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SCIENTISTS REVEAL BRAIN CIRCUITRY INVOLVED IN POST-TRAUMATIC STRESS AND RELATED DISORDERS

"Light switch" in rodent brain turns off depressive behaviors; altered brain circuitry that presents potential risk factor for PTSD identified; rodent study on extinguishing bad memories

NEW ORLEANS — Researchers report new insights into how the brain responds to extreme stress, whether from combat, natural disasters, or repeated violent competition. The insights offer hope for detecting and treating several widespread and debilitating neuropsychiatric disorders, and were presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Post-traumatic stress disorder (PTSD) is a severe anxiety disorder that can develop after experience of a traumatic or terrifying event, such as those experienced in combat or from sexual aggression. Such events can overwhelm the individual's ability to cope and lead to a long-lasting disorder. Symptoms include re-experiencing the original trauma through flashbacks or nightmares, often triggered by seemingly innocuous events. PTSD can harm an individual's relationships, ability to work, to sleep, and other aspects of life.

The lifetime prevalence of PTSD among adult Americans is 8 percent. Neither drug nor behavioral treatments currently available are consistently effective in treating PTSD. Therefore, scientists are studying brain changes associated with PTSD and related cognitive disorders, looking for clues to help in the development of new treatments.

Today's findings show that:

- A fast-acting antidepressant, ketamine, appears to aid the formation of new nerve connections in the brain, helping to extinguish fearful memories. The mouse study could possibly lead to new PTSD treatments (Neil Fournier, PhD, abstract 399.09, see attached summary).
- In a mouse model, when dopamine neurons in the brain's reward system are turned on and off with a genetically engineered "light switch," depressive symptoms also come and go. The research highlights the importance of this neural circuit as a potential target for new depression treatments (Dipesh Chaudhury, PhD, abstract 522.01, see attached summary).
- Brain images of adolescents taken before and after the 2011 Japanese earthquake reveal that pre-existing weakness in certain brain connections could be a risk factor for intensified anxiety and PTSD after a traumatic life experience (Atsushi Sekiguchi, MD, PhD, abstract 168.12, see attached summary).
- Rodent studies show that repeated violent, competitive encounters drive changes in brain activity that shapes the ongoing behavior of losers and winners in distinct ways, and can contribute to depression and/or anxiety (Tamara Franklin, PhD, abstract 399.10, see attached summary).

Other recent findings discussed show:

- How exposure to stress causes molecular changes that weaken the ability of the prefrontal cortex to regulate behavior, thought, and emotion, while strengthening more primitive brain circuits (Amy Arnsten, PhD, abstract 310, see attached speaker summary).

– more –

“New methods for looking deep into the brain are revealing a dynamic landscape that changes as it must to cope with trauma,” said press conference moderator Sheena Josselyn, PhD, from the Hospital for Sick Children in Toronto, Ontario, an expert on the neural basis of brain function. “The more we learn about those changes, and how experiences remodel the brain, the more tools we will acquire for treating disorders that affect millions of people.”

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 399.09 Summary

Lead author: Neil Fournier, PhD (203) 974-7849
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Rapid-acting Antidepressant Could Improve Treatment for Post-Traumatic Stress Disorder

Ketamine appears to help extinguish learned fears in rodents

A rodent study finds that ketamine, a rapid-acting antidepressant, may offer new options for treating post-traumatic stress disorder (PTSD), in combination with therapy. The study finds that ketamine encourages the formation of new nerve connections in the brain that enable mice to forget their fear. The findings were presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Traumatic memories recur repeatedly and uncontrollably with PTSD and can be almost impossible to extinguish; current drug treatments are largely ineffective. Behavioral therapy also falls short. "Exposure-based" PTSD therapy repeatedly exposes patients to stimuli — such as a sudden loud noise — associated with the original trauma. While such therapy can gradually reduce the depth of fear, core PTSD symptoms often remain untouched. Neil Fournier, PhD, of Yale University School of Medicine, reported on the new potential treatment.

"There is an urgent need to develop new drugs that improve current therapies," Fournier said. "To extinguish fear, brain circuits must be remodeled and new nerve connections made, particularly in the brain's medial prefrontal cortex. It now appears that ketamine spurs these kinds of changes."

The researchers conditioned rats to fear a certain tone. They then administered either ketamine or saline to the animals. Twenty-four hours later, they retrained the animals to not fear the tone. Later, they tested the recall of this new, more positive memory association. The rats given ketamine had significantly improved memory of the new association, measured by a decrease in fear-related freezing behavior upon hearing the tone.

The researchers conclude that, in combination with exposure-therapy, ketamine may provide a rapid and novel approach to improve treatment for PTSD and related anxiety disorders.

Research was supported with funds from the National Institute of Mental Health and the Canadian Institutes of Health Research.

Scientific Presentation: Monday, Oct.15, 8– 9 a.m., Hall F-J

399.09, Treatment with the rapid antidepressant ketamine accelerates the extinction of fear memory in rats: Implications for the treatment of Post-Traumatic Stress Disorder
***N. M. FOURNIER**, P. LICZNERSKI, M. BANASR, *R. S. DUMAN; Yale Univ. Sch. Med., NEW HAVEN, CT

TECHNICAL ABSTRACT: Post-traumatic stress disorder (PTSD) is characterized by an inability to extinguish a previously acquired fearful memory. It is believed that extinction-related impairments play a role in the persistence of PTSD and its related symptoms. However, despite extensive research to better understand the neurobiology of PTSD, therapeutic options are still limited and are not effective in the vast majority of patients. As such, the development of novel agents that improve the extinction of fear memory is warranted. Recently, it has been demonstrated that administration of a single dose of ketamine can produce rapid and lasting antidepressant effects in patients resistant to classical antidepressant treatments. In addition, preliminary studies have found that patients receiving perioperative ketamine have a lower prevalence of PTSD than those that did not. Our laboratory has shown that the therapeutic effects of ketamine on depressive behavior require dendritic spine and synapse formation within the medial prefrontal cortex. Given that extinction of conditioned fear memories also requires plasticity in this brain region, we used auditory fear conditioning to investigate whether ketamine improves fear extinction learning. To test this possibility, rats received ketamine (10 mg/kg; i.p.) or saline twenty-four hours after conditioning and were then subjected to an extinction training paradigm the next day. We found that although ketamine treatment did not influence conditioned freezing responses during extinction training, freezing behavior was significantly lower the next day during an extinction recall session. Pretreatment with ketamine 2 hrs before extinction training did not enhance extinction learning. Interestingly, treatment with another rapid antidepressant scopolamine, which works through a different mechanism of action than ketamine, did not improve extinction recall. Taken together, our findings suggest that ketamine-induced plasticity encourages the formation of new neuronal circuits that promote extinction learning thus providing a rapid and novel pharmacological approach that when combined with behavioral extinction training can result in an improved treatment of PTSD and related symptomology. Studies are currently underway to characterize the role of glutamate-AMPA receptors, downstream signaling, and molecular changes that promote enhanced fear extinction after ketamine treatment.

Abstract 522.01 Summary

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Tamping Down Dopamine Neurons Can Control Depression in Mice

Genetically engineered light switch in brain controls reward system and depressive symptoms

Research in an animal model shows that activity of dopamine neurons in the brain's reward system directly affects the development of depression. In mice, high activity levels of these neurons bring on depression-like behaviors, whereas inhibiting their activity eases them. The findings were presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Major depressive disorder affects some 121 million people worldwide and is the third leading contributor to the global burden of disease. But with current treatments effectively treating only about 40 percent of depressed patients, there is an urgent need for new therapeutic approaches.

Lead authors Dipesh Chaudhury, PhD, and Jessica Walsh in Ming-Hu Han's laboratory at the Mount Sinai School of Medicine, examined the possible dysfunction of dopamine neurons in the brain's ventral tegmental area (VTA), the seat of the reward system. These neurons produce dopamine, a biochemical that regulates reward-seeking behavior.

"Depression and other psychiatric disorders are typically regarded as either chemical imbalances or the result of brain injury," Chaudhury said. "Mounting evidence suggests they result from the malfunction of neural circuits, interconnected groups of neurons with a common function. Our results do indicate that the dopamine reward circuit could be a promising target for new depression treatments."

The study employed a combination of optogenetic and behavioral research techniques. With optogenetics, scientists genetically engineer molecules that can be targeted to specific neurons and allow their activity to be activated or silenced by light.

By optically increasing the activity of dopamine neurons in mice that had endured a social defeat, the researchers produced "depressed" behavior — namely, avoidance of other mice and of a sweet treat. Inhibiting the activity of dopamine neurons in these mice eased their depressive-like behavior. Identification of this circuit in depression-like behavior provides a specific target for developing treatments for depression.

Research was supported with funds from the National Institute of Mental Health, Johnson & Johnson, the International Mental Health Research Organization, and the National Institutes of Health.

Scientific Presentation: Tuesday, Oct. 16, 8–10:45 a.m., Room 273

522.01, Optogenetic dissection of the functional role of the firing patterns of ventral tegmental area dopamine neurons in encoding behavioral susceptibility to social defeat stress
*__D. CHAUDHURY__, J. J. WALSH, B. JUAREZ, A. K. FRIEDMAN, J. KOO, D. FERGUSON, H.-C. TSAI, L. POMERANZ, S. KU, D. J. CHRISTOFFEL, E. MOUZON, M. LOBO, R. L. NEVE, J. M. FRIEDMAN, S. RUSSO, K. DEISSEROTH, E. J. NESTLER, M.-H. HAN; Pharmacol. and Therapeut., Mount Sinai Sch. Of Med., New York, NY; Stanford Univ., Stanford, CA; Rockefeller Univ., New York, NY; Univ. of Maryland, Baltimore, MD; MIT, Cambridge, MA

TECHNICAL ABSTRACT: The role of high frequency phasic firing of ventral tegmental area (VTA) dopamine (DA) neurons in mediating stress vulnerability is not completely understood. In a chronic social defeat model of depression, our recent studies found that mice exhibiting a susceptible (depressive), but not resilient (non-depressive) phenotype, exhibited consistently increased phasic firing of VTA DA neurons. To investigate the casual relationship between phasic firing in these neurons and susceptibility to social defeat in freely-behaving mice, we selectively targeted DA cells by injecting a Cre-dependent viral vector AAV-DIO-ChR2 (channel rhodopsin2), into the VTA of transgenic TH-Cre mice. First, through in vitro and in vivo electrophysiological recordings, we demonstrated that light activation of ChR2 reliably generated physiologically relevant low frequency tonic and high frequency phasic firing patterns in VTA DA neurons. We then showed that optogenetic induction of phasic, but not tonic, firing, in VTA DA neurons of mice, during a social interaction test, 24 hours after undergoing a subthreshold social defeat paradigm, induced a susceptible phenotype as measured by increased social avoidance and decreased sucrose preference (anhedonia). Furthermore, optogenetic phasic stimulation of previously resilient mice induced the susceptible phenotype. To further explore the importance of neuronal firing

in modulating behavioral susceptibility to social defeat stress we are performing ‘rescue' experiments. Here, we are utilizing the Cre-dependent viral vector AAV-DIO-NpHR (Halorhodopsin 3.0) to decrease the activity of VTA DA neurons of previously susceptible mice in order to promote the resilient phenotype. These studies provide direct evidence showing that the phasic firing pattern of VTA DA neurons in the brain reward circuitry encodes a signal for stress vulnerability.

Abstract 168.12 Summary

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Trauma Induced by Japanese Earthquake Reveals Telling Brain Patterns for Post-Traumatic Stress Disorder

Changes in brain's white matter could be risk factor for anxiety disorder

The catastrophic 2011 earthquake in Japan has provided a valuable opportunity to examine changes in the brain's white matter after a major disaster. The study authors find that people who had weak neural connections on the front, right side of the brain prior to the earthquake were more likely to develop extreme anxiety after it. The study is the first report of a long-term investigation of changes in the brain's white matter before and after a severe disaster. The findings were presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The brain's white matter is dense with axons, nerve fibers that extend from nerve cell bodies. These axons make connections and transmit signals from one brain region to another. Prior research showed that white matter changes in people with post-traumatic stress disorder (PTSD), and in those who encounter highly stressful life events. But it has been difficult to ascertain which atypical neural connections existed prior to trauma, thus heightening PTSD risk, and which are a direct result of the stressful experience. Research reported by lead author Atsushi Sekiguchi, MD, PhD, from Tohoku University, is the first long-term study able to examine this question.

The researchers used a brain-image database that had been gathered from a group of healthy adolescents before the earthquake struck. Thirty participants permitted the researchers to re-examine their brains' white matter and measure their anxiety levels three to four months after the earthquake.

The scientists found that weak connections observed in an area of the brain's front right side before the earthquake were a pre-existing factor correlated with increased vulnerability to high anxiety after the earthquake. On the other hand, stronger connections in white matter in the front left sides after the earthquake correlated with post-event anxiety.

"The extremely traumatic Tohoku Earthquake provided us a rare opportunity to investigate changes in the brain's white matter specifically associated with a large-scale disaster," Sekiguchi said. "Our results provide new evidence of the neural network changes soon after a stressful life event, and may ultimately enable the quick detection of emerging PTSD in survivors."

Research was supported with funds from the Ministry of Health, Labour and Welfare in Japan.

Scientific Presentation: Sunday, Oct. 14, 11 a.m.–12 p.m., Hall F-J

168.12, Brain structural changes as vulnerability factors and acquired signs of post-earthquake distress
*__A. SEKIGUCHI__, M. SUGIURA, Y. TAKI, Y. KOTOZAKI, R. NOUCHI, H. TAKEUCHI, T. ARAKI, S. HANAWA, S. NAKAGAWA, C. M. MIYAUCHI, A. SAKUMA, R. KAWASHIMA,; Sendai, Japan; Functional Brain Imaging, Developmental Cognitive Neuroscience., Smart Ageing Intl. Res. Ctr., IDAC, Tohoku Univ., Sendai, Japan; Intl. Res. Inst. of Disaster Science, Tohoku Univ., Sendai, Japan

TECHNICAL ABSTRACT: Many survivors of severe disasters, even those without posttraumatic stress disorder (PTSD), need psychological support. To understand the pathogenesis of PTSD symptoms and prevent the development of PTSD, the critical issue is to distinguish neurological abnormalities as vulnerability factors from acquired signs of emotional distress in the early stage of adaptation to the trauma in the normal population. The neurological underpinnings of PTSD have been well characterized, but the causal relationships with the traumatic event are still unclear, because of difficulties with prospective studies.
We had obtained magnetic resonance images from a group of healthy adolescents before the Great East Japan Earthquake in multiple studies performed in our laboratory. Therefore, the severe magnitude 9.0 earthquake has provided an opportunity to study longitudinal brain structural changes. We examined thirty non-PTSD subjects using voxel-based analyses in a longitudinal diffusion-tensor imaging (DTI) study before and after the earthquake. We found that the state anxiety level after the earthquake was negatively associated with fractional anisotropy (FA) in the right anterior cingulum (Cg) before the earthquake, and positively associated with increased FA in the left anterior Cg and uncinate fasciculus (Uf) before and after the earthquake. Our results demonstrated that reduced FA in the

right anterior Cg was a vulnerability factor, and increased FA in the left anterior Cg and Uf was an acquired sign of state anxiety after the earthquake. As the Cg is involved in fear and anxiety processing, our results indicate that this processing is related to vulnerability to anxiety after the earthquake. Furthermore, increased FA in the left anterior Cg and Uf was induced by frequent emotional processing and regulation access in the early stage of trauma adaptation. These findings provide new evidence of neural network-level posttraumatic responses soon after the traumatic event, and may contribute to the development of effective methods to prevent PTSD.

Abstract 399.10 Summary

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Relentless Competition Changes the Brain and Alters Behavior

Mouse study reveals how competitive encounters affect the brains of winners and losers

Rodent studies show that repeated competitive encounters disrupt the normal balance between decision-making and emotion-processing centers in the brain. The findings also suggest that repeated aggressive encounters alter the baseline connectivity between particular brain areas, possibly affecting subsequent choices in social encounters. The findings were presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Male mice are typically territorial, and ones that find themselves perpetual losers in violent encounters with other male mice develop more passive behaviors (a strategy thought to be related to depression in humans). Those mice that typically come out on top develop more aggressive behaviors. Both losers and winners develop anxiety-like behavior. Now, new research reported by lead author Tamara Franklin, PhD, of the European Molecular Biology Laboratory (EMBL) has found reduced communication between the frontal cortex, a brain region controlling planning and decision-making, and lower brainstem areas in the socially defeated mice, perhaps blocking more defensive, aggressive action and potentially also leading to enhanced fear and anxiety.

"Our findings explain how repeated winning and losing reprograms the brain to prepare for future encounters," Franklin said. "By studying brain changes induced by repeated victory or defeat, we can learn about the brain circuits that control depression-like behavior."

In the lab, researchers observed the behavior of mice during social encounters, while monitoring electrical activity in different parts of their brains, and later analyzing levels of specific brain molecules associated with brain activity. The researchers found that repeated losing caused a decrease in brain activity in the frontal cortex, and repeated winning caused an increase in activity in the same area. The findings could ultimately lead to an understanding of how to block or reverse inappropriate coping strategies.

Research was supported with funds from the European Molecular Biology Laboratory and the Swiss Foundation for Grants in Medicine and Biology.

Scientific Presentation: Monday, Oct. 15, 9–10 a.m., Hall F-J

399.10, Changes in functional connectivity resulting from repeated competitive encounters in mice
*__T. B. FRANKLIN__, A. VYSSOTSKI, C. GROSS; Mouse Biol. Unit, European Mol. Biol. Lab., Monterotondo, Italy; Inst. of Neuroinformatics, Univ. of Zurich/ETH Zurich, Zurich, Switzerland

TECHNICAL ABSTRACT: Previous experience during competitive encounters greatly affects behavioral choices in subsequent social encounters, and in potentially stressful environments. Mice that have been exposed to chronic social defeat develop a tendency to use passive rather than active coping responses, while mice exposed to repeated victories display enhanced aggression and dominance behaviors. In order to investigate this induced change in behavioral strategy, we use a combination of in vivo electrophysiology and protein quantification in mice. In brain areas previously associated with the defense response, chronic winning or losing has contrasting effects on a marker of long-term plasticity, deltaFosB. In addition, we have used in vivo electrophysiology and observed changes in functional connectivity between these brain areas, even in the absence of any external social stimuli. This suggests that the baseline connectivity of particular brain areas is altered by repeated aggressive encounters, providing a possible factor underlying the likelihood that an animal takes a passive rather than an active role during social confrontations. Findings provided here further highlight plasticity in the adult brain as a result of social interactions, and have implications for the functional neuroanatomy underlying depression.

Speaker's Summary

Speaker: Amy Arnsten, PhD (203) 785-4431
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Special Lecture**: Going to Hell in a Hand Basket: Molecular Weakening of Prefrontal Cortical Regulation during Stress (310)**

Monday, Oct.15, 11:30 a.m.–12:40 p.m., Hall D

This lecture describes the regulation of behavior, thought and emotion by the highly evolved prefrontal cortex, and how these "top-down" circuits are weakened by molecular events during stress exposure. In contrast, more primitive brain circuits are strengthened by stress signaling mechanisms. Many of the genetic links in neuropsychiatric illness involve insults to the molecular brakes on stress-signaling pathways, leading to increased susceptibility to prefrontal cortical dysfunction.