2017 Summary of Advances Nominations: January 2017 – April 2017

### Question 1 (Screening and Diagnosis)

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<th>Joshua Gordon</th>
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<td>Walter Koroshetz</td>
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<td>Jennifer Johnson</td>
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Using magnetic resonance imaging (MRI) in infants with older siblings with autism, researchers from around the country were able to correctly predict 80 percent of those infants who would later meet criteria for autism at two years of age.

In this prospective neuroimaging study of 106 infants at high familial risk of ASD and 42 low-risk infants, we show that hyperexpansion of the cortical surface area between 6 and 12 months of age precedes brain volume overgrowth observed between 12 and 24 months in 15 high-risk infants who were diagnosed with autism at 24 months. Brain volume overgrowth was linked to the emergence and severity of autistic social deficits. A deep-learning algorithm that primarily uses surface area information from magnetic resonance imaging of the brain of 6-12-month-old individuals predicted the diagnosis of autism in individual high-risk children at 24 months (with a positive predictive value of 81% and a sensitivity of 88%). These findings demonstrate that early brain changes occur during the period in which autistic behaviours are first emerging.

Joshua Gordon  

Longitudinal diffusion tensor imaging data were collected from 217 infants at high familial risk for ASD. Forty-four of these infants were diagnosed with ASD at age 2. Targeted cortical, cerebellar, and striatal white matter pathways were defined and measured at ages 6, 12, and 24 months. Dependent variables included the Repetitive Behavior Scale-Revised and the Sensory Experiences
Questionnaire. Findings suggest that restricted and repetitive behaviors contributing to a diagnosis of ASD at age 2 years are associated with structural properties of callosal and cerebellar white matter pathways measured during infancy and toddlerhood. They further identified that repetitive behaviors and unusual sensory response patterns co-occur and share common brain-behavior relationships. These brain-behavior relationships were remarkably specific, suggesting a possible neurobiological mechanism wherein atypical neural development in infancy precedes the emergence of core autistic features within the domain of restricted and repetitive behaviors. Identifying pre-symptomatic markers of later behavior in ASD also affords the possibility of developing enhanced approaches to screening and preventative interventions.

**Question 2 (Underlying Biology)**

**Walter Koroshetz**


This study explored sex differences in ASD that may be related to normative differences in brain structure phenotype. The authors conducted MRI scans on high-functioning ASD adults (n=98) and matched neurotypical control adults (n=98) 18-42 years of age, and developed predictive models of biological sex based on cortical thickness. Analyses of the neuroanatomical diversity and patterns revealed that more male-typical patterns of brain anatomy among biological females led to three-fold increase in risk for ASD as compared to biological females with a more female characteristic brain phenotype. In addition, the patterns of regional neuroanatomical variability and their correlations with low or high ASD risk were sex specific, and were observed in regions that have been linked to core ASD behavioral deficits. This paper sheds light on potential neurobiological mechanisms that may underpin sex differences in ASD and points to the need for consideration of brain structure phenotype when assessing ASD risk.


Approximately 50% of males with Fragile X Syndrome (FXS) are diagnosed with autism. Loss of functional FMRP, which causes FXS, leads to abnormal intracellular signaling and altered synthesis of synaptic proteins. This study identified and manipulated a pathway by which these changes occur that involves type 1 adenylyl cyclase (ADCY1) mRNA and protein synthesis pathways. In Fmr1 mutant mice, genetic reduction of ADCY1 protein normalized the aberrant signaling cascades that are mediated by ERK1/2 and PI3K, and attenuated autism-related repetitive and social behaviors and audiogenic seizures. Peripheral administration of an experimental compound that suppresses ADCY1 activity also reduced the behavioral deficiencies in the Fmr1
mutant mice. Gq-coupled muscarinic acetylcholine receptors are also upregulated in Fmr1 mutant mice and implicated in the ERK1/2 and PI3K signaling cascades, and thus may represent a novel target for pharmacological intervention in ASD.

Question 3 (Risk Factors)

Joshua Gordon


Nat Genet. 2017 Apr;49(4):504-510. [PMID: 28191890] (suggested by Thomas Lehner; NIMH-funded study)

Recent research has uncovered an important role for de novo variation in neurodevelopmental disorders. Using aggregated data from 9,246 families with autism spectrum disorder, intellectual disability, or developmental delay, the authors found that ~1/3 of de novo variants are independently present as standing variation in the Exome Aggregation Consortium's cohort of 60,706 adults, and these de novo variants do not contribute to neurodevelopmental risk. They further used a loss-of-function (LoF)-intolerance metric, pLI, to identify a subset of LoF-intolerant genes containing the observed signal of associated de novo protein-truncating variants (PTVs) in neurodevelopmental disorders. LoF-intolerant genes also carry a modest excess of inherited PTVs, although the strongest de novo–affected genes contribute little to this excess, thus suggesting that the excess of inherited risk resides in lower-penetrant genes. These findings illustrate the importance of population-based reference cohorts for the interpretation of candidate pathogenic variants, even for analyses of complex diseases and de novo variation.

Walter Koroshetz


mSphere. 2017 Feb 22;2(1). [PMID: 28251181]

This study using a large birth cohort identifies an association between HSV infection and ASD. Maternal infections during pregnancy are associated with risk of neurodevelopmental disorders, including autism spectrum disorders (ASDs). Proposed pathogenetic mechanisms include fetal infection, placental inflammation, and maternal cytokines or antibodies that cross the placenta. The Autism Birth Cohort comprises mothers, fathers, and offspring recruited in Norway in 1999 to 2008. Through questionnaire screening, referrals, and linkages to a national patient registry, 442 mothers of children with ASD were identified, and 464 frequency-matched controls were selected. Immunoglobulin G (IgG) antibodies to Toxoplasma gondii, rubella virus, cytomegalovirus (CMV), herpes simplex virus 1 (HSV-1), and HSV-2 in plasma collected at midpregnancy and after delivery were measured by multiplexed immunoassays. High levels of HSV-2 IgG antibodies in maternal midpregnancy plasma were associated with increased risk of ASD in male offspring (an increase in HSV-2 IgG levels from 240
to 640 arbitrary units/ml was associated with an odds ratio of 2.07; 95% confidence interval, 1.06 to 4.06; P = 0.03) when adjusted for parity and child’s birth year. No association was found between ASD and the presence of IgG antibodies to Toxoplasma gondii, rubella virus, CMV, or HSV-1. Additional studies are needed to test for replicability of risk and specificity of the sex effect and to examine risk associated with other infections.

**Walter Koroshetz**


*This study explored whether gene-sex-environment interactions can explain sex-differences in incidence of ASD. They found that maternal immune activation by lipopolysaccharide in a genetic mouse model of ASD led to male-specific deficits in social behaviors. The genetic, environmental, and sex related factors had cumulative effects on ultrasonic vocalizations as 3 days of age, and only mice exposed to all three factors showed deficits in social recognition in adulthood. Three-way interaction was also found in corticotropin-releasing hormone receptor 1 (Crhr1) in the left hippocampus, which was also associated with epigenetic methylation over the Crhr promoter, implicating a role for stress-related genes in these effects. This study helps provide further insight into potential causes and mechanisms underlying sex-differences in ASD.*

**Walter Koroshetz**


*This study used single-molecule inversion programs (smMIPs) to sequence 208 candidate genes for neurodevelopmental disorders (ASD, intellectual disability, and developmental delay) from greater than 11,700 cases and greater than 2,800 controls. In total, 91 (44%) of the candidate genes reached locus-specific significance for disruptive mutations in 5.7% of patients. Secondary analysis of genetic burden and patient follow-up revealed 25 genes preferentially associated with ASD versus ID/DD diagnosis. The 25 genes were biased for de novo missense mutations suggesting less severe mutations may be involved in ASD without ID, and highlighted genes that may implicate early developmental programs responsible for neuronal proliferation, patterning, differentiation, and axonal guidance. Three genes without previous phenotypic information reached a high level of de novo significance – NAA15, KMT5B, ASH1L – and clinical follow-up assessments suggested new syndromic and nonsyndromic forms of ASD.*
Ruth Etzel  

Additional studies are needed to evaluate this interesting association.

Geraldine Dawson  

This is a report of sequencing of 5,205 samples from families with ASD, accompanied by clinical information, creating a database accessible on a cloud platform and through a controlled-access internet portal. The research team identified 18 new candidate ASD-risk genes.

**Question 4 (Treatments and Interventions)**

Geraldine Dawson  

Executive function deficits are common and impairing symptoms of ASD. There are no evidence-based treatments for EF deficits in ASD. The protocol described here will provide important preliminary data on the feasibility and efficacy of 20 Hz rTMS to DLPFC for EF deficits in ASD.

Geraldine Dawson  

This study is the first to show that an early parent-mediated intervention delivered to high risk infants before onset of ASD has the potential to impact the brain systems underpinning social attention in infants at familial risk for ASD. Compared to infants who only received assessment and monitoring, infants who received the intervention showed improvements in neurocognitive metrics of social attention, as reflected in a greater reduction in habitation times to face versus object stimuli between 6 and 12 months, maintained at 18 months; a greater increase in frontal EEG theta power between 6 and 12
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<th>April 26, 2017 IACC Meeting</th>
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<td><strong>Joshua Gordon</strong></td>
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| Lake JK, Denton D, Lunsky Y, Shui AM, Veenstra-VanderWeele J, Anagnostou E.  
| This study aimed to describe rates of antipsychotic medication use and the association between their use and demographics, clinical variables, and the use of behavioral/educational services among children with ASD. For children with ASD ages 2–11 (n = 4749) and those 12–17 (n = 401), 5.4 and 17.7% were prescribed at least one atypical antipsychotic medication (aripiprazole, risperidone, olanzapine, quetiapine, and ziprasidone) respectively. In young children, older age, use of multiple psychotropic medications, prior ASD diagnosis, non-white Hispanic race/ethnicity, and oppositional defiant problems were associated with antipsychotic use. Among older children, only older age was associated with antipsychotic use. In at least one age group, antipsychotic medication use was also related to behavior, family and occupational therapy, public insurance, site region, externalizing problems, body mass index, and sleep and gastrointestinal problems. Young children with ASD prescribed atypical antipsychotic medication were more likely to experience feeling tired, but had fewer problems with sleep onset delay and falling asleep in the car. Older children were more likely to experience gastrointestinal problems. Across both age groups, children were also more often overweight or obese compared to children who were not prescribed this medication.  |
| **Walter Koroshetz** |
| Ruskin DN, Murphy MI, Slade SL, Masino SA.  
| This study explored the potential for ketogenic diet to reverse ASD symptoms in a mouse model of ASD. Pregnant mice were exposed to maternal immune activation to induce ASD phenotype in offspring, who were then fed a ketogenic or control diet for three weeks after weaning. The ketogenic diet reversed the ASD-related social behaviors among the male offspring exposed to maternal immune activation. It did not have any effect on social behaviors in female mice, who were unaffected by the maternal immune activation. Metabolic changes were confirmed in both sexes exposed to the ketogenic diet by evidence of reduced blood glucose and elevated blood ketones. This study demonstrates clear benefit of ketogenic diet in a mouse model of ASD, suggesting potential utility for metabolic therapy in improving core ASD symptoms. Six years after the intervention, children whose parents were trained using the PACT model showed improved parent-child interaction skills, and fewer were considered to have “severe” autism as compared to the comparison group. Results were published on 25 October in The Lancet.  |
| **Question 5 (Services)** |
| David Mandell  
Julie Lounds Taylor  |
| Kerns CM, Newschaffer CJ, Berkowitz S, Lee BK.  
**Brief report: examining the association of autism and adverse childhood experiences in the National Survey of Children’s Health: the important role of income and co-occurring**  |
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<td><strong>Julie Lounds Taylor</strong></td>
<td>Although the sample is small (60), they found that parent-reported AND self-reported recreational activities buffered the effects of stress on quality of life. Interestingly, it was recreational activities that were important and not social activities. It gives some food for thought about what interventions might be more or less important to improve self-perceived quality of life.</td>
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<td><strong>David Mandell</strong></td>
<td>Prior studies have shown that children with ASD use emergency medical services more than other children. This study focuses specifically on adolescents, an understudied group. This study estimates that risk as four-fold, and greater for those who are older or live in rural areas. The use of the ED for females with autism is increasing over time. To the extent that ED use represents a failure of the health care system to provide more timely and less restrictive services, this study shows the importance of developing crisis prevention and management services for these groups.</td>
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<td><strong>Nathenson RA, Zablotsky B.</strong> The transition to the adult health care system among youths with autism spectrum disorder. Psychiatr Serv. 2017 Mar 15;appips201600239. [Epub ahead of print] [PMID: 28292222]</td>
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<td><strong>Julie Lounds Taylor</strong></td>
<td>In this administrative database study in one state, use of all services except emergency services decreased with age for youth with ASD. The fact that ED service use does not increase with age suggests that need is still there, but that services are not accessible for this group.</td>
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<td><strong>Joshua Gordon</strong></td>
<td>Researchers identified individuals with a diagnosis of autism who died between 1999 and 2014 by screening causes of death in the multiple cause-of-death data files in the National Vital Statistics System based on the ICD-10. During the study period, 1367 deaths (1043 males and 324 females) in individuals with autism were recorded in the United States. The mean age at death for individuals with autism was 36.2 years (SD = 20.9 years), compared with 72.0 years (SD = 19.2 years) for the general population. Of the deaths in individuals with autism, 381 (27.9%) were attributed to injury, with suffocation being the leading cause of injury mortality, followed by asphyxiation ($n = 78; PMR = 13.50; 95% CI = 10.68, 16.85$) and drowning ($n = 74; PMR = 39.89; 95% CI = 31.34, 50.06$). The</td>
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researchers concluded that individuals with autism appear to be at substantially heightened risk for death from injury.

Limitations of the study noted by the researchers:
First, in the absence of population data on autism, we were unable to calculate the death rates and cause-specific standardized mortality ratios. Instead, we relied on proportionate mortality analysis to explore the relative burden of injury mortality in individuals with autism. In proportionate mortality analysis, a cause-specific PMR is influenced by changes in the number of deaths from the specific cause or the number of deaths from all other causes. Consequently, the heightened PMR from injury observed in individuals with autism may not necessarily measure the excess risk of injury mortality in individuals with autism as compared with the general population. Second, our study was limited to death certificate data. The accuracy of data on death certificates filed by medical examiners and coroners varies with the cause of death and the types of disease. Therefore, autism as a contributing cause of death is likely underreported.

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<td>Walter Koroshetz</td>
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This study evaluated 889 10-year-old children from the Extremely Low Gestational Age Newborn (ELGAN) birth cohort (delivered at 23-27 weeks’ gestation in 2002-2004) to assess prevalence of ASD in extremely pre-term children versus the general population. Children were first screened using the Social Communication Questionnaire, then further evaluated with the ADI-R, and final diagnosis was made with the ADOS-2. Prevalence of 7.1% was found, and the analyses revealed an inverse relationship between ASD risk and gestational age. Forty percent of ASD children had intellectual disability, and the male to female ratio was 2.1:1, which is lower than the 4:1 ratio observed in the general population. This study underscores the need for enhanced ASD screening for preterm children, and for further exploration of the relationship between risk factors associated with preterm birth that may play a role in ASD etiology.