

**Civitan International / Simpson-Ramsey
Neurodevelopment Symposium
April 20, 2017**

UAB Student Hill Center
1400 University Boulevard
Birmingham, AL 35294

8:00 am	Sign-in and Continental Breakfast
8:30 am	Opening Remarks Alan Percy, M.D., Professor, Department of Pediatrics, Interim Director, Civitan International Research Center Director
	Rita Cowell, Ph.D., Associate Professor, Dept. Psychiatry & Behavioral Neurobiology, Associate Director of Communications and Outreach, CIRC

Session I

8:45 am	Adaptive Behavior Profiles in Autism and Neurodevelopmental Disorders: Implications for Functional Independence Celine A. Saulnier, Ph.D., Director of Research Operations, Marcus Autism Center Associate Professor, Division of Autism and Related Disorders
9:15 am	Characterizing the Heterogeneity in Autism Spectrum Disorder using Brain Connectivity Underlying Social Cognition Melissa Thye, Graduate Student, Lifespan Developmental Psychology PhD Program
9:30 am	Developmental Social Neuroscience Meets Public Health Challenge: A New System of Healthcare Delivery for Infants and Toddlers with Autism Spectrum Disorder Ami Klin, Ph.D., Director, Marcus Autism Center, Children's Healthcare of Atlanta Georgia Research Alliance Eminent Scholar Professor & Chief, Emory

10:20 am	Break
----------	-------

Session II

10:35 am	Adult Neurogenesis and Klotho Gwendalyn King, Ph.D., Assistant Professor, SPIN Director, Department of Neurobiology, UAB
11:05 am	Amygdalar Expression of the microRNA miR-101a and its Target Ezh2 Contribute to Rodent Anxiety-like Behavior Josh Cohen, Neuroscience Graduate Research Assistant, M.D., Ph.D. Program
11:20 am	A Theory of Cognitive Failure in Alzheimer's Disease Paul Worley, M.D., Professor Neuroscience and Neurology, The Johns Hopkins School of Medicine
12:10 pm	Lunch

Session III

- 1:15 pm **History of the Simpson-Ramsey Lectureship**
Fred Biasini, Ph.D., Associate Professor, Director, Lifespan Developmental Psychology Program
- 1:25 pm **Describing the Development, Behavior and Autism Symptom Profiles of Individuals with Pitt-Hopkins Syndrome**
Kristi Guest, Ph.D., Assistant Professor, Disabilities Services Coordinator, Research Coordinator, UAB Civitan-Sparks Clinics
- 1:55 pm **The Choice of Musical Instrument and its Effects on Auditory Working Memory and Perception in Adolescents**
Abby Turnbough, Audiology Intern, Sparks Center for Development & Learning Disorders
- 2:10 pm **Interests, Reward, and Experience in Autism: Clues on the Road to Treatment Development and Service Delivery**
Jim Bodfish, Ph.D., Professor, Dept of Hearing & Speech Sciences, Psych and Neuroscience, Vanderbilt Brain Institute and Vanderbilt Kennedy Center
- 3:00 pm **Adjourn to Poster Session**
- 3:30- 5:30 pm **Poster Session and Reception**
The Edge of Chaos
4th Floor
Lister Hill Library

Interests, Reward, and Experience in Autism: Clues on the Road to Treatment Development and Service Delivery

Jim Bodfish, Ph.D.

Professor, Departments of Hearing & Speech Sciences, Psychiatry, and Neuroscience

Member, Vanderbilt Brain Institute, and Vanderbilt Kennedy Center
Vanderbilt University School of Medicine



Dr. Jim Bodfish is a psychologist and is a Professor in the Departments of Hearing & Speech Science, Psychiatry, & Neuroscience at the Vanderbilt University School of Medicine. He is a member of the Vanderbilt Brain Institute, the Vanderbilt Bill Wilkerson Center, and the Vanderbilt Kennedy Center. He has devoted his career exclusively to research, teaching, and clinical activities in the field of autism and developmental disabilities. His research has focused on the pathogenesis and treatment of autism and related developmental disabilities and has been published in a variety of journals. His clinical work focuses on the integration of behavioral and medical approaches for treatment-resistant cases.

Summary:

What interests people with autism and how does this influence how they choose to “spend” their attention and time? As parents know, children with autism can spend a disproportionate amount of time seeking out and engaging in often highly focused and primarily nonsocial patterns of behavior and interest. They can quickly become “experts” all on their own in these very specific things that capture their interest. When viewed from the perspective of experience-dependent brain and behavioral development, such a focused nonsocial pattern of behavior and interests can lead to strengths and skills but may also diminish social experience and opportunities for social learning and development. The work in my lab is guided by the goal of arriving at a deeper understanding of this natural pattern of behavioral disposition and development in autism. We conduct studies designed (1) to examine brain-behavior mechanisms associated with the development of interests in autism, and (2) to leverage this mechanistic understanding in the development of novel approaches to intervention and services for that subset of the autism spectrum that tend to need the most support and services – i.e. children with diminished language development and challenging behaviors that can limit their response to conventional interventions. Some of the questions that guide our work are: Does this pattern of development in autism unfold as a result of a tendency to avoid social stimulation (e.g. anxiety), or a predisposition to approach nonsocial stimulation (e.g. reward)? How early do nonsocial interests emerge in autism? Do autism-typical patterns of interest relate to differences in activation of brain reward circuitry and connectivity of reward circuitry with other brain networks? Can clinical findings on interest patterns be translated to guide preclinical models in autism and to the development of novel approaches for early intervention? In my talk, I hope to show how we’ve tried to address these questions through a translational program of research, and to tell what we think we’ve learned about autism along the way.

Developmental Social Neuroscience meets Public Health Challenge: A New System of Healthcare Delivery for Infants and Toddlers with Autism Spectrum Disorder

Ami Klin, Ph.D.

Director, Marcus Autism Center, Children's Healthcare of Atlanta; Georgia Research Alliance Eminent Scholar Professor & Chief, Division of Autism & Related Disorders, Department of Pediatrics, Emory University School of Medicine; Emory Center for Translational Social Neuroscience. Shorter affiliation: Marcus Autism Center, Children's Healthcare of Atlanta and Emory University School of Medicine.



Ami Klin, Ph.D. is the Georgia Research Alliance Eminent Scholar Professor and Chief of the Division of Autism and Developmental Disabilities at Emory University School of Medicine, and Director of the Marcus Autism Center, Children's Healthcare of Atlanta. He obtained his Ph.D. from the University of London, and completed clinical and research post-doctoral fellowships at the Yale Child Study Center. He directed the Autism Program at the Yale Child Study Center, Yale University School of Medicine until 2010, where he was the Harris Professor of Child Psychology & Psychiatry. The Marcus Autism Center is one of the largest centers of clinical care in the country.

Summary:

This presentation highlights the critical role of early diagnosis and intervention in attenuating the symptoms of autism. Data will be presented on early diagnostic indicators obtained through eye-tracking-based behavioral assays that quantify the social disabilities in autism. The results of these assays were used to generate "growth charts" of normative social engagement, and the deviations from the norm were taken as early indicators of risk. These methods yielded high sensitivity and specificity for the screening of infants. The ultimate goal of this effort is to develop objectified and quantified tools for the detection of autism in infancy, tools that might be deployed in primary care and pediatricians' offices. This work will be contextualized in terms of recent developmental social neuroscience research with toddlers with autism, which implicated developmentally very early emerging, and evolutionarily highly conserved, mechanisms of social adaptation that set the stage for reciprocal social interaction, which in turn represent the platform for early social brain development. These mechanisms of socialization are under stringent genetic control, setting the scientific basis for parent-delivered, community-viable, early treatment in which social engagement is "engineered" via daily activities, thus impacting a child's development during every moment of social interaction. Effective screening of infants would be unethical without a clinical infrastructure providing access to family support and early intervention for those screened positive. Through a collaboration with Dr. Amy Wetherby, we are now establishing tools and procedures for the full integration of primary care physicians and early intervention providers with the goal of establishing a new system of healthcare delivery for infants & toddlers with autism spectrum disorders. This system deploys "Early Social Interaction" as its modality of parent-delivered treatment.

Adaptive Behavior Profiles in Autism and Neurodevelopmental Disorders: Implications for Functional Independence

Celine Saulnier, Ph.D.

Director of Research Operations

Marcus Autism Center, Children's Healthcare of Atlanta

Associate Professor, Division of Autism and Related Disorders

Department of Pediatrics, Emory University School of Medicine



Dr. Saulnier obtained her doctorate in Clinical Psychology from the University of Connecticut, after which she completed a postdoctoral fellowship at the Yale Child Study Center under the mentorship of Dr. Ami Klin. After her postdoc, Dr. Saulnier joined the Yale faculty, where she became both the Clinical Director and the Training Director for the Autism Program, managing and supervising multidisciplinary diagnostic evaluations on individuals with autism spectrum and related disorders from infancy through young adulthood.

At the Marcus Autism Center, Dr. Saulnier oversees all activities related to the diagnostic characterization of individuals participating in clinical research, and she is the Director of the Clinical Assessment Core for the NIH Autism Center of Excellence grant. Her research focuses on profiles of adaptive behavior in autism spectrum disorders, particularly on the discrepancy between cognitive ability and the application of functional skills to daily contexts and routines.

Dr. Saulnier is an avid lecturer and educator on ASD, having conducted hundreds of workshops and seminars nationwide over the past decade. She is also co-author of the book, *Essentials of Autism Spectrum Disorders Evaluation and Assessment*. She is also an Associated Assistant Professor in the Department of Psychology at Emory College of Arts and Sciences

Summary:

Adaptive behavior is generally defined as the independent performance of daily activities that are required for personal and social self-sufficiency. Deficits in adaptive behavior are, by definition, criteria for Intellectual Disability. Yet in autism, adaptive delays tend to be above and beyond what would be expected based on cognitive impairments, alone. This gap between cognition and adaptive behavior appears to widen with age and impedes functional independence into adulthood. This presentation will outline these profiles of adaptive behavior and discuss the importance of assessing for and teaching adaptive skills from initial diagnosis throughout the lifespan.

A Theory of Cognitive Failure in Alzheimer's Disease

Paul Worley, M.D.

Professor Neuroscience and Neurology
The Johns Hopkins School of Medicine



Paul Worley's laboratory examines the molecular basis of learning and memory. In particular, his laboratory has cloned a set of immediate early genes (IEGs) that are rapidly transcribed in neurons involved in information processing, and that are essential for long term memory. IEG proteins can directly modify synapses and provide insight into cellular mechanisms that support synapse-specific plasticity. For example, Narp is secreted and induces excitatory synapse formation. Homer catalyzes conformational coupling of multi-protein machines involved in calcium signaling. Rheb regulates mTor (target of rapamycin) and protein translation. Arc induces the formation of endosomes that function in trafficking of glutamate receptors. Thus, rapid de novo transcription provides novel insights into the cellular and neural network basis of behavioral plasticity.

Adult Neurogenesis and Klotho

Gwendalyn King, Ph.D.

Assistant Professor

SPIN Director

Department of Neurobiology

University of Alabama at Birmingham



Dr. King received her Bachelor's Degree in Molecular Biology from Purdue University. She received Master and Ph.D. degrees from the University of Michigan. She was a postdoctoral fellow under Drs. Maria Castro and Pedro Lowenstein at Cedars-Sinai Medical Center/UCLA where she was awarded an F32 fellowship from NINDS. Her work focused on neuroimmunology and the development of novel glioma therapeutics using adenoviral vectors. She worked with Carmela Abraham at Boston University School of Medicine as an Instructor to understand the role of the anti-aging gene Klotho in the brain. At BUSM she was awarded a K99/R00 from NIA. She joined the faculty at UAB in 2011.

Summary:

Only about 4% of genes expressed by the brain show changes in expression as people age. Among these is the gene responsible for making the klotho protein. When klotho is absent from mice it causes lifespan to be shortened and for cognitive impairment to develop extremely rapidly. When mice have more klotho they live longer and show cognitive enhancement in behavioral tasks that utilize the hippocampus. While it may seem logical to see opposite effects when a single protein is up or down-regulated, it occurs very rarely. Making klotho even more interesting, a common polymorphism in the gene that causes more klotho to be circulating in the blood stream correlates with increased executive function in humans across lifespan. We are interested in determining how klotho functions within to explain such dramatic affects on cognitive function. Our recent data show premature aging of the hippocampal neurogenic niche in klotho-deficient mice as evidenced by reduced numbers of neural stem cells, decreased proliferation, and impaired maturation of immature neurons. Klotho-deficient neurospheres show reduced proliferation and size that is rescued by supplementation of shed klotho protein. Conversely, 6 month old klotho overexpressing mice exhibit increased numbers of neural stem cells, increased proliferation, and more immature neurons with enhanced dendritic arborization. In both models, the cellular phenotypes correlate with behavioral measures of dentate gyrus function with klotho overexpression protecting against normal age-related loss of object location memory. Together these data show that klotho is a novel regulator of postnatal neurogenesis affecting neural stem cell proliferation and maturation sufficient to impact cognitive function.

Describing the Development, Behavior and Autism Symptom Profiles of Individuals with Pitt-Hopkins Syndrome

Kristi Guest, Ph.D.

Assistant Professor

Department of Psychology

University of Alabama at Birmingham



Dr. Kristi Carter Guest is the Disabilities Services Coordinator for the [UAB Early Head Start Program](#), Research Coordinator for the [UAB Civitan-Sparks Clinics](#) and the [UAB Leadership Education in Neurodevelopmental and Related Disabilities](#) (LEND) and is an Assistant Professor in the Department of Psychology. She serves on the Executive Board for the Central Alabama Early Intervention Council and is on the planning committee for the statewide Alabama Early Intervention Conference.

Dr. Guest received clinical training at the UAB Civitan-Sparks Clinics performing hundreds of developmental assessments with children who were at-risk for developmental delay. Currently she participates in the interdisciplinary diagnostic observations of children suspected of having Autism Spectrum Disorders in the UAB Civitan-Sparks ASD Clinic. With the UAB Early Head Start Program, Dr. Guest provides clinical services for children with disabilities and their families to initiate and facilitate early intervention and school based services. With the UAB Early Head Start program, she coordinates all of the developmental screenings for children in the program.

Summary:

Available clinical studies describe individuals with Pitt-Hopkins Syndrome (PTHS) as exhibiting some of the core symptoms of Autism Spectrum Disorder (ASD), including difficulties in verbal and nonverbal communication, sensory sensitivity, and social interaction difficulties. Significant developmental delays, including motor delays and intellectual disability are also reported in individuals with PTHS. The current study focused on obtaining demographic information as well as standardized caregiver-report measures of development, behavior, and ASD symptoms to clarify and characterize the presence of ASD symptoms in this population, with particular emphasis on the social, communication, adaptive, developmental, and repetitive behaviors of individuals with PTHS. Information regarding ASD symptoms and patterns of behavior within genetic syndromes such as PTHS may be helpful in characterizing a broader ASD phenotype. Further, a better understanding of social communication and behavioral difficulties in individuals with known genetic differences and developmental delays may help guide more informed recommendations for intervention.

TRAINEE SPEAKERS

Amygdalar Expression of the microRNA miR-101a and its Target Ezh2 Contribute to Rodent Anxiety-like Behavior

Joshua L. Cowen

jcohen@uab.edu

Scientific Abstract

A greater understanding of neural mechanisms contributing to anxiety is needed in order to develop better therapeutic interventions. The current study interrogates a novel molecular mechanism that shapes anxiety-like behavior, demonstrating that the microRNA miR-101a-3p and its target, enhancer of zeste homolog 2 (*Ezh2*) in the amygdala, contribute to rodent anxiety-like behavior. We utilized rats that were selectively-bred for differences in emotionality and stress reactivity, showing that high novelty responding (HR) rats, which display low trait anxiety, have lower miR-101a-3p levels in the amygdala compared to low novelty responding (LR) rats that characteristically display high trait anxiety. To determine if there is a causal relationship between amygdalar miR-101a-3p and anxiety behavior, we used a viral approach to over-express miR-101a-3p in the amygdala of HR rats and test whether it would increase their typically low levels of anxiety-like behavior. We found that increasing miR-101a-3p in the amygdala increased HRs' anxiety-like behavior in the open field test and elevated plus maze. Viral-mediated miR-101a-3p over-expression also reduced expression of the histone methyltransferase *Ezh2*, which mediates gene silencing via tri-methylation of histone 3 at lysine 27 (H3K27me3). Knockdown of *Ezh2* with short-interfering RNA (siRNA) also increased HRs' anxiety-like behavior, but to a lesser degree than miR-101a-3p over-expression. Overall our data demonstrate that increasing miR-101a-3p expression in the amygdala increases anxiety-like behavior and that this effect is at least partially mediated via repression of *Ezh2*. This work adds to the growing body of evidence implicating miRNAs and epigenetic regulation as molecular mediators of anxiety behavior.

Lay Abstract

A greater understanding of neural mechanisms contributing to anxiety is needed in order to develop better therapeutic interventions. Rodent models of anxiety-like behavior offer useful tools that can be exploited towards this end. The current study utilized rats that were selectively-bred to display high and low anxiety-like behavior. We identified differences in expression of key epigenetic regulators in the amygdala, a region important to anxiety and stress behavior, in these animals. We show that manipulation of these regulators, microRNA miR-101a-3p and enhancer of zeste homolog 2 (*Ezh2*), is sufficient to increase anxiety-like behavior in rodents. This work provides evidence for a novel molecular network's contribution to anxiety behavior.

Characterizing the Heterogeneity in Autism Spectrum Disorder using Brain Connectivity Underlying Social Cognition

Melissa Thye

mthye@uab.edu

Scientific Abstract

Behavioral and neural heterogeneity is a key feature of individuals with Autism Spectrum Disorder (ASD). Previous neuroimaging studies report alterations in the theory-of-mind (ToM) network in ASD. However, most of these studies relied on analyses which concatenate results to arrive at a group-level model which may not accurately represent many participants within a heterogeneous group. A novel analytical approach, the *Group Iterative Multiple Model Estimation* (GIMME) algorithm, reveals divergent subgroups based on patterns of functional connectivity among a priori regions of interest (ROI) using a structural equation modeling framework. The primary objective of this study was to characterize the neural heterogeneity across ASD and typically developing (TD) participants in a functional magnetic resonance imaging (fMRI) study of ToM processing. A total of 63 participants (32 ASD and 31 age-and-IQ-matched TD) watched animations of geometrical shapes depicting intentional or random action in the scanner. In the intentional/ToM condition, two subgroups were identified. Subgroup A (28% ASD; 39% TD) was characterized by increased connectivity from LPCUN to RpSTS as well as increased connectivity from MPFC to RIFG. Conversely, Subgroup B (72% ASD; 61% TD) showed comparatively weaker connectivity with no additional pathways emerging above the group level model. Statistical comparisons of the individuals comprising the two subgroups revealed stronger connectivity of the group level connection from LpSTS to MPFC in Subgroup A compared to Subgroup B. This pattern of results suggests possible underconnectivity in the group containing the largest percentage of ASD participants. Implications for individualized neuroimaging data analysis will be discussed.

Lay Abstract

Autism spectrum disorder (ASD) is characterized by difficulty in reading the minds of others, an ability known as theory-of-mind (ToM). There are also widespread differences across individuals with autism, and such differences are usually ignored in studies examining the brain in autism. To address this problem, we used a novel data analysis approach known as *Group Iterative Multiple Model Estimation* (GIMME) which identifies both group level information and individual level information. In particular, we were interested in the variability in brain connectivity which measures the coordination of different regions in the brain over time. Thus, this analysis will subgroup participants based on the similarity of the individual participant's brain connectivity. In an MRI scanner, participants watched movement of geometrical shapes engaged in intentional or random motion. We found two subgroups of participants with different profiles of connectivity. The subgroup containing the largest percentage of ASD participants showed overall weaker brain connectivity among brain regions known to respond to ToM tasks. These results impact how we study ASD specifically and how we account for variability in the study of brain connectivity and functioning more generally.

The Choice of Musical Instrument and its Effects on Auditory Working Memory and Perception in Adolescents

Abby Turnbough

anturnbo@uab.edu

Abstract

Research examining the human asymmetry of handedness has spanned several decades; this has included exploring the relationship among handedness and the auditory modality. Bannatyne and Wichiarijote (1969) found a positive correlation between unlearned left handedness and auditory digit span memory test scores in third grade children. Authors attributed this outcome to processing digits in a similar fashion to music notes. Additionally, musicians whose dexterity involves both hands have more symmetric neural processing as a result of the sensory-motor experience they've had with their instrument (Gaser & Schlaug, 2003). However, there is little research translating these neurological differences in musicians to determine if more symmetry in regions enhanced by musical training would manifest into advantages for auditory processing. In an attempt to identify perceptual advantages of instrumental training involving both hands during stages when the central auditory nervous system (CANS) is still developing, monaural and binaural listening tasks, as well as working memory tasks were collected on adolescent musicians. The outcomes indicate that regardless of instrumental choice musical training would benefit individuals with difficulty segregating binaural input and temporal auditory organization difficulties.

Bannatyne, A. D., & Wichiarijote, P. (1969). Hemispheric Dominance, Handedness, Mirror Imaging, and Auditory Sequencing. *Exceptional Children*, 36(1), 27-36.

Gaser, C. & Schlaug, G. (2003). Brain structures differ between musicians and nonmusicians. *Journal of Neuroscience*, 23, 9240-9245.

Civitan International / Simpson Ramsay
Neurodevelopment Symposium
Poster Session
The Edge of Chaos
April 20, 2017

1.	Attribution of Social Meaning to Non-Human Actors and Superior Temporal Sulcus Response in Autism Spectrum Disorders - Carla J. Ammons and Rajesh K. Kana
2.	Topographic Mapping of the Primary Visual Cortex in Autism Spectrum Disorder Jamie Bice, Carla J. Ammons, Wesley Burge, Thomas DeRamus, & Rajesh K. Kana
3.	Amygdalar expression of the microRNA miR-101a and its target Ezh2 contribute to rodent anxiety-like behavior - Joshua L. Cohen, Nateka L. Jackson, Mary E. Ballestas, William M. Webb, Farah D. Lubin, and Sarah Clinton
4.	Characterization of G Protein-Coupled Estrogen Receptor Expression in Zebrafish Embryos Hailey E. Edwards and Daniel A. Gorelick
5.	Estimation of Frequency-Specific Behavioral Thresholds from Chirp ABR Responses Annie Gordon, Saravanan Elangovan, and Shannon Bramlette
6.	Variance in Language Abilities in Autism as a function of Hemispheric Lateralization and Functional Connectivity - Abbey J. Herringshaw and Rajesh K. Kana
7.	KPT-350 ameliorates Duchenne muscular dystrophy symptoms in dystrophic zebrafish and mice Rylie M. Hightower, Devin E. Gibbs, Christopher S. Lee, Janelle M. Spinazzola, Lillian C. Mead, Jeffrey J. Widrick, Sharon Tamir, Shelton Cochran, Yosef Landesman, Louis M. Kunkel, Matthew S. Alexander
8.	Relationships between Gross Motor Ability and Social Function in Young Children with Autism Spectrum Disorders - Jamie M. Holloway, Morghen Smith, Ashley Cooper, and Fred Biasini
9.	Regional Homogeneity of Brain Activity and Its Relationship to Social Impairment in Autism Spectrum Disorder - Niharika Loomba, Carla Ammons, Omar Maximo, and Rajesh K. Kana
10.	Alterations in Brain Entropy in Autism Spectrum Disorders Jose O. Maximo, Donna L. Murdaugh, and Rajesh K. Kana
11.	Stronger contribution and impaired LTP of hippocampal inputs to the medial prefrontal cortex in the MeCP2 mouse model of Rett syndrome - Mary Phillips and Lucas Pozzo-Miller
12.	The topography of fusiform face area response during implicit face processing in autism spectrum disorder - Victoria Seghatol-Eslami, Carla Ammons, and Rajesh Kana
13.	Congenital MCMV infection is associated with Sensorineural Hearing Loss (SNHL) Cathy Yea Won Sung and William Britt
14.	Characterizing the Heterogeneity in Autism Spectrum Disorder using Brain Connectivity Underlying Social Cognition - Melissa D. Thye and Rajesh K. Kana
15.	The choice of musical instrument and its effects on auditory working memory and perception in adolescents - Abby N. Turnbough and Aurora J. Weaver
16.	Role of Hatha Yoga Therapy as an Effective Treatment for Chronic Migraine Varshini Venkatesan and Dr. Grace Arnold
17.	Regulation of α_{2A} Adrenergic Receptor Trafficking and Signaling by Amyloid Precursor Protein Fang Zhang, Mary Gannon, Yunjia Chen, Kai Jiao, and Qin Wang

Carla Ammons
cjammons@uab.edu

Attribution of Social Meaning to Non-Human Actors and Superior Temporal Sulcus Response in Autism Spectrum Disorders

Carla J. Ammons and Rajesh K. Kana

Scientific Abstract

Background: Attributing intentions and beliefs to non-human entities is an innate human tendency called anthropomorphism (Hutson, 2012). However, children with autism spectrum disorder (ASD) are less likely to use anthropomorphic language (Hieder & Simmel, 1944) and often struggle to accurately attribute emotions and intentions to others. Neuroimaging has shown reduced activation in mentalizing regions of the brain (superior temporal sulcus, STS; medial prefrontal cortex, MPFC) during social attribution (Kana et al., 2009; 2015) and biological motion processing (Pelphrey et al., 2005) in ASD.

Objective: To examine the neural correlates of anthropomorphism in ASD.

Methods: 34 age-and-IQ-matched participants (17 ASD) viewed animations of stick figures or geometrical shapes engaged in random or socially meaningful movements (i.e. bullying, helping) during fMRI.

Results: ASD and TD participants were equally accurate at identifying social movement by human and non-human characters [Diagnosis x Movement x Character: $F(1,28)=.103, \text{NS}$]. Observation of social movement, regardless of character, activated bilateral posterior STS, bilateral MPFC, and precuneus in TD; but only right pSTS and left MPFC in ASD (cluster corrected $p<.005$). Attributing social motives to shapes elicited greater left pSTS and bilateral MPFC activation only for TD participants.

Conclusion: Greater bilateral recruitment of pSTS in TD may reflect a stronger propensity for anthropomorphism in ambiguous situations which is not seen in those with ASD.

Lay Abstract

Attributing human intentions to animals or characters is an innate tendency called anthropomorphism. However, children with autism spectrum disorder (ASD) are less likely to attribute mental states and often struggle to understand the emotions and intentions of others. Reduced participation of social brain regions associated with thinking about the mental states of others (like the superior temporal sulcus, STS, and medial prefrontal cortex, MPFC) is also seen during interpretation of social and biological movements in ASD. Yet, the brain bases of anthropomorphism are less well known and are the subject of this study. 17 ASD and 17 typically developing (TD) participants watched videos of human stick figures or triangles moving in random or socially meaningful ways (i.e. bullying, helping) while in an fMRI scanner. Activity of different brain regions was compared for each type of movement between ASD and TD participants. Both groups were equally accurate at identifying social movements. However, watching socially moving shapes resulted in greater left pSTS and bilateral MPFC activity only in the TD group. When the groups were directly compared, we found reduced left pSTS activity in ASD when viewing anthropomorphic scenes. Greater engagement of pSTS in TD may reflect a stronger inclination toward anthropomorphism in ambiguous situations. Individuals with ASD may be less likely to identify socially oriented movement or meaning in their environment paving the way for social difficulties.

Jamie Bice
jamiebic@uab.edu

Topographic Mapping of the Primary Visual Cortex in Autism Spectrum Disorder

Jamie Bice, Carla J. Ammons, Wesley Burge, Thomas DeRamus, & Rajesh K. Kana

Scientific Abstract

Background: Enhanced visuospatial processing seen in autism spectrum disorder (ASD) has been well-documented (Kana et al., 2013), although its underlying neural mechanism is less established. A previous structural neuroimaging study examined the visual cortex and found no difference in central/peripheral visual field representation between ASD and controls (Hadjikhani et al., 2004).

Objective: The goal of this structural MRI study is to examine the topography of the primary visual cortex (V1) in ASD and typically developing individuals (TD). We hypothesized that enhanced visuospatial processing in ASD may relate to neuroanatomical differences in the subregions of V1.

Method: Structural MRI data acquired from 55 participants [28 ASD (ages 8-40 years), 27 TD (ages 8-36 years)] were analyzed measuring surface area, cortical thickness, cortical thickness standard deviation, and grey matter volume using Freesurfer software. In each hemisphere, V1 was parcellated into 9 sub-regions and these parameters were extracted from each region. Group differences were calculated using a mixed effects general linear model (GLM).

Results: Overall, structural differences were found between ASD and TD in the V1 region most associated with central vision. For V1 region 1, ASD had an overall lower GMV but a higher average cortical thickness compared to the TD group (GMV: $F(1)=4.67$, $p<.05$; Thickness: $F(1)=5.88$, $p<.05$). However, significant age x diagnosis interactions were also found in this region for GMV ($F(1)=6.45$, $p<.05$), cortical thickness ($F(1)=5.53$, $p<.05$), and cortical thickness SD ($F(1)=4.12$, $p<.05$). GMV, cortical thickness, and cortical thickness SD decreased with age in individuals with ASD, while these parameters increased with age in the TD group.

Conclusion: Morphometric alterations in sub-regions associated with the most central representations of the visual field suggest changes in V1 anatomy in ASD. Our findings may provide more insight into the detail-oriented processing and its impact on the deficits in social communication seen in ASD. This study is the first, to our knowledge, to examine the topography of V1 in ASD and provides more insight into the visual advantage in ASD.

Lay Abstract

Autism Spectrum Disorder (ASD) is characterized by social difficulties and restricted and repetitive behaviors. People with ASD are generally better at visual thinking. However, what is behind this visual advantage, at the brain level, is unknown. In this study we wanted to look at the structure of the visual area of the brain, the primary visual cortex (V1) and see how it is organized in people with autism. Using MRI scans collected from participants with autism and controls, we divided V1 into 9 different subregions and measured the thickness and volume of that tissue. We found that the thickness and volume of a few subregions, not all, differed in our participants with autism when compared to control participants. These findings provide insight into central and peripheral use of the visual field in people with autism to understand their environment.

Joshua Cohen
jcohen@uab.edu

Amygdalar expression of the microRNA miR-101a and its target Ezh2 contribute to rodent anxiety-like behavior

Joshua L. Cohen, Nateka L. Jackson, Mary E. Ballestas, William M. Webb, Farah D. Lubin, and Sarah Clinton

Scientific Abstract

A greater understanding of neural mechanisms contributing to anxiety is needed in order to develop better therapeutic interventions. The current study interrogates a novel molecular mechanism that shapes anxiety-like behavior, demonstrating that the microRNA miR-101a-3p and its target, enhancer of zeste homolog 2 (*Ezh2*) in the amygdala, contribute to rodent anxiety-like behavior. We utilized rats that were selectively-bred for differences in emotionality and stress reactivity, showing that high novelty responding (HR) rats, which display low trait anxiety, have lower miR-101a-3p levels in the amygdala compared to low novelty responding (LR) rats that characteristically display high trait anxiety. To determine if there is a causal relationship between amygdalar miR-101a-3p and anxiety behavior, we used a viral approach to over-express miR-101a-3p in the amygdala of HR rats and test whether it would increase their typically low levels of anxiety-like behavior. We found that increasing miR-101a-3p in the amygdala increased HRs' anxiety-like behavior in the open field test and elevated plus maze. Viral-mediated miR-101a-3p over-expression also reduced expression of the histone methyltransferase *Ezh2*, which mediates gene silencing via tri-methylation of histone 3 at lysine 27 (H3K27me3). Knockdown of *Ezh2* with short-interfering RNA (siRNA) also increased HRs' anxiety-like behavior, but to a lesser degree than miR-101a-3p over-expression. Overall our data demonstrate that increasing miR-101a-3p expression in the amygdala increases anxiety-like behavior and that this effect is at least partially mediated via repression of *Ezh2*. This work adds to the growing body of evidence implicating miRNAs and epigenetic regulation as molecular mediators of anxiety behavior.

Lay Abstract

A greater understanding of neural mechanisms contributing to anxiety is needed in order to develop better therapeutic interventions. Rodent models of anxiety-like behavior offer useful tools that can be exploited towards this end. The current study utilized rats that were selectively-bred to display high and low anxiety-like behavior. We identified differences in expression of key epigenetic regulators in the amygdala, a region important to anxiety and stress behavior, in these animals. We show that manipulation of these regulators, microRNA miR-101a-3p and enhancer of zeste homolog 2 (*Ezh2*), is sufficient to increase anxiety-like behavior in rodents. This work provides evidence for a novel molecular network's contribution to anxiety behavior.

Hailey Edwards
hedwa329@uab.edu

Characterization of G Protein-Coupled Estrogen Receptor Expression in Zebrafish Embryos

Hailey E. Edwards and Daniel A. Gorelick

Scientific Abstract

Estrogens act by binding to either nuclear estrogen receptors, ligand activated transcription factors, or to the G protein-coupled estrogen receptor (GPER), a transmembrane receptor. We demonstrated that estradiol increases heart rate via GPER in zebrafish embryos. However, it is not known whether GPER acts in the heart to affect heart rate, or whether GPER acts in the brain to affect heart rate. To determine where GPER acts to regulate heart rate, we assayed GPER localization. Using colorimetric whole mount *in situ* hybridization, we detected GPER transcript in the brain but not the heart. GPER expression was observed in three discrete regions of the brain: olfactory and preoptic areas and the pituitary. It is unknown whether GPER interacts with nuclear estrogen receptors or whether GPER acts as an autonomous estrogen receptor *in vivo*. If GPER and nuclear estrogen receptor signaling pathways interact, then we would expect GPER and nuclear estrogen receptors to be expressed within the same cells. We utilized fluorescent whole mount *in situ* hybridization to determine if GPER and the canonical nuclear estrogen receptors are expressed in the same cells in the brain. We found that GPER was co-localized with nuclear estrogen receptors in parts of the pituitary, but there was no co-localization in the olfactory and preoptic areas. Our results suggest that GPER acts in the brain to regulate heart rate and that GPER may act independently of nuclear estrogen receptors in specific regions of the brain.

Lay Abstract

Estradiol increases heart rate in zebrafish embryos via the G protein-coupled estrogen receptor (GPER). We detect GPER in the brain, but not in the heart. It remains unclear how GPER expression in the brain regulates heart rate and if GPER can act independently of other estrogen receptors. We labeled GPER expressing cells, other estrogen receptor expressing cells, and some specific cell types using whole mount *in situ* hybridization. Our results show only a subpopulation of GPER expressing cells express other estrogen receptors, suggesting GPER acts autonomously in some regions of the brain.

Annie Gordon
agordon1@uab.edu

Estimation of Frequency-Specific Behavioral Thresholds from Chirp ABR Responses

Annie Gordon, Saravanan Elangovan, and Shannon Bramlette

Scientific Abstract

The tone-burst Auditory Brainstem Response (ABR) is currently the gold standard for physiological estimation of an audiogram (JCIH, 2007). The narrowband (NB) Chirp stimuli have been purported as an alternate ABR stimulus, particularly for threshold estimation. A chirp stimulus is low frequency leading meaning it temporally rises from lower to higher frequencies in order to compensate for the temporal dispersion subsequent to the traveling wave delay within the cochlea. Research has shown ABRs to chirps display higher amplitude responses than click (Hood & Maloff, 2013) and tone-burst (Rodrigues et al. 2013) stimuli, creating improved threshold estimation accuracy. We examined a group of normal hearing and hearing impaired adults with traditional behavioral audiology and estimated ABR thresholds using the Interacoustics Eclipse AEP System. Comparable recording measures were utilized to record ABR responses for the following test stimuli: click, tone-burst (500, 1000, 2000, 4000 Hz), broadband & narrowband CE-Chirp (500, 1000, 2000, 4000 Hz). Results revealed ABR responses recorded with narrowband chirp stimuli estimated thresholds at significantly lower levels than those estimated by equivalent tone-burst stimuli, have significantly shorter ABR wave V latencies (broadband, .5, 1, 2, 4 kHz stimuli) and larger amplitudes (broadband, 2 & 4 kHz stimuli) at lower presentation levels (40 dB nHL). Findings suggest NB chirp stimuli may improve testing efficiency and reliability resulting in important implications in the hearing assessment of infants and difficult-to-test populations.

Lay Abstract

The tone-burst Auditory Brainstem Responses (ABR) is currently the gold standard used clinically for the objective estimation of a behavioral pure tone audiogram (JCIH, 2007). Research has shown ABRs to another stimulus, the Chirp, display better responses than traditionally used click (Hood & Maloff, 2013) and tone-burst (Rodrigues et al. 2013) stimuli. In the present study, we recorded and compared thresholds estimated by both the tone-burst and chirp stimuli with those estimated by the traditional behavioral pure tone audiogram. Our results support the notion that ABR responses recorded with Chirp stimuli may improve test efficiency and reliability of estimating frequency-specific hearing acuity. These results have important implications in the hearing assessment of infants and difficult-to-test populations.

Abbey Herringshaw
abbeyjh@uab.edu

Variance in Language Abilities in Autism as a function of Hemispheric Lateralization and Functional Connectivity

Abbey J. Herringshaw and Rajesh K. Kana

Scientific Abstract

The brain's language network is often more right lateralized in autism spectrum disorders (ASD) than in typically developing (TD) individuals, which may be either detrimental or compensatory. TD individuals may compensate for weak/atypical language lateralization with greater interhemispheric functional connectivity (Tzourio-Mazoyer et al., 2015), which is consequential considering reported connectivity disruptions in ASD. This study tested whether functional lateralization and connectivity of language areas predicts variance in language abilities. ASD ($N=15$) and TD ($N=17$) adults matched on performance IQ but not verbal IQ (VIQ) read sentences in a Siemens 3.0 Tesla fMRI scanner. Regions-of-interest (ROIs) were defined using Brodmann areas 44/45 (Broca's area) and 22 (Wernicke's area). ROI lateralization indices (LI) and ROI-to-ROI functional connectivity were calculated in SPM12 and the LI and CONN toolboxes. LI values and beta-weights of connectivity between RH and LH homologues served as independent variables in two 3-way ANOVAs (group x LI x connectivity) predicting VIQ. VIQ was predicted by the group x LI x connectivity interaction in BA22, $F(1,24)= 7.407, p<.05$, and the group x LI interaction in BA44/45, $F(3,28)= 4.319, p<.05$. An additional two-way ANOVA (group x BA44/45 LI) predicted interhemispheric BA44/45 connectivity, $F(3,28)= 3.658, p<.05$. These results reflect VIQ variation in ASD dependent on BA22 connectivity and lateralization: in ASD a combination of weaker connectivity and reduced LH dominance predicted some of the lowest VIQ's observed. In BA44/45, greater left lateralized activity predicted higher VIQ in TD, while ASD showed the opposite pattern. ASD also lacked connectivity increases with weakening lateralization.

Lay Abstract

A relatively well-accepted finding in brain research is the left-hemisphere dominance for language. Estimates indicate >90% of the population shares this pattern. Research suggests that the brain's language network is often more right lateralized in autism spectrum disorders (ASD) than in typically developing (TD) individuals. However, the impact of this on language abilities is unclear. A minority of TD individuals with less left hemisphere language dominance may make more connections between left and right brain areas in order to compensate for this difference. This is important, because individuals with ASD also show fewer brain connections in general. This study tested whether left vs. right brain organization and connections between right and left language areas affect language abilities in individuals with and without ASD. 15 ASD and 17 TD adults read sentences in an MRI scanner. Two major hubs of the brain's language network (Broca's area and Wernicke's area) were studied. For each hub, the amount of brain area used on each side was calculated, as was the extent to which the sides were coordinating. In the first hub, language abilities of the ASD group changed depending on connections and left vs. right organization; ASD participants with both less leftward organization and less cooperation between sides had the worst language.

Rylie Hightower
rylieh@uab.edu

KPT-350 Ameliorates Duchenne Muscular Dystrophy Symptoms in Dystrophic Zebrafish and Mice

Rylie M. Hightower, Devin E. Gibbs, Christopher S. Lee, Janelle M. Spinazzola, Lillian C. Mead, Jeffrey J. Widrick, Sharon Tamir, Shelton Cochran, Yosef Landesman, Louis M. Kunkel, Matthew S. Alexander

Scientific Abstract

DMD is an X-linked disorder that afflicts approximately 1:5000 live male births, making it the most common form of muscular dystrophy worldwide. The nuclear export protein XPO1/CRM1 is a promising target for the treatment of neurological disorders with inflammatory pathology, such as DMD. KPT-350 is a potent, orally available, slowly-reversible, small molecule inhibitor of XPO1. KPT-350 treatment induces nuclear retention of I κ B α , a protein cargo of XPO1 and potent inhibitor of NF- κ B transcriptional activity, making it a potential therapeutic for DMD. Both short- and long-term effects of treatment with KPT-350 were assessed by characterization of muscle architecture, mobility, and survivability. Furthermore, we tested oral KPT-350 (5 mg/kg body weight) in adult *mdx* (DMD) and WT control mice 3 times a week for 8 weeks in a blinded fashion. In short-term treatment studies, KPT-350-treated *sapje* zebrafish showed significant prevention of muscle degeneration associated with dystrophin-deficiency as well as improved overall muscle architecture. With long-term treatment, KPT-350 extended the lifespan of the *sapje* zebrafish and reduced overall dystrophic pathology. In *mdx* (DMD) mice, KPT-350 treatment blocked muscle inflammation, ameliorated histological hallmarks of DMD, improved overall neuromuscular physiology, and reduced overall dystrophic symptoms compared to vehicle controls. Our studies demonstrate that KPT-350 is a promising small molecule therapeutic that can attenuate neuromuscular symptoms and early pathological progression of DMD.

Lay Abstract

Duchenne muscular dystrophy (DMD) is an X-linked disorder that afflicts approximately 1:5000 live male births, making it the most common form of muscular dystrophy worldwide. Patients with DMD typically lose their ability to walk by the time they reach their teenage years. They also develop severe cardiac and respiratory problems that contribute to the debilitating nature of this disease. One important symptom in patients with DMD is inflammation, which worsens many other disease symptoms like muscle function. KPT-350 is a therapeutic drug that has been developed for neurological disorders that involve inflammation as part of their disease process. Inside cells, the nucleus is an important site for the regulation of when genes get “turned on” and “turned off.” The goal of KPT-350 treatment is to prevent genes involved in inflammation from getting “turned on.” With inflammatory genes “turned off”, patients would hopefully experience less inflammation. With less inflammation, symptoms like muscle function would be improved. To test this, we administered KPT-350 to zebrafish and mice with DMD. When zebrafish were given KPT-350, their muscles weren’t as damaged and they lived longer than the DMD zebrafish that weren’t given the drug. When mice were given KPT-350, they could run and walk better and longer, their muscles weren’t as damaged, and they had less inflammation than the DMD mice that weren’t given the drug. Our experiments show that KPT-350 is helping to alleviate symptoms of DMD

Jamie Holloway

jmh27@uab.edu

Relationships between Gross Motor Ability and Social Function in Young Children with Autism Spectrum Disorders

Jamie M. Holloway, Morghen Smith, Ashley Cooper, and Fred Biasini

Scientific Abstract

In addition to social and communication impairments, children with autism spectrum disorder (ASD) often exhibit additional delays in motor abilities. In children who are typically developing, motor ability is related to social function. However, the extent to which motor ability and social function are related in children with ASD is unknown. The purpose of this study is to examine the relationship between gross motor ability and social function in young children with ASD. Children with ASD between the ages of 48-71 months were invited to participate in the study. The gross motor subscales of the *Peabody Developmental Motor Scales 2nd Ed (PDMS-2)* were administered to determine each participant's level of gross motor function. Social function was measured using the Social Skills Improvement System (SSIS) Rating Scales and the Preschool Activity Card Sort (PACS). Eleven children with ASD participated in the study. Participants ranged from 48 to 68 months of age (Mean=57.7 mths). Eight children demonstrated delayed gross motor skills on the PDMS-2 as indicated by a GMQ <1.5 SD below the mean. Spearman's rank-order correlation revealed a strong, positive relationship between PDMS-2 GMQ and SSIS Social Skills standard scores ($rs=0.747$, $p=.008$) and the Social subscale of the PACS ($rs=0.745$, $p=.008$). The results support previous findings that suggest that gross motor delays are common in children with ASD. In addition, a positive relationship between gross motor ability and social function was found.

Lay Abstract

In addition to social and communication impairments, children with autism spectrum disorder (ASD) often have additional delays in motor abilities. In children who are typically developing, motor ability is related to social function. However, the extent to which motor ability and social function are related in children with ASD is unknown. The purpose of this study is to examine the relationship between gross motor ability and social function in young children with ASD. Children 4 and 5 years of age with ASD were invited to participate in the study. Gross motor skills and social function were measured using standardized tests. Eleven children with ASD participated. Participants ranged from 48 to 68 months of age. Eight children demonstrated delayed gross motor skills. The results support previous findings that suggest that gross motor delays are common in children with ASD. In addition, gross motor ability and overall social function were positively correlated. Children with ASD who had higher gross motor skills also had higher social skills.

Niharika LLoomba
nloomba@uab.edu

Regional Homogeneity of Brain Activity and Its Relationship to Social Impairment in Autism Spectrum Disorder

Niharika Loomba, Carla Ammons, Omar Maximo, and Rajesh K. Kana

Introduction: Individuals with autism spectrum disorder (ASD) often show characteristic social deficits. Disruption in brain connectivity has been emerging as a model of the neuropathology of autism. Regional homogeneity (ReHo), a measure of local connectivity (synchronization of brain activity of proximal areas), has been found to be increased in relatively posterior brain regions but decreased anterior regions in ASD compared to typically developing (TD) individuals (Keown et al., 2013). This study aims to characterize the patterns of local connectivity differences and relate it with social impairments in individuals with ASD.

Methods: Eyes closed resting state-fMRI data from 26 ASD and 23 TD participants [matched for head motion ($p= 0.94$) and age (range=18-64 years, $p= 0.89$)] from the ABIDE-II consortium were obtained and preprocessed through a standard pipeline. Individual voxel-wise ReHo maps were obtained and standardized. All participants completed the Social Responsiveness Scale (SRS) at time of scan. T-scores for SRS Total and SRS Social Awareness, a subscale of the SRS, were correlated with the standardized ReHo maps.

Results: SRS Total scores were negatively correlated with ReHo in the medial prefrontal cortex, middle and inferior occipital gyrus, and lingual gyrus. There was positive correlation between SRS Total and ReHo in the superior temporal gyrus. All results were significant at a cluster-corrected level of $p<.05$ (uncorrected $p<.01$ with a cluster size > 31 voxels).

Discussion: The findings of inverse relationship between social symptoms in autism and local connectivity underscore the role of network organization in cognitive and behavioral functioning. The findings show that disruptions in the synchronization of brain regions may influence behavioral impairments that are characteristic to ASD.

Jose Maximo
omaximo@uab.edu

Alterations in Brain Entropy in Autism Spectrum Disorders

Jose O. Maximo, Donna L. Murdaugh, and Rajesh K. Kana

Scientific Abstract

Background: Sample entropy is a novel approach to characterize the temporal dynamics of the brain. Estimating entropy is especially important in clinical populations such as autism spectrum disorders (ASD) as higher entropy would entail brain disease. We hypothesize increased brain entropy in children with ASD compared to typically developing (TD) children.

Methods: Resting state fMRI data from the ABIDE II consortium were used and consisted of 45 high-functioning children with ASD and 45 age-and-IQ-matched TD children. Data were preprocessed using a standard resting state preprocessing pipeline. Sample entropy was then calculated in two ways: by cortical region (Frontal, temporal, parietal, and occipital) and whole brain. Group differences were assessed using a two-way ANOVA (Group x region) and a two-sample *t*-test. Brain-behavior correlations were calculated using sample entropy and Social Responsiveness Scale (SRS) total scores in the ASD group.

Results: The main results are: I) a main effect of Region; II) significantly reduced sample entropy (TD > ASD) in frontal gyrus and increased sample entropy (ASD > TD) in left parietal and temporal regions; and III) positive correlations of sample entropy with SRS scores in left parietal and temporal regions.

Conclusions: Increased SampEn in the ASD group in posterior areas indicate increased randomness of a system, meaning the dynamic system activity is less predictable and less organized. The correlation of increased sample entropy with ASD symptoms underscores the clinical implications of this neurobiological index. Our preliminary results suggest that SampEn may be a reliable tool to assess brain dynamics in ASD.

Lay Abstract

Biological systems typically exhibit complex behavior with nonlinear dynamic properties. Nonlinear signal processing techniques such as sample entropy is a novel approach to characterize the temporal dynamics of the brain. Estimating entropy, the state of uncertainty of a system, is especially important in clinical populations such as autism spectrum disorders (ASD) as higher entropy would entail brain disease.

Resting state fMRI data from the ABIDE II consortium were used from 45 ASD children and 45 neurotypical ones. Sample entropy was calculated between the two groups and brain-behavior correlations were calculated using Social Responsiveness Scale (SRS) total scores.

Significantly reduced sample entropy (TD > ASD) in frontal gyrus and increased sample entropy (ASD > TD) in left parietal and temporal regions; and positive correlations of sample entropy with SRS scores in left parietal and temporal regions.

Increased SampEn in the ASD group in posterior areas indicate increased randomness of a system, meaning the dynamic system activity is less predictable and less organized. The correlation of increased sample entropy with ASD symptoms underscores the clinical implications of this neurobiological index.

Mary Phillips
Mphil10@uab.edu

Stronger Contribution and Impaired LTP of Hippocampal Inputs to the Medial Prefrontal Cortex in the *Mecp2* Mouse Model of Rett Syndrome

Mary Phillips and Lucas Pozzo-Miller

Scientific Abstract

An imbalance between synaptic excitation and inhibition (E/I) is a cornerstone pathophysiology in autism, including the monogenic autism-associated disorder Rett syndrome (RTT). E/I imbalance results in altered levels of neuronal activity, which disrupts neural networks and the associated behaviors. We characterized network activity by imaging voltage-sensitive dye (VSD) signals in slices from symptomatic male *Mecp2* knockout (KO) mice. VSD signals evoked by single synaptic potentials are larger, longer lasting, and wider spreading in slices of the ventral hippocampus (vHIP) from *Mecp2* KO mice compared to wildtype (WT) slices. In contrast, VSD signals in slices from the medial prefrontal cortex (mPFC) of *Mecp2* KO mice are shorter lasting and less spreading. However, stimulation of identified vHIP fibers in mPFC slices evoked larger and wider spreading VSD signals in *Mecp2* KO slices. Normalized to intra-cortical stimulation in the same slices, there is a stronger contribution of vHIP inputs to the *Mecp2* KO mPFC suggesting that vHIP inputs drive hyperactivation of the mPFC network in *Mecp2* KO mice, in contrast to the hypoactivity evoked by stimulation of local intra-cortical fibers. High-frequency stimulation of vHIP fibers triggers long-term potentiation (LTP) of VSD signals in mPFC slices from WT mice, which is absent in *Mecp2* KO mice. The mPFC pathway is selectively activated following a social encounter, as estimated by higher levels of the immediate early gene c-Fos, thus atypically strong vHIP inputs to the mPFC and their lack of LTP in *Mecp2* KO mice may underlie atypical social behaviors and deficits in social memory.

Lay Abstract

Rett syndrome (RTT) is a neurodevelopmental, autism spectrum disorder causing motor and sensory impairments, intellectual disability, and loss of spoken language. The brain of these individuals and experimental mouse models show altered levels of nerve cell activity resulting from an imbalance in synaptic excitation and inhibition. However, the direction of the imbalance is different depending on the brain region: the ventral hippocampus (vHIP) is *hyper*-active, and the medial prefrontal cortex (mPFC) is *hypo*active. The fact that the vHIP makes direct excitatory connections with the mPFC raises the possibility that the opposing network imbalances are causally related. Indeed, selective stimulation of vHIP inputs in slices of the mPFC causes hyper-activation in the mouse model of RTT, but not in wildtype mice. In addition, the synaptic connections between the vHIP and the mPFC in RTT mice lack the long-term changes in strength thought to underlie learning and memory. As the mPFC is involved in social behaviors, the inability of these synapses to be strengthened may underlie atypical social encounters and lack of social memory in RTT mice. We hope our studies will identify novel targets for rational therapeutic interventions

Victoria Seghatol-Eslami
Vs129@uab.edu

The topography of fusiform face area response during implicit face processing in autism spectrum disorder

Victoria Seghatol-Eslami, Carla Ammons, and Rajesh Kana

Abstract

Social impairment is a hallmark feature of individuals with autism spectrum disorder (ASD). Implicit face processing, paying attention to human faces without explicit instructions, is relatively automatic and commonly seen in the social interactions of typically developing (TD) individuals. Individuals with ASD may be less likely to attend and process implicit information from faces in social situations, leading to poor interpersonal interactions. The fusiform face area (FFA), part of the fusiform gyrus (FG), has been implicated in face processing (Kanwisher, et al., 1997). The mid fusiform sulcus (MFS) is a shallow longitudinal sulcus separating face-selective regions on the lateral FG from place-selective regions on the medial FG, which has not directly been studied in ASD. Functional magnetic resonance imaging (fMRI) data were acquired from 21 high-functioning adults with ASD and 22 TD control participants while making judgments about the means (how an action is performed) and intention (why an action is performed) of a model's actions. In addition to characterizing the neuroanatomy of the MFS in our data, we examined the location of fusiform brain activity to implicit processing in relation to the MFS during task conditions (intention and means) versus fixation. Both TD and ASD individuals showed activity in FG regions lateral to the MFS in response to implicit face processing. While the TD activation was predominately in the right hemisphere, ASD activation was in lateral FG regions in both hemispheres during the combined task of intention and means. However, group differences did not survive multiple comparison correction.

Cathy Sung
cysung@uab.edu

Congenital MCMV Infection is Associated with Sensorineural Hearing Loss (SNHL)
Cathy Yea Won Sung and William Britt

Scientific Abstract

Congenital HCMV infection can cause sensorineural hearing loss (SNHL) in approximately 15% of infants ranging from moderate to severe and unilateral to bilateral hearing loss. However, the mechanism(s) of disease leading to SNHL in infants with congenital HCMV infection are unknown. Thus, we developed a murine model of hearing loss in congenital MCMV infection using intraperitoneal (IP) inoculation in newborn mice that results in hematogenous spread to the inner ear. We detected hearing loss in 50-60% of infected mice with increased hearing threshold of approximately 20dB across all frequencies of sound. This phenotype closely resembles the characteristics of hearing loss in infants with congenital HCMV infection. Therefore, we have used this model to investigate the impact of MCMV infection on the development of the auditory pathway.

Virus was detected in the cochlea as early as four days post infection in the lateral wall and in the spiral ganglion neurons. Inflammatory cells were abundant in the inner ear and numerous genes that initiate inflammation and cell death pathways were activated in the infected cochlea. Further histological analyses of the inner ear in mice with increased ABR thresholds exhibited uniformly preserved hair cells in the Organ of Corti after MCMV infection, even in mice with hearing loss. However, the number of spiral ganglion neurons (SGN) and synapses that connect the cochlear hair cells and SGN nerve terminals were decreased. Additionally, staining of the unmyelinated nerve fibers in the cochlear sensory epithelium revealed disorganized and degenerating nerve terminals in the MCMV-infected mice with hearing loss. These observed damages in the cochlea of MCMV-infected mice may be a possible mechanism of hearing loss. Ongoing studies will confirm these observations of hearing loss in this model and identify the mechanisms that potentially result in these phenotypes.

Lay Abstract

HCMV is known to be the most common cause of sensorineural hearing loss (SNHL) in the United States with up to 15% of children with congenital HCMV infection displaying some level of hearing loss. However, the mechanism(s) of disease leading to SNHL in infants with congenital HCMV infection are unknown. Thus, we developed a mouse model of hearing loss in congenital CMV infection to study the mechanism of disease. We detected 50-60% of infected mice resulting in hearing loss. Additionally, virus was detected in the inner ear and inflammatory response was significantly increased during infection. Further analysis in the cochlear structures in mice with hearing loss exhibits damage in the spiral ganglion neurons. These observations in the cochlea may be a possible mechanism of hearing loss during MCMV infection in mice.

Melissa Thye
mthye@uab.edu

Characterizing the Heterogeneity in Autism Spectrum Disorder using Brain Connectivity Underlying Social Cognition

Melissa D. Thye and Rajesh K. Kana

Scientific Abstract

Behavioral and neural heterogeneity is a key feature of individuals with Autism Spectrum Disorder (ASD). Previous neuroimaging studies report alterations in the theory-of-mind (ToM) network in ASD. However, most of these studies relied on analyses which concatenate results to arrive at a group-level model which may not accurately represent many participants within a heterogeneous group. A novel analytical approach, the *Group Iterative Multiple Model Estimation* (GIMME) algorithm, reveals divergent subgroups based on patterns of functional connectivity among a priori regions of interest (ROI) using a structural equation modeling framework. The primary objective of this study was to characterize the neural heterogeneity across ASD and typically developing (TD) participants in a functional magnetic resonance imaging (fMRI) study of ToM processing. A total of 63 participants (32 ASD and 31 age-and-IQ-matched TD) watched animations of geometrical shapes depicting intentional or random action in the scanner. In the intentional/ToM condition, two subgroups were identified. Subgroup A (28% ASD; 39% TD) was characterized by increased connectivity from LPCUN to RpSTS as well as increased connectivity from MPFC to RIFG. Conversely, Subgroup B (72% ASD; 61% TD) showed comparatively weaker connectivity with no additional pathways emerging above the group level model. Statistical comparisons of the individuals comprising the two subgroups revealed stronger connectivity of the group level connection from LpSTS to MPFC in Subgroup A compared to Subgroup B. This pattern of results suggests possible underconnectivity in the group containing the largest percentage of ASD participants. Implications for individualized neuroimaging data analysis will be discussed.

Lay Abstract

Autism spectrum disorder (ASD) is characterized by difficulty in reading the minds of others, an ability known as theory-of-mind (ToM). There are also widespread differences across individuals with autism, and such differences are usually ignored in studies examining the brain in autism. To address this problem, we used a novel data analysis approach known as *Group Iterative Multiple Model Estimation* (GIMME) which identifies both group level information and individual level information. In particular, we were interested in the variability in brain connectivity which measures the coordination of different regions in the brain over time. Thus, this analysis will subgroup participants based on the similarity of the individual participant's brain connectivity. In an MRI scanner, participants watched movement of geometrical shapes engaged in intentional or random motion. We found two subgroups of participants with different profiles of connectivity. The subgroup containing the largest percentage of ASD participants showed overall weaker brain connectivity among brain regions known to respond to ToM tasks. These results impact how we study ASD specifically and how we account for variability in the study of brain connectivity and functioning more generally.

Abby Turnbough
anturnbo@uab.edu

The choice of musical instrument and its effects on auditory working memory and perception in adolescents

Abby N. Turnbough and Aurora J. Weaver

Abstract

Research examining the human asymmetry of handedness has spanned several decades; this has included exploring the relationship among handedness and the auditory modality. Bannatyne and Wichiarijote (1969) found a positive correlation between unlearned left handedness and auditory digit span memory test scores in third grade children. Authors attributed this outcome to processing digits in a similar fashion to music notes. Additionally, musicians whose dexterity involves both hands have more symmetric neural processing as a result of the sensory-motor experience they've had with their instrument (Gaser & Schlaug, 2003). However, there is little research translating these neurological differences in musicians to determine if more symmetry in regions enhanced by musical training would manifest into advantages for auditory processing. In an attempt to identify perceptual advantages of instrumental training involving both hands during stages when the central auditory nervous system (CANS) is still developing, monaural and binaural listening tasks, as well as working memory tasks were collected on adolescent musicians. The outcomes indicate that regardless of instrumental choice musical training would benefit individuals with difficulty segregating binaural input and temporal auditory organization difficulties.

Bannatyne, A. D., & Wichiarijote, P. (1969). Hemispheric Dominance, Handedness, Mirror Imaging, and Auditory Sequencing. *Exceptional Children*, 36(1), 27-36.

Gaser, C. & Schlaug, G. (2003). Brain structures differ between musicians and nonmusicians. *Journal of Neuroscience*, 23, 9240-9245.

Varshini Venkatesan
varshini@uab.edu

Role of Hatha Yoga Therapy as an Effective Treatment for Chronic Migraine

Varshini Venkatesan and Dr. Grace Arnold

Scientific Abstract

Migraine headache is a chronic pain condition that is characterized by unilateral, throbbing head pain, which is moderate to severe in intensity and is often aggravated by physical activity. Even as the second most common disorder in the United States, the cause of chronic migraine has been debated for decades, with no definite cure. However, there are several treatment options to alleviate the impact of chronic migraine and they range from acute and prophylactic medications to non-pharmacological strategies. Among these non-pharmacological options, yoga therapy, specifically Hatha Yoga, has been proven to be effective in treating chronic migraine, especially in managing it long-term. This study explores the reasons behind the effectiveness of Hatha Yoga as a treatment option for chronic migraine, by not only examining its pathophysiology in terms of central sensitization and peripheral sensitization, but also comparing its pathophysiology to that of prophylactic medications. The pathophysiology of migraine headaches implicates central sensitization and peripheral sensitization of the trigeminovascular pathway. The components of the pathway have each been targeted specifically by different therapy types, resulting in a range of varying degrees of pain relief and comfort. Yoga therapy, however, does not have specific biological targets. Instead, the breathing techniques involved in hatha yoga prevent the first step of peripheral sensitization, thus proving to be an efficient treatment option for chronic migraine.

Lay Abstract

Migraine headache is a chronic pain condition that is characterized by unilateral, throbbing head pain, which is moderate to severe in intensity and is often aggravated by physical activity. There are several treatment options to alleviate the impact of chronic migraine and they vary from acute and prophylactic medications to non-pharmacological ones. Among these non-pharmacological options, yoga therapy, specifically Hatha Yoga, has been proven to be effective in treating chronic migraine. This study explores the reasons behind the effectiveness of Hatha Yoga as a treatment option for chronic migraine, by not only examining its pathophysiology in terms of central sensitization and peripheral sensitization, but also comparing its pathophysiology to that of prophylactic medications.

Fang Zhang
fangzh@uab.edu

Regulation of α_2A Adrenergic Receptor Trafficking and Signaling by Amyloid Precursor Protein

Fang Zhang, Mary Gannon, Yunjia Chen, Kai Jiao, and Qin Wang

Scientific Abstract

The pathogenic effect of the Amyloid Precursor Protein (APP) cleavage product A β in Alzheimer's disease is well established. However, less is known about the physiological function of APP outside of the disease state. While it has been implicated in several functions, including neuronal development, intracellular transport, and neuronal homeostasis, whether and how APP may regulate GPCR functions have not been addressed. In this study, we identified a novel direct interaction between APP and the α_2A Adrenergic Receptor (α_2AAR) that occurred at the intracellular domains of both proteins. The APP interaction with α_2AAR was promoted by agonist binding and competes with arrestin binding to the receptor. Consistent with reduced arrestin interaction with α_2AAR in the presence of APP, agonist driven internalization of α_2AAR was reduced, and desensitization of α_2AAR -induced ERK1/2 activation was also attenuated. Further, arrestin recruitment to the cell membrane in both N2a cells and primary SCG neurons is increased in cells in which APP was knocked down using siRNA. Our study suggests that APP, as a novel interacting partner of α_2AAR , stabilizes α_2AAR at the cell surface and prolongs its signaling. Given the important role of α_2AAR in the noradrenergic system, this novel regulation of α_2AAR by APP may have an impact on modulation of noradrenergic tone in the brain.

Lay Abstract

The pathogenic effect of the Amyloid Precursor Protein (APP) cleavage product A β in Alzheimer's disease is well established. However, less is known about the physiological function of APP outside of the disease state. While it has been implicated in several functions, including neuronal development, intracellular transport, and neuronal homeostasis, whether and how APP may regulate GPCR functions have not been addressed. In this study, we identified a novel direct interaction between APP and the α_2A Adrenergic Receptor (α_2AAR) that occurred at the intracellular domains of both proteins. The APP interaction with α_2AAR was promoted by agonist binding and competes with arrestin binding to the receptor. Consistent with reduced arrestin interaction with α_2AAR in the presence of APP, agonist driven internalization of α_2AAR was reduced, and desensitization of α_2AAR -induced ERK1/2 activation was also attenuated. Further, arrestin recruitment to the cell membrane in both N2a cells and primary SCG neurons is increased in cells in which APP was knocked down using siRNA. Our study suggests that APP, as a novel interacting partner of α_2AAR , stabilizes α_2AAR at the cell surface and prolongs its signaling. Given the important role of α_2AAR in the noradrenergic system, this novel regulation of α_2AAR by APP may have an impact on modulation of noradrenergic tone in the brain.

Guest Speakers

Jim Bodfish, Ph.D.

Professor

Departments of Hearing & Speech Sciences, Psychiatry, and Neuroscience
Vanderbilt Brain Institute, and Vanderbilt Kennedy Center
Vanderbilt University School of Medicine

Ami Klin, Ph.D.

Director, Marcus Autism Center, Children's Healthcare of Atlanta
Georgia Research Alliance Eminent Scholar Professor & Chief, Division of Autism & Related Disorders, Department of Pediatrics, Emory University School of Medicine; Emory Center for Translational Social Neuroscience. Shorter affiliation: Marcus Autism Center, Children's Healthcare of Atlanta and Emory University School of Medicine.

Celine Saulnier, Ph.D.

Director of Research Operations

Marcus Autism Center, Children's Healthcare of Atlanta
Associate Professor, Division of Autism and Related Disorders
Department of Pediatrics, Emory University School of Medicine

Local Speakers

Kristi Guest, Ph.D.

Assistant Professor

Disabilities Services Coordinator
Department of Psychology
University of Alabama at Birmingham

Gwendalyn King, Ph.D.

Assistant Professor

Summer Program in Neuroscience (SPIN) Director
Department of Neurobiology
University of Alabama at Birmingham

Trainees

Josh Cohen

Graduate Research Assistant
MD/PhD Program
Neuroscience

Melissa Thye

Graduate Student
Lifespan Developmental
Psychology PhD Program

Abby Turnbough

Audiology Intern
Sparks Center for
Development & Learning
Disorders