Meeting of the Interagency Autism Coordinating Committee

October 26, 2016

National Institutes of Health
31 Center Drive
Building 31, C Wing, 6th Floor, Conference Room 6
Bethesda, MD 20892

Conference Call Access:
Phone: 888-469-2037
Access Code: 3353029

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Meeting of the IACC

Morning Agenda

9:00 AM Welcome, Introductions, Roll Call and Approval of Minutes

Joshua Gordon, M.D., Ph.D.
Director, NIMH and Chair, IACC

Bruce Cuthbert, Ph.D.
Director, Research Domain Criteria Unit, NIMH

Susan Daniels, Ph.D.
Director, OARC, NIMH and Executive Secretary, IACC

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Meeting of the IACC

Morning Agenda – continued

10:00  Update from Office of the National Autism Coordinator

Thomas Novotny, M.D.
Deputy Assistant Secretary for Health and National Autism Coordinator
Department of Health and Human Services

10:05  Tackling Early Death in Autism

Jon Spiers
Chief Executive
Autistica, United Kingdom
Meeting of the IACC

Morning Agenda - continued

10:05 Tackling Early Death in Autism – continued

James Cusack, Ph.D.
Director, Science
Autistica, United Kingdom

10:55 Morning Break
Tackling early death in autism
About Autistica

• The UK’s leading autism research charity

• We want to give everyone affected by autism the chance of a long, happy, healthy life

• Our research strategy is driven by the views of the autism community
Overview

• The data on mortality in autism

• New research directions

• Autistica’s report and campaign

• Policy, information and awareness

• Developing a global response
Data on mortality

• The largest ever autism mortality study (ASD n = 27,122; matched controls n = 2,672,185) was recently published, finding increased risk of early death in autism, OR:2.56 (2.38-2.76) (Hirvikoski et al., 2015).

• Autistic and intellectually disabled at highest risk of early death (OR: 5.78) with neurological conditions (epilepsy) the leading cause (OR: 40.56)

• In autistic people with no intellectual disability increased risk of death is also found (OR: 2.18) with suicide being a leading cause (OR:9.40).

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Total n ASD</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouridsen</td>
<td>Denmark</td>
<td>341</td>
<td>1.9 (1.3-2.8)</td>
</tr>
<tr>
<td>Pickett</td>
<td>USA</td>
<td>13111</td>
<td>2.5</td>
</tr>
<tr>
<td>Gillberg</td>
<td>Sweden</td>
<td>120</td>
<td>5.6 (2.5-10.5)</td>
</tr>
<tr>
<td>Bilder</td>
<td>USA</td>
<td>305</td>
<td>9.9 (5.7-17.2)</td>
</tr>
<tr>
<td>Schendel</td>
<td>Denmark</td>
<td>20,492</td>
<td>2.0 (1.4-3.0)</td>
</tr>
</tbody>
</table>

Data from other studies on mortality
Autism and epilepsy

• 20-40% of autistic people also end up having epilepsy (Bolton et al., 2011)

• Altered developmental trajectory, often occurring later.

• Seizures may be more frequent in frontal lobe/social centres, resistant to treatment, harder to identify.
Mental Health and Suicide

• Autistic children are at increased risk of mental health problems: 70% having one; 40% having two or more (Simonoff et al., 2008). Approximately half of 5-10 year olds have an anxiety disorder.

• 80% of adults have reported having a psychiatric disorder. 57.2% reported having depression, 53.2% anxiety (Lever & Geurts, 2016)

• 66% of autistic adults with no intellectual disability have considered suicide. 35% have made plans or attempts at suicide (Cassidy et al., 2014).
Other causes of death

Autistic people experience worse physical health than the general population and are at significantly increased risk of heart disease, stroke, diabetes and respiratory conditions.

Causes are complex and poorly understood but likely to be multi-factorial.

<table>
<thead>
<tr>
<th>Causes</th>
<th>Odds Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulatory</td>
<td>1.49 (1.27-1.75)</td>
</tr>
<tr>
<td>Congenital</td>
<td>19.10 (11.94-30.55)</td>
</tr>
<tr>
<td>Digestive</td>
<td>3.31 (2.25-4.87)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>3.70 (2.34-587)</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>1.80 (1.46-2.23)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2.68 (1.99-3.62)</td>
</tr>
</tbody>
</table>

Hirvikoski et al., 2015

<table>
<thead>
<tr>
<th>Illnesses</th>
<th>Odds Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>2.54 (2.13-3.02)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.18 (1.62-2.93)</td>
</tr>
<tr>
<td>Parkinson’s</td>
<td>32.73 (7.76-137.96)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.12 (1.03-4.37)</td>
</tr>
</tbody>
</table>

Croen et al., 2015
Autistica’s scientific response

We aim to raise and leverage £10m in five years to fund new research into epilepsy, suicide and the other major causes of death for autistic people.
Autistica’s scientific response

Why?
- Scoping research need

The solution
- Each area: stakeholder meetings to develop research strategy

Potential Research
- Open competition for a centre, novel treatment trials
- Network, small grants aimed towards prevention
- Applied health and social care research

The result
- Autistic people will live longer, happier, healthier lives.
The need for a global response

We cannot tackle this enormous challenge alone.

Autistica has committed to raise awareness of this shocking situation, first in the UK and Europe and now internationally.

Our first report in March 2016 aimed to:

• Raise awareness of the hidden mortality crisis
• Increase other funders’ investment in research
• Ensure services actively reduce premature death
• Make recommendations for action by politicians
Influencing policymakers

We are calling for:
• Premature deaths in autism to be a national priority
• Better data collection and analysis
• Better support for autistic people (health checks, risk plans, screening, new therapies)
• More training for healthcare professionals
• More research
Influencing policymakers

In the UK, we have:

• Secured autism as a theme in a National Mortality Review
• Published a Parliamentary Commission report on early death and access to healthcare
• Improved autism data collection by doctors
• Integrated autism into the National Suicide Prevention Alliance and a national suicide enquiry
• Met leading politicians and civil servants
• Held a three hour debate in Parliament
Awareness

Over 120 newspapers, TV and radio stations and news websites have covered the issue.

We briefed the leading UK autism charities and presented our report at Autism Europe Congress 2016.

We continue to spread the word nationally and internationally.
This is new to the vast majority of the autism community.

We must take care how and when we communicate the risks, be clear on what we do and don’t yet know, and be sensitive to autistic people’s needs.

We are soon to publish new information resources for individuals and families.
Driving a global response

Together, we should be aiming to give everyone affected by autism the chance of a long, happy, healthy life

- New basic, translational and epidemiological studies
- International collaborations to accelerate progress
- Open source resources for the autism community
- Coordinated policy responses
Thank you.

james.cusack@autistica.org.uk
jon.spiers@autistica.org.uk

www.autistica.org.uk
Meeting of the IACC

Break
Meeting of the IACC

Morning Agenda - continued

11:10 Committee Business

Susan Daniels, Ph.D.
Director, Office of Autism Research Coordination, NIMH and Executive Secretary, IACC

IACC Strategic Plan Update
• Update on working group activities
• Discussion of duplication of effort statement
• Discussion of budgetary requirements
• Discussion of objective development

12:00 PM Lunch

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Meeting of the IACC

Committee Business

Susan Daniels, Ph.D.
Director, Office of Autism Research Coordination, NIMH
and Executive Secretary, IACC

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IACC Committee
Business

Susan A. Daniels, Ph.D.
Director, Office of Autism Research Coordination
Executive Secretary, IACC
National Institute of Mental Health

IACC Full Committee Meeting
October 26, 2016
IACC Responsibilities

• Develop and annually update a strategic plan for ASD
• Develop and annually update a summary of advances in ASD research
• Monitor Federal activities with respect to ASD
• Make recommendations to the HHS Secretary regarding research or public participation in decisions regarding ASD

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Seven working groups composed of IACC Members and invited external experts have been convened to cover the 7 Strategic Plan Questions.
IACC Strategic Plan Working Groups

- Question 1: When Should I Be Concerned? (Screening/Diagnosis)
- Question 3: What Caused This to Happen and Can It Be Prevented? (Risk Factors)
- Question 4: Which Treatments and Interventions Will Help? (Interventions)
- Question 5: Where Can I Turn for Services? (Services)
- Question 6: What Does the Future Hold, Particularly for Adults? (Lifespan Issues)
- Question 7: What Other Infrastructure and Surveillance Needs Must Be Met? (Infrastructure, Surveillance, Outreach, Collaboration)

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Working Group Activities

Each of the 7 working groups held 2 conference calls in September and October to discuss:

• Progress toward the current Strategic Plan Objectives
  – Based on information from the 2013 analysis of research funded by federal and private funders

• Progress in the field:
  – Research advances
  – Practice to research
  – Gaps, needs, barriers and opportunities
  – New programs and policies
  – New research evidence that can inform policy
  – Services needs/gaps, needed policy changes

• Aspirational Goal; Chapter Title

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Working Group Activities

Each of the 7 working groups is in the process of or has already scheduled a third conference call where we will discuss:

• Draft chapter outline for each Question that describes progress in the field, gaps/needs, barriers and opportunities

• Development of 3 broad objectives for each Question, including examples of responsive research projects, and services or policy activities

• **Today: IACC suggestions re: areas to target in objectives?**

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Strategic Plan Update Requirements

- The Autism CARES Act requires the IACC in its Strategic plan to provide:
  
  “Recommendations to ensure that autism spectrum disorder research, and services and support activities to the extent practicable, of the Department of Health and Human Services and of other Federal departments and agencies are not unnecessarily duplicative.”

- This requirement was based on a 2013 report by the GAO that stated concerns about potential for duplication in the research portfolio, but not services

- IACC public members responded to the report

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Strategic Plan Update Requirements

- IACC Public Member Response Letter

Key Points:

- Efforts by multiple agencies with different mission areas to address different aspects of broad, complex issues related to autism spectrum disorders research is important and necessary

- Emphasized the need for corroboration and replication of research

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Strategic Plan Update Requirements

• Feedback collected from working groups regarding duplication:
  – Emphasized the importance of replication of research and reproducibility
  – Saw role for closer coordination of large genomic sequencing efforts to avoid resequencing same individuals, more transparency and data sharing to prevent duplication of effort
  – Ensuring that the new Strategic Plan objectives have minimal overlap will make it easier to review the portfolio for potential duplication
  – Other suggestions from the committee?

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Strategic Plan Update Requirements

• Next steps:
  – IACC needs to prepare a 1-2 paragraph statement on recommendations to ensure that unnecessary duplication of effort is minimized
  – Volunteer(s) to draft a statement for feedback from the working groups and then review by the full committee in January?
  – Text of IACC letter is available as a resource

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Strategic Plan Update Requirements

• The Autism CARES Act requires the IACC Strategic Plan to include “proposed budgetary requirements.”

• The previous Strategic Plan provided estimated budgetary requirements for each objective

• *Does the committee want to develop budgetary requirements based on the objectives, the questions, or the overall plan, keeping in mind that the new objectives will be broad and inclusive of both research and services activities?*

• *Does the committee want to try to estimate actual budgets or project percentage increases, decreases, etc.? Growth over time?*
Strategic Plan Next Steps

• Working Group Calls to be held in November

• Working groups to begin writing chapters in November

• Chapter drafts will be shared with committee in January, with goal of publication of new Strategic Plan in April 2017

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Susan Daniels, Ph.D., Director
Ben Feldman, Ph.D., Science Policy Analyst
Angelice Mitrakas, B.A., Operations Coordinator
Karen Mowrer, Ph.D., Science Policy Analyst
Miguelina Perez, B.A., Management Analyst
Julianna Rava, M.P. H., Science Policy Analyst
Jeff Wiegand, B.S., Web Development Manager
Meeting of the IACC

Lunch
Meeting of the IACC

Afternoon Agenda

1:00    Oral Public Comment Session

1:30    Summary of Written Public Comments
        Karen Mowrer, Ph.D.
        Health Science Policy Analyst
        OARC, NIMH

1:40    Request for Public Comment
        Susan Daniels, Ph.D.
        Director, OARC and Executive Secretary, IACC

1:45    IACC Committee Member Discussion of Public Comments

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Summary of Written Public Comments

Karen Mowrer, Ph.D.
Health Science Policy Analyst
Office of Autism Research Coordination, NIMH

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Meeting of the IACC

Request for Public Comments on IACC Strategic Plan

Susan Daniels, Ph.D.
Director, Office of Autism Research Coordination, NIMH
Executive Secretary, IACC

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2016 IACC Strategic Plan Request for Public Comment

Susan A. Daniels, Ph.D.
Director, Office of Autism Research Coordination
Executive Secretary, IACC
National Institute of Mental Health

IACC Full Committee Meeting
October 26, 2016
2016 IACC Strategic Plan
Request for Public Comment

• On behalf of the IACC, OARC issued a Federal Register Notice soliciting public comment on the research, service, and policy priorities for the topics addressed by the current strategic plan:
  • Q1 Diagnosis and Screening
  • Q2 Underlying Biology
  • Q3 Risk Factors
  • Q4 Treatments & Interventions
  • Q5 Services
  • Q6 Lifespan
  • Q7 Research Infrastructure and Surveillance

• Comments were provided to Strategic Plan Working Groups and all comments are now publicly available on the IACC website

• Within each question comments are grouped by themes addressed

• Over 1,100 comments were received
Respondent Categories

- Parents and family members
- Service providers
- Researchers
- Advocates/Professional Societies
- Educators
- Medical/Therapy Practitioners
- Family Assistance/Navigation
- Self advocates
- Research trainees
- Government employees
- International

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Question 1: Diagnosis & Screening

- Need better recognition and diagnosis of subgroups
- Need better understanding of early signs and symptoms
- Families need emotional support following diagnosis and assistance in navigating access to services
- Improve accuracy and awareness of diagnosis in females/address sex and gender disparities in diagnosis
- Improvements in the accuracy and usability of screening and diagnosis tools
- Need more and increased access to genetic screening
- Need greater research and identification of biomarkers, and use of these biomarkers in screening and diagnosis
- Need improvements in access and accuracy of adult and adolescent diagnosis
- Need to address the multifaceted disparities in diagnosis across racial, cultural, socioeconomic, and regional lines
- Need to increase/decrease early screening and diagnosis of ASD in children
- Need to reduce the time to diagnosis by improving service access and diagnostic tools/process
- Need to strengthen link between initial diagnosis and access to services and interventions
- Parents and caregivers need greater education so that they can recognize signs and symptoms
- Practitioners need to listen to and consider parent concerns about early signs and symptoms
- Universal screening for ASD is needed
- Workforce development, including access to qualified practitioners and improvements in the training of the existing workforce
- Current priorities are appropriate (diagnosis and screening tools, early signs, symptoms and biomarkers, identification of subgroups, disparities in diagnosis)
Question 2: Underlying Biology

- Need further research on the genetics of autism, and genetic tests should be more accessible
- Need more developmental biology research
- Need more research and a better understanding of genetic syndromes related to ASD
- Need more research and better understanding of the biomarkers and symptoms of ASD, and the heterogeneity of symptoms
- Need more research into the contribution of immune and metabolic pathways to autism
- Need more research on cognitive and behavioral biology
- Need more research on the basic neuroscience of ASD
- Need more research on the biology and relationship of co-occurring conditions in ASD
- Need more research on the molecular biology of ASD
- Need more research on sex and gender differences, inclusive of both biological sex and self-identified gender
- Need research to better understand, differentiate, and treat subgroups of people with autism
- Need more research to better understand sensory processing and motor function in ASD
- Need more translational and interdisciplinary research to improve the lives of people with ASD
- Need to prioritize gut-brain interaction research
- Current priorities are appropriate (molecular biology and neuroscience, developmental biology, cognitive and behavioral biology, genetic syndromes related to ASD, sex differences, immune and metabolic aspects, and co-occurring conditions in ASD)
- Understanding the biology of ASD is not a priority, relative to other areas (i.e. treatment and services)

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Question 3: Risk Factors

- Need better methods for testing contributions of risk factors from multiple domains to better understand risk of autism
- Need more research into better understanding of environmental risk factors, defined broadly to including both chemical and social environments
- Need more research on epigenetic risk factors
- Need more research on genetic risk factors
- Need more research on immune and metabolic risk factors
- Need more research on maternal and prenatal factors
- Need more research on the interaction of genetic and environmental factors
- Need more research on the risk factors for co-occurring conditions in autism
- Need more research on the role of the microbiome and gastrointestinal risk factors
- Need more research to better understand heritability and risk of autism in families
- Need more research to understand the role of vaccines in causing autism
- Need less/no additional research on the role of vaccines in autism
- Current priorities are appropriate (genetic and environmental risk factors, gene-environment interactions, and the potential role of epigenetics and the microbiome)
- The cause and prevention of autism are not a priority, either because resources can be better used in other areas or because preventing autism should not be a goal
Question 4: Treatments & Interventions (385 responses rec’d as of 6/29)

- Need a qualified workforce trained in providing treatments and interventions; need both a greater number and improved training of current clinicians, therapists, and school employees
- Need to prioritize early intervention
- Need to educate parents about available treatments and interventions, and to help provide these interventions
- Endorsement of specialized or ASD specific treatments and interventions
- Improve availability and efficacy of treatments and interventions specifically for adult and adolescents with ASD
- Improve efficacy and availability of behavioral treatments and interventions
- Improve efficacy and availability of interventions in educational settings
- Improve the evidence base for treatments and interventions, and make that information more readily available and widely used
- Personalized combinations and types of treatments and interventions will be the most efficacious
- Positive and negative comments about searching for a “cure” rather than treatments or interventions
- Research and availability of technology based or assistive technology treatments and interventions
- Research and availability of treatments and interventions for co-occurring conditions
- Need research on biomedical and pharmacological treatments and interventions to improve efficacy and reduce side effects
- Need research on the efficacy and availability of complementary, alternative or integrative treatments and interventions
- Need research on long term outcomes of treatments and intervention, as well as the translation and implementation of research based treatments and interventions
- Improve coordination of treatments and interventions between services and practitioners
- Current priorities are appropriate (behavioral, medical/pharmacologic, educational, technology-based, and complementary/integrative interventions)

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Question 5: Services

responses rec’d as of 6/29

- Access to early intervention services is a priority
- Disparities in access to services should be addressed
- Families need access to services to reduce the mental and emotional burden of caring for those with ASD
- Improve the efficacy and cost effectiveness of services and service delivery
- Improve the quality and availability of services within the educational systems
- Improve the service systems and service models
- Increase the accessibility and utilization of services.
- Need better coordination between service providers, taking into account what is relevant for the individual and the choices of those with ASD and their families/caregivers
- Need for an adequately trained and compensated workforce to improve available services and service delivery
- Need for better services to foster community inclusion of those with ASD
- Need to be more and better access to specialized services for ASD
- Parents/caregivers need assistance navigating complicated service systems.
- Prioritize services to improve the health and safety, including addressing interactions with law enforcement and wandering
- The broader community needs to be better educated about ASD, to lead to better understanding and inclusion
- The cost of services is prohibitive, and research and policies are needed to reduce these barriers to access
- Current priorities are appropriate (service access and utilization, service systems, education, family well-being, efficacious and cost-effective service delivery, health and safety issues affecting children, and community inclusion)
- Focus on the treatment or cause of autism rather than the delivery of services
Question 6: Lifespan

- Improve access to and quality of adult services, including additional research to improve evidence based services for adults
- Improve access to diagnosis for adolescents and adults
- Improve community integration/inclusion, including social isolation and community education about ASD
- Improve the quality, accessibility of housing options
- Improve transition services, and provide better assistance for young adults and their families during transitions
- Long term and financial planning are a priority for research, services, and policy
- Need assistance for adults with autism and their families in navigating available adult services
- Need for a larger, better trained and compensated workforce for adults with ASD
- Research and services to improve health, medical care, safety and quality of life across the lifespan
- Research, services and policies are needed to improve vocational/employment and post-secondary education opportunities
- Services and research should take into account the perspective and choices of adults and their families/caregivers
- Current priorities are all important/relevant (health and quality of life across the lifespan, aging, transition, and adult services, including education, vocational training, employment, housing, financial planning and community integration.)
- Focus should be on early intervention or developing effective treatments; adults/lifespan are not a research priority
- Improve caregiver support

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Question 7: Research Infrastructure and Surveillance

- Improve services infrastructure
- Increase collaboration and coordination among services providers
- Increase collaboration and coordination of research including interdisciplinary research
- Increase the dissemination of research, and the translation of research into practice
- Need greater development of the research workforce
- Need more and improved surveillance of ASD prevalence, including by race/ethnicity, gender and age
- Need research infrastructure, i.e. databases, research and clinical trial policies
- Research should include the voices and participation of individuals with autism and their families
- Current priorities are appropriate/important (research infrastructure needs, ASD surveillance research, research workforce development, dissemination of research information, and strengthening collaboration)
- Prioritize services and interventions rather than research
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• Prioritize services and interventions rather than research
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IACC Committee
Member Discussion of Public Comments

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Discussion of Nominated 2016 Science Advances

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2016 Summary of Advances Nominations
July - October
Q1. When should I be concerned?

No articles were nominated in July - October 2016 for Question 1
Q2. How can I understand what is happening?

Altered proliferation and networks in neural cells derived from idiopathic autistic individuals

Salience Network Connectivity in Autism Is Related to Brain and Behavioral Markers of Sensory Overresponsivity
Green SA, Hernandez L, Bookheimer SY, Dapretto M
Q2. How can I understand what is happening?

Infants’ observation of tool-use events over the first year of life
Libertus K, Greif ML, Needham AW, Pelphrey K

Functional Connectivity of the Amygdala Is Disrupted in Preschool-Aged Children With Autism Spectrum Disorder
Shen MD, Li DD, Keown CL, Lee A, Johnson RT, Angkustsiri K, Rogers SJ, Müller RA, Amaral DG, Nordahl CW
Q3. What caused this to happen and can it be prevented?

Maternal Consumption of Seafood in Pregnancy and Child Neuropsychological Development: A Longitudinal Study Based on a Population With High Consumption Levels


Project TENDR: Targeting Environmental Neuro-Developmental Risks. The TENDR Consensus Statement


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Q3. What caused this to happen and can it be prevented?

Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms
Q4. Which treatments and interventions will help?

Research in Autism Spectrum Disorders

The effects of embodied rhythm and robotic interventions on the spontaneous and responsive social attention patterns of children with Autism Spectrum Disorder (ASD): A pilot randomized controlled trial
Srinivasan SM, Eigsti IM, Neelly L, Bhat AN

Longitudinal Effects of Adaptive Interventions With a Speech-Generating Device in Minimally Verbal Children With ASD

Social network analysis of children with autism spectrum disorder: Predictors of fragmentation and connectivity in elementary school classrooms
Anderson A, Locke J, Kretzmann M, Kasari C; AIR-B Network

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Q5. Where can I turn for services?

No articles were nominated in July - October 2016 for Question 5
Q6. What does the future hold, particularly for adults?

*No articles were nominated in July - October 2016 for Question 6*
Q7. What other infrastructure and surveillance needs must be met?

No articles were nominated in July - October 2016 for Question 7
IACC Summary of Advances

Susan A. Daniels, Ph.D.
Director, Office of Autism Research Coordination
Executive Secretary, IACC
National Institute of Mental Health

IACC Full Committee Meeting
October 26, 2016
2016 Summary of Advances Process

- The committee has been receiving quarterly data calls for submission of nominations
- Submitted nominations are discussed at each meeting; nominations require a written justification
- Issues:
  - Few nominations received; some Question areas not covered well
  - Will those areas be covered in the final data call in December?
  - All nominations do not have a justification; do we want to keep that requirement?

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End of year process:

- Final nominations for 2016 submitted in December; discussed in January (if large number of submissions, we can either set aside more time for discussion or not discuss all nominations)

- Then committee voting process to select top 20 advances? Or certain number of advances per Question to ensure coverage of all questions?

- OARC to provided short, lay-friendly summaries of the selected articles, as previously?

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Break
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Afternoon Agenda - continued

2:45  Panel on Autism in Women and Girls

2:45  Introduction

Kevin Pelphrey, Ph.D.
IACC Member and Panel Chair
Director, Autism and Neurodevelopmental Disorders Institute
George Washington University and Children’s National Medical Center

2:50  Somer Bishop, Ph.D.
Assistant Professor
University of California, San Francisco

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Meeting of the IACC

Afternoon Agenda - continued

3:10  The Autism Sisters Project

Alison Singer, M.B.A.
IACC Member
President, Autism Science Foundation

3:20  The Role of Genetics and Sex-Differential Biology in Risk for Autism

Donna Werling, Ph.D.
Postdoctoral Scholar, Department of Psychiatry
University of California San Francisco School of Medicine
Phenotypic differences between males and females with autism spectrum disorders (ASD)

Somer L. Bishop, PhD
Department of Psychiatry and Weill Institute for Neurosciences
University of California, San Francisco
10/26/2016
Outline

• State of current knowledge
  – Discrepant findings
  – Methodological limitations
Outline

• State of current knowledge
  – Discrepant findings
  – Methodological limitations

(CONFUSED)
Outline

• State of current knowledge
  – Discrepant findings
  – Methodological limitations

• Moving forward
  – Donna, Kevin, and Alison
Outline

• State of current knowledge
  – Discrepant findings
  – Methodological limitations

• Moving forward
  – Alison, Donna, and Kevin
    (HOPEFUL FOR THE FUTURE!)
Mix of consistencies and inconsistencies

• More males with ASD than females
  – Many changes in epidemiological trends, but preponderance of males remains (though ratio varies across samples)

• Relative to overall sex ratio in ASD, females are over-represented at the lower end of the IQ continuum and under-represented at the higher end
Nonverbal IQ: Simons Simplex Collection

SSC Males

Mean = 86.22
Std. Dev. = 25.426
N = 1,907

SSC Females

Mean = 77.91
Std. Dev. = 26.236
N = 299
Mix of consistencies and inconsistencies

- More males with ASD than females
  - Many changes in epidemiological trends, but preponderance of males remains (though ratio varies across samples)
- Relative to overall sex ratio in ASD, females are over-represented at the lower end of the IQ continuum and under-represented at the higher end
- Longstanding interest in examining sex differences
  - Discrepant findings related to phenotype
Social-communication

- Similar levels of ASD symptoms (Lord et al., 1982)
- Toddler/preschool boys had higher language, motor and social-competence (Carter et al., 2007)
- Preschool girls had fewer social-communication impairments (Zwaigenbaum et al., 2012)
- Adult females had fewer social-communication difficulties (Lai et al., 2011)
- Girls had fewer teacher-reported behavior problems (Mandy et al., 2012)
Restricted and repetitive behaviors

- Females exhibited lower repetitive behavior scores (e.g., Hartley et al., 2009; Mandy et al., 2011; Frazier et al., 2014)
  - Seen across multiple measures (3Di, ADI-R, RBS-R, ADOS)
- No sex differences in community-based sample of 288 toddlers with ASD (54 girls) (Reinhardt et al, 2014)
Questions persist

• Clinicians and researchers continue to wonder (and worry) about sex differences in behavioral manifestations of ASD
# Clinician perceptions

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female: 86% (n=91)</th>
<th>Male: 14% (n=15)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Involvement in dx</td>
<td>57% make dx (n=58)</td>
<td>31% perform assessments (n=32)</td>
<td>12% participate in evaluation (n=12)</td>
</tr>
<tr>
<td>Years experience</td>
<td>58% have 10+ years (n=56)</td>
<td>26% have spent 6-9 years (n=25)</td>
<td>13% have 1-5 years experience (n=12)</td>
</tr>
<tr>
<td>Primary age range seen</td>
<td>7% see mostly adults (n=7)</td>
<td>9% see primarily adolescents (n=8)</td>
<td>37% work with school age children (n=35)</td>
</tr>
<tr>
<td>Number seen per month</td>
<td>Mean = 15.8 people, median = 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of females seen per month</td>
<td>Mean = 3.4 females, median = 2</td>
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<td></td>
</tr>
</tbody>
</table>

Jamison, Huerta, Bishop, & Halladay (under review).
Observed differences in core and associated symptoms

Jamison, Huerta, Bishop, & Halladay (under review).
Observed differences in social-communication

Jamison, Huerta, Bishop, & Halladay (under review).
Observed differences in RRBs

Jamison, Huerta, Bishop, & Halladay (under review).
Clinical observations vs. empirical data

• Why the mismatch?
  – Measurement issues
  – Sampling issues
  – Methodological issues
Measurement issues

- Existing measures may lack sensitivity for detecting some females with ASD
  - Diagnostic constructs (which in turn are reflected on measures) could be sex-biased
- Scores on ASD measures are affected by individual factors like IQ and emotional/behavioral problems (EBP)
ADI-R scores by diagnostic group and level of EBP

SRS scores by diagnostic group and level of EBP

Sampling Issues

• Measurement issues can affect ascertainment
  – Over-reliance on standardized screening or diagnostic measures could skew samples (e.g., toward girls with lower IQ and/or more behavior problems)
Referral bias

Mean T scores in preschoolers with ASD (N=102) and non-ASD diagnoses (N=57)

Sampling Issues

• Measurement issues can affect ascertainment
  – Over-reliance on standardized screening or diagnostic measures could skew samples (e.g., toward girls with lower IQ and/or more behavior problems)

• Small clinical samples
  – Ns for females are particularly small
  – May not be powered to properly account for other important individual differences
School-aged/adolescent; verbally fluent

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Participants</td>
<td>396</td>
<td>85</td>
</tr>
<tr>
<td>Age in years, $M (SD)$</td>
<td>8.9 (2.9)</td>
<td>8.7 (2.8)</td>
</tr>
<tr>
<td>VIQ, $M (SD)$</td>
<td>99.6 (18.9)</td>
<td>104.6 (16.7)</td>
</tr>
<tr>
<td>NVIQ, $M (SD)$</td>
<td>104.7 (15.5)</td>
<td>104.3 (14.8)</td>
</tr>
</tbody>
</table>

Calibrated severity scores (CSS)

- Controlling for VIQ and age, sex significantly predicted:
  - Overall CSS ($B = -.57$, CI 95% -1.08 to -0.06, $p = .03$)
  - RRB Domain Calibrated Scores ($B = -.89$, CI 95% -1.4 to -.34, $p = .002$)

- In this sample, even females with lower scores (including those who scored below instrument cut-offs) still received best-estimate clinical diagnoses of ASD

Methodological issues

- Detecting meaningful differences relies on identification of appropriate comparison groups
  - Who is a relevant control? (e.g., IQ/age matched males with ASD vs. IQ/age matched non-ASD female?)

- Clear need for longitudinal data
Employment/PSE at the First Time Point after High School Exit

Methodological issues

• Detecting meaningful differences relies on identification of appropriate comparison groups
  – Who is a relevant control? (e.g., IQ/age matched males with ASD vs. IQ/age matched non-ASD female?)

• Clear need for longitudinal data

• Need to move existing behavioral measures

• Incorporate different measurement strategies
Conclusions

• There do appear to be at least subtle sex differences in phenotype within certain groups
  – Ascertainment and measurement issues present major challenges
• Sex is one stratification variable worth considering, but it needs to be considered in the context of other behavioral and biological variables that we know are important
Thank you

- UMACC/CADB families, clinicians and researchers
- Alycia Halladay
- Alexandra Havdahl
- Marisela Huerta
- Rene Jamison
- Catherine Lord
- Shanping Qiu
- Michael Sweeney
- Julie Taylor
### Direction of Clinician Responses: Early Childhood

<table>
<thead>
<tr>
<th>Criteria / Severity</th>
<th>Less Severe (M&lt;F)</th>
<th>Similar (M=F)</th>
<th>More Severe (F&gt;M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social reciprocity</td>
<td>33% (n=22)</td>
<td>62% (n=41)</td>
<td>5% (n=3)</td>
</tr>
<tr>
<td>Nonverbal behaviors</td>
<td>33% (n=22)</td>
<td>60% (n=39)</td>
<td>6% (n=4)</td>
</tr>
<tr>
<td>Developing, maintaining relationships</td>
<td>23% (n=15)</td>
<td>71% (n=46)</td>
<td>6% (n=4)</td>
</tr>
<tr>
<td>Stereotyped/Repetitive Behaviors</td>
<td>32% (n=21)</td>
<td>65% (n=43)</td>
<td>3% (n=2)</td>
</tr>
<tr>
<td>Insistence on Sameness</td>
<td>24% (n=16)</td>
<td>71% (n=47)</td>
<td>5% (n=3)</td>
</tr>
<tr>
<td>Restricted/Fixated Interests</td>
<td>33% (n=22)</td>
<td>65% (n=43)</td>
<td>2% (n=1)</td>
</tr>
<tr>
<td>Hyperreactivity to sensory</td>
<td>9% (n=6)</td>
<td>86% (n=55)</td>
<td>5% (n=3)</td>
</tr>
<tr>
<td>Hyporeactivity to sensory</td>
<td>17% (n=11)</td>
<td>67% (n=43)</td>
<td>16% (n=10)</td>
</tr>
</tbody>
</table>

Jamison, Huerta, Bishop, & Halladay (under review).
Direction of Clinician Responses: School Age

<table>
<thead>
<tr>
<th>Criteria / Severity</th>
<th>Less Severe (M&lt;F)</th>
<th>Similar (M=F)</th>
<th>More Severe (F&gt;M)</th>
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</thead>
<tbody>
<tr>
<td>Social reciprocity</td>
<td>48% (n=30)</td>
<td>48% (n=30)</td>
<td>3% (n=2)</td>
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<tr>
<td>Nonverbal behaviors</td>
<td>44% (n=27)</td>
<td>54% (n=33)</td>
<td>2% (n=1)</td>
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<tr>
<td>Developing, maintaining relationships</td>
<td>25% (n=15)</td>
<td>70% (n=43)</td>
<td>5% (n=3)</td>
</tr>
<tr>
<td>Stereotyped/Repetitive Behaviors</td>
<td>55% (n=34)</td>
<td>40% (n=25)</td>
<td>5% (n=3)</td>
</tr>
<tr>
<td>Insistence on Sameness</td>
<td>23% (n=14)</td>
<td>73% (n=45)</td>
<td>5% (n=3)</td>
</tr>
<tr>
<td>Restricted / Fixated Interests</td>
<td>38% (n=23)</td>
<td>59% (n=36)</td>
<td>3% (n=2)</td>
</tr>
<tr>
<td>Hyper-reactivity to Sensory</td>
<td>8% (n=5)</td>
<td>85% (n=52)</td>
<td>5% (n=3)</td>
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<tr>
<td>Hypo-reactivity to Sensory</td>
<td>19% (n=11)</td>
<td>76% (n=43)</td>
<td>7% (n=4)</td>
</tr>
</tbody>
</table>

Jamison, Huerta, Bishop, & Halladay (under review).
Direction of Clinician Responses: Adolescence

<table>
<thead>
<tr>
<th>Criteria / Severity</th>
<th>Less Severe (M&lt;F)</th>
<th>Similar (M=F)</th>
<th>More Severe (F&gt;M)</th>
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</thead>
<tbody>
<tr>
<td>Social reciprocity</td>
<td>37% (n=23)</td>
<td>55% (n=34)</td>
<td>8% (n=3)</td>
</tr>
<tr>
<td>Nonverbal behaviors</td>
<td>41% (n=25)</td>
<td>56% (n=34)</td>
<td>3% (n=2)</td>
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<tr>
<td>Developing, maintaining relationships</td>
<td>16% (n=10)</td>
<td>69% (n=42)</td>
<td>15% (n=9)</td>
</tr>
<tr>
<td>Stereotyped/Repetitive Behaviors</td>
<td>47% (n=29)</td>
<td>48% (n=30)</td>
<td>5% (n=3)</td>
</tr>
<tr>
<td>Insistence on Sameness</td>
<td>21% (n=13)</td>
<td>71% (n=44)</td>
<td>8% (n=5)</td>
</tr>
<tr>
<td>Restricted / Fixated Interests</td>
<td>31% (n=19)</td>
<td>63% (n=39)</td>
<td>6% (n=4)</td>
</tr>
<tr>
<td>Hyper-reactivity to Sensory</td>
<td>8% (n=5)</td>
<td>87% (n=52)</td>
<td>5% (n=3)</td>
</tr>
<tr>
<td>Hypo-reactivity to Sensory</td>
<td>23% (n=14)</td>
<td>74% (n=45)</td>
<td>3% (n=2)</td>
</tr>
</tbody>
</table>

Jamison, Huerta, Bishop, & Halladay (under review).
Direction of Clinician Responses: Adult

<table>
<thead>
<tr>
<th>Criteria / Severity</th>
<th>Less Severe (M&lt;F)</th>
<th>Similar (M=F)</th>
<th>More Severe (F&gt;M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reciprocity</td>
<td>31% (n=17)</td>
<td>59% (n=32)</td>
<td>9% (n=5)</td>
</tr>
<tr>
<td>Nonverbal behaviors</td>
<td>41% (n=22)</td>
<td>52% (n=28)</td>
<td>7% (n=4)</td>
</tr>
<tr>
<td>Developing, maintaining relationships</td>
<td>17% (n=9)</td>
<td>74% (n=39)</td>
<td>9% (n=5)</td>
</tr>
<tr>
<td>Stereotyped/Repetitive Behaviors</td>
<td>36% (n=19)</td>
<td>64% (n=34)</td>
<td>0% (n=0)</td>
</tr>
<tr>
<td>Insistence on Sameness</td>
<td>19% (n=10)</td>
<td>78% (n=42)</td>
<td>4% (n=2)</td>
</tr>
<tr>
<td>Restricted / Fixated Interests</td>
<td>22% (n=12)</td>
<td>76% (n=41)</td>
<td>2% (n=1)</td>
</tr>
<tr>
<td>Hyper-reactivity to Sensory</td>
<td>8% (n=4)</td>
<td>87% (n=45)</td>
<td>6% (n=3)</td>
</tr>
<tr>
<td>Hypo-reactivity to Sensory</td>
<td>13% (n=7)</td>
<td>80% (n=43)</td>
<td>7% (n=4)</td>
</tr>
</tbody>
</table>

Jamison, Huerta, Bishop, & Halladay (under review).
ADOS items showing significant score discrepancies by sex

ADOS scores by diagnostic group and level of EBP

• Listening to our Daughters: Girls & Women with Autism will Inform Novel Treatments

Kevin Pelphrey
Carbonell Family Professor and Director
Autism and Neurodevelopmental Disorders Institute

October 26, 2016
Brain Systems for Social Cognition

Pelphrey et al. (2003) *Journal of Neuroscience*
Can we see autism’s signature in the individual brain?
Classification Analysis

Discovery → Replication

S L I D E  3
A weak response to biological motion is a marker of autism in boys (but not girls!)

Björnsdotter et al., JAMA: Psychiatry, 2016
Autism Center of Excellence: Girls Network

**125 Boys with ASD**
**75 TD Boys**
**125 Girls with ASD**
**75 TD Girls**

Unaffected siblings:
**50 boys & 50 girls**
<table>
<thead>
<tr>
<th>Milestones</th>
<th>April 1 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target: Total Recruitment</td>
<td>374</td>
</tr>
<tr>
<td>Actual: Total Recruitment</td>
<td>454</td>
</tr>
<tr>
<td>Actual/Target Ratio: Total Recruitment</td>
<td><strong>121%</strong></td>
</tr>
<tr>
<td>Target: Racial Minority Recruitment</td>
<td>65</td>
</tr>
<tr>
<td>Actual: Racial Minority Recruitment</td>
<td>110</td>
</tr>
<tr>
<td>Actual/Target Ratio: Racial Minority Recruitment</td>
<td><strong>169%</strong></td>
</tr>
<tr>
<td>Target: Hispanic Ethnicity Recruitment</td>
<td>33</td>
</tr>
<tr>
<td>Actual: Hispanic Ethnicity Recruitment</td>
<td>60</td>
</tr>
<tr>
<td>Actual/Target Ratio: Hispanic Ethnicity Recruitment</td>
<td><strong>182%</strong></td>
</tr>
</tbody>
</table>
Sex differences in brain response to coherent versus scrambled biological motion: ASD ♀ > ASD ♂

- Male ASD liability threshold: Mean + 2.1SD
- Female ASD liability threshold: Mean + 2.7SD
- 1.3% ASD prevalence
- 4:1 sex bias

ASD females vs. TD females: dmPFC, dPFC, pSTS, FFG, ITG
ASD males vs. TD males: Right hemisphere view

Female: ♀; Male: ♂; dmPFC: dorsomedial prefrontal cortex; FFG: fusiform gyrus; ITG: inferior temporal gyrus; pSTS: posterior superior temporal sulcus; vmPFC: ventromedial prefrontal cortex

ASD ♀ > ASD ♂
How do we translate basic science into practicable treatments aimed at target engagement?
IMPRECISION MEDICINE

For every person they do help (blue), the ten highest-grossing drugs in the United States fail to improve the conditions of between 3 and 24 people (red).

1. ABILIFY (aripiprazole)
   Schizophrenia

2. NEXIUM (esomeprazole)
   Heartburn

3. HUMIRA (adalimumab)
   Arthritis

4. CRESTOR (rosuvastatin)
   High cholesterol

5. CYMBALTA (duloxetine)
   Depression

6. ADVAIR DISKUS (fluticasone propionate)
   Asthma

7. ENBREL (etanercept)
   Psoriasis

8. REMICADE (infliximab)
   Crohn’s disease

9. COPAXONE (glatiramer acetate)
   Multiple sclerosis

10. NEULASTA (pegfilgrastim)
    Neutropenia

Based on published number needed to treat (NNT) figures. For a full list of references, see Supplementary Information at dx.nature.com/4dr?8.

Pivotal Response Training (PRT)
Change in Behavior: Social Responsiveness Scale (SRS)

Yang et al. (in press) *Nature: Translational Psychiatry*
Neuro-prediction of treatment response

Yang et al. (in press)
*Nature: Translational Psychiatry*
Change in brain, driving change in behavior

Yang et al. (in press)
Nature: Translational Psychiatry
R inferior frontal gyrus
R precentral gyrus

M ASD > F ASD

Boys
-15.67
-3.98

Girls

Vineland - Socialization Change: PRT vs. Waitlist

WLCBoys
WLCGirls
Boys
Girls

-1.20
3.50
1.82
7.25
Can we boost brain responses before treatment, to make treatment work

Art by Charlotte Pretzsch
Intranasal Oxytocin – Social Judgments

Gordon et al. (2013) *Proceedings of the National Academy of Sciences*
Linking neural signatures, genes, and behavior in to shape developmental trajectories
Results: fNIRS (LR and HR 3-Month-Old Infants)

LEFT

Low Risk

High Risk

RIGHT

Low Risk

High Risk

Hemoglobin change (micromolar)

Time (in tenths of seconds)

BIOLOGICAL

SCRAMBLED
Acknowledgments

The Carbonell Family
NIMH
NICHD
NINDS
Simons Foundation
Autism Speaks
Hilibrand Foundation
John Merck Scholars Fund
Autism Science Foundation

I thank the participants and their families for participating in our research.
I thank my colleagues who make this work so much fun.
kevinpelphrey@gwu.edu
The role of genetics and sex-differential biology in risk for autism

Donna Werling, PhD
Sanders & State Labs, UCSF
October 26, 2016
Autism prevalence is sex-biased

- ~4:1 males:females have a diagnosis of autism spectrum disorder (ASD)

<table>
<thead>
<tr>
<th>Male:female ratio – logarithmic scale</th>
<th>Female</th>
<th>Mean age (yrs)</th>
<th>ASD</th>
<th>Cervical, ovarian, breast and uterine cancer</th>
<th>Assault</th>
<th>Conflict</th>
<th>Prostate hypertrophy</th>
<th>Prostate cancer</th>
<th>Bladder/Esophageal cancer</th>
<th>Cancer</th>
<th>Dementia</th>
<th>Hypertensive Heart disease</th>
<th>Perinatal/ Congenital conditions</th>
<th>Migraine</th>
<th>Depression</th>
<th>Rheumatoid arthritis</th>
<th>Chlamydia</th>
<th>Pregnancy related</th>
<th>Cervical, ovarian, breast and uterine cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>10:1</td>
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<td>2:1</td>
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<td>1:10</td>
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</tbody>
</table>

Autism prevalence is sex-biased

• ~4:1 males:females have a diagnosis of autism spectrum disorder (ASD)¹

• 8 males and 3 females in the 11 cases originally reported by Leo Kanner, 1943²

• Male bias consistent over time and across countries¹

Why study sex bias in ASD from a biological perspective?

**Sex** appears to be a potent modulator of ASD risk

Males: 1 in 42 diagnosed  
Females: 1 in 189 diagnosed
Why study sex bias in ASD from a biological perspective?

Sex appears to be a potent modulator of ASD risk

Males: 1 in 42 diagnosed

Females: 1 in 189 diagnosed
Why study sex bias in ASD from a biological perspective?

**Sex** appears to be a potent modulator of ASD risk

- Treatment development
- Novel/key insights into fundamental biology of ASD
Female Protective Effect (FPE) Model for ASD = Liability model

Population mean

Liability for ASD

i.e. exposure to risk factors such as genetic variants
Female Protective Effect (FPE) Model for ASD = Liability model

No. individuals in population

Population mean

Liability for ASD

Diagnosed individuals

i.e. exposure to risk factors such as genetic variants
Female Protective Effect (FPE) Model for ASD = *Multiple threshold* liability model

- Differential risk factors decrease liability threshold
- Differential protective factors increase liability threshold

Liability for ASD

i.e. exposure to risk factors such as genetic variants
Female Protective Effect (FPE) Model for ASD = *Multiple threshold* liability model

- differential risk factors decrease liability threshold

- differential protective factors increase liability threshold

i.e. exposure to risk factors such as genetic variants
FPE model predicts that diagnosed females carry greater risk than males.
FPE model predicts that diagnosed females carry greater risk than males.
FPE model predicts that diagnosed females carry greater risk than males.
FPE model predicts that diagnosed females carry greater risk than males.
FPE model predicts that diagnosed females carry greater risk than males.
Higher incidence of disruptive, *de novo* variants in ASD females

Copy number variants (CNVs)

- Duplications
- Deletions

Insertion/Deletions (Indels)

- De novo indels per individual
  - All
  - Brain

Single nucleotide variants (SNVs)

- De novo SNVs per individual
  - ASD genes
    - LoF
    - Missense

Inferred genetic risk for ASD

Genetic risk in diagnosed

Siblings of female cases have higher ASD traits than siblings of male cases

Robinson et al, PNAS, 2013

Autistic traits in siblings?
Siblings of female cases have higher ASD traits than siblings of male cases

Robinson et al, PNAS, 2013
FPE model predicts that females respond differently to liability that is sufficient for diagnosis in males.
FPE model predicts that females respond differently to liability that is sufficient for diagnosis in males

1. Quantitative:
   Females are protected and have neurotypical phenotype.

2. Qualitative:
   Females present symptoms differently than males, and are not diagnosed.
FPE model predicts that females respond differently to liability that is sufficient for diagnosis in males.

Hypothesis:

*Sex-differential biology contributes to male and female differences in ASD risk and/or symptom presentation*.

1. Quantitative:
   
   Females are protected and have neurotypical phenotype.

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1. Identify genes with sex-differential expression levels in the human brain

2. Characterize the relationship between sex-DEX genes and ASD biology
# BRAINSPAN
ATLAS OF THE DEVELOPING HUMAN BRAIN

## Table 1: Periods of human development and adulthood as defined in this study

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Odds ratio for enrichment: 34.5 - 0.03
Male-DEX genes show enrichment for microglial and endothelial cell markers
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**Convergence between male-typical and ASD neurobiology**
Enrichment evidence suggests a male sensitization model of ASD risk.

- Differential risk factors decrease liability threshold
- Differential protective factors increase liability threshold

Liability for ASD:
- i.e. exposure to risk factors such as genetic variants
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Diagram:
- Population mean
- Differential risk factors decrease liability threshold
- Liability for ASD
  - i.e. exposure to risk factors such as genetic variants
- Diagnosed individuals

No. individuals in population
Enrichment evidence suggests a male sensitization model of ASD risk

Large overlap leads to male sensitization

Small overlap leads to relative female protection

Male-enriched neurobiology

Neurobiology shared between sexes

Female-enriched neurobiology
Enrichment evidence suggests a male sensitization model of ASD risk

To understand ASD sex bias, we must characterize the intersection of typical male neurobiology and ASD neurobiology.

![Diagram showing the relationship between male-enriched neurobiology, neurobiology shared between sexes, and female-enriched neurobiology. The diagram illustrates large overlap leading to male sensitization and small overlap leading to relative female protection.]
Summary

• Intersection of ASD neurobiology and sex-differential neurobiology provides an approach to understand sex bias

• Male-biased expression:
  – Microglial genes
  – Collagen genes and endothelial cell markers
  – Glial genes dysregulated in ASD brain, suggesting a male-sensitization effect

• Validation in independent samples is needed
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Looking forward

- Well powered, foundational data sets comparing males and females will be required for:
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**Data types**

- RNA sequencing for gene expression
- ChIP-seq for identifying gene targets of the estrogen and androgen receptors

**2x2 design**

**Developmental stages**

- Fetal
- Perinatal
- Early postnatal/childhood
- Puberty
- Adulthood

**Cell types**

- Neurons
- Microglia
- Astrocytes

**Brain regions**

- Neocortex
- Thalamus
- Striatum
- Cerebellum

**Organisms**

- Human
- Primate
- Mouse
The role of genetics and sex-differential biology in risk for autism

Donna Werling, PhD
Sanders & State Labs, UCSF
October 26, 2016
Autism prevalence is sex-biased

• ~4:1 males:females have a diagnosis of autism spectrum disorder (ASD)

Autism prevalence is sex-biased

- ~4:1 males:females have a diagnosis of autism spectrum disorder (ASD)\(^1\)
- 8 males and 3 females in the 11 cases originally reported by Leo Kanner, 1943\(^2\)
- Male bias consistent over time and across countries\(^1\)

---

\(^1\) Fombonne, 2009, Pediatr Res. \(^2\) Kanner, 1943, Nervous Child.
Why study sex bias in ASD from a biological perspective?

**Sex** appears to be a potent modulator of ASD risk

Males: 1 in 42 diagnosed

Females: 1 in 189 diagnosed
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Why study sex bias in ASD from a biological perspective?

**Sex** appears to be a potent modulator of ASD risk

- Treatment development
- Novel/key insights into fundamental biology of ASD
Female Protective Effect (FPE) Model for ASD = Liability model

No. individuals in population

Population mean

Liability for ASD
i.e. exposure to risk factors such as genetic variants
Female Protective Effect (FPE) Model for ASD = Liability model

Liability for ASD → Diagnosed individuals
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FPE model predicts that diagnosed females carry greater risk than males.
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Higher incidence of disruptive, *de novo* variants in ASD females

Copy number variants (CNVs)$^1$

Insertion/Deletions (Indels)$^2$

Single nucleotide variants (SNVs)$^3$

Siblings of female cases have higher ASD traits than siblings of male cases.
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Module: M6, M12, M31, M35, M45, M63
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ASD Control
Males
Females

Data types

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Acknowledgements

Stephan Sanders
UCSF

Matt State
UCSF

Nenad Sestan
Yale

This work was supported by a grant to SS from the Simons Foundation (SFARI #307705), and a fellowship to DW from the Autism Science Foundation (ASF #16-009)
Meeting of the IACC

Afternoon Agenda - continued

3:40  Listening to our Daughters: How Working with Girls and Women on the Spectrum Informs our Understanding of Autism

Kevin Pelphrey, Ph.D.
IACC Member and Panel Chair

4:00  Questions and Discussion
Meeting of the IACC

Questions and Discussion

These slides do not reflect decisions of the IACC and are for discussion purposes only.
Meeting of the IACC

Afternoon Agenda - continued

4:25 Round Robin

4:55 Closing Remarks

5:00 Adjournment
Meeting of the IACC

Round Robin

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NIMH Round Robin Update

Joshua Gordon, M.D., Ph.D.
Director, National Institute of Mental Health
Chair, IACC

IACC Full Committee Meeting
October 26, 2016
NIMH ServASD Program

- NIMH responded to the need identified in the IACC Strategic Plan for improved access to and effectiveness of ASD services with the ServASD I request for applications (RFA).

- In 2014, NIMH awarded 12 research grants aimed at testing strategies for early screening, referral and engagement in services for young children, developing service coordination approaches for transition-aged youth, and projects to test strategies to improve and support the community functioning of adults with ASD.

- In October 2015, the ServASD II initiative was re-issued for pilot studies of services strategies for Adults and Youth with ASD. 34 applications were received/reviewed, with awards expected in early 2017.

  

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Round Robin Update

Susan Daniels, Ph.D.
Director, OARC, NIMH and Executive Secretary, IACC

IACC Full Committee Meeting
October 26, 2016
Interagency Committee on Disability Research
Draft Government Wide Strategic Plan

• The ICDR invites the general public and other public agencies to comment on the Draft Government Wide Strategic Plan for FY 2017-2020, and the strategic goals and objectives the ICDR will pursue over the next three years.


Written comments must be received by November 4, 2016.
Closing Remarks