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MENTAL ILLNESS:
PROBING THE CAUSES OF SCHIZOPHRENIA, DEPRESSION, & ANXIETY
New understanding of brain systems suggests new treatment options

Washington — New research identifies the brain chemicals and circuits involved in mental illnesses like schizophrenia, depression, and anxiety, giving potential new directions to their treatment. In addition, research with children shows that early-life depression and anxiety changes the structure of the developing brain. The findings were presented at Neuroscience 2011, the Society for Neuroscience's annual meeting and the world's largest source of emerging news about brain science and health.

One in 17 Americans suffer from a serious mental illness, such as schizophrenia, major depression, or bipolar disorder, making it one of the leading causes of disability. Yet science is only beginning to understand the underlying physical causes of these diseases.

Today's new findings show:

- Childhood anxiety and depression alter the way the amygdala connects to other regions of the brain. This finding may help explain how early life stress can lead to future emotional and behavioral issues (Shaozheng Qin, PhD, abstract 927.06, see attached summary).
- In animal studies, a link between two factors associated with schizophrenia, prenatal infection and impaired function of a molecule important in memory (Melissa Burt, abstract 763.11, see attached summary).
- Researchers have identified a brain chemical important to antidepressant response in mice. The findings may help in the design of therapies for major depression (Maha Elsayed, abstract 904.10, see attached summary).
- The connections between two specific areas of the brain — the prefrontal cortex and the dorsal raphe nucleus — may contribute to depression. Stimulating these circuits in rats had an antidepressant effect (Melissa Warden, PhD, abstract 306.15, see attached summary).
- An enzyme called STEP is elevated in the brains of people with schizophrenia. Mice lacking this chemical did not develop schizophrenia-like behaviors (Nikisha Carty, PhD, abstract 238.03, see attached summary).

"If we can fully understand the roots of mental illness in brain circuitry and systems, we may be able to develop better treatment targets for the millions suffering from these diseases," said press conference moderator Carol Tamminga, MD, of the University of Texas Southwestern, who is an expert on schizophrenia.

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

– more –

Related Presentations:

Minisymposium: **Neural Bases of Self-Regulation and Their Disruption in Childhood Psychiatric Disorders**
Tuesday, Nov. 15, 1:30–4 p.m., Room 145B

Peter and Patricia Gruber Lecture: **Rett Syndrome: Linking Epigenetics and Neuronal Plasticity**
Sunday, Nov. 13, 2:30–3:40 p.m., Hall D

Special Lecture: **The Neurobiology of Mood: The Search Continues**
Wednesday, Nov. 16, 1–2:10 p.m., Hall D
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Abstract 927.06 Summary

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Childhood Anxiety and Depression Alter Brain Circuitry

Findings suggest childhood disorders increase connections between the amygdala and other parts of the brain

Anxiety and depression in childhood can alter brain circuitry, according to new research presented at Neuroscience 2011, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The findings are important for understanding how early life stress and anxiety affect the development of cognitive, emotional, and social skills.

Childhood stress and trauma have been linked to higher rates of emotional and psychiatric problems later in life. The amygdala and its circuits form a brain system for processing negative emotions. However, little is known about how this circuit is altered in young children who suffer from anxiety and depression.

To study this, researchers scanned the brains of 60 children, ages 7 to 9. The children were assessed for anxiety and depression using those portions of the Child Behavior Checklist. The researchers found the most anxious or depressed children displayed increased connectivity between the amygdala and other parts of the brain involved in emotional processing and regulation.

"Our study is the first to show that anxiety and depression problems during childhood alter the intrinsic functional connectivity of the amygdala in the developing brain," said lead author Shaozheng Qin, PhD, a postdoctoral scholar at Stanford University. "Our findings provide initial evidence to suggest that early life anxiety and depression problems may play a role in brain dysfunction observed in adults with various psychiatric disorders," Qin said.

The research was supported by the National Institute of Health and the Netherlands Organization for Scientific Research.

Scientific Presentation: Wednesday, Nov. 16, 2–3 p.m., Halls A–C

927.06, Increased intrinsic functional connectivity of amygdala in young children with high anxiety and depression problems
S. QIN, C. B. YOUNG, V. MENON; Dept. of Psychiatry and Behavioral Sci., Stanford Univ., Stanford, CA

TECHNICAL ABSTRACT: The human brain undergoes rapid development during childhood, with dramatic changes in emotional function. The amygdala and its connected circuitry are the core of emotion function, and are thus more vulnerable to the negative effects caused by emotion problems. Early life stress, anxiety and depression are believed to play a critical role in hindering healthy emotion development. However, little is known about how these anxiety and depression problems in young children alter intrinsic functioning of the developing brain, particularly for amygdala-centered emotion networks. Using resting-state functional magnetic resonance imaging (fMRI), we investigated amygdala-centered intrinsic functional connectivity in 60 typically developing children (ages 7-9 years). Anatomically defined regions of interest for the functional connectivity analyses included the left and right amygdala. Anxiety and depression problems were assessed using the subscales of the Child Behavior Checklist, completed by a parent of each child. First, we replicated amygdala-centered intrinsic functional connectivity networks observed in the adult brain, including subcortical, limbic and paralimbic regions, a set of regions in prefrontal and posterior midline structures, and the cerebellum. More importantly, we found that the strength of connectivity of the amygdala with caudate, bilateral insular cortex and lateral prefrontal cortex positively correlated with parent-reported each child's anxiety and depression problems. Furthermore, we found significantly increased functional connectivity of the amygdala with left medial prefrontal cortex, bilateral posterior insular and regions in posterior midline structures in children with high anxiety and depression problems as compared to those with no problems. Our study demonstrates that young children with high anxiety and depression problems show increased functional connectivity of the amygdala with medial prefrontal, insula and posterior visual cortices. These alterations might result from relatively greater metabolic changes in these structures due to the constant exposure to stressful situations. Similar effects have been seen in adults with various psychiatric disorders characterized by greater susceptibility to anxiety and/or depression. Thus, our findings provide initial evidence to suggest that early life anxiety and depression problems may play an important role in brain dysfunction observed in adults with various psychiatric disorders.

Abstract 763.11 Summary

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Animal Study May Explain Link between Prenatal Infection and Schizophrenia

Prenatal infection reduced function of brain protein thought to be important in schizophrenia

New findings show prenatal infection — a known risk factor for schizophrenia — can cause changes in the brain and behavior comparable to certain aspects of schizophrenia. The animal study shows that prenatal infection decreases functioning in key brain chemical receptors vital for long-term memory. The findings were presented at Neuroscience 2011, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Schizophrenia is thought to reduce the function of proteins important in brain cell communication called N-methyl-D-aspartate receptors (NMDAR). The new study, led by Melissa Burt, at McGill University, suggests prenatal infection could lead to schizophrenia by decreasing NMDAR function.

To simulate prenatal infection, the researchers administered a bacterial toxin to pregnant rats. When the offspring reached adolescence, they showed reduced NMDAR function in the hippocampus, a brain structure important in memory. The animals also had deficits in spatial memory. People with schizophrenia often show memory deficits. "Understanding how specific environmental factors, like prenatal infection, increase the risk for schizophrenia is necessary in order to devise preventive strategies for this serious disorder," Burt said.

The research was supported by the Canadian Institutes of Health Research.

Scientific Presentation: Wednesday, Nov. 16, 10–11 a.m., Halls A–C

763.11, Prenatal infection, a risk factor for schizophrenia, produces spatial processing deficits and N-methyl-D-aspartate receptor (NMDAR) hypofunction in the hippocampus of adolescent male rat offspring.
M. A. BURT[1,2], *Y. C. TSE[1,3], P. BOKSA[1,2,3], T. P. WONG[1,2,3,4]; [1]Douglas Mental Hlth. Univ., Montreal, QC, Canada; [2]Neurol. and Neurosurg., [3]Psychiatry, [4]Pharmacol. and Therapeut., McGill Univ., Montreal, QC, Canada

TECHNICAL ABSTRACT: N-methyl-D-aspartate receptor (NMDAR) hypofunction has been hypothesized as a pathological change in schizophrenia and suggested to account for many symptoms manifested in this disorder. Nonetheless, the etiology is still unknown for this neurodevelopmental disorder. In recent years, however, prenatal infection has been identified as an environmental risk factor for schizophrenia. A rat model of prenatal infection was developed, where the bacterial endotoxin, lipopolysaccharide (LPS), is administered during prenatal development. This model has reproduced schizophrenia-related behavioral changes and alterations in the hippocampus, a structure susceptible to deficits within the schizophrenia population, in offspring. We hypothesized that prenatal infection could reduce NMDAR function in the hippocampus and impair normal spatial processing of the offspring. Sprague-Dawley rats were administered 100 μg/kg of LPS or saline control on both gestational days 15 and 16 and the adolescent male offspring were utilized. First, we examined NMDAR function by measuring NMDAR-mediated fEPSP slope across increasing fiber volley sizes in hippocampal CA1 slices. Also, we measured NMDAR/α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) EPSC ratio in individual CA1 pyramidal neurons. We found that prenatal LPS treatment caused a significant reduction in NMDAR function in both field and whole cell recordings. Next, we investigated NMDAR-dependent synaptic plasticity. Previous studies found no differences in long-term potentiation (LTP), a cellular model for learning and memory; therefore we looked at another form of plasticity, long-term depression (LTD). We utilized an NMDAR-dependent LTD protocol, paired-pulse (PP) LTD, in hippocampal CA1 slices, and found prenatal LPS treatment abolished NMDAR-dependent PP-LTD. Finally, we were examined spatial memory in the Morris water maze (MWM) using a short, 1 day training protocol followed by a 24 hour retention probe. We found that rats treated prenatally with LPS were impaired, having no significant memory for the platform location in the probe trial. This is interesting because NMDAR-dependent LTD in the CA1 has previously been implicated in consolidation of spatial memory in the MWM. Such results indicate that NMDAR function in the hippocampus, a structure of noteworthy vulnerability in schizophrenia, is particularly susceptible to the deleterious effects of prenatal infection.

Abstract 904.10 Summary

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Brain Chemical Is Key to Antidepressant Response

Animal study finds molecule important in restoring cell production and behavior after stress

A brain chemical called fibroblast growth factor-2 (FGF2) may protect against depression, suggests a new animal study. The research was presented at Neuroscience 2011, 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 a new mechanism to explore in creating faster, more effective antidepressant medications.

Recent studies indicate people with depression have fewer brain cells called glia, and animal studies show that loss of these cells can trigger depression. FGF2 supports the growth of new glia.

In the current study, researchers led by Maha Elsayed, of Yale University, found FGF2 restored glia cells lost to stress and improved depressive-like behavior in mice. The team exposed mice to natural stressors until the mice showed behaviors akin to depression. The stressed mice that were given FGF2 produced new glia cells and behaved in tests as if they were not depressed.

"Our study confirms that FGF2 can alleviate symptoms of depression in animals, and goes one step further in providing a new targeted mechanism for treating depression," said Elsayed. "Our results show that FGF2 promotes the formation of new glia cells, restoring the glia deficits triggered by stress," she said.

The research was supported by National Institute of Mental Health and the State of Connecticut.

Scientific Presentation: Wednesday, Nov. 16, 2–3 p.m., Halls A–C

904.10, FGF2 is necessary and sufficient for the gliogenic and behavioral actions of antidepressants
M. ELSAYED, M. BANASR, V. DURIC, N. FOURNIER, P. LICZNERSKI, R. DUMAN; Yale university, NEW HAVEN, CT

TECHNICAL ABSTRACT: Preclinical studies have demonstrated that chronic stress decreases glial number in the prefrontal cortex (PFC), a cellular deficit consistently reported in postmortem studies of major depressive disorder (MDD) patients. Antidepressants on the other hand, oppose these cellular abnormalities, in part by increasing the generation of new oligodendrocytes. Given that MDD subjects treated with antidepressants no longer show decreases in the expression of a potent mitogen, fibroblast growth factor-2 (FGF2), we asked whether FGF2 signaling could underlie the opposing actions of stress and antidepressant treatment on gliogenesis as well as behavior in models of depression. We found that: 1) chronic intracerebroventricular (icv) infusion of FGF2 in mice blocks the decrease in PFC gliogenesis caused by chronic unpredictable stress (CUS). Double labeling studies show that the cells regulated by stress and FGF2 are NG2+, although other populations of cells could also be altered (currently under investigation). Furthermore, FGF2 infusions blocked CUS-induced anhedonia, a core symptom of MDD. 2) We also found that chronic administration of the antidepressant fluoxetine increases the expression of FGF2 as well as FGF receptor-1 (FGFR1) in the PFC, leading to studies of a selective inhibitor of this receptor. 3) When FGFR1 is blocked by SU5402 infusion (icv), fluoxetine-induction of gliogenesis in the PFC is abolished. Furthermore, SU5402 infusion blocked the actions of fluoxetine in models of behavioral despair. 4) Finally, we found that direct infusions of FGF2 into rat PFC decreased immobility in the forced swim test and reduced the latency to feed in novelty suppressed feeding test. Taken together, these findings demonstrate that FGF2-FGFR1 signaling is sufficient and necessary for the gliogenic, as well as the behavioral actions of antidepressant treatment, providing further evidence for a role of FGF2 in the pathophysiology and treatment of MDD. The work above is supported by NIMH grants MH45481 and MH93897, and the State of CT.

Abstract 306.15 Summary

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Activating Certain Neurons Prevents "Depressed" Behavior

Animal study identifies a brain circuit involved in depression

Stimulating a particular brain circuit produces antidepressant effects, according to new animal research presented at Neuroscience 2011, 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 the circuit connecting the prefrontal cortex and the dorsal raphe nucleus is key to understanding and potentially developing treatments for depression.

Researchers led by Melissa Warden, PhD, of Stanford University, tested whether this circuit is involved in depression using optogenetics and a swim test. The researchers injected rats with a substance designed to turn on specific neurons in the circuit when they were exposed to blue light. Activating these neurons with a mini-fiberoptic laser light had an immediate antidepressant effect: these rats spent more time trying to escape a tank of water. (In this swim test, passively floating is thought to indicate a depression-like state.)

When the team recorded the rats' neural activity, they identified prefrontal cortex neurons that only turned off when the rats were floating. These same neurons remained active during normal activity in their cages, and when actively trying to escape the water.

"These results demonstrate the importance of the connection between the prefrontal cortex and the dorsal raphe in depression-related behavior," said Warden. "These findings help pinpoint the dysfunctional circuitry underlying depression and will likely reveal new avenues for therapeutic intervention," she said.

Research was supported by National Institute of Mental Health, National Institute of Drug Abuse, National Institute of Neurological Disorders and Stroke, U.S. Defense Advanced Research Projects Agency, the Keck Foundation, the Michael J. Fox Foundation, and the California Institute for Regenerative Medicine.

Scientific Presentation: Sunday, Nov. 13, 3–4 p.m., Halls A–C

306.15, Optogenetic control and neurophysiology of the medial prefrontal-dorsal raphe projection during depression-related behavior
M. R. WARDEN[1], A. SELIMBEYOGLU[2], K. M. TYE[1], S.-Y. KIM[1], J. MIRZABEKOV[1], L. M. FRANK[4], K. DEISSEROTH[1,3,5]; [1]Bioengineering, [2]Neurosciences, [3]Psychiatry and Behavioral Sci., Stanford Univ., Stanford, CA; [4]Univ. of California, San Francisco, CA; [5]HHMI, Stanford, CA

TECHNICAL ABSTRACT: Major depression is common (lifetime prevalence 17%), yet is poorly understood and current treatments are often inadequate. Parallel streams of evidence suggest that both the prefrontal cortex (PFC) and the dorsal raphe nucleus (DRN), the major source of serotonin (5-HT) to the forebrain, may be involved; in addition, the projection from the medial PFC (mPFC) to the DRN is thought to be important but has never been directly and specifically shown to have a causal role in depression-related behaviors. We describe here a combined projection-specific optogenetic and electrophysiological approach to this circuit in awake, behaving rats. First, we selectively transduced excitatory neurons bilaterally in the mPFC of male Long Evans rats with adeno-associated virus containing ChR2-EYFP under the control of the CaMKIIα promoter. When the axons of these neurons in the DRN were illuminated, rats showed a reversible and repeatable antidepressant-like phenotype in the forced swim test (FST), while control rats that were injected with EYFP did not show this effect (ChR2-EYFP, n=15; EYFP, n=12; $p<0.01$). We next investigated the neuronal correlates of depression-related behavior in this projection by recording from identified single neurons in the mPFC that project to the DRN while rats were engaged in the FST. These neurons comprised 8% of the total population of recorded mPFC neurons (10/118) and were modulated during the FST in a manner consistent with the behavioral response to optogenetic stimulation. These results demonstrate the causal significance of the mPFC-DRN projecting cells in depression-related behaviors, in this case the generation and expression of motivated actions in challenging situations.

Abstract 238.03 Summary

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Potential New Drug Target for Schizophrenia Identified

People with schizophrenia have more of a specific brain chemical

According to a new study, people with schizophrenia have elevated levels of an enzyme called striatal-enriched tyrosine phosphatase (STEP). The study found antipsychotic medications commonly prescribed for schizophrenia reduce STEP levels in mice. The findings were presented at Neuroscience 2011, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Schizophrenia alters important molecules called N-methyl-D-aspartate receptors (NMDAR), which are necessary for communication between neurons. Previous studies showed that elevated levels of STEP equate to lower levels of NMDAR, which are required for many aspects of cognition.

To test whether antipsychotics improve cognition by reducing STEP in the brain, researchers led by Nikisha Carty, PhD, at Yale University, bred mice that do not have STEP, and gave them a drug that causes schizophrenia-like symptoms. After exposure to the drug, mice without STEP did not develop schizophrenia-like behaviors and showed increased amounts of NMDAR.

Antipsychotic medications, while effective, often cause adverse side effects and do not improve cognition. Moreover, many people show drug resistance. "Ultimately, these promising new results indicate that developing drugs that lower STEP levels may prove to be a more effective therapeutic strategy in the treatment of schizophrenia," Carty said.

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

Scientific Presentation: Sunday, Nov. 13, 3–4 p.m., Halls A–C

238.03, Striatal-enriched protein tyrosine phosphatase (STEP): Implications in schizophrenia and molecular mechanisms of Neuroleptics.
N. C. CARTY[1], P. KURUP[1], J. XU[1], T. PANG[1], D. AUSTIN[3], G. CHEN[3], C. PITTENGER[2], P. LOMBROSO[1]; [1]Child Study Ctr., [2]Yale OCD Res. Clin., Yale Univ. Sch. of Med., New Haven, CT; [3]Lab. of Mol. Pathophysiology, Mood and Anxiety Disorders Program, NIMH-IRP, Bethesda, MD

TECHNICAL ABSTRACT: Glutamatergic receptor function is critical in mediating synaptic plasticity, and disruptions in glutamatergic signaling are proposed to give rise to behavioral abnormalities and cognitive deficits. The more recent glutamate hypothesis of schizophrenia (SZ) posits a hypoglutamatergic state in the disease, possibly through changes in GluN2B containing NMDA receptor trafficking. Aberrant NMDAR trafficking results in loss of NMDARs on neuronal membranes, thus, affecting synaptic plasticity and is proposed to contribute to cognitive dysfunction. STEP61 is a brain-specific tyrosine phosphatase that dephosphorylates a regulatory Tyr1472 on the NR2B subunit, leading to the internalization of NMDA (NR1/NR2B) receptors. Here we find a significant increase in active STEP61 in human cingulate cortex of SZ patients, establishing an important link between elevated STEP levels and aberrant glutamate receptor signaling involved in SZ. One possible underlying mechanism mediating STEP accumulation involves the ubiquitin-proteasome system (UPS) which mediates protein degradation. In the present study we establish that acute blockade of the NMDAR with MK801 lead to a significant increase in STEP61 protein levels as well as a significant decrease in the phosphorylation levels STEP61 and of the several STEP substrates including pERK, pPYK2 and pNR2B. Thus, blockade of the NMDAR results in aberrant accumulation of STEP61 via decreased Ca++ mediated activation of the UPS degratory pathway. While typical and atypical antipsychotic medications are most effective in the treatment of positive symptoms of SZ, the underlying cellular mechanisms responsible for these beneficial effects remains unclear. Here we propose the novel hypothesis that STEP mediates the beneficial effects of antipsychotic medications. Furthermore, we demonstrate that dopamine D2R blockade leads to the phosphorylation and inactivation of STEP61 and restore NMDA receptors to neuronal surfaces in vitro. We also show that the antipsychotic drugs haloperidol, clozapine and risperidone lead to a DR2/PKA-mediated phosphorylation and inactivation of STEP61. Inactivation of STEP61 leads to increased trafficking of glutamate receptors to neuronal surfaces. We also show that STEP knockout mice show an attenuated response to the psychotomimetic effects of acute and chronic administration of phencyclidine in both locomotor activity and learning and memory tasks. The present findings connect the dopamine D2 receptor signaling pathway with the restoration of surface NR1/NR2B receptors. Ultimately, these results indicate that STEP inhibitors may prove therapeutic in the treatment of SZ.