Embargoed until Oct. 19, 3 p.m. CST
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Contacts: Emily Ortman, (202) 962-4090
Anne Nicholas, (202) 962-4060

Studies Expand Understanding of Social Behavior

Research points to possible therapeutic targets for autism spectrum disorder

CHICAGO — Research released today uncovers the neural mechanisms driving social behavior, suggesting possible new approaches to diagnosing and treating autism spectrum disorder, Rett syndrome, and anxiety disorders. The findings were presented at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The prevalence of autism spectrum disorders is increasing; in the United States, currently 1 in 68 children are affected. Children with autism have deficits in social interaction and communication, but treatments that improve social behavior have not yet been identified. Other diseases that are related to autism and also involve social behavioral problems, such as Fragile X syndrome and Rett syndrome, lack promising treatments as well.

Today's new findings show that:

- A protein implicated in autism is required for the proper pruning of synaptic connections in mice, identifying a possible target to correct the excessive connections seen in the disease (Chia-Wei Chang, abstract 392.08, see attached summary).
- A molecule that mimics the action of a key protein in the brain improves synaptic plasticity and locomotion in a mouse model of Rett syndrome (Lucas Pozzo-Miller, abstract 586.03, see attached summary).
- The brain makes quick assessments of the emotion and approachability of crowds, and people with anxiety exhibit differences in their reactions. The finding may help the development of behavioral diagnostics for mental health issues (Hee Yeon Im, abstract 564.10, see attached summary).

"The findings released today expand our understanding of the neurobiology of social behavior," said press conference moderator Sue Carter, PhD, of Indiana University, an expert in social bonding and behavior. "Uncovering these mechanisms will drive the creation of better therapies for disorders like autism."

This research was supported by national funding agencies such as the National Institutes of Health, as well as other private and philanthropic organizations. Find out more about social behavior and the brain at *BrainFacts.org.*

Related Neuroscience 2015 Presentation:
Presidential Special Lecture: Themes and Variations in Circuits and Behavior
Saturday, Oct. 17, 5:15-6:25 p.m., Hall B1

Abstract 392.08 Summary

Lead Author: Chia-Wei Chang (469) 286-5476
University of Texas Southwestern Medical Center chia-wei.chang@UTSW.edu
Dallas

Autism-Linked Protein Helps Regulate Number of Synaptic Connections in Mice

Excess synaptic connections can impair neuronal function and communication

A protein implicated in autism is required for pruning excess synaptic connections, according to an animal study released today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. Excess synaptic connections can impair the function of neuronal circuits and coordination between brain regions, possibly leading to the social behavioral deficits seen in autism.

Neuronal activity is required for regulating synaptic connections; the connections that are used are strengthened and reinforced, while inactive connections are pruned away. Recent studies have shown that individuals with autism have an increased number of synaptic connections between neurons — possibly due to a deficit in pruning during development — that might lead to disrupted neuronal activity and the impaired social behavior seen in autism. However, the molecular mechanisms and durations of electrical activity required to cause sufficient pruning are unknown.

Mutations in the myocyte enhancer factor 2 (MEF2) gene have been found in some people with autism. The gene makes the MEF2 protein, which is believed to help control synapse number following neuronal activity. The loss of the fragile X mental retardation protein (FMRP) causes Fragile X syndrome, an inherited intellectual disability that is often comorbid with autism spectrum disorders. Without FMRP, neurons have an overabundance of synaptic connections. Previous work suggests that MEF2 and FMRP work together to regulate synapse number.

Using optogenetics, a technique that involves stimulating neurons with light, the researchers activated brain tissue from mice and tested which proteins are required for synaptic pruning following both brief (one hour) and chronic (one day) stimulation. Deleting MEF2 proteins blocked pruning following brief, but not chronic, stimulation. Surprisingly, FMRP was not required for synapse elimination in either of the two stimulation conditions. Therefore, the results indicate that MEF2 is necessary for pruning after brief neuronal activity, but FMRP is not. The findings reveal the neural activity patterns that lead to synapse pruning and do so through distinct autism-linked genes.

"Our discoveries increase our understanding of how neuronal connections can be pruned and how autism-linked genes contribute to pruning," said lead author Chia-Wei Chang of the University of Texas Southwestern Medical Center. "By understanding this mechanism, we can develop various methods to promote pruning in patients with autism."

Research was supported with funds from the Simons Foundation Autism Research Initiative and the National Institutes of Health.

Scientific Presentation: Monday, Oct. 19, 4-5 p.m., Hall A

392.08, Distinct mechanisms of activity-dependent synapse elimination by brief and chronic postsynaptic action potential firing: Roles of MEF2 and FMRP
***C.-W. CHANG**, J. R. WILKERSON, C. F. HALE, J. R. GIBSON, K. M. HUBER;
Dept. of Neurosci., Univ. of Texas Southwestern Med. Ctr., Dallas, TX

TECHNICAL ABSTRACT: Experience and activity-dependent synapse elimination plays an important role in the refinement of neuronal circuits during early postnatal development and is implicated in learning and memory. Myocyte Enhancer Factor 2 (MEF2), a transcription factor that is activated by neuronal depolarization and Ca2+ influx, is implicated in pruning or elimination of excitatory synapses and spines onto cortical neurons (Flavell et al., 2006). The Fragile X Mental Retardation Protein (FMRP), an RNA binding protein that is linked to human intellectual disability and autism, is required for synapse elimination induced by overexpression of constitutively active MEF2 (Pfeiffer et al., 2010). The physiological patterns of neural activity that activate MEF2 and lead to MEF2 and FMRP-dependent synapse elimination are unknown. To address this question, we examined the role of MEF2 genes and FMRP in activity-dependent synapse elimination in organotypic hippocampal slice cultures. To control and drive action potential firing in individual neurons we biolistically transfected channelrhodopsin 2 (ChR2) into CA1 neurons in slice culture and induced firing with a patterned photostimulation protocol (PPS, 50ms pulses of blue light at 3 Hz) for either 1 (brief) or 24 hours (chronic). Both brief and chronic PPS activate MEF2- transcriptional activity in CA1 neurons, as measured by the transcriptional reporter, MRE-GFP, and caused functional synapse elimination as measured by decreases in evoked EPSCs and mEPSC frequency 24 hours after PPS onset (Goold and Nicoll, 2010). Interestingly, postsynaptic, cell autonomous deletion of MEF2A and MEF2D, the major MEF2 family members expressed in CA1, blocked functional synapse elimination induced by brief, but not chronic PPS. Our results reveal distinct mechanisms of synapse elimination induced by either brief or chronic postsynaptic action potential firing and suggest that other activity-regulated transcription factors in synapse elimination in response to chronic activity. Surprisingly, brief and chronic PPS induce synapse elimination independently of *Fmr1* implicating different mechanisms in synapse elimination induced by activity and that induced by overexpression of MEF2.

Abstract 586.03 Summary

Senior Author: Lucas Pozzo-Miller, PhD
University of Alabama at Birmingham (205) 975-4659
Birmingham, Ala. lucaspm@uab.edu

Mimicking BDNF Signaling Improves Rett Syndrome Symptoms in Mice

A small synthetic molecule improves locomotion and synaptic plasticity in mouse model

New animal research reveals a molecule that mimics the signaling of a key protein in the brain may help improve motor symptoms and restore cellular activity in Rett syndrome, according to a study released today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Rett syndrome is the most common form of inherited, severe intellectual disability in females, and affected individuals often have lack of speech, social difficulties, seizures, and problems with movement, such as trouble walking, difficulty with voluntary actions, and repetitive hand motions. The disorder is caused by a mutation in the gene coding for the methyl-CpG-binding protein 2 (MeCP2), making the MeCP2 protein inactive. MeCP2 normally modulates the expression of brain-derived neurotrophic factor (BDNF), a protein important for synaptic plasticity and neuronal survival. People with Rett syndrome have low levels of BDNF, but increasing levels therapeutically is problematic, as BDNF does not cross the blood-brain barrier.

For this study, the researchers tested the effects of a mimetic — a synthetic molecule that mimics a naturally occurring one — in a mouse model of Rett syndrome. The mimetic LM22A-4 acts like BDNF in the brain but is able to cross the blood-brain barrier.

The researchers injected LM22A-4 or a placebo into female wild-type mice and female mice that have only one copy of the *Mecp2* gene. After two months of daily treatments, the *Mecp2* mutant mice treated with LM22A-4 improved on tests of locomotion and coordination that included exploring open areas and the ability to walk across a wooden rod. When treated with a placebo, the mutant mice had reduced long-term potentiation — a measure of synaptic plasticity — but when treated with the mimetic, measures of synaptic plasticity were restored to wild-type levels.

"The findings from this study provide further evidence for the promise of small-molecule mimetics of BDNF as effective treatments," said lead author Lucas Pozzo-Miller of the University of Alabama at Birmingham. "Expanding upon previous work by David Katz and Frank Longo showing reversal of breathing abnormalities in Rett mice treated with LM22A-4, we now have evidence that this mimetic of BDNF is able to restore neural network stability and improve synaptic plasticity in the hippocampus, while also improving locomotor activity in the Rett model mouse."

Research was supported with funds from Rettsyndrome.org, the Rett Syndrome Research Trust, the National Institute of Neurological Disorders and Stroke, and the National Institute of Child Health and Human Development.

Scientific Presentation: Tuesday, Oct. 20, 3-4 p.m., Hall A

586.03, The TrkB ligand LM22A-4 rescues hippocampal LTP and Rett-like behavioral phenotypes in Mecp2 knockout mice
W. LI[2], T. YANG[3], F. LONGO[3]; ***L. POZZO-MILLER**[1],
[1]Neurobio., Univ. Alabama-Birmingham, Birmingham, AL; [2]Neurobio., The Univ. of Alabama At Birmingham, Birmingham, AL; [3]Neurol. and Neurolog. Sci., Stanford Univ., Stanford, CA

TECHNICAL ABSTRACT: Rett syndrome (RTT) is an autism-linked disorder caused by loss-of-function mutations in the gene encoding methyl-CpG-binding protein 2 (MeCP2), a transcriptional regulator that modulates expression of many genes, including the neurotrophin *Bdnf*. BDNF deregulation accounts for many sensory, motor, and cognitive deficits in RTT individuals, as well as in mouse models that recapitulate RTT phenotypic traits. We previously demonstrated that naïve hippocampal CA3->CA1 synapses are potentiated in slices from male *Mecp2* KO mice, thus saturating long-term potentiation (LTP) (WL & LP-M, SfN 2014). Restoration of BDNF function has a great potential to rescue these features, but BDNF's inability to cross the blood-brain barrier has limited its pharmacotherapeutic use for systemic/peripheral treatment. Here, we used the small molecule LM22A-4, which has sufficient brain penetration and pharmacokinetics, and mimics BDNF signaling by occupying the binding pocket of the BDNF receptor TrkB (Massa et al. 2010). We treated female *Mecp2* heterozygous (Het) mice at 4 months of age with LM22A-4 for 2 months (twice daily i.p. injections). Western immunoblots of hippocampal homogenates confirmed the activation of TrkB receptors and downstream signaling pathways in LM22A-4-treated *Mecp2* Het mice. The general behavioral phenotype score, open field test, and dowel crossing test all showed significant improvements in locomotor activity and motor coordination in LM22A-4-treated *Mecp2* Het mice. At the end of the 2-month treatment, acute slices were used for simultaneous electrophysiology and voltage-sensitive dye (VSD) imaging. Basal transmission at CA3->CA1 synapses and evoked spatio-temporal spread of VSD signals in area CA1 were enhanced in Mecp2 Het mice compared to age-matched female wildtype (WT) controls. In addition, LTP of fEPSPs and VSD signals were smaller in female *Mecp2* slices than in WT slices. The 2-month LM22A-4 treatment reduced basal synaptic transmission and the spatio-temporal spread of VSD signals to WT levels, and restored LTP of fEPSPs and VSD signals to levels comparable to those observed in WT slices. Our findings provide preclinical evidence that the BDNF loop-domain mimetic LM22A-4 improves hippocampal function and RTT-related behavioral deficits, thus establishing the rationale for the treatment of RTT and other neurodevelopmental disorders with autistic features associated with MeCP2 dysfunction.

Abstract 564.10 Summary

Lead Author: Hee Yeon Im, PhD (617) 726-0309
Harvard Medical School him3@mgh.harvard.edu
Charlestown, Mass.

The Brain Quickly Assesses Emotion of Crowds

Type of emotion and gender influence processing of a group of faces

People quickly discern the mood of crowds, but those with higher levels of anxiety make more errors in evaluating crowd emotions, according to a study released today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. In a task involving evaluating emotions of crowds, the specific emotion expressed and gender of the faces influences perception of the crowd's mood.

Previous work on how people perceive emotion has focused on looking at one face at a time, but often we must process many faces in a crowd of people. Identifying the mood of a crowd, whether it's friendly or threatening, is a critical social skill. However, people who have problems responding appropriately to emotional cues, such as those with anxiety disorders, may struggle with this and become overwhelmed in crowds.

To investigate how people process the emotion of crowds, the researchers morphed the faces of six different individuals (three men and three women) to show emotions that ranged from neutral to extremely happy and neutral to extremely angry.

Participants were simultaneously presented with two crowds of four to six faces (one crowd in each visual field) and asked to press a key to indicate which group looked more approachable. Each group of faces showed a range of one emotion (faces displaying different levels of happiness, for example). Participants answered faster when shown angry crowds. Happy female crowds and angry male crowds were identified more accurately than happy male and angry female crowds. People with higher levels of self-reported anxiety made more errors when looking at happy crowds, suggesting disrupted recognition of happy crowds and less inclination to approach them. Finally, the researchers tracked the eye movements of the participants as they looked at the crowds. Participants' eyes first went to the face displaying the most extreme emotion, suggesting the brain directs the gaze to prioritize extreme emotions when evaluating crowds.

"We found that humans have a remarkable ability to integrate different facial cues to evaluate the collective mood of a crowd of faces and decide rapidly whether to approach or avoid it," said lead author Hee Yeon Im, PhD, of Harvard Medical School. "Understanding how this is achieved may allow us to use this test as a behavioral diagnostic to identify mental health problems, instead of relying on self-reports."

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

Scientific Presentation: Tuesday, Oct. 20, 1-4 p.m., N228

564.10, The integrative process of reading emotional expressions from a crowd of faces
***H. IM**[1], D. ALBOHN[3], R. B. ADAMS, Jr[3], K. KVERAGA[2];
[1]Harvard Med. Sch. / Massachusetts Gen. Hos, Somerville, MA; [2]Harvard Med. Sch. / Massachusetts Gen. Hos, Charlestown, MA; [3]The Pennsylvania State Univ., University Park, PA

TECHNICAL ABSTRACT: The vast majority of affective perception research has employed single faces as stimuli. Yet, when we face a crowd of strangers, we may need to rapidly evaluate the crowd's collective mood and decide whether to approach or avoid it. One efficient way to do this is to read facial expressions in the crowd. Here we tested how humans extract emotion from groups of faces (termed "crowd emotion") with average crowd emotion ranging from happy to angry. We created 'morphed' faces from emotionally extreme faces of 6 different identities (3 female/3 male). In Study 1, two crowds of 4 or 6 morphed faces of a single identity were presented in the left and right visual fields for 1 sec. Subjects (N = 18) were asked to indicate via a key press whether the group on the left or right looked more approachable. We found that overall accuracy (63.7%) was significantly higher than chance, suggesting they could reliably extract the average emotion from two crowds of faces. The accuracy increased with the average emotional distance between the two face crowds (60.97% for ±5 and 67.22% for ±9 emotional units). We also found the tendency towards faster RTs for angrier crowds than happier crowds indicating more rapid processing of potential threat. There was no set size effect on accuracy or RT, suggesting that crowd emotion can be extracted without requiring serial processing. Finally, happy female crowds were identified more accurately than happy male crowds, while the opposite was true for angry male vs. angry female crowds. This suggests that crowd emotion perception is modulated by sex-specific identity cues (masculinity or femininity of a crowd), an effect also found for processing individual faces (Adams, Hess, & Kleck, 2015).
In Study 2, we tested the effect of facial identity on perceived crowd emotion with a new cohort (N=18). The same morphed faces were intermixed to create crowds of 4 or 6 different identities. Although there was a slight drop in overall accuracy (60.31%) compared to Study 1, indicating interference of identity cues with emotion cues, we replicated the findings from Study 1: increased accuracy with average emotional distance, faster RTs for angrier vs. happier crowds, and no set size effects. In Study 3, we tracked subjects' eye movements and found that the first saccade was made to the happiest face in the crowd more frequently than to any other faces, indicating that the eye movement system prioritizes extreme expressions in evaluating crowd emotion. In conclusion, average crowd emotion can be reliably extracted from crowds with varying emotional expressions, and its perception is modulated by identity cues and emotional valence.