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RESEARCH FINDS NEW EVIDENCE THAT CHRONIC AND SHORT-TERM STRESS CAUSES WIDE-RANGING CHANGES IN BRAIN STRUCTURE AND PERFORMANCE

Early-life stress, chronic stress, and even short-term stress change how the brain is shaped — and how it functions

Washington, DC — Research released today reports new evidence that a wide range of stressful experiences change the physical structure and function of the brain, potentially affecting child development, adult brain wiring, and cognitive performance. The findings were reported at Neuroscience 2008, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The new findings show:

- Early-life stress physically alters brain structures associated with the regulation of stress and emotions, according to animal research. Researchers speculate that enlargement of the regions during childhood may indicate vulnerability to neuropsychiatric diseases caused by stress (Simona Spinelli, abstract 477.6, see attached summary).
- Children who have experienced early-life stress are more likely to use brain circuits involved in emotion, according to new imaging research. Children who spent time in institutions as infants use different brain circuits than other children when performing an emotionally arousing task (Nim Tottenham, abstract 281.10, see attached summary).
- Short-term stress — even that lasting just a few hours — can reduce cellular connections in the hippocampus, a brain region involved in learning and memory. Previous research had shown the impact of long-term stress; this study shows the same effect for short-term stress and identifies a drug that may prevent stress's harmful effect (Yuncai Chen, abstract 282.15, see attached summary).
- Chronic stress shrinks the hippocampus. This study resolves controversial findings in people with post-traumatic stress disorder and illustrates the damaging effect of stress on the brain (Fred Helmstetter, abstract 283.24, see attached summary).
- Short-term stress impairs decision-making in adult rats. Animals exposed to stress had greater difficulty choosing among options that maximized a reward payoff (Lauren Jones, abstract 489.16, see attached summary).

"We know that life experience changes the nervous system, and we are learning more about the troubling effect of stress in brain structure and performance," said press conference moderator Bruce McEwen, PhD, head of the Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology at The Rockefeller University in New York. "These effects are particularly worrying in the developing brain, which appears to be programmed by early stressful experience. Given today's rapid pace of life, these findings help to shed light on stress and raise the important question of how to manage it effectively."

# # #

Abstract 477.6 Summary

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Early-Life Stress Changes Structure of Brain

Structural changes may be early indicators of stress-induced brain disorders

Early-life stress has long-term consequences on brain structure, according to new animal research. The study, released at Neuroscience 2008, the Society for Neuroscience annual meeting and the world's largest source of emerging news about brain science and health, shows that stress during infancy increases the size of several brain regions important for the regulation of stress and emotions. Enlargement of these brain structures during childhood may indicate vulnerability to neuropsychiatric diseases caused by stress.

The researchers, led by Simona Spinelli, PhD, at the National Institutes of Health, compared rhesus monkeys raised for the first six months of life by their mothers (unstressed) to those raised with their peers (stressed). At six months of age, both groups of monkeys joined larger social groups. Several months later, the researchers took magnetic resonance images of the monkeys' brains.

The monkeys that had experienced early-life stress showed enlargement of brain regions involved in the regulation of stress and emotion, including the medial prefrontal cortex, dorsal anterior cingulate cortex, and cerebellar vermis. These findings are consistent with human brain imaging studies showing structural changes in the brains of children and adults exposed to early-life stress. However, in humans, it has been difficult to determine whether the structural abnormalities were present at birth, or occurred as a result of early-life stress.

"Our study shows that exposure to a stressful early-life environment has long-term consequences on brain development," said Spinelli. "Our data suggest that increased size of brain regions important for stress and emotional regulation observed during childhood may be a structural indicator for an increased risk of developing stress-related neuropsychiatric disorders in humans."

The researchers plan to continue the study, examining brain scans of these monkeys when they reach adolescence and adulthood.

This work was supported by the Intramural Research Programs of the U.S. National Institute on Alcohol Abuse and Alcoholism, the National Institute on Drug Abuse, and the National Institute of Child Health and Human Development.

Scientific Presentation: Monday, November 17, 2–3 p.m., Washington Convention Center, Hall A-C

477.6, Stress during a critical developmental period induces long-term morphological changes in primate brain
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TECHNICAL ABSTRACT: Traumatic experiences in early childhood are associated with increased risk for developing stress-related disorders which are linked to structural brain abnormalities in adults and children. However it is unclear if these volumetric brain changes are present before the disease onset or reflect the consequences of the disease progression. Therefore, the purpose of the current study was to investigate long-term effect of chronic exposure to an adverse environment during infancy on the morphology of several hypothesized vulnerable brain structures in juvenile Rhesus monkeys. To this aim we acquired antomical brain images on a 3 Tesla Siemens Magnetom Allegra scanner in mother-reared (MR) (7 males, 8 females)) and peer-reared (PR) (7 males, 6 females) animals, between 23 and 32 months of age, and measured the volume of the following brain areas: cerebellar vermis (CB-V), hippocampus (HC), corpus callosum (CC), medial prefrontal (MPF) and dorsal anterior cingulate (dACC) cortex. Image processing was performed with ANALYZE 7.5 (Biomedical Imaging Mayo Foundation). In addition to volumetric measurements, 5-HIAA level in CSF and ACTH and cortisol concentration in plasma were assessed. ACTH was lower in

PR monkeys ($F_{1,24}=7.6$, $p<0.02$), but there was no effect of rearing on cortisol or 5-HIAA concentration. Two-way ANOVA revealed an enlarged CB-V ($F_{1,24}=8.92$, $p<0.007$), mPFC ($F_{1,46}$, $p<0.05$) and dACC ($F_{1,24}=4.46$, $p<05$) in PR compared to MR group. There was no effect of rearing on total intracranial volume and on CC, however, as expected, males had bigger brain volumes (97097.8$\pm$1828 mm^3) than females (87190.1 ± 1510.3 mm^3) ($F_{1,24}=17.75$, $p<0.0003$). We also found reduced absolute HC volume in PR females \($F_{1,26}=8.9$, $p<0.006$) and positive correlation between ACTH level and both right and left HC volume in PR females (right side: $r2=0.62$, $p<0.04$; left side: $r2=0.69$ $p<0.03$), but not in PR males or MR animals. Notably, this effect was evident before the gender-specific hormonal influences that occur during puberty, suggesting that increased female vulnerability to mood and anxiety disorders may be present prior to adolescence. Our data suggest that enlargement of several brain areas vulnerable to the effect of an early-life adverse environment could be a structural phenotype for a high risk to stress-related neuropsychiatric disorders in human.
Support Contributed By: NIDA-, NIAAA- and NICHD--IRP.

Abstract 281.10 Summary

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Greater Tendency Toward Use of Emotional Brain Circuits in Children Adopted From Institutions

Findings suggest early-life stress may affect development of brain's emotional centers

Children who have experienced early-life stress are more likely to use brain circuits involved in emotion, according to new imaging research. The study, released at Neuroscience 2008, the Society for Neuroscience annual meeting and the world's largest source of emerging news about brain science and health, shows that children who spent time in institutions as infants use different brain circuits than other children when performing an emotionally arousing task. The findings suggest that adverse conditions in early life can affect the development of brain circuits involved in emotion.

"Children in the United States who have been adopted from orphanages abroad have experienced an upbringing that is outside of the bounds of a typical infancy," said Nim Tottenham, PhD, of the Sackler Institute at Weill Medical College of Cornell University, who led the study with senior researcher BJ Casey, PhD. "These types of experiences may lead to increased anxiety and difficulty regulating emotions."

Tottenham and her colleagues used functional magnetic resonance imaging to scan children while they performed a task: The children were shown images of fearful or neutral faces and were asked to indicate when a neutral expression appeared and abstain when a fearful face was shown. Children performed similarly on the task, regardless of where they were raised.

However, the brain circuits used by the two groups of children differed. Children raised in typical conditions showed increased activity in brain regions involved in cognition and perception, including the fusiform gyrus and inferior frontal gyrus. However, children who had spent time in institutions showed increased activity in brain regions involved in emotion, including the amygdala and ventral medial prefrontal cortex.

"Our findings suggest that adverse experiences in infancy increase emotional reactivity and activity in associated neural systems," said Tottenham. "These findings show an association between early-life stress and atypical development of emotion-related brain systems."

The research was supported by the U.S. National Institute of Mental Health.

Scientific Presentation: Sunday, November 16, 2–3 p.m., Washington Convention Center, Hall A-C

281.10, Early-life stress is associated with a neural bias towards emotionality

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TECHNICAL ABSTRACT: Early-life stress is associated with a neural bias towards emotionality

Adverse rearing environments can produce long-lasting change in responsivity to arousing stimuli and the ability to regulate emotion. Children who had been institutionally reared during infancy (n=19) were scanned using fMRI while engaged in an emotional go-nogo task (Hare et al., 2005, 2008), which measures cognitive control in the context of highly arousing stimuli. There were no group differences in accuracy on the task ($F(1,35) = 0.45$) relative to an age-matched sample (N=18). However, there were differences in the neural systems that the two groups recruited to perform the task. Unlike typical rearing, which resulted in a recruitment of a perceptuo-cognitive network, including fusiform gyrus and inferior frontal gyrus, early life adversity was associated with a greater tendency to engage an emotional network, including amygdala and ventral medial prefrontal cortex. Thus, although behavioral performance did not differ between groups, the neural circuit recruited by the previously institutionalized children tended towards an emotional one. These findings extend our earlier work showing an association between early life stress and atypically large amygdala volume and suggest that stressful experiences in infancy increase the bias towards recruitment of emotional systems.

Abstract 282.15 Summary

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Even Short-Term Stress Reduces Brain Cell Connections

Animal research identifies potential drug target to diminish effects of stress

New animal research shows that a few hours of severe stress can reduce cellular connections in the hippocampus, a brain region involved in learning and memory. Previous research showed that long-term stress reduced brain cell connections and impaired memory. The new study, presented at Neuroscience 2008, the Society for Neuroscience annual meeting and the world's largest source of emerging news about brain science and health, shows that relatively short stress induces the same effect and identifies a previously unsuspected stress hormone produced in the brain as a contributor. The findings help explain how stress impacts the brain and memory, and may hold a key to preventing this problem.

In the brain, cells called neurons receive information from other neurons at specialized spike-like outgrowths called dendritic spines. Researchers had shown that chronic stress reduced the number of dendritic spines in the hippocampus. In the current study, Tallie Z. Baram, MD PhD, and her colleagues at the University of California, Irvine, including lead author Yuncai Chen, PhD, found that just a few hours of severe emotional stress had the same effect.

However, the researchers found that chronic and short-term stress may use different hormones to shape brain cell connections. The stress hormone cortisol, which circulates throughout the body, is thought to be involved in reducing the number of dendritic spines following chronic stress. Following short-term stress, Baram and colleagues found that a different stress hormone, corticotropin-releasing hormone (CRH) — which is produced solely in the brain — is involved.

Baram blocked the decline in dendritic spines in mice that had experienced short-term stress with a drug that prevents CRH from interacting with its receptor. "Our findings can play an important role in the development of drugs that might prevent the undesirable effects of stress and offer insights into why some people are forgetful or have difficulty retaining information during stressful situations," Baram said.

The research was supported by the U.S. National Institutes of Health and the National Alliance for Research on Schizophrenia and Depression.

Scientific Presentation: Sunday, November 16, 3–4 p.m., Washington Convention Center, Hall A-C

282.15, Stress induces dendritic spine loss within hours in adult hippocampus: novel mechanisms
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TECHNICAL ABSTRACT: Rationale: Chronic stress leads to dendritic remodeling in the hippocampus, and this is likely a result of loss of dendritic spines. However, whether acute stress provokes loss of spines in hippocampal pyramidal cells has not been fully investigated. In addition, the nature of the mechanisms underlying spine and dendritic reduction with stress is unclear. Corticotropin-releasing hormone (CRH) is released in hippocampus by stress, and activates the CRH receptor CRFR1 on pyramidal neurons (Chen et al., 2004, 2006). CRH exposure leads to a rapid spine loss in hippocampal organotypic cultures, which is blocked by a selective CRFR1 antagonist (Chen et al., 2008). Here, we tested whether exposure of adult rodents to acute stress induces loss of dendritic spines, as well as the functional consequences.
Methods: Adult Thy1-YFP transgenic mice were exposed to a 5 hrs restraint and noise stress. At the end of this stress experience, spine densities on apical dendrites of CA3 pyramidal cells were compared among the following groups: (1) stressed, (2) stress-free controls, (3) pre-infused (icv) with the CRFR1 antagonist NBI 30775 (15 μg in 1 μl) 30 min prior to the 5 hr stress, and (4) stress-free and antagonist-infused.
Results: Stress induced a rapid reduction of spine density in apical dendrites of CA3 neurons, primarily on the 3rd and 4th order dendritic branches, the main postsynaptic target of excitatory commissural/associational fibers. The selective CRFR1 antagonist, abolished the stress-induced decline of spine density. In further support of a role for CRH in rapid spine loss after stress, two-photon live imaging demonstrated an increased spine retraction within minutes after the infusion of the peptide to organotypic cultures of hippocampus.
Conclusions: (1) Acute stress induces a rapid (within hours) spine loss in selective dendritic domains of adult hippocampus; (2) The activation of CRFR1, most likely by its endogenous ligand CRH, is involved in this process; and (3) CRH may promote spine loss via selective acceleration of spine retraction.

Abstract 283.24 Summary

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Chronic Stress Selectively Shrinks Brain Structure Important in Memory

Animal study resolves controversial finding in people with post-traumatic stress disorder

New animal research shows for the first time that chronic stress shrinks the hippocampus, a brain region important in learning and memory. The study, released at Neuroscience 2008, the Society for Neuroscience annual meeting and the world's largest source of emerging news about brain science and health, resolves controversial findings in humans and illustrates the damaging effect of stress on the brain.

"Smaller hippocampi have been observed in imaging studies of people suffering from post-traumatic stress disorder, or PTSD, but these measurements were completed only after diagnosis," said Fred Helmstetter, PhD, of the University of Wisconsin, Milwaukee, who led the study. "That made it impossible to determine whether the traumatic experience caused hippocampal size reduction, or if people with smaller hippocampi are more prone to develop PTSD."

To resolve the controversy, Helmstetter and colleagues used high-resolution 3-D magnetic resonance imaging to measure hippocampal volumes in rats before and after exposure to several weeks of chronic stress. They found that chronic stress reduced hippocampal size by more than 3 percent. However, chronic stress failed to alter the size of any other brain structure.

According to Helmstetter, these findings are consistent with studies in both animals and humans showing that stress impairs memory.

The research was supported by the U.S. National Institute of Mental Health and the University of Wisconsin, Milwaukee Research Growth Initiative.

Scientific Presentation: Sunday, November 16, 4–5 p.m., Washington Convention Center, Hall A-C

283.24, Chronic stress selectively reduces hippocampal volume in rats
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TECHNICAL ABSTACT: It is well-documented that stress can exert physiological changes in the hippocampus, a structure implicated in the formation of long-term declarative memory in humans and spatial memory in rodents. As it increases in duration and/or intensity, uncontrollable stress will exacerbate neuronal endangerment in rodent hippocampus and correlate with hippocampal volume reduction in humans, particularly in posttraumatic stress disorder (PTSD) patients such as combat veterans. However, since human imaging studies cannot address the causal link between stress and hippocampal changes, the notion of stress-induced diminution of hippocampal volume remains controversial.
To address these issues, the present study used a longitudinal, within-subjects design and compared hippocampal volumes in rats before and after exposure to chronic stress. Twenty Long-Evans rats (weight: 300-325 g) initially received a magnetic resonance imaging (MRI) scan to acquire T1-weighted brain images (spatial resolution: .068 x .068 x .75 mm) at 9.4T and then were divided into two groups: stress (n=10) and control (n=10). For 21 days, the stress group received 6-hour daily restraint/immobilization while controls stayed in their home cage. During the restraint, controls were deprived of food and water for the same amount of time to match food access in the stress group. After stress, all the animals received the same strructural MRI scan again to measure volume changes in the brain.
Comparisons of hippocampal volume revealed approximately 3% of hippocampal volume loss in the stress group. However, stress related volume changes were not found in other structures, such as the anterior cingulate cortex, retrosplenial granular cortex, or the adrenal gland. In addition to hippocampal volume loss, restraint procedures produced a drop in food intake and body weight compared to controls. In sum, chronic stress selectively reduces hippocampal volume within subjects without significantly modifying other brain structures or adrenal size. These novel findings directly support the idea that stress can alter the size of the hippocampus.

Abstract 489.16 Summary

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Short-Term Stress Impairs Decision-Making in Rats

Findings suggest stress adversely affects cognitive processes

New animal research shows that stress impairs decision-making. The findings, released at Neuroscience 2008, the Society for Neuroscience annual meeting and the world's largest source of emerging news about brain science and health, suggest that even short-term stress can affect cognition.

Previous research has shown that, given two options, rats will choose the one with the greatest or most likely reward. However, in this study, researchers at the University of Washington, led by graduate student Lauren Jones, found that after rats experienced an hour of stress, they had difficulty making the decision.

The researchers trained the rats on a track shaped like a figure eight lying on its side. Whether the rats chose to explore the left or right loop of the track, they were equally likely to receive a reward. When the researchers increased the size or the probability of reward on one side but not the other, the rats visited that side with greater frequency. However, stressed rats took longer to change their preference to reflect the bigger reward payoff.

"If uncontrollable stress disrupts rats' abilities to adjust their behavior toward greater reward for the same amount of work, how influenced by stress are people's frequent and complex daily decisions?" Jones asks. "Research on the effects of stress on cognitive processes such as learning, memory, and decision-making will help to characterize the potential problems stressed people face in their hectic lives."

The research was supported by the U.S. National Institute of Mental Health and the University of Washington.

Scientific Presentation: Monday, November 17, 4–5 p.m., Washington Convention Center, Hall A-C

489.16, Acute uncontrollable stress alters subsequent decision-making processes in rats
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TECHNICAL ABSTRACT: Patterns of decision-making between multiple reward options may be influenced by the qualitative value of each reward, the relative amount of each reward, the likelihood of the reward occurrence, and the degree of difficulty to obtain the reward. Using an automated figure-8 maze (Pedigo et al., 2006; Yoon et al., 2008), we have investigated the effects of stress on decision-making choice behavior in male Sprague-Dawley rats. Animals were trained until they were able to complete 40 laps (trials) in less than 30 minutes. From the center arm of the maze, the rat entered either the right or the left arm to obtain a reward. Afterwards, the animal returned to the center arm, where there was another reward and a new trial began. During initial training, each reward volume was equal (0.04 ml), and the probability of reward on any trial was .8 for each arm of the maze. Under these training parameters, the animals exhibited relatively stable numbers of left and right arm visits. Rats reliably increased their responses to one side of the maze in two conditions: when the reward volume was increased relative to the other reward, and when the probability of one reward was reduced from the initial value. However, given a combined test of volume increase and probability decrease of one reward, rats resumed their initial baseline response pattern, approximately half to each side. After experiencing acute uncontrollable stress (60 min restraint + 60 intermittent tailshocks), rats were significantly impaired in biasing their behavior toward the maze arm providing relatively larger reward. These results indicate that stress impairs decision-making processes in rats.