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Press Room, Nov. 12–16: (202) 249-4080

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RESEARCH PROVIDES CLUES TO NEURODEVELOPEMENTAL DISORDERS

Findings show how brain's structure and genes affect autism and fragile X syndrome

Washington — Research released today shows that scientists are finding new tools to help understand neurodevelopmental disorders like autism and fragile X syndrome. These studies show in new detail how the brain's connections, chemicals, and genes interact to affect behavior. The research 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 health.

Neurodevelopmental disorders like autism-spectrum disorders and fragile X syndrome are often diagnosed as the brain is developing and a child's difficulty communicating and interacting with others is perceptible. One in every 110 children is diagnosed with an autism-spectrum disorder.

Today's new findings show that:

- Children with bipolar disorder look at facial features other than the eyes when determining facial expressions. The findings may explain why they have difficulty identifying emotions, like children with autism (Pilyoung Kim, PhD, abstract 299.10, see attached summary).
- An enzyme called STEP is elevated in a mouse study of fragile X syndrome. Removing that protein makes the mice more social, suggesting a new therapeutic target (Susan Goebel-Goody, PhD, abstract 238.02, see attached summary).
- The gene that causes fragile X syndrome is associated with brain structure and working memory in healthy men, a finding that may explain why its loss causes disease (Susan Rivera, PhD, abstract 645.08, see attached summary).

Another recent finding discussed shows that:

- Animal studies explore synaptic and behavioral abnormalities related to a candidate gene for autism and the autism-related disorder Phelan-McDermid Syndrome (Joseph Buxbaum, PhD, see attached speaker summary).

"This research is imperative in investigating the causes of neurodevelopmental disorders, which begin early in development and change the trajectory of so many lives," said press conference moderator and child neurologist Emanuel DiCicco-Bloom, MD, of the UMDNJ-Robert Wood Johnson Medical School. "With the help of further research, scientists and clinicians can lay a foundation for effective education, early intervention, and new treatments."

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

Related Presentation:

Symposia: **Autism at the Synapse: Human Genetics and Animal Models of Shank Mutations CME**
Saturday, Nov. 12, 1:30–4 p.m., Ballroom B

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Abstract 299.10 Summary

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Children with Bipolar Disorder Focus on Different Facial Features

Finding may explain difficulty identifying emotions in affected children

Children with bipolar disorder (BD) or severe mood dysregulation (SMD) may look at faces in a way that impairs their ability to determine emotional expressions, according to new research. The study shows children with BD or SMD spend less time looking at the eyes compared with healthy children when trying to identify facial expressions. The new 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.

Studies have shown children with psychiatric disorders including autism make more errors than other children when labeling emotional facial expressions (happy, sad, fearful, and angry) at least, in part, because they pay less attention to the eyes. Children with BD and SMD have similar deficits in identifying expressions, and the current study sought to find out why.

Researchers led by Pilyoung Kim, PhD, of the National Institute of Mental Health, tracked eye movements in children viewing emotional faces. Across all emotional expressions, all children spent more time looking at the eyes, the component of expression that conveys the most information about emotion, relative to other facial features. However, BD and SMD children paid less attention to the eyes and more attention to the noses and mouths when compared with healthy children.

"In combination with other studies, our findings indicate the potential value of treatment programs that teach children how to identify emotions by looking at others' eyes," said Kim. "If such training helps children to process the emotional information in their world more accurately, that may in turn increase their ability to regulate their emotional reactions to social situations."

Research was supported by the Intramural Research Program of the National Institute of Mental Health.

Scientific Presentation: Sunday, Nov. 13, 2–3 p.m., Halls A–C

299.10, Abnormal eye-movement among children with bipolar disorder or severe mood dysregulation during face emotion processing
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TECHNICAL ABSTRACT: Introduction: Children with bipolar disorder (BD) or severe mood dysregulation (SMD) have deficits in face emotion labeling. Face emotion labeling deficit among BD children may be associated with abnormal eye-movement in response to facial stimuli. Adult BD patients and children with other psychiatric disorders such as autism or high psychopathic traits have deficits in face emotion labeling, and the deficits are further linked to reduced fixations on emotionally salient facial features such as eye regions. Thus, the current study examined whether decreased attentions to eye regions among children with BD or SMD may be associated with their face emotion labeling deficits. Methods: Participants included children with BD (N=17), or SMD (N=28), and healthy volunteer (HV) children (N=14). No between-group difference in age, IQ and gender was found. Eye movements were measured with an EyeLink II head-mounted eye-tracker (SR Research, Mississauga, ON, Canada), and sampled pupil centroid at 500 Hz. Before starting the task, eyes were calibrated and validated, and a drift correction was performed every 5 trials during the task. During the task, participants saw photographs of four emotional faces (happy, sad, anger, and fear) and a neutral face. After a fixation cross (300 ms), and each picture (2s) are shown, participants labeled the emotion of each face. A fixation cross was shown during the inter-trial intervals (average 1s) between trials. Rectangular areas-of-interest (AOIs) were drawn for each face around eyes, nose, and mouth. Data is analyzed using a repeated-measures analysis of covariance (ANOVA) where group (BD, SMD and control) is the between-group factor and emotion and AOI were the within-group factors. Results: Behaviorally, SMD children had lower accuracy relative to BD and HV children across emotions, $F(2,57)= 4.53$, $p<.05$, whereas BD children showed slower reaction time relative to SMD and HV children across emotion, $F(2,57)= 2.78$, $p<.10$. For fixation duration, the group X AOI interaction was found, $F(4,2187)=12,33$, $p<.001$. Across all emotions, in the eye regions, both BD and SMD children showed shorter fixation duration to HV children. In the nose regions, BD children showed longer fixation whereas in the mouth regions, SMD children showed longer duration compared to other groups. No difference was found for fixation numbers. Discussion: Abnormal eye-movements such as decreased attentions to eye regions among BD and SMD children may be an underlying mechanism for their face emotion labeling deficits.

Abstract 238.02 Summary

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Reducing Brain Chemical Corrects Social Deficits in Mouse Model of Fragile X Syndrome

Chemical could be new drug target for fragile X and autism

Reducing levels of an enzyme called striatal-enriched tyrosine phosphatase (STEP) increases social behavior in a mouse model of fragile X syndrome. Fragile X syndrome shares some common symptoms with autism spectrum disorders, including high seizure rates and social deficits. The findings, which suggest a new drug target, 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.

Fragile X syndrome is caused by the loss of fragile X mental retardation protein (FMRP). FMRP normally suppresses the production of other proteins. Without it, the production of some proteins goes unchecked. Previous research showed that FMRP interacts with STEP. To study whether STEP proteins may be responsible for behavioral deficits characterized by the disorder, researchers led by Susan Goebel-Goody, PhD, of Yale University Medical School, studied mice lacking FMRP (which show fragile X-like symptoms), and bred them with mice without STEP.

Mice lacking FMRP typically behave in avoidant and anxious ways; however, researchers found the fragile X mice with reduced levels of STEP were *more* social, behaving similarly to the mouse control group. When presented with the option to socialize with a stranger mouse or explore a new object, mice with reduced levels of STEP spent more time per visit with the stranger mouse than fragile X mice, demonstrating that reducing STEP reversed their social deficit.

"Our results highlight the possibility that pharmacological interventions that reduce STEP activity might be successful strategies to treat fragile X syndrome and autism," Goebel-Goody said.

This research was supported by the National Institute for Mental Health and the FRAXA Research Foundation.

Scientific Presentation: Sunday, Nov. 13, 2–3 p.m., Halls A–C

238.02, Removal of striatal-enriched tyrosine phosphatase (STEP) ameliorates social deficits in a mouse model of fragile X syndrome
S. M. GOEBEL-GOODY, E. D. WILSON-WALLIS, P. J. LOMBROSO; Child Study Ctr., Yale Univ., NEW HAVEN, CT

TECHNICAL ABSTRACT: Individuals with fragile X syndrome (FXS) exhibit avoidant and anxious behaviors, and ~30% of boys with FXS meet the criteria for autism. Deficits in social interaction are therefore a severe impairment in FXS and are often associated with lower cognitive ability, adaptive behavior, and language ability. FXS mouse models also show impairments in sociability, suggesting that potential therapeutic targets aimed at improving social behavior can be assessed in these rodents. Given that FXS is characterized by a loss of the translation-suppressing protein fragile X mental retardation protein (FMRP), a number of mRNAs that are normally regulated by FMRP have been implicated as possible targets. One excellent candidate is striatal-enriched protein tyrosine phosphatase (STEP). STEP is a brain-specific phosphatase that dephosphorylates and inactivates ERK1/2, p38, Fyn, NMDA receptors (NMDARs), and AMPA receptors (AMPARs). STEP has been implicated in FXS since STEP mRNA associates with FMRP and increased STEP translation mediates AMPAR endocytosis following metabotropic glutamate receptor stimulation. To determine whether reducing STEP ameliorates social deficits in FXS, we genetically reduced STEP levels in Fmr1 KOs by cross-breeding STEP KO mice with Fmr1 KO mice. Progeny of various genotypes (WT, Fmr1 KO, STEP Het/Fmr1 KO, and STEP/Fmr1 double KO) were then subjected to a three-chambered social choice task, where they were presented with the option to socialize with a stranger mouse contained in an inverted wire cup in one chamber (stranger) or to explore an inverted wire cup alone in the opposite chamber (object). All genotypes spent more time socializing with the stranger mouse rather than the object, and the time spent in close proximity to the stranger mouse was also relatively equal among genotypes. However, Fmr1 KOs had more entries in close proximity to the stranger mouse than the other genotypes. Consequently, Fmr1 KOs spent less time per entry in close proximity to the stranger mouse relative to the other groups, demonstrating that genetically reducing STEP reverses this social deficit. The time and number of entries in close proximity to the object were not different between genotypes, revealing that the impairment in Fmr1 KOs was specific to the social aspect of the task. These findings suggest that Fmr1 KOs display impairments in social approach and maintenance and support the hypothesis that reducing STEP levels in Fmr1 KOs ameliorates social anxiety. Moreover, our results highlight the possibility that pharmacological interventions that reduce STEP activity might be successful strategies to treat FXS and autism.

Abstract 645.08 Summary

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Gene Responsible for Fragile X Syndrome Linked to Healthy Brain Function

Gene associated with working memory in healthy men

The gene responsible for fragile X syndrome is associated with brain structural connectivity and working memory in healthy men, 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.

Fragile X syndrome, the most common inherited cause of intellectual disability, is caused by the loss of fragile X mental retardation protein, which is made by the fragile X mental retardation 1 *(FMR1)* gene. The new study, led by the senior author Susan Rivera, PhD, and the lead author, Jun Yi Wang, PhD, at University of California, Davis, shows that in the healthy brain, *FMR1* is involved in working memory, a central component of intelligence.

The researchers measured *FMR1* messenger RNA (mRNA) expression in healthy adult men. They also administered a working memory test and performed imaging scans of participants' brains. They found that lower levels of *FMR1* mRNA were associated with higher working memory performance as well as stronger, more organized brain cell connections.

"The study demonstrates for the first time the *FMR1* gene's contribution to brain structural connectivity and working memory in the normal population. Our findings call for further investigations to determine the biological mechanisms underlying the associations," Rivera said.

This work was supported by the National Institutes of Health.

Scientific Presentation: Tuesday, Nov. 15, 2:45–3 p.m., Room 201

645.08, The associations of FMR1 expression, white matter connectivity, and cognition in healthy males
J. Y. WANG[1], D. HESSL[3], A. SCHNEIDER[3], R. J. HAGERMAN[3], F. TASSONE[3], **S. M. RIVERA[2]**; [1]Ctr. for Mind and Brain, [2]Univ. of California, Davis, Davis, CA; [3]Med. Investigation of Neurodevelopmental Disorders (MIND) Inst., Univ. of California-Davis, Sch. of Med., Sacramento, CA

TECHNICAL ABSTRACT: The role of fragile X mental retardation 1 (*FMR1*) gene in synaptogenesis at postsynaptic terminals is well-established. Less well-known is the gene's function at presynaptic sites including translation regulation of myelin related proteins, axon pruning, and growth cone collapse. Previous neuroimaging studies have concentrated on investigating the effect of abnormal *FMR1* expressions on the brain and revealed altered frontostriatal pathway associated with lack of *FMR1* expression in fragile X full mutation, and late-onset axonal degeneration due to *FMR1* mRNA elevation in premutation. The goal of the current study was to explore the associations between *FMR1*, white matter connectivity, and cognition in healthy males.
We acquired neuroimaging and measured lymphocytic CGG repeat size and *FMR1* mRNA level and cognitive performance from 34 healthy males (18-80 years, mean ± SD = 43.6 ± 18.4 years). The analyses were performed at three levels: (1) diffusion tensor tractography at the tract level for 11 major fiber tracts, (2) tract-based spatial statistics (TBSS) at the voxel level, and (3) gray and white matter volume and integrity at the global level. Multiple linear regression was used to examine the associations while controlling for age. To correct family-wise errors, false discovery rate was used, and to test the generalization of the results, leave-one-out procedure of partial least square (PLS) regression was applied. All three methods detected significant associations with *FMR1* mRNA. For tractography measurements, seven tracts showed significant correlations between *FMR1* mRNA and structural connectivity (negative correlations for fractional anisotropy and positive for mean diffusivity). These tracts comprised the cerebral peduncular fibers, extreme capsule fibers, cingulum, arcuate fasciculus, inferior longitudinal and frontooccipital fasciculi, and corpus callosum. Subsequent TBSS analyses revealed that radial diffusivity, not axial diffusivity, contributed to the significant associations. In addition, *FMR1* mRNA correlated negatively with working memory, with all of the above tracts except for extreme capsule fibers and inferior frontooccipital fasciculus contributing significantly to this function. Notably, these seven fiber tracts predicted working memory, executive function, and dexterity in functionally relevant manners and with results highly generalizable as indicated by the leave-one-out procedure of PLS regression. These findings suggest *FMR1* as a potential common genetic factor for working memory and structural connectivity. Replication is underway to verify this novel association in the normal population.

Speaker's Summary

Speaker: Joseph Buxbaum, PhD (212) 659-8862
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Haploinsufficiency of Full-Length SHANK3 Leads to Deficits in Synaptic Function (3.03)
Symposium: Human Genetics and Animal Models of Shank Mutations
Saturday, Nov. 12, 2:10–2:45 p.m., Washington Convention Center, Ballroom B

Many autism-related genetic differences in humans affect synaptic function as a final common pathway. Mutations in the synaptic scaffolding gene *SHANK3* in particular have been identified in autistic patients by independent groups; SHANK3 is a likely candidate gene for the autism-related disorder Phelan-McDermid Syndrome. Symposium speakers will examine links between *SHANK* genes and autism and relate synaptic and behavioral abnormalities in animal and *in vitro* models of *SHANK3* mutations.

Dr. Buxbaum's team has an FDA waiver for a clinical trial and has a shared patent with Mount Sinai School of Medicine on a potential approach to treatment in *SHANK3*-deficiency.

Research was supported by the National Institute of Health, The Seaver Foundation, The Simons Foundation, and a gift from William Gibson and Paulina Rychenkova.