### Question 1 (Screening and Diagnosis)

**Joshua Gordon**


Funded by NIMH and NICHD; highlighted in NIMH and NIH press releases, as well as Dr. Collins’ blog:

**Geraldine Dawson**


*This systematic review suggests that individuals with autism spectrum conditions display typical sex/gender differences in core autism spectrum condition traits, suggesting that diagnostic criteria based on these symptoms should take into account typical sex/gender differences.*

**Joshua Gordon**


*This study uses data from 260 infants at 6 and 12 months of age, including 116 infants with longitudinal data. Diffusion data was used to obtain measures of the length and strength of connections between brain regions to compute network efficiency. Group differences were assessed in efficiency within linear mixed-effects models determined by the Akaike information criterion. Inefficiencies in high-risk infants later classified with ASD were detected from 6 months onward in regions involved in low-level sensory processing. In addition, within the high-risk infants, these inefficiencies predicted 24-month symptom severity. These results suggest that infants with ASD, even before 6 months of age, have deficits in connectivity related to low-level processing, which contribute to a developmental cascade affecting brain organization and eventually higher-level cognitive processes and social behavior.*

**Geraldine Dawson**


*This study of 1,081 individuals did not find evidence that SPCD is qualitatively distinct from ASD. Rather, it appears to lie on the borderlands of the autism spectrum, describing those with autistic traits that fall just below the threshold for an ASD diagnosis. SPCD may have clinical utility for identifying*
people with autistic traits that are insufficiently severe for ASD diagnosis, but who nevertheless require support.

**Question 2 (Underlying Biology)**

**Joshua Gordon**


In the attached paper, the authors report that variation in viewing of social scenes, including levels of preferential attention and the timing, direction and targeting of individual eye movements, is strongly influenced by genetic factors, with effects directly traceable to the active seeking of social information. In a series of eye-tracking experiments conducted with 338 toddlers, including 166 epidemiologically ascertained twins (enrolled by representative sampling from the general population), 88 non-twins with autism and 84 singleton controls, we find high monozygotic twin–twin concordance (0.91) and relatively low dizygotic concordance (0.35). Moreover, the characteristics that are the most highly heritable, preferential attention to eye and mouth regions of the face, are also those that are differentially decreased in children with autism (χ² = 64.03, P < 0.0001). These results implicate social visual engagement as a neurodevelopmental endophenotype not only for autism, but also for population-wide variation in social-information seeking.

**Geraldine Dawson**

Joshua Gordon


This study suggests that Childhood Disintegrative Disorder (CDD), a rare form of ASD characterized by late-onset, severe regression, is biologically distinct from other forms of autism. CDD candidate genes were found to be more highly expressed in non-neocortical regions than neocortical regions. This expression profile was similar to that of an independent cohort of ASD probands with regression. The non-neocortical regions overlapped with those identified by fMRI as abnormally hyperactive in response to viewing faces, such as the thalamus, cerebellum, caudate, and hippocampus. Eye-tracking analysis showed that, among individuals with ASD, subjects with CDD focused on eyes the most when shown pictures of faces. These results suggest differences between CDD and other forms of ASD on the neurobiological as well as clinical level.

**Walter Koroshetz**


Heterogeneity in ASD, and small sample sizes in previous studies, have led to inconclusive evidence on a potential role of cortical thickness abnormalities in autism. This current study used a subset of data from the Autism Brain Imaging Data Exchange (ABIDE) data set to determine age-specific differences in cortical thickness in ASD and its relation to symptom severity. The study included 560 male subjects (266 ASD and 294 controls; age = 6-35 years) and computed
cortical thickness measurements using the CIVET process followed by stringent multi-reviewer quality control procedures. Data were analyzed for age-related abnormalities and explored for association with symptom severity based on ADOS scores. The data showed significantly increased cortical thickness between ages 6 and 14; the effect was more pronounced in the left hemisphere. There was also a significant positive correlation between residual cortical thickness and severity scores for social affect and communication symptoms. This study used a robust data set to explore an unanswered question regarding brain structure abnormalities in autism. Longitudinal studies across the life span are needed to further explore the relationship between brain structure and development in ASD.

**Joshua Gordon**


Among the 3,166,542 children (1,547,266 females and 1,619,174 males; mean [SD] age, 11.2 [4.7] years) in the study, the prevalence of ASD was 1.96% (95% CI, 1.94%-1.98%) among males and 0.50% (95% CI, 0.49%-0.51%) among females. When a male was associated with risk in the family, ASD was diagnosed in 4.2% (95% CI, 3.8%-4.7%) of female siblings and 12.9% (95% CI, 12.2%-13.6%) of male siblings. When a female was associated with risk in the family, ASD was diagnosed in 7.6% (95% CI, 6.5%-8.9%) of female siblings and 16.7% (95% CI, 15.2%-18.4%) of male siblings. These findings are in agreement with the higher rates of ASD observed among males than among females in the general population. The study provides more specific guidance for the screening and counseling of families and may help inform future investigations into the environmental and genetic factors that confer risk of ASD.

**Question 3 (Risk Factors)**

**Linda Birnbaum**


Advance: Studies of environmental risk factors for autism are hampered by the difficulty in assessing exposures and their timing during etiologically relevant periods of early development, which occur years before diagnosis. The authors address this challenge and demonstrate the utility of tooth matrix exposure biomarkers for identifying different temporal patterns of uptake of essential and toxic metals in ASD cases and controls.

Summary: This study used teeth collected from twins that either were concordant or discordant for ASD diagnosis, and examined levels of both essential and toxic metals in precise layers of dentine from shed deciduous teeth (baby teeth) during prenatal and early postnatal periods. Levels of lead were elevated in ASD cases, particularly in the early postnatal period (5-20 weeks post-birth). Levels of the essential metals manganese and zinc also differed in ASD cases vs. controls. Manganese levels were lower in ASD cases during two time frames, one prenatally (10 weeks prior to birth) and the other during an early postnatal phase (5-20 weeks after birth). Zinc levels, meanwhile, were only
lower during a latter prenatal to early postnatal phase (10 weeks prior to birth until 5 weeks after). Furthermore, metal levels at three months after birth were predictive of severity of ASD later in life. This study is an important advance for identifying biomarkers of exposure to environmental risk factors during critical windows of development and supports the idea that ASD may be associated with altered regulation of essential and toxic metals.

**Joshua Gordon**


The current study sought out to deepen our understanding of genetic risk for Neurodevelopmental disorders (NDD). The research focused on identifying novel, previously less studied-missense mutations associated with NDD. Using a genome wide approach, utilizing publicly available large sample sequencing data, the research team has identified 200 genes with significant clustering of novel patient specific, protein coding missense mutations. Further analysis of the identified hotspot genes showed enrichment for synaptic signaling, and chromatin mediated regulation of transcription pathways both previously implicated in ASD and other psychiatric disorders. The current findings are a significant step forward in the complex process of identification and refinement of potential functional genetic targets that can lead to better understanding of disease etiology, course, outcome and possible personalized targeted treatment development.

**Linda Birnbaum**


Advance: This study demonstrates that environmental exposures can have effects across multiple generations. As we seek to understand autism risk and etiology, it is important to consider how we will study and measure these exposures across generations.

Summary: This study used data from the Avon Longitudinal Study of Parents and Children, a long-running population-based British study of how environment and genotype affect health outcomes. Parents of children enrolled in this study were asked about their parents’ smoking habits—whether they ever smoked and if mothers smoked during pregnancy. The relationship between grandparental smoking and social and communication traits predictive of autism were studied. Granddaughters of maternal grandmothers who smoked had increased odds of adverse scores in social communication and repetitive behaviors. Smoking by maternal grandmothers was also associated with autism diagnosis, particularly in grandsons (this might be in part related to the sex bias in diagnosis; there were only 212 diagnosed cases and 4 males for every female diagnosed).
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<td><strong>Geraldine Dawson</strong></td>
<td>Data from this study of mice suggest that defined gut commensal bacteria with a propensity to induce TH17 cells may increase the risk of neurodevelopmental disorders in the offspring of pregnant mothers undergoing immune system activation owing to infections or autoimmune syndromes.</td>
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<tr>
<td><strong>Linda Birnbaum</strong></td>
<td>The joint effect of air pollution exposure and copy number variation on risk for autism. Autism Res. 2017 Apr 27. [Epub ahead of print]</td>
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<td>David Amaral</td>
<td>Pardo CA, Farmer CA, Thurm A, Shebl FM, Ilieva J, Kalra S, Swedo S. <strong>Serum and cerebrospinal fluid immune mediators in children with autistic disorder: a longitudinal study.</strong> Mol Autism. 2017 Jan 5;8:1. [PMID: 28070266]</td>
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<tr>
<td>Joshua Gordon</td>
<td>Turner TN, Coe BP, Dickel DE, Hoekzema K, Nelson BJ, Zody MC, Kronenberg ZN, Hormozdiari F, Raja A, Pennacchio LA, Darnell RB, Eichler EE. <strong>Genomic patterns of de novo mutation in simplex autism.</strong> Cell. 2017 Sep 27. pii: S0092-8674(17)31006-1. [PMID: 28965761]</td>
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<td>Geraldine Dawson</td>
<td>Viktorin A, Uher R, Reichenberg A, Levine SZ, Sandin S. <strong>Autism risk following antidepressant medication during pregnancy.</strong> Psychol Med. 2017 May 22:1-10. [Epub ahead of print] [PMID: 28528584]</td>
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October 24, 2017 IACC Meeting

 confirms that common and rare variation act additively to create risk for autism spectrum disorders. Nat Genet. 2017 May 15. [Epub ahead of print] [PMID: 28504703]

Using a novel approach called the polygenic transmission disequilibrium test and data from 6,454 families with a child with ASD, this study shows that polygenic risk for ASD, schizophrenia, and greater educational attainment is over-transmitted to children with ASD. These findings hold independent of proband IQ. It is found that polygenic variation contributes additively to risk in ASD cases who carry a strongly acting de novo variant. Lastly, the study shows that elements of polygenic risk are independent and differ in their relationship with phenotype. These results confirm that the genetic influences on ASD are additive and suggest that they create risk through at least partially distinct etiologic pathways.

First, common polygenic risk -- the tiny little effects of common genetic variation spread throughout the genome -- appear relevant, and almost equally so, to all groups examined. Regardless of whether the cases had intellectual disability or not, were male or female, or carried a large impact de novo mutation, common polygenic risk was a significant contributor. Second, evidence was presented showing that genetic risk for ASD comes in many different flavors. The very large impact de novo variants that create risk for ASD, for example, are strongly associated with intellectual disability, epilepsy, and motor delays. The common variant risk factors are comparatively neurologically gentle. They don't show those associations. In fact, common polygenic risk for ASD is associated with higher IQ in general population samples.

Question 4 (Treatments and Interventions)

Alison Singer  

Another randomized clinical trial – multisite no less – shows the effectiveness of targeting very early behaviors for the treatment of autism.

Larry Wexler  

Commons and colleagues created a behavior-developmental scale to predict performance in students with Autism Spectrum Disorder (ASD). Forty-two children were given the Autism Developmental Task Sequence (ADTS). Using the Rasch Analysis, researchers ascertained the order of hierarchical complexity (MHC) of various tasks, including the behavioral developmental difficulty of task items. The scale derived from the Rasch Analysis will help create interventions and provide diagnostic data. Furthermore, this tool could improve progress monitoring strategies for children with ASD. In turn, such improvements could strengthen the design of behavioral and educational materials.

Larry Wexler  
Corbett and colleagues examined the impact of peer-mediated, theatre-based intervention on reducing anxiety and stress. Thirty youth with autism spectrum disorder (ASD) (ages 8-14) participated in the study. Seventeen youth were randomized into the experimental (EXP) group. Sixteen participants were randomized into the waitlist (WLC) control group. The EXP group received interventions during a 10-week period. The WLC group received interventions during a 10-week summer session after the EXP group had completed their trial. Results indicated a reduction in trait-anxiety and an overall increase in social competence for the EXP group. Recommendations include continued studies in this area with the incorporation of physiological and self-report metrics of stress or anxiety and the use of other anxiety reduction techniques. Students with ASD often exhibit greater anxiety in comparison to typically developing peers. This study provides an innovative approach to identify strategies that support children with ASD in reducing anxiety.

Geraldine Dawson


A systematic review of nutritional and dietary interventions for autism. It was concluded that there is little evidence to support the use of nutritional supplements or dietary therapies for children with ASD. Note that there is an accompany editorial, which I am not nominating as an advance but might be of interest to the committee: https://www.ncbi.nlm.nih.gov/pubmed/28562291

Larry Wexler


Using an effectiveness-implementation hybrid design in tandem with the Joint Attention, Symbolic Play, Engagement, and Regulation model (JASPER), Shire and colleagues tested 113 children enrolled in local public early intervention classrooms in low SES settings. Shire and colleagues addressed the practicability of supervised teacher assistant (TA)-implemented JASPER within an early intervention program and the influence of intervention on children’s core developmental challenges concerning JASPER related skills. Results indicated fidelity of implementation by paraprofessionals and notable increases in engagement between children and paraprofessionals. Students receiving JASPER interventions demonstrated gains in joint engagement, joint attention, and play skills. Recommendations include formal evaluation of supervisor’s TA coaching, adding additional measures to more fully understand clinical significance of staff questionnaire scores, and extension of intervention analysis. This study is consequential because paraprofessionals are often assigned to work with children with ASD. This study shows how to support paraprofessionals in implementing an intervention with fidelity.

Larry Wexler


Strain described a 4-year follow-up study from the Learning Experiences and Alternative Program for Preschoolers and their Parents (LEAP) randomized trial.
In the previous randomized study trial, moderate to large effect size differences were evident for students receiving the complete LEAP inclusion model. Due to such promising outcomes, Strain and colleagues received funding for the 4-year follow-up study. In this study, Strain outlined four a-priori questions: What is the stability of classroom placement across 4 years (K-3)? What is driving initial kindergarten placement decisions? How did classroom quality vary across settings? What do children in the LEAP Randomized Control Trial (RCT) look like 4 years away from intervention? Initial decisions about placement seemed to be made according to preestablished district perceptions of students with autism, not based on individual student need. Statistically significant differences were observed, with students in inclusive settings performing better than those in segregated settings. Recommendations include program replication and further longitudinal studies. This article is noteworthy because it shows that a decision about a child’s placement (which appeared to be based more on district policy then a child’s individualized need) can significantly impact their developmental trajectory and their academic success.

**Geraldine Dawson**


A systematic review of interventions targeting sensory challenges in autism. It was concluded that some interventions may yield modest short-term (<6 months) improvements in sensory- and ASD symptom severity-related outcomes; the evidence base is small, and the durability of the effects is unclear. Although some therapies may hold promise, substantial needs exist for continuing improvements in methodologic rigor.

**Question 5 (Services)**

**David Mandell**


This study comprises the most rigorous study to date of the effects of states’ autism insurance mandates on service use and spending among children with autism. The study finds that mandates result in substantial increases in spending on autism-specific services, although the effect is not apparent until two years after the mandates are passed. A notable finding is that the effect is concentrated among younger children and dissipates among adolescents, suggesting the need for additional strategies to improve service access and use among older children with autism.

**Larry Wexler**


Caron and colleagues reviewed studies, within a ten-year period, related to Early Intensive Behavior Interventions (EIBI). These interventions were provided to children with autism spectrum disorders (ASD). Researchers catalogued program implementation components evidenced in the studies. Twenty-eight studies met the selection criteria. Implementation components included dosage,
adherence, differentiation, quality, and participation. Variables related to dosage and adherence were well described throughout selected studies, while the majority of studies did not report on participation, differentiation, or quality. Recommendations include examining the fidelity of EIBI interventions, a more comprehensive definition of EIBI programs, and enhanced evaluations of implementation in practice. This study is significant because it provides an expansive overview of EIBI interventions through the examination of current research.

**Larry Wexler**  

Chou and colleagues considered the differences in self-determination between students with autism spectrum disorders (ASD), students with intellectual disability (ID), and students with learning disabilities (LD). Researchers selected 222 participants, with equal numbers in disability categories. Using a multivariate analysis of covariance (MANCOVA), Chou and colleagues examined four dependent variables: autonomy, self-regulation, psychological empowerment, and self-realization. Students with ASD scored lower in the categories of autonomy and psychological empowerment than students with ID or LD. However, students with ASD did not demonstrate significant variance from students with ID or LD in self-regulation. Implications for educators include, but are not limited to, selection of domain interventions based upon profile distinctions and increasing educational opportunities for students with ASD to develop self-determination skills and participate in inclusive settings. This study should be considered because students with disabilities typically do not demonstrate self-determination practices to the degree of their general education peers. Therefore, engaging in studies that examine such behaviors may lead to increased strategies for self-determination practices among students with disabilities.

**Geraldine Dawson**  

This study determined the effect of early intensive behavioral treatment of young children with autism on health care service use and costs. In the postintervention period, compared with children who had earlier received treatment as usual in community settings, children in the early intervention group used less ABA/EIBI, occupational/physical therapy, and speech therapy services, resulting in significant cost savings in the amount of about $19,000 per year per child. Costs associated with ESDM treatment were fully offset within a few years after the intervention because of reductions in other service use and associated costs.

**David Mandell**  
Jamison JM, Fourie E, Siper PM, Trelles MP, George-Jones J, Buxbaum Grice A, Krata J, Holl E, Shaoul J, Hernandez B, Mitchell L, McKay MM, Buxbaum JD, Kolevzon A. *Examining the efficacy of a family peer advocate model for black
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<td>This study comprises a randomized trial of a relatively inexpensive intervention to improve outcomes for poor and ethnic minority caregivers of children with autism. The study found that the intervention increased parent knowledge of autism and reduced parent stress, but had no effect on service use, suggesting that interventions like these may be necessary but not sufficient for improving overall parent and child outcomes.</td>
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<td>David Mandell</td>
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<td>This paper is emblematic of a body of work coming from this group that merges Medicaid claims data with national survey data and uses ecological associations to examine the effects of different state Medicaid policies on child and family outcomes. This particular study examines the effect of the generosity of Medicaid waivers on parents' workforce participation. Prior research has demonstrated that mothers of children with autism are much more likely than parents of other children to drop out of the workforce. The present study finds that parents of children with autism who live in states with more generous Medicaid waivers are more likely to stay in the workforce, suggesting that these state policies have important economic implications beyond the immediate care for which they pay.</td>
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<td>Geraldine Dawson</td>
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<td>Study compared barriers to autism spectrum disorder (ASD) diagnosis and current ASD-related service use among non-Latino white (NLW) families and Latino families with English proficiency (L-EP) or limited English proficiency (L-LEP). English proficiency was an important marker for barriers to ASD diagnosis and treatment in Latinos. Increasing ASD-related knowledge and provider trust may decrease disparities in the diagnosis and treatment of ASD among US Latinos.</td>
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<td>Question 6 (Lifespan Issues)</td>
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<td>Julie Lounds Taylor</td>
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<td>There have been a handful of studies that have used vocational rehabilitation databases to determine which individual services are associated with employment outcomes at case closure. This study also uses the voc rehab database (i.e., the Rehabilitative Service Databases), but instead of looking at individual contribution of services, they used social network analysis to examine patterns/combinations of services that might facilitate employment outcomes for adults with ASD in the VR system. Using this method, they were able to identify six “core services” (assessment, job placement assistance, counseling, job search assistance, on-the-job support, transportation) – for every one...</td>
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Nearly all studies of employment outcomes use data collected at one point in time, and thus cannot speak to issues around maintaining vocational positions once obtained. This study, using detailed longitudinal data collected from a small sample (n = 36), examined the proportion of youth with ASD who experienced instability in vocational/education in the first 2-3 after high school exit, as well as whether behavioral and family factors measured in high school distinguished those who did versus did not experienced instability. Although most youth transitioned into some sort of post-secondary activity, 50% experienced instability in those activities. Maternal and family functioning – and not the characteristics of the youth with ASD – distinguished those who did versus did not experience instability. This study suggests that the factors that predict whether youth with ASD get a job or go to college might be different from the factors that predict maintaining those activities.

This study examined social media use, anxiety, and friendship quality in 44 adolescents with ASD and 56 clinical comparison controls. More time on social media and greater social media utility was associated with higher friendship quality as rated by both parents and adolescent with ASD – particularly for those with lower parent-rated anxiety. There were no relationships between friendship quality and social media use for control group adolescents. This study suggests that adolescents with ASD may be a unique subgroup in terms of their capacity to benefit from social media.


ASD prevalence and 95% confidence intervals (CIs) were computed from population-based surveillance, census, and survey data. SES categories were defined using area-level education, income, and poverty indicators. ASD was ascertained in 13,396 of 1,308,641 8-year-old children under surveillance. The prevalence of ASD increased with increasing SES during each surveillance year among White, Black, and Hispanic children. The prevalence difference between high- and low-SES groups was relatively constant over time (3.9/1000 [95% CI = 3.3, 4.5] in 2002 and 4.1/1000 [95% CI = 3.6, 4.6] in the period 2006-2010). Significant racial/ethnic differences in ASD prevalence remained after stratification by SES. A positive SES gradient in ASD prevalence according to US
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<td><strong>surveillance data prevailed between 2002 and 2010, and racial and ethnic disparities in prevalence persisted during this time among low-SES children.</strong></td>
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