress and those mice that lacked the receptor subtype both exhibited a dramatically increased response on the very first day they received cocaine. Analysis also revealed that mice exposed to early-life stress had reduced levels of the $GABA_AR$ subtype in the brain's reward center, identifying a potential link between early-life trauma, reduced expression of a chemical receptor, and the response to cocaine in mice.

Research was supported with funds from the Medical Research Council (UK) and Wellbeing of Women (UK).

Scientific Presentation: Wednesday, Nov. 19, 1–2 p.m., Halls A-C

782.13, The effects of early-life stress on nucleus accumbens GABAA receptor function and cocaine-mediated behavior
***S. J. MITCHELL**[1], E. P. MAGUIRE[1], B. G. GUNN[1], L. CUNNINGHAM[1], M. B. HERD[1], S. L. KING[2], D. STEPHENS[2], J. D. SWINNY[3], D. BELELLI[1], J. J. LAMBERT[1]; [1]Div. of Neurosci., Dundee Univ., Dundee, United Kingdom; [2]Sch. of Psychology, Univ. of Sussex, Brighton, United Kingdom; [3]Sch. of Pharm. and Biomed. Sci., Univ. of Portsmouth, Portsmouth, United Kingdom

TECHNICAL ABSTRACT: The nucleus accumbens (NAc) consists primarily of GABAergic neurons, and is an essential integration site within the natural reward-pathway, which is 'hijacked' by drugs of abuse. We have previously shown for accumbal medium spiny neurons (MSNs) that α2-subunit containing $GABA_A$ receptors (α2-$GABA_AR$s), mediate phasic inhibition and that their genetic inactivation ($\alpha2^{-/-}$) abolishes behavioral sensitization to cocaine. Recently, linkage association studies in humans revealed a genetic association of GABRA2 haplotypes with cocaine addiction, which was evident only in individuals who had experienced childhood trauma. Collectively, these studies indicate an association of childhood trauma, drug addiction, and the GABARA2 haplotype.

Here, we have utilized a mouse model of early life stress (ELS) to investigate the impact of early-life adverse experiences on cocaine-induced behaviors and the putative role of NAc α2-$GABA_A$Rs in this interaction. A fragmented maternal care paradigm was implemented to produce ELS. Adult wild type (WT) control mice received a daily *i.p* injection of cocaine (10 mg/kg) for 10 days, which resulted in behavioral sensitization, manifest as enhanced cocaine-induced increase of locomotor activity *cf.* saline-injected controls. In contrast, adult ELS mice did not sensitize to cocaine, but exhibited a significantly increased acute locomotor response to a single cocaine injection (10 mg/kg) *cf.* WT control. Interestingly, but in contrast to a previous report, both features were exhibited by non-stressed $\alpha2^{-/-}$ mice. Whole-cell voltage-clamp recordings of NAc MSNs of adult mice, previously exposed to the ELS paradigm, revealed a significant reduction in the amplitude and frequency of miniature inhibitory post-synaptic currents (mIPSCs) *cf.* WT controls. Non-stressed $\alpha2^{-/-}$ mice exhibited similar alterations of mIPSCs properties *cf.* WT controls. Complementary immunohistochemical analysis revealed a significant and selective reduction of $GABA_A$R α2, but not α1 subunit staining in the NAc core of adult ELS *cf.* WT control mice, indicating that ELS selectively decreases α2-$GABA_A$R expression. In conclusion, ELS and $\alpha2^{-/-}$ mice share a selective α2-$GABA_A$R mediated reduction of inhibitory phasic transmission, which is accompanied under these experimental conditions for both models by an increased acute cocaine locomotor response and blunting of further behavioral sensitization to cocaine. Collectively, these findings complement the human studies and suggest that such mouse models may prove useful in permitting a better understanding of the complex association of cocaine abuse, childhood trauma and the GABRA2 gene.

Abstract 675.11 Summary

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Childhood Maltreatment May Alter Brain Circuits Regulating Emotions, Impulses

Findings may have implications for potential early detection and treatment strategies for depression, addiction

A new study finds that childhood neglect and abuse may alter the development of brain circuitry in adolescents, especially in the prefrontal cortex, a part of the brain that is important in emotion and impulse regulation. The findings were presented today 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 gained a rare window into how childhood neglect and abuse — both physical and emotional — alter the patterns of brain circuits during adolescence," said lead author Elizabeth Cox of Yale University. "These findings can help guide the development of early detection and intervention strategies for disorders such as depression and addiction."

Adolescence is a critical period in brain development, especially for the brain circuits that help to regulate emotions and impulses. It is also a time when disorders such as depression and substance abuse often develop.

The researchers conducted clinical and behavioral assessments and brain scans of adolescents who had been neglected or abused during childhood. They assessed the adolescents twice: first when the adolescents were about 15 years old and second about two and a half years later. Both times, magnetic resonance imaging scans provided information on brain structure and connectivity.

The findings suggest that maltreatment alters the brain circuitry both within the prefrontal cortex and from that region to other brain regions that are important in emotion and impulse control, potentially altering the function of the circuits connecting these regions.

Researchers also found preliminary evidence that the consequences of maltreatment differ between females and males, supporting earlier research that suggested females exposed to childhood maltreatment have a higher risk of developing depression, while males are more likely to struggle with substance abuse.

Research was supported with funds from the National Institute on Drug Abuse, National Institute of Mental Health, National Institutes of Health Roadmap for Medical Research Common Fund, International Bipolar Foundation, the American Foundation for Suicide Prevention, the Brain and Behavior Research Foundation, and the Women's Health Research at Yale.

Scientific Presentation: Wednesday, Nov. 19, 8–11:15 a.m., Room 206

675.11, Child maltreatment and corticostriatolimbic development in adolescence: Effects of maltreatment subtype and gender
***E. T. COX**, F. WANG, J. JOHNSTON, L. SPENCER, C. M. MAZURE, R. SINHA, L. MAYES, H. P. BLUMBERG; Yale Univ., New Haven, CT

TECHNICAL ABSTRACT: The adolescent/young adult epoch is a critical period in the development of corticostriatolimbic (CSL) neural systems that subserve impulse and emotional regulation. During adolescence, emotional symptoms and risky and addictive behaviors often emerge, with rates higher in individuals who have experienced childhood maltreatment (CM). Previous cross-sectional findings suggest CM has effects on CSL systems in adolescence, potentially contributing to these detrimental behavioral outcomes. In this longitudinal study, 44 adolescents/young adults with a history of CM (57% female) participated in two clinical and behavioral assessments, including completion of the Childhood Trauma Questionnaire (CTQ), and multimodal structural, diffusion tensor and functional imaging during emotional face processing. At initial scan the average age was 15.6 years, and at follow-up 18.3 years, with an average inter-scan interval of 2.7 years. The relationship between CTQ scores, including total and subscale scores, and structural and functional CSL trajectories were assessed. Findings were especially robust for white matter (WM) and included an inverse association between total CTQ scores with ventral frontal WM structural integrity

over time ($p<0.05$). Physical abuse was associated with frontal, temporal, and striatal WM structural integrity decreases ($p<0.05$) over time. Gender-related associations with emotional abuse were observed. Both sexes showed frontal WM findings, but only males showed a significant inverse association between CTQ scores with striatal WM structural integrity and females with temporopolar WM structural integrity ($p<0.05$). Functional imaging findings demonstrated effects especially for responses to fearful faces, for example, demonstrating effects for physical neglect in anterior cingulate cortex ($p<0.05$). Results extend previous cross-sectional CSL findings associated with CM, demonstrating their progression over adolescence. These include evidence for differing effects of CM subtypes on CSL trajectories. Gender-specific findings observed may be related to divergent CM associations in behavioral outcomes in males and females, observed previously and in this study, with highly stressed males more likely to develop externalizing behaviors and highly stressed females more likely to develop internalizing and depressive symptoms.

Abstract 836.02 Summary

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Presence of Caregiver Improves Children's Regulation of Their Emotions

By adolescence, brain circuitry is more developed and caregiver's presence has little effect

The presence of a caregiver may influence the function of children's brain circuits responsible for emotional regulation. With a caregiver present, those brain circuits act in a more mature fashion, resembling an adolescent pattern. In contrast, during adolescence, the presence of a caregiver has little effect on the function of these brain circuits, which have likely already matured. 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.

"Our research indicates a critical 'sensitive period' in the development of circuits responsible for emotional regulation," said lead author Dylan Gee of the University of California, Los Angeles. "The children in this study were all between 4 and 10 years of age. This appears to be a time when the outside environment is particularly influential in shaping development."

The brain's amygdala plays a key role in emotional reactions, and the prefrontal cortex in turn regulates the amygdala. The researchers investigated sensitive periods in the development of amygdala-prefrontal cortex circuitry.

They used functional magnetic resonance imaging to scan the brains of children and adolescents while they viewed either their mother or a stranger. The researchers also measured how well participants could regulate their responses to emotional stimuli while they were sitting with their mother versus when they were sitting with a stranger. Twenty-three children (ages 4-10) and 30 adolescents (ages 11-17) participated in the study.

The results showed that viewing their mother reduced amygdala reactivity in children and resulted in stronger communication between the amygdala and prefrontal cortex. Children also had better regulatory behavior in the presence of their mothers. In addition, children whose mothers had greater effects on their amygdala-prefrontal circuitry had lower anxiety and more secure parent-child attachment. In contrast, for adolescents, the presence of their mother had little impact on the function of these brain circuits, which have likely already matured.

The study reveals a potential neurobiological mechanism through which a caregiver provides an external source of emotional regulation in childhood before the brain circuitry supporting emotion regulation has fully developed.

Research was supported with funds from the National Institute of Mental Health, the National Science Foundation, and the Dana Foundation.

Scientific Presentation: Wednesday, Nov. 19, 1–5 p.m., Halls A-C

836.02, Maternal buffering of human amygdala-prefrontal circuitry specifically during childhood
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TECHNICAL ABSTRACT: Mature amygdala-medial prefrontal cortex (mPFC) circuitry provides regulation of affect in adulthood; however, this circuitry is late to develop. In (semi-) altricial species, caregivers provide potent regulation of affect in the absence of mature regulatory circuitry, buffering against stress reactivity and emotional over-arousal. The present investigation examined the effects of maternal stimuli on human amygdala-mPFC circuitry and related emotion-regulation behaviors. Children (n=23; ages: 4-10) showed greater suppression of right amygdala reactivity in the presence of maternal stimuli, which had no effect on adolescents' (n=30; ages: 11-17) amygdala reactivity (independent samples t-test for mother versus stranger: p=.049).

In the absence of maternal stimuli, children exhibited an immature connectivity pattern. However, in the presence of maternal stimuli, connectivity exhibited a mature pattern (i.e., negative connectivity) resembling the adolescent pattern (mother/stranger condition x age group interaction: p=.034). This pattern of

responding suggests that children are able to recruit more mature patterns of connectivity when in the presence of maternal stimuli. Maternal effects on amygdala-mPFC circuitry were associated with maternal buffering effects on behavior, such that affect-related regulation skills during an emotional face go/nogo were improved (i.e., fewer commission errors) when children were in the presence of their mother ($p=.015$). Individual differences emerged as well: greater maternal influence on amygdala-mPFC circuitry was associated with lower separation anxiety, more secure attachment, and more modulation of behavioral regulation by the mother in daily life. Taken together, the present findings suggest a neural mechanism through which caregivers modulate children's regulatory behavior by inducing a mature pattern of amygdala-prefrontal connectivity and buffering against heightened amygdala reactivity.

Speaker Summary (584.01)

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Maternal Stress Exacerbates the Effects of Prenatal Air Pollution Exposure on Offspring Anxiety, Cognition, and Neuroimmune Function in a Sex-Specific Manner

Nanosymposium: Early Exposure to Stress: Environmental Factors

Tuesday, Nov. 18, 1–3:45 p.m., Room 147B

Our research indicates that prenatal exposure to air pollution synergizes with maternal stress during pregnancy to increase the risk of mental health disorders in offspring.

Areas of low socioeconomic status experience the greatest burden of air pollution and other environmental toxins, along with fewer resources and high psychosocial stress. These unfavorable conditions are most hazardous for expectant mothers and their developing children, as a mother's well-being during pregnancy is a crucial determinant of the lifelong physical and mental health of her children. The rising rate of neurodevelopmental disorders, such as autism, has recently been associated with high levels of air pollution, which is one of the most pervasive environmental toxins in the modern world and thus of great concern for public health policy.

Stress may be most harmful for populations made vulnerable by other factors. For instance, stress exacerbates many forms of physical and mental health conditions, ranging from cardiovascular disease to schizophrenia. Maternal stress is especially harmful during the critical period of fetal development (e.g., maternal stress increases childhood asthma risk when experienced in combination with prenatal exposure to tobacco smoke or high levels of air pollution). This interaction is believed to be due to the action of stress and environmental toxins on common biological pathways, such as the immune system, but less is known about the effects on the developing brain.

To investigate how the experience of combined environmental and social stressors during pregnancy influences offspring brain function, female mice were exposed to air pollution (diesel exhaust particles) or a harmless control substance every three days throughout pregnancy. During the second half of pregnancy, half of the mice in each group were also given less nesting material, which is a novel model of maternal stress. Just prior to birth, moms were returned to normal housing conditions, in order to restrict our study to stressors experienced only indirectly by the offspring in the womb. Once the offspring grew up, we performed a series of behavioral tests that revealed increased levels of anxiety only in animals whose mothers had received exposure to both air pollution and stress during pregnancy. Intriguingly, the male offspring of this combined exposure group also exhibited a striking memory deficit, although the female offspring did not. This sex difference is consistent with many neurodevelopmental disorders, including autism.

These behavioral results suggest that the combination of prenatal exposure to air pollution and maternal stress may alter brain development during a critical period, resulting in long-term changes in brain function. As air pollution and stress are both known to act on the immune system, and the immune system is capable of altering brain function, we next investigated whether the immune system in the brain was changed long-term by prenatal air pollution and stress exposure. We found a significant shift to an inflammatory state in the brains of male, but not female, offspring that had been exposed to air pollution and stress prenatally, in a manner that was clearly correlated with the observed behavioral changes.

Overall, the findings from this study demonstrate that maternal stress can serve as a vulnerability factor, permitting an environmental toxin to permanently alter the trajectory of brain development, when it would have been insufficient to do so in isolation. Our results add to those from previous studies that have found that a mother's environment and experiences during pregnancy can affect her child's risk for neurodevelopmental disorders and mental health problems into adulthood. Ultimately, further research in this area can inform public health policy and environmental regulations, as well as aid the development of social and clinical interventions.

This research was supported with funds from the U.S. Environmental Protection Agency's Children's Environmental Health Center, the Duke Institute for Brain Sciences, and the National Science Foundation.