IACC Working Group: Improving Health Outcomes for Individuals on the Autism Spectrum

Thursday, September 27, 2018

National Institutes of Health

Neuroscience Center

Rooms C, D & E

6001 Executive Blvd

Rockville, MD, 20892

Conference Call Access:
Phone: 800-369-1744
Participant Passcode: 6697418

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

Meeting of the IACC

Morning Agenda

8:30 AM **Welcome, Introductions**

Susan Daniels, Ph.D.

Director, Office of Autism Research Coordination, National Institute of Mental Health, and Executive Secretary, IACC

Working Group Co-Chairs

David G. Amaral, Ph.D.

Distinguished Professor, Department of Psychiatry and Behavioral Science, University of California, Davis (UC), UC Davis MIND Institute

Julie Lounds Taylor, Ph.D.

Assistant Professor, Pediatrics and Special Education, Vanderbilt University, and Investigator, Vanderbilt Kennedy Center

IACC Working Group: Improving Health Outcomes for Individuals on the Autism Spectrum

September 27, 2018

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

Improving Health Outcomes for Individuals on the Autism Spectrum WG

- The IACC voted to convene a working group on health and wellness issues for individuals with ASD

- The Working Group will explore ways to:
  - Support research to better understand the health conditions that affect individuals on the autism spectrum
  - Increase community/provider awareness of these conditions and their treatment
  - Foster development of practice guidelines, policies, service approaches and other efforts to improve the health and quality of life of people on the autism spectrum

Working Group Scope

- Health and general wellness for people with ASD
- Co-occurring physical and mental health conditions
- Premature mortality
- Patient-provider interactions (including medical practitioner training)
- Parental/family mental health

Expected Working Group Activities and Products

- **Workshop: Addressing the Health Needs of People on the Autism Spectrum**
  - Health epidemiology
  - Patient-provider interactions
  - Co-occurring health conditions

- A written document providing an update on issues

- Continued discussions in Working Group conference calls, Working Group meetings, and/or IACC full committee meetings

- Working Group activities will run from September 2018 – September 2019

Working Group Members

Co-Chairs

- David Amaral, Ph.D., University of California, Davis
- Julie Lounds Taylor, Ph.D., Vanderbilt University

IACC and Federal Members

- Patricia Dietz, Dr.P.H., M.P.H., Centers for Disease Control and Prevention
- Jennifer Johnson, Ed.D., Administration for Community Living
- Alice Kau, Ph.D., *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
- Kevin Pelphrey, Ph.D., George Washington University and Children's National Medical Center ●
- Denise Juliano-Bult, M.S.W., National Institute of Mental Health
- Scott Michael Robertson, Ph.D., U.S. Department of Labor ●
- Marcella Ronyak, Ph.D., LCSW, CDP, Indian Health Service ●
- Nina Schor, M.D., Ph.D., National Institute of Neurological Disorders and Stroke
- Alison Tepper Singer, M.B.A., Autism Science Foundation ●

● Self-advocate ● Parent/Family member

Working Group Members

External Members

- Gregory Barnes, M.D., Ph.D., University of Louisville School of Medicine
- Timothy Buie, M.D., Harvard Medical School
- Dan Coury, M.D., The Ohio State University College of Medicine
- Lisa Croen, Ph.D. Kaiser Permanente Northern California
- Orrin Devinsky, M.D., New York University
- Sarah Gardner, MIND Institute, University of California, Davis ●
- Dena Gassner, M.S.W., Adelphi University ● ●
- Antonio Hardan, M.D., Stanford University Medical Center
- Joseph Joyce, M.B.A., Autism Society of America ●
- Connor Kerns, Ph.D., University of British Columbia
- Bryan King, M.D., M.B.A., University of California, San Francisco

● Self-advocate ● Parent/Family member

Working Group Members

External Members

- Clarissa Kripke, M.D., University of California, San Francisco
- Beth Ann Malow, M.D., M.S., Vanderbilt University Medical Center ●
- Micah Mazurek, Ph.D., University of Virginia
- Donna Murray, Ph.D., University of Cincinnati
- Christina Nicolaidis, M.D., M.P.H., Oregon Health and Science University ●
- Dora Raymaker, Ph.D., Portland State University ●
- Elliott Sherr, M.D., Ph.D., University of California, San Francisco
- Matthew Siegel, M.D., Tufts University
- Sarah Spence, M.D., Ph.D., Harvard Medical School
- Jeremy Veenstra-VanderWeele, M.D., Columbia University

● Self-advocate ● Parent/Family member

Meeting of the IACC

Morning Agenda

8:45 AM **Health and Healthcare for Adults on the Autism Spectrum: The Newcastle University Adulthood and Ageing Research Programme**

Jeremy Parr, M.D.
Professor of Pediatric Neurodisability, Newcastle University Institute of Neuroscience, United Kingdom

2018 IACC Workshop: Addressing the Health Needs of People on the Autism Spectrum

Health and healthcare for adults on the autism spectrum: The Newcastle University adulthood and ageing research programme

Jeremy Parr

Professor of Paediatric Neurodisability

@jeremyrparr

Funding, and conflicts of interest

I have no financial conflicts of interest

The autism spectrum adulthood and ageing research programme is funded by the UK autism charity Autistica

Received funding from the UK MRC, NIHR and charities for research described

Editorial Committee for the *Autism in Adulthood* journal

Lots of work by lots of people

Autistic people and relatives, parents of children, children

Tom Berney, Carla Black, Sam Brice, Tracy Finch, Mark Freeston, Deborah Garland, The Goth, Vicki Grahame, Jahnese Hamilton, Barry Ingham, Ann Le Couteur, David Mason, Joan Macintosh, Morag Maskey, Helen McConachie, Cos Michael, Chris Mitchell, Alex Petrou, Jacqui Rodgers, Sarah Wigham, Colin Wilson, Marc Woodbury-Smith

Autism specific health checks consortium

Many other colleagues nationally and internationally. The Programme Advisory and Steering committee

Newcastle University
UK | Malaysia | Singapore

Institute of Neuroscience

Institute for Ageing

Research priorities: Longitudinal cohort study re the lives of autistic people. Their quality of life, mental health, physical health

Engagement strategies

https://research.ncl.ac.uk/adultautismspectrum/newsevents/

International leaders in autism research registers/databases, and cohorts (cross sectional and longitudinal data); web based, paper materials

- Hypothesis driven research
- Improve research infrastructure

UK research registers/databases (with consent); 80 health providers (NHS Trusts)

ASD-UK: Over 4500 families of children; 2000 local (55% of local ASD families – largest internationally). Co-existing conditions, age at diagnosis

Longitudinal cohorts (consent); work with 60 NHS Trusts, plus community

Adult ASC-UK: Over 1700 adults on the autism spectrum, 700 relatives of adults. Among the largest internationally. Mental health, physical health, how lives change with time; mixed methods

Expertise and materials shared and exported (Ireland, US, Canada)

2018: Newcastle University research programme on autism lifecourse and ageing

Designing intervention: Methods and measures used in diagnosis

Understanding: Uncertain futures for autistic people and relatives (Rodgers)

Design intervention: Personalised phobia treatment

Designing intervention: Post diagnostic support

Survey, design intervention & RCT: Personalised anxiety treatment

Survey, design intervention & RCT: Accessing health care

Survey, design intervention & RCT: Autism specific health checks in Primary care

Measurement: Quality of life WHO-QoL-BREF and ASQoL

Top ten questions for autism research

AUTISTICA

Building brighter futures through autism research

1	Which interventions improve mental health or reduce mental health problems in autistic people? How should mental health interventions be adapted for the needs of autistic people?
2	Which interventions are effective in the development of communication/language skills in autism?
3	What are the most effective ways to support/provide social care for autistic adults?
4	Which interventions reduce anxiety in autistic people?
5	Which environments/supports are most appropriate in terms of achieving the best education/life/social skills outcomes in autistic people?
6	How can parents and family members be supported/educated to care for and better understand an autistic relative?
7	How can autism diagnostic criteria be made more relevant for the adult population? And how do we ensure that autistic adults are appropriately diagnosed?
8	How can we encourage employers to apply person-centred interventions and support to help autistic people maximise their potential and performance in the workplace?
9	How can sensory processing in autism be better understood?
10	How should service delivery for autistic people be improved and adapted in order to meet their needs?

How are autistic people and the research team working together?

- Collaborative working started when shaping the project. Autistic people were not integrated into a pre-designed project
- Autistic people were asked what outcomes we wanted

The autistic researchers' job is ongoing. We meet regularly to:

- suggest ways the research team can engage with autistic adults
- advise on the range of communication methods possible for gathering information
- advise on tailoring autism friendly environments for meeting contributors
- advise on respecting autistic preferences and behavioural traits
- make suggestions, such as providing feedback and updates on progress, to promote inclusion and help keep people engaged over the longer term

Characteristics

The adult cohort includes 54% males, 44% females, and 2% who report another gender

30% need support to complete materials

130 people who are unable to consent for themselves (consultee consent)

Age range 16-80 years

50% age 16-35 years, 20% 36-45 years and 30% over age 46; more than 150 people aged over 56 years

Consent to recontact: update information, give new information, many agreed to meet

Predictors of Quality of Life for Autistic Adults

Autism Research

David Mason, Helen McConachie, Deborah Garland, Alex Petrou, Jacqui Rodgers, and Jeremy R. Parr

N=370; Autistic adults have lower QoL than the general population

	Positive Predictors		Negative Predictors	
Physical	Employed	β = .112*	Female Mental health condition SRS total	β = -.133* β = -.211*** β = -.413***
Psychological			Female Mental health condition SRS total	β = -.150** β = -.274*** β = -.378***
Social	In a relationship Receiving support	β = .285*** β = .129*	Older age Mental health condition SRS total	β = -.187** β = -.194** β = -.260***
Environment	Receiving support	β = .180**	Female Mental health condition SRS total	β = -.160** β = -.250*** β = -.442***

*$p < .05$, **$p < .01$, and ***$p < .001$

Enhancing the Validity of a Quality of Life Measure for Autistic People

Journal of Autism and Developmental Disorders
https://doi.org/10.1007/s10803-017-3402-z

Helen McConachie[1,5] · David Mason[1] · Jeremy R. Parr[2] · Deborah Garland[3] · Colin Wilson[4] · Jacqui Rodgers[2]

424 autistic adults participated

Impact: Reliability and validity of the WHOQoL BREF for the measurement of QoL for autistic adults

9 ASQoL items created that can be used by researchers internationally; freely available online and can be downloaded at:

(Search: ASQoL Newcastle)

https://research.ncl.ac.uk/neurodisability/leafletsandmeasures/autismqualityoflifemeasure/

Email: Jeremy.Parr@ncl.ac.uk or Jacqui.Rodgers@ncl.ac.uk

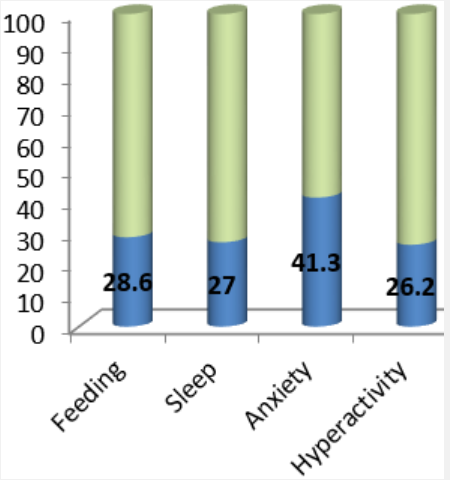
Co-existing conditions of children

Data from 3900 families of children (often or frequent):

	Boys	Girls	Total
Sleep problems	74.6 (2356)	78.0 (583)	75.2 (2939)
Hyperactivity	83.0 (2622)	82.3 (615)	82.9 (3727)
Injury to self	41.7 (1317)	42.6 (318)	41.9 (1635)
Anxiety, fears, or phobias	80.3 (2538)	83.3 (622)	80.9 (3160)
Feeding problems	80.0 (2527)	77.8 (581)	79.6 (3108)

Equally prevalent in children with and without intellectual disability

Unmet clinical need



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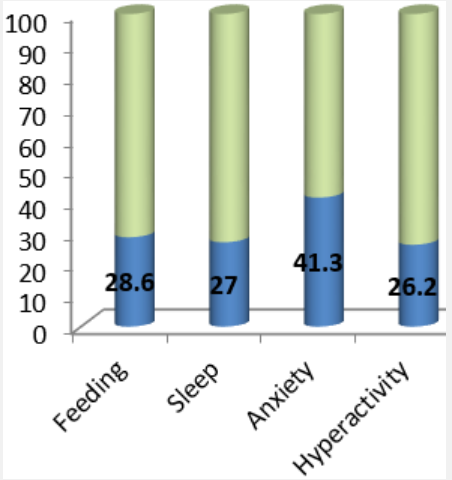
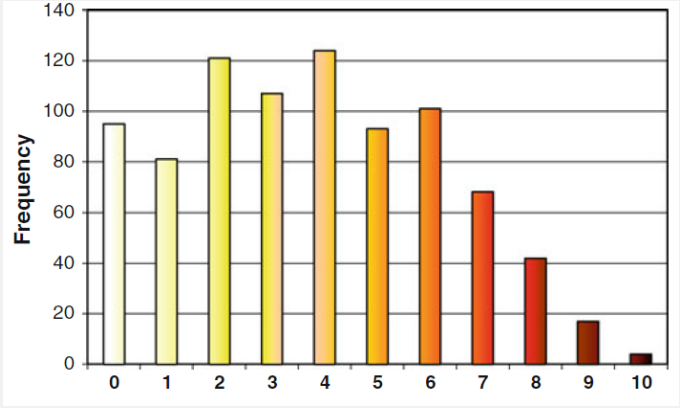
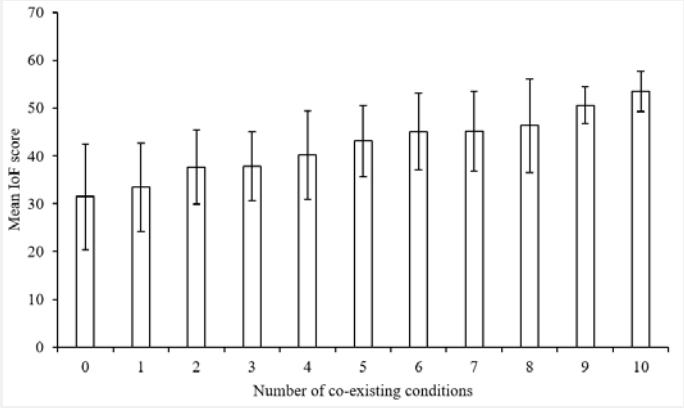






Mental health conditions (equal numbers autistic adults: males and females (n=1198) Petrou el al., in preparation

	n (%) or Mean (SD)					
	16-25 (n=315)	26-40 (n=407)	41-60 (n=408)	61+ (n=68)	Total (n=1198)	Association between age groups
SRS total	107.0 (34.3)	115.7 (25.6)	112.9 (25.5)	103.3 (29.7)	111.7 (28.5)	$X^2(3)=12.5$, p=.006
Mental health/neurological conditions						
ADHD	45 (14.3)	44 (10.8)	25 (6.1)	8 (11.8)	122 (10.2)	$X^2(3)=13.5$, p=.004
Anxiety	158 (50.2)	226 (55.5)	228 (55.9)	27 (39.7)	639 (53.3)	$X^2(3)=8.20$, p=.042
Depression	111 (35.2)	210 (51.6)	221 (54.2)	29 (42.6)	571 (47.7)	$X^2(3)=29.6$, p<.001
Access to mental health services						
Tried to access mental health services	194 (61.6)	308 (75.7)	293 (71.8)	45 (66.2)	843 (70.1)	$X^2(3)=17.87$, p<.001
Accessed the mental health services needed	128 (40.6)	187 (45.9)	164 (40.2)	26 (38.2)	505 (42.2)	$X^2(3)=15.20$, p=.002

Mental health conditions (equal numbers autistic adults: males and females (n=1198) Petrou el al., in preparation

	n (%) or Mean (SD)					
	16-25 (n=315)	26-40 (n=407)	41-60 (n=408)	61+ (n=68)	Total (n=1198)	Association between age groups
Physical health conditions						
Arthritis	5 (1.6)	16 (3.9)	57 (14.0)	19 (27.9)	97 (8.1)	$X^2(3)=82.33$, $p<.001$
Diabetes	5 (1.6)	14 (3.4)	35 (8.6)	7 (10.3)	61 (5.1)	$X^2(3)=24.38$, $p<.001$
Gastrointestinal problems	35 (11.1)	83 (20.4)	118 (28.9)	22 (32.4)	258 (21.5)	$X^2(3)=38.45$, $p<.001$
Irritable bowel syndrome	34 (10.8)	57 (14.0)	73 (17.9)	12 (17.6)	176 (14.7)	$X^2(3)=7.78$, $p=.05$
Obesity	17 (5.4)	59 (14.5)	53 (13.0)	9 (13.2)	138 (11.5)	$X^2(3)=16.19$, $p<.001$
Sleep problems	76 (24.1)	96 (23.6)	116 (28.4)	13 (19.1)	301 (25.1)	$X^2(3)=4.35$, $p=.226$

Health care adjustments / Accommodations: Data from >500 autistic adults and relatives, >100 parents of children (Brice, Wigham; in preparation)

For anxiety: some examples, needed most frequently but infrequently provided

Therapists with expertise in autism (not just therapy)
Information pre clinic about what to expect
Waiting rooms small, with appropriate activities
Meeting people's sensory needs (lighting, noise)
Health summary document (eg health passport)
Tailoring the appointment according to information given by the person/relative
Follow up appointments to enable further discussion

'It was in an unfamiliar place in an unfamiliar town, though this was my fault because I tend to avoid going out. What was particularly hard was that the building had an outside intercom that, had I been alone, I would not have used, would have panicked instead and returned home'

AUTISM AND AGEING

PHYSICAL HEALTH AND WELLBEING

Thursday 28th - Friday 29th September 2017

Newcastle University, United Kingdom

Workshop Report: Establishing Priority Research Areas to Improve the Physical Health and Well-Being of Autistic Adults and Older People

AUTISM IN ADULTHOOD
Volume 1, Number 1, 2018

Georgina Warner, MA, PhD[1] Jeremy R. Parr, MBChB, MD[2] and James Cusack, MA, PhD[1]

39 people; 11 research priorities, initial research outlines

1. Tailoring of existing measures of pain to better suit autistic people.
2. An international collaborative effort to agree a core set of demographic, health behavior and health outcome indicators most relevant to autistic people that can be compared with general population data.
3. Investigation of healthcare self-advocacy strategies and potential barriers to effective healthcare self-advocacy for autistic people.
4. Development of a tool to improve understanding of how factors influence personal well-being for autistic people.
5. A review of evidence on autism-specific health service accommodations and service design to inform what an autism-friendly health service looks like.
6. Adaptation of an online healthcare "toolkit" developed in the United States to facilitate the primary healthcare of autistic adults for use in the UK.
7. Development and evaluation of a personalized annual health check program for autistic people.
8. Evaluation of the types of cardiovascular and gut problems most prominent in older autistic adults, contributory factors, and treatment effectiveness.
9. Engagement with autistic people regarding opportunities to use knowledge about genetics and biology to improve health and well-being.
10. Exploration of the research priorities regarding sexual development and health in autism.
11. Investigation of autistic people's use and experiences of residential facilities for older people.

Design and initial evaluation of an autism-specific health check for use with autistic adults in UK National Health Service Primary Care

Funded in response to competitive, open call for proposals regarding design and evaluation of an autism specific health check (primary care)

In partnership with autistic people and relatives, and professionals, design web based autism specific health check, and trial use in the UK NHS (2019-22); includes Nicolaidis, Raymaker, Urbanowicz. Commissioners, managers, clinicians

Autistic people and relatives involved throughout: Priority setting, developing outline, co-investigators in the consortium designing and writing the application

Outcomes: Acceptability, feasibility, access, health outcomes. Utilise standard NHS datasets, in addition to research data collected

Some key messages

Value in research programmes that build critical mass in autism adulthood and ageing

An integrated research approach: use basic science, improved understanding to design trials, improve interventions and services, implement change

Longitudinal studies allow investigation of personal change, and accelerated cohort studies; ideally, across the lifecourse

Build datasets through informed consent, enabling sharing of anonymised data

Ensure access to usual healthcare and other data, big datasets; UK NHS is an ideal environment for this

National and international collaborations will lead to early results – using parallel protocols and measures

Thank You

Jeremy.Parr@ncl.ac.uk

@jeremyrparr

https://research.ncl.ac.uk/neurodisability/conditionsandtopics/autismspectrumdisorderasd/

Newcastle University research programme: Jeremy.Parr@ncl.ac.uk; @jeremyrparr

Designing intervention: Methods and measures used in diagnosis

Understanding: Uncertain futures for autistic people and relatives (Rodgers)

Design intervention: Personalised phobia treatment

Designing intervention: Post diagnostic support

Survey, design intervention & RCT: Personalised anxiety treatment

Survey, design intervention & RCT: Accessing health care

Survey, design intervention & RCT: Autism specific health checks in Primary care

Measurement: Quality of life WHO-QoL-BREF and ASQoL

Autism Spectrum, Adulthood and Ageing

Adult Autism Spectrum Cohort-UK

Register with the Adult Autism Spectrum Cohort - UK

Some challenges

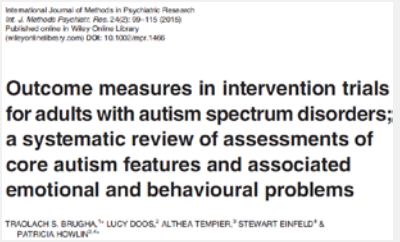
What to measure? When to measure it? When to re-measure?

Who to ask? Adults – but relatives too? Relatives lives? Relatives views about adults lives? (what's acceptable?)

What to measure with? Are our measures fit for purpose? Acceptable, psychometric properties?

Comparison (control) data; comparison between adults; different settings or countries? Or compare with the general population?

(National, and International collaboration)


International Journal of Methods in Psychiatric Research
Int. J. Methods Psychiatr. Res. 24(2): 99–115 (2015)
Published online in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/mpr.1466

Outcome measures in intervention trials for adults with autism spectrum disorders; a systematic review of assessments of core autism features and associated emotional and behavioural problems

TRAOLACH S. BRUGHA,[1]* LUCY DOOS,[2] ALTHEA TEMPIER,[3] STEWART EINFELD[4] & PATRICIA HOWLIN[2,5]

Discussion

Meeting of the IACC

Morning Agenda

9:30	**Physical and Mental Health in Autism – Epidemiology of Co-occurring Conditions** **Lisa Croen, Ph.D.** Senior Research Scientist, Division of Research, Kaiser Permanente Northern California, and Director, Kaiser Permanente Autism Research Program
10:15	**Break**
10:30	**Oral Public Comments**
11:00	**Written Public Comments**
11:15	**Working Group Discussion of Comments**

Physical and Mental Health in Autism – Epidemiology of Co-occurring Conditions

Lisa Croen, Ph.D.
Senior Research Scientist, Division of Research, Kaiser Permanente Northern California, and Director, Kaiser Permanente Autism Research Program

What do we know?

Individuals with ASD have higher burden of medical and psychiatric conditions than individuals without ASD

- Higher utilization of healthcare services and higher associated costs

Common co-occurring conditions with ASD

- Common medical: GI, sleep, seizure, overweight/obesity, allergy/immune
- Common psychiatric: depression, anxiety

Less prevalent conditions also occur more often in individuals with ASD than general popn

- Medical: neurologic, metabolic, endocrine, ophthalmologic, cardiovascular, genetic
- Psychiatric: suicide/suicidal ideation, bipolar disorder, OCD, tic

What do we know?

Co-occurring conditions cluster together in individuals with ASD

- E.g., sleep and constipation, feeding and speech disorders

Co-occurring conditions – emergence across the lifespan

- Early childhood – GI, sleep, seizure, overweight, immune conditions
- Middle childhood/adolescence – obesity, depression, anxiety
- Adulthood – cardiovascular conditions, diabetes, Parkinsons, dementia

What gaps need to be addressed?

What do co-occurring conditions tell us about biologic pathways? Etiology of ASD?

- Temporality of co-occurring conditions
  - Share cause with ASD?
    - E.g., shared genetics
  - Conditions are consequence of core ASD symptoms?
    - E.g. obesity consequence of poor diet, tx with antipsychotics
  - Conditions share environmental risk factor with ASD
    - E.g., maternal metabolic disorders during pregnancy associated with ASD and obesity

How can co-occurring conditions aid detection of ASD?

- Are there patterns of co-occurring conditions that signal ASD?
- Can pattern of emergence of co-occurring health conditions in first years of life be used as an early warning sign/red flag, early screening tool for ASD?

What gaps need to be addressed?

What is natural history of co-occurring medical and psychiatric disorders among individuals with ASD?

- How are genetic and environmental risk factors for ASD associated with the trajectories of co-occurring conditions (type, timing of emergence, clustering of conditions, expression over the life course)?

Health service provision

- Healthcare provider education
- Health system, clinic, and practice organization to accommodate patients with ASD and complex health needs
- Transition from pediatric to adult care
  - Communication gap between pediatric and adult providers

Discussion

Break

Meeting of the IACC

Morning Agenda

10:30	**Oral Public Comments**
11:00	**Written Public Comments**
11:15	**Working Group Discussion of Comments**
11:30	**Epilepsy in Individuals with Autism – State of the Science**
	Basic Science: Shared Mechanisms
	Gregory Barnes, M.D., Ph.D., Director, University of Louisville Autism Center, and Associate Professor, Child Neurology, Department of Neurology, University of Louisville School of Medicine

Oral Public Comments

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

Written Public Comments

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

Meeting of the IACC

Morning Agenda

11:30 **Epilepsy in Individuals with Autism – State of the Science**

Basic Science: Shared Mechanisms

Gregory Barnes, M.D., Ph.D.,
Director, University of Louisville Autism Center, and Associate Professor, Child Neurology, Department of Neurology, University of Louisville School of Medicine

11:45 **Clinical Science: Epidemiology and Management**

Sarah Spence, M.D., Ph.D.,
Co-Director, Autism Spectrum Center, Boston Children's Hospital, and Assistant Professor of Neurology, Harvard Medical School

12:30 PM **Lunch**

The University *of* Louisville

UL Autism Center

Epilepsy in Autism Spectrum Disorders: Shared Mechanisms

Gregory Neal Barnes MD/PhD

UL Autism Center & BioImaging Laboratory,
Departments of Bioengineering and Neurology

University of Louisville

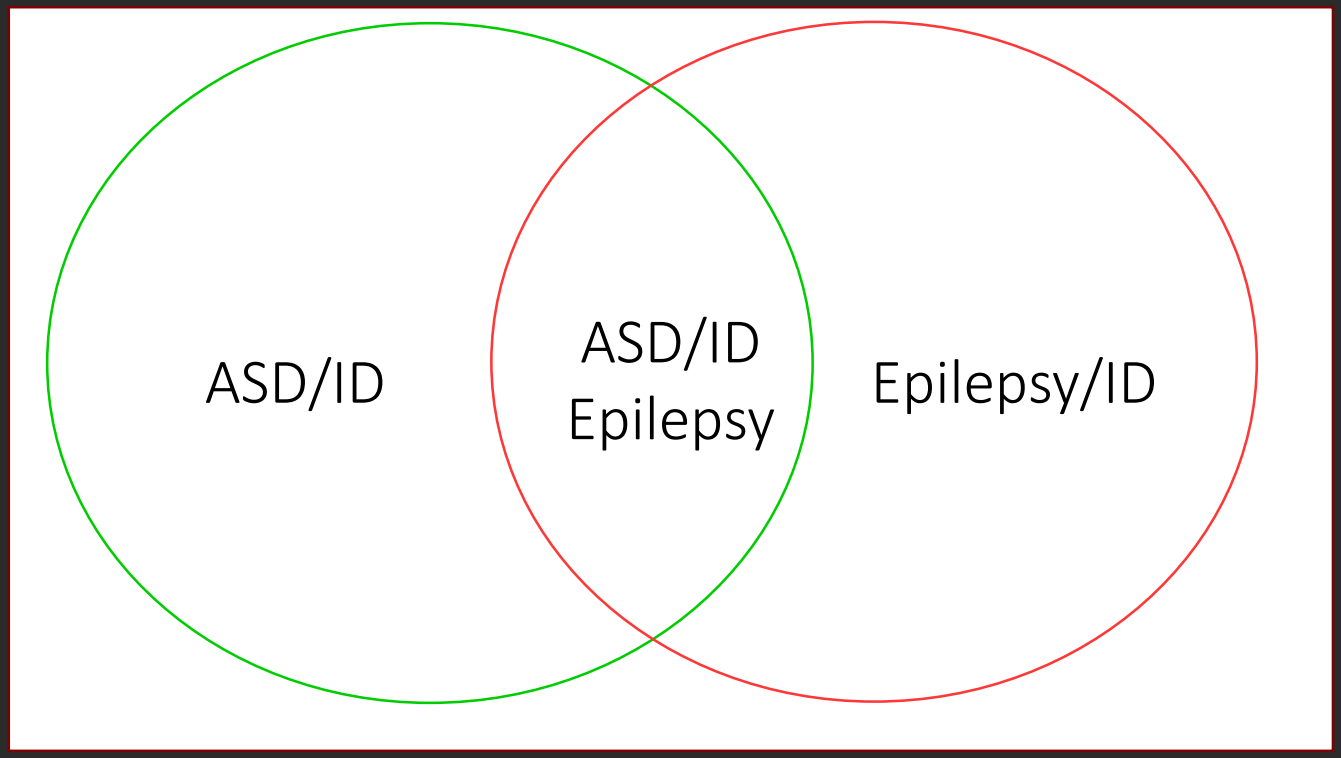
BIL BIOIMAGING LAB

UofL

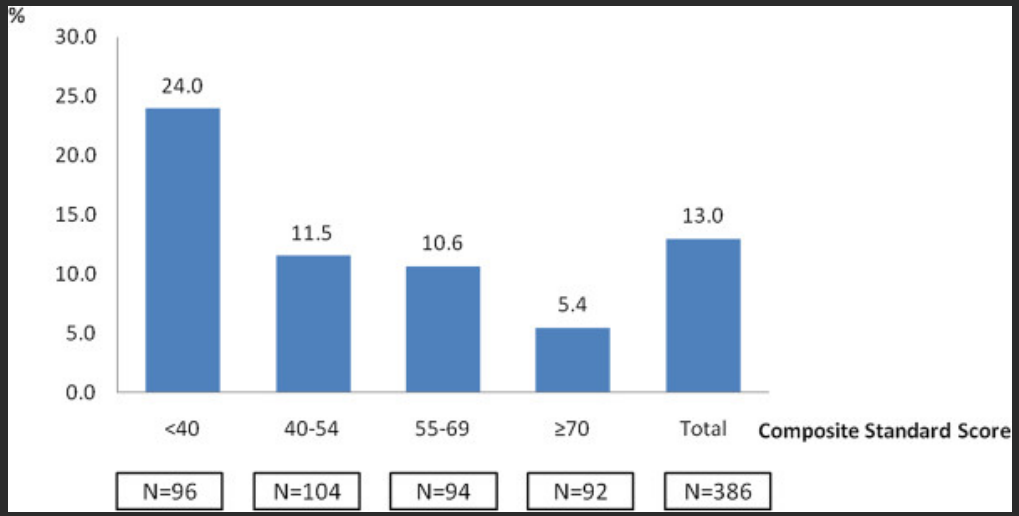
Disclosures

Investigator and Research Grant Funding from GW Pharmaceuticals

Common Mechanism of ASD and Epilepsy

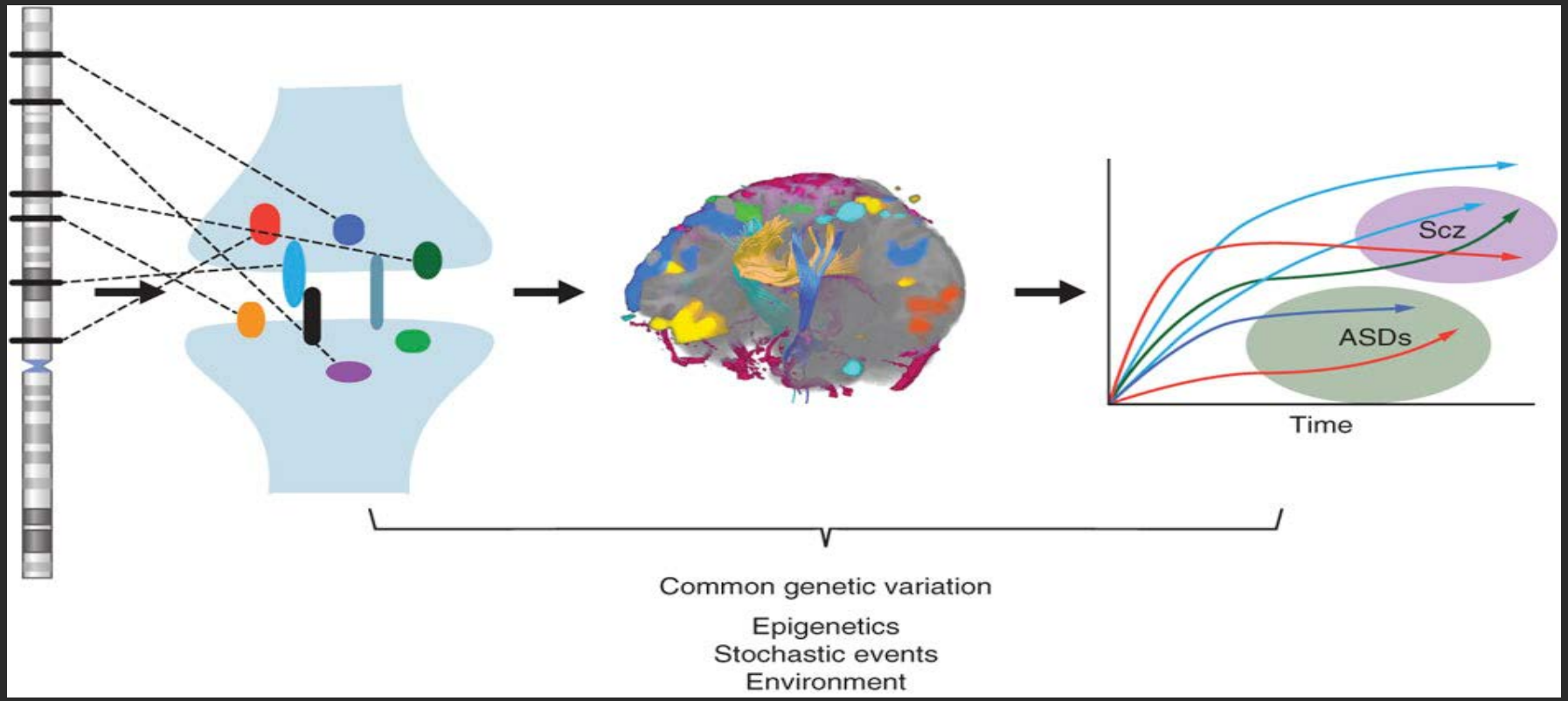


Common Mechanism of ASD and Epilepsy



threefold increased risk of epilepsy for children with a composite standard score <70 [45/294 (15.3%)] comparing children with a composite standard score ≥70 [5/92 (5.4%)] (OR=3.1; 95% CI: 1.2 to 10.5; *P*=0.015)

ASD and Epilepsy



Intellectual Disability

Shared Neurobiology of ASD and Epilepsy

Both disorders largely involving the synapse

Both disorders of activity dependent pathways

Seizures can dysregulate autism-related protein cascades

Evidence for epilepsy in human autism syndromes and animal models

Both occurring in critical periods

Both disorder have similar neuroanatomical and functional alterations of shared brain circuitry

Possible Mechanisms

Cells Involved

Forebrain excitatory neurons

Forebrain inhibitory neurons (PV+- social, SS+- repetitive behaviors)

Serotoninergic neurons

Basal forebrain cholinergic neurons

Cerebellar Purkinje neurons

Hulbert and Jiang, 2017

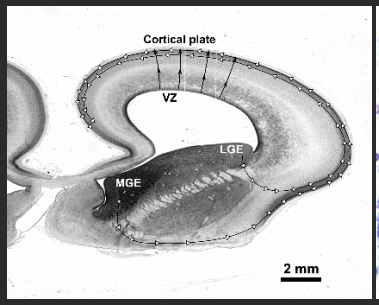
Early life epilepsy (30%)

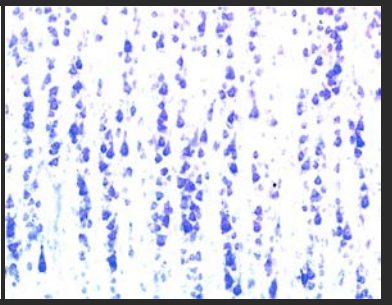
Altered organization of mini-columns are associated with defects in local GABAergic circuits and their $GABA_A$ receptors in the setting of ID

NeuroPathological Findings in Autism

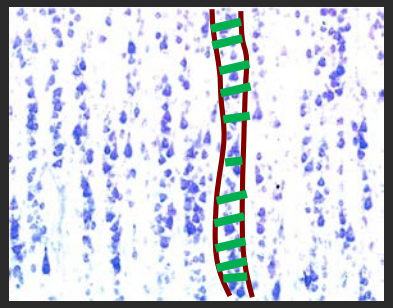
What is the minicolumn?

- The minicolumn is a vertical arrangement of neurons that grows in the cortical surface.

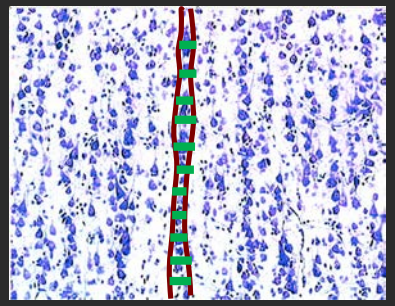




Microscopic Image



Control Subject

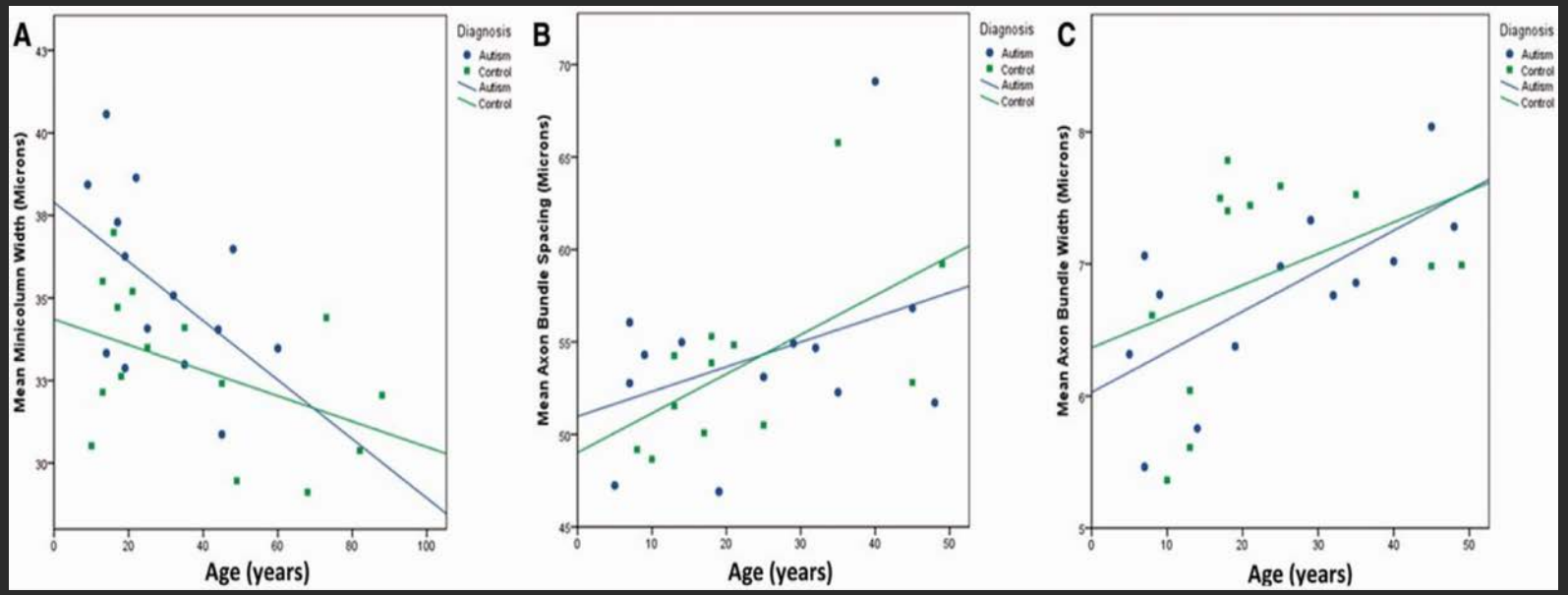


Autistic Subject

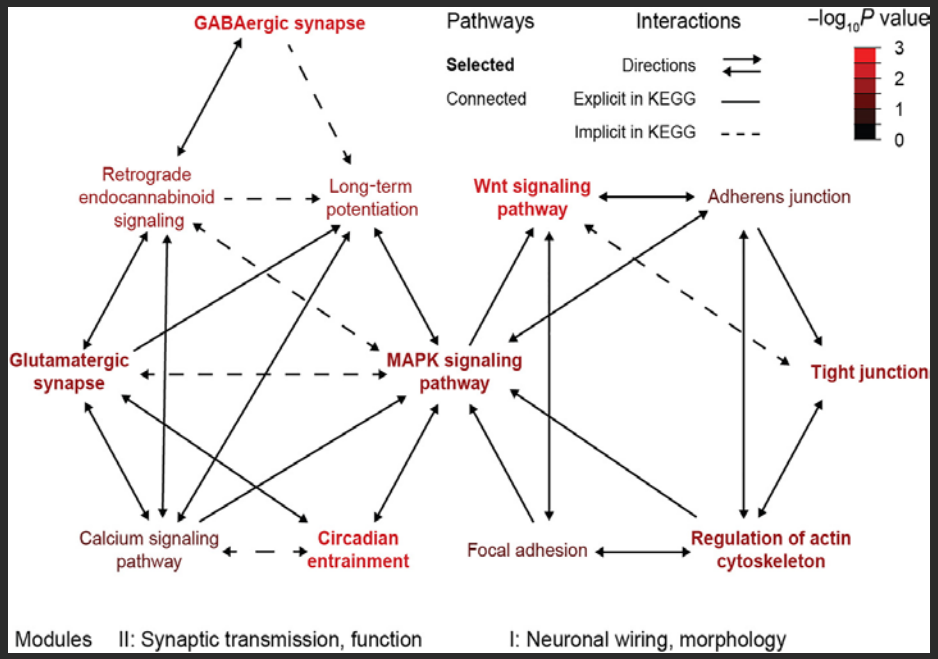
Findings*: Autistic subjects had smaller minicolumns whose dimensions varied according to neocortical area. The greatest difference between autistic and control groups was observed in area 44.

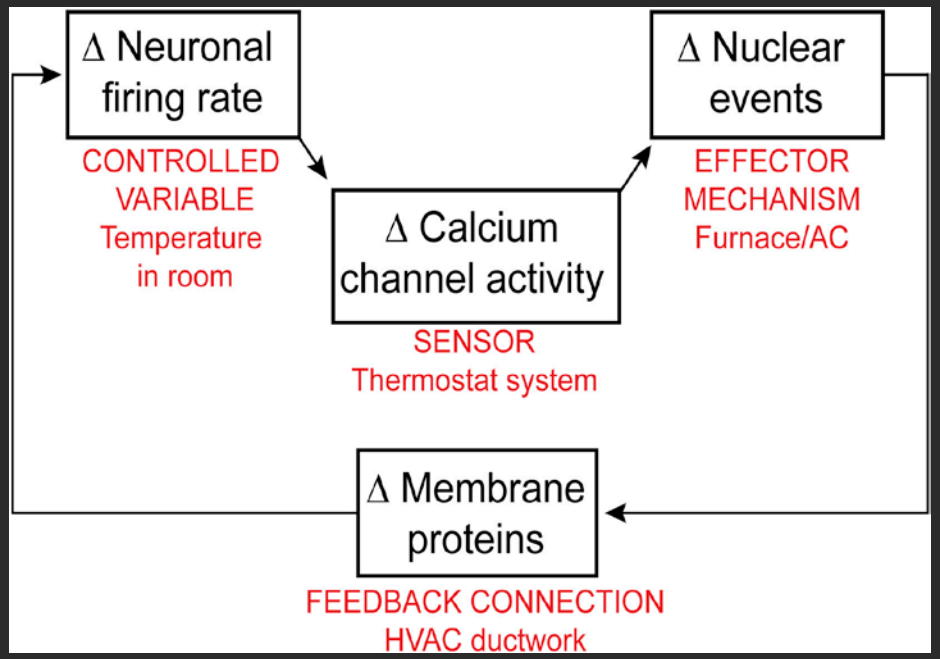
*M. Casanova, A. El-Baz, E. Vanbogaert, P. Narahari, and A. Switala, "A Topographic Study of Minicolumnar Core Width by Lamina Comparison between Autistic Subjects and Controls: Possible Minicolumnar Disruption Due to an Anatomical Element in-Common to Multiple Laminae," *Brain Pathology, vol. 20, no. 2, pp. 451–458, March 2010.*

Variation by Age?

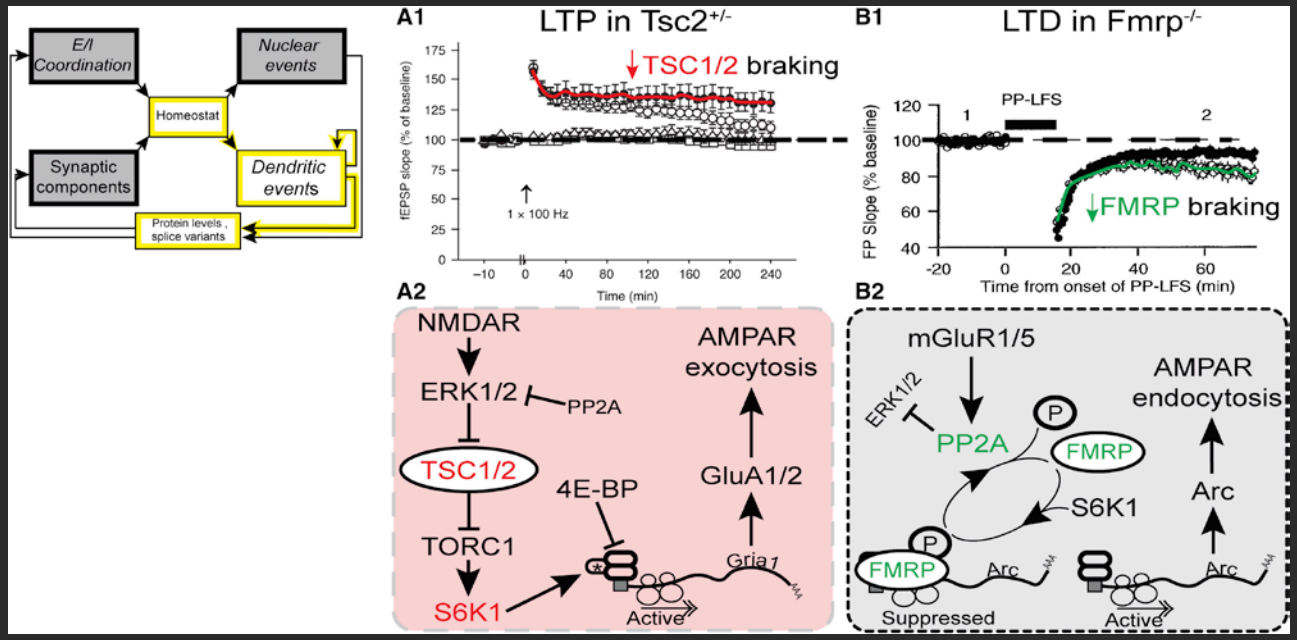


Superpathways of ASD Genes: Homeostatic Regulation





Large Effect Size Genes Impact GABA Signaling



Impacted Function of GABA Signaling

Genes:

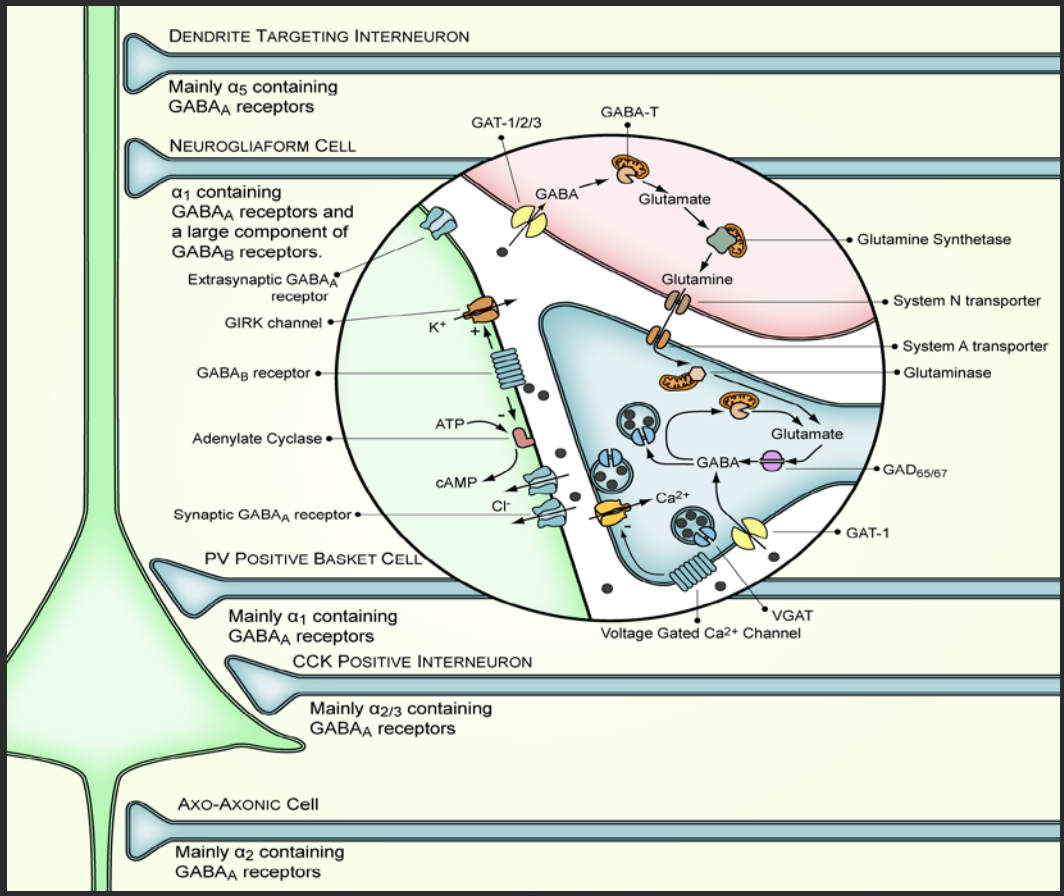
GABA transaminase

GABA transporters

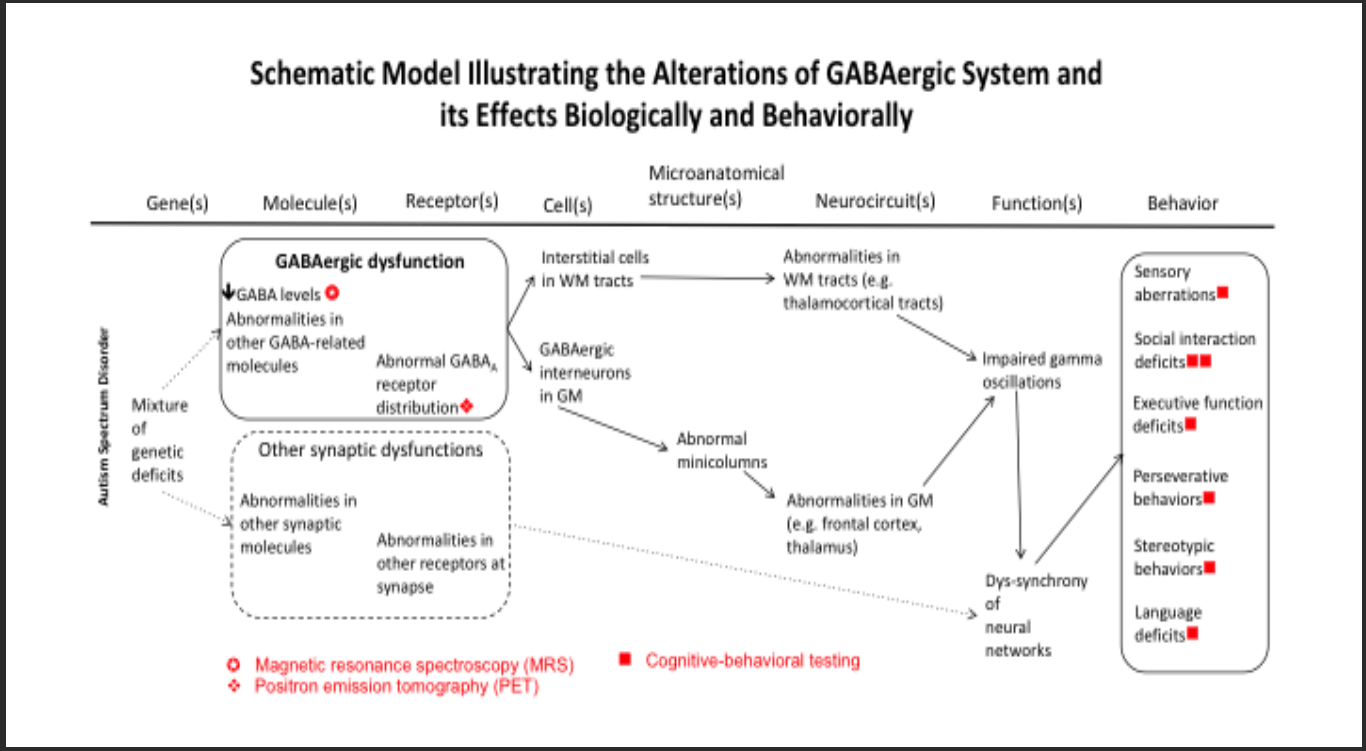
Gephyrin

$GABA_A$ Receptors

Voltage gated calcium channels



Impacted Function of GABA Signaling in ASD



Shared Neurobiology of ASD and Epilepsy

Both disorders largely involving the synapse

Both disorders of activity dependent pathways

Seizures can dysregulate autism-related protein cascades

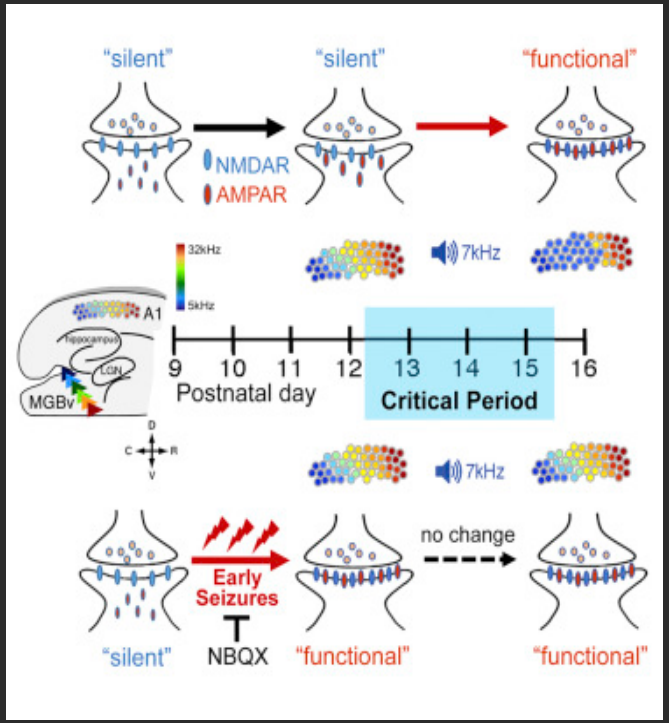
Evidence for epilepsy in human autism syndromes and animal models

Both occurring in critical periods

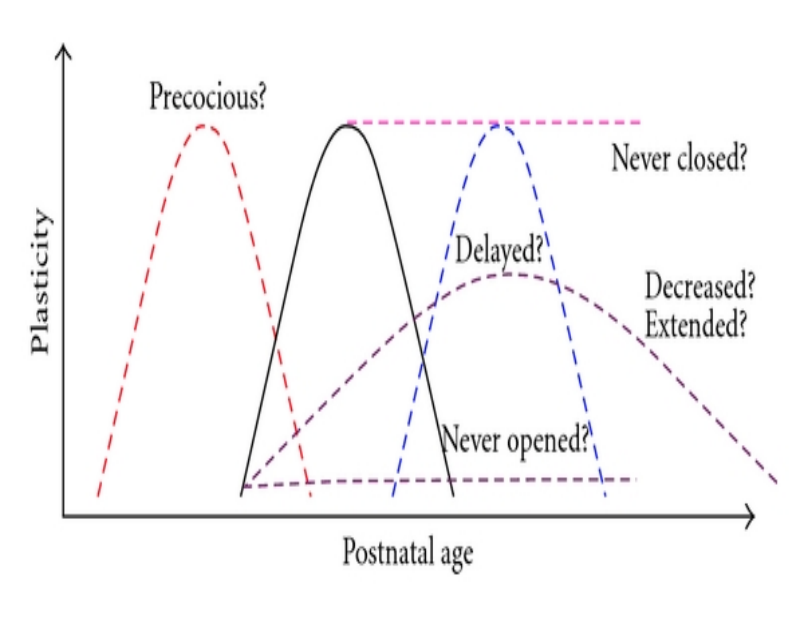
Both disorder have similar neuroanatomical and functional alterations of shared brain circuitry

Impact of Premature Activity on Critical Periods in Sensory Perception

- Critical Periods occur in many brain circuits relevant to ASD
- Humans
- Social, intellectual, cognitive skills: age 2 years
- Hearing: age 7 years
- Vision: age 8 years



Impact of Premature Activity on Critical Periods in ASD



A brain that is too plastic at the wrong times could result in noisy and unstable processing.

A brain that lacks plasticity early in life might remain hyper- or hypoconnected and unresponsive to environmental changes early in life.

Mechanisms: GABAergic or Excitatory

Shared Neurobiology of ASD and Epilepsy

Both disorders largely involving the synapse

Both disorders of activity dependent pathways

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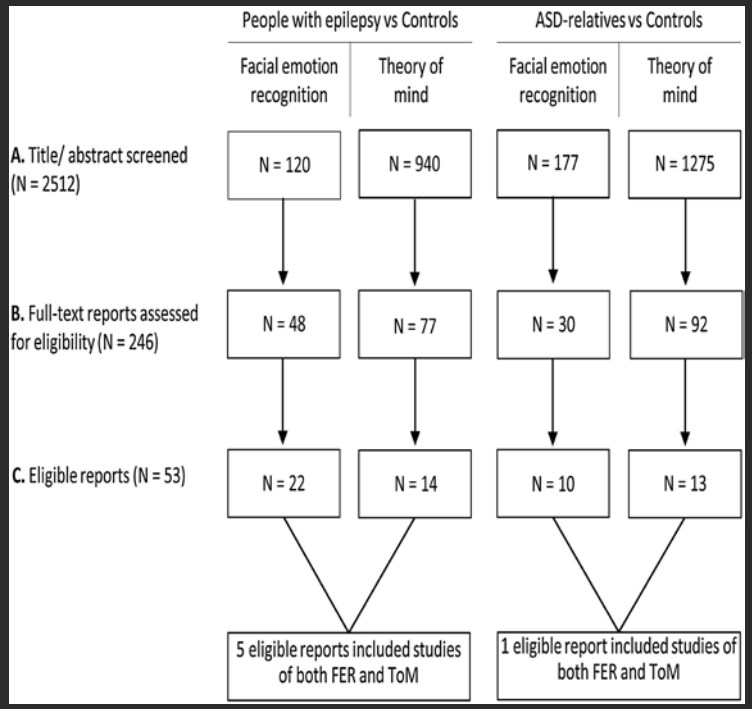
Both disorder have similar neuroanatomical and functional alterations of shared brain circuitry

Functional Connectivity MRI Studies



PWE had deficits in Theory of Mind and Facial Emotion Recognition Tasks > TD controls

Deficits in PWE were less than deficits of ASD relatives

Both groups were free of ID

Deficits in PWE groups were independent of epilepsy characteristics

Common histopathology: focal cortical dysplasia, heterotopias, increased dendritic spine density

Shared Neurobiology of ASD and Epilepsy

Both disorders largely involving the synapse

Both disorders of activity dependent pathways

Seizures can dysregulate autism-related protein cascades

Evidence for epilepsy in human autism syndromes and animal models

All in the setting of shared genetics

Both occurring in critical periods

Both disorder have similar neuroanatomical and functional alterations of shared brain circuitry

Thanks to Our Collaborators

UL Bioengineering

Dr Ayman El-Baz

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Dr Rekha Jagadapillai

South Carolina

Dr Manual Casanova

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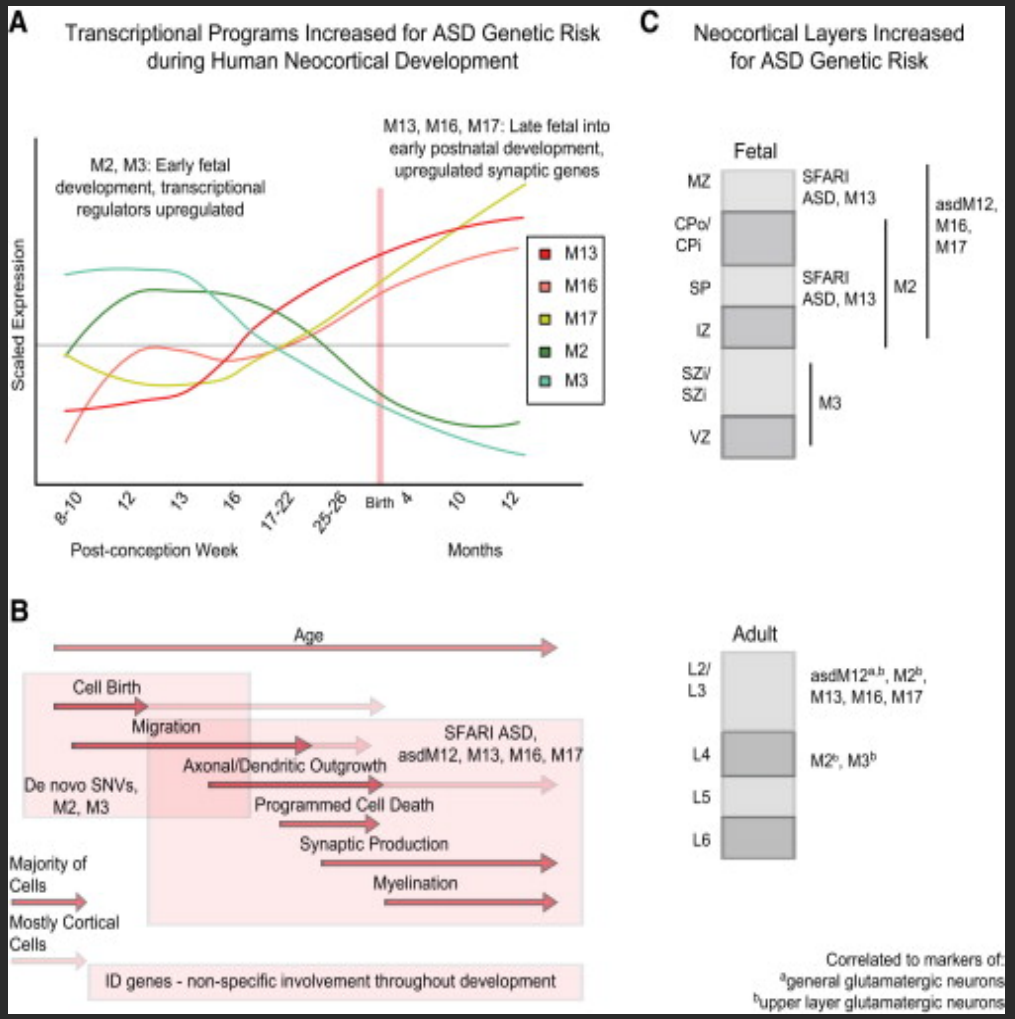
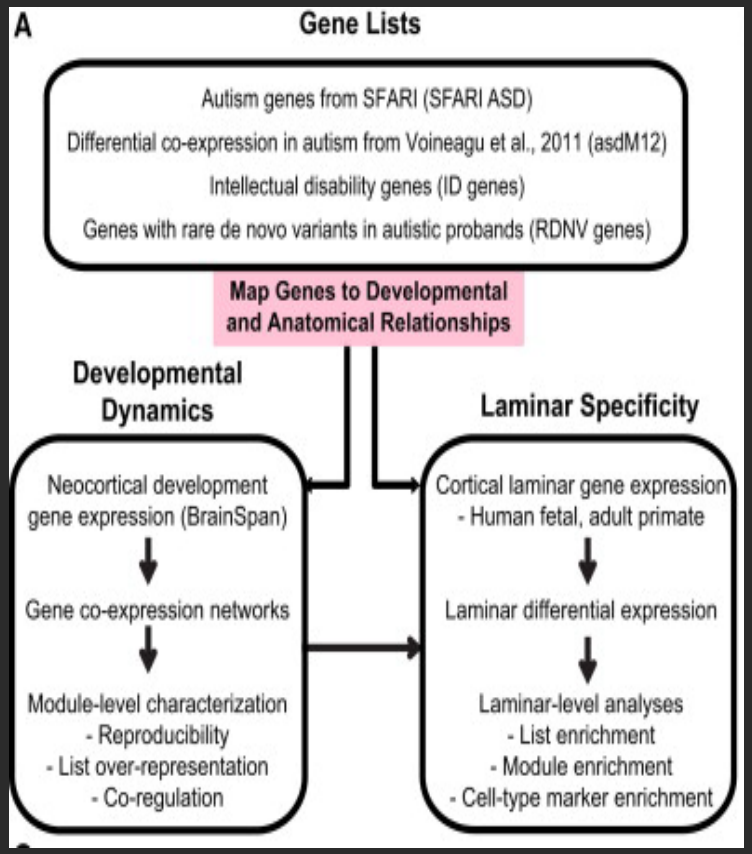
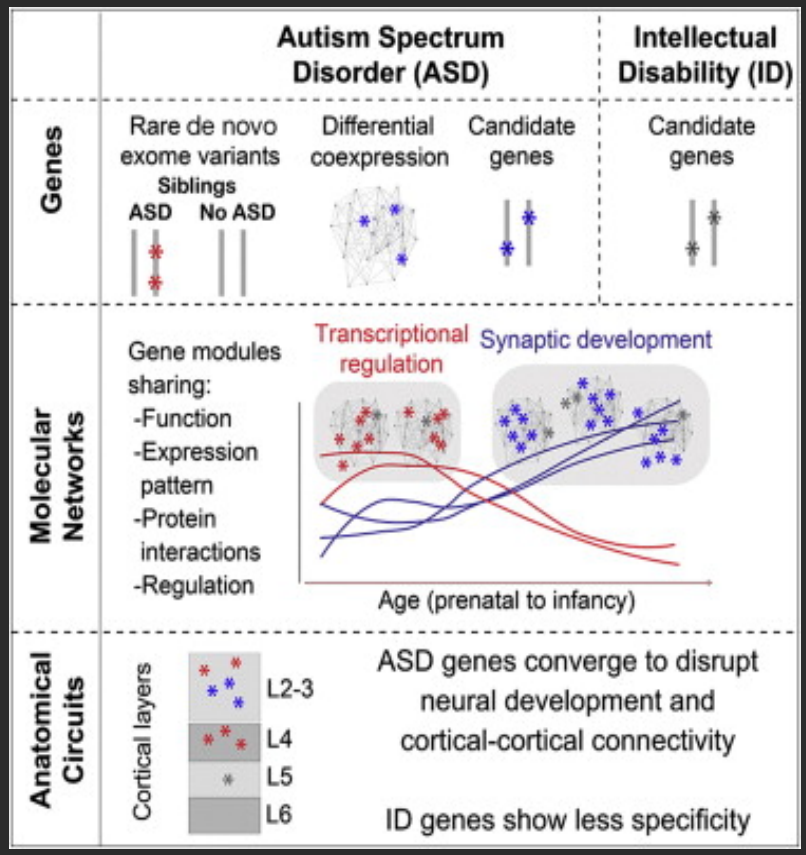

A
Transcriptional Programs Increased for ASD Genetic Risk during Human Neocortical Development
M2, M3: Early fetal development, transcriptional regulators upregulated
M13, M16, M17: Late fetal into early postnatal development, upregulated synaptic genes
Scaled Expression
M13
M16
M17
M2
M3
8-10
12
13
16
17-22
25-26
Birth
4
10
12
Post-conception Week
Months
B
Age
Cell Birth
Migration
Axonal/Dendritic Outgrowth
De novo SNVs, M2, M3
SFARI ASD, asdM12, M13, M16, M17
Programmed Cell Death
Synaptic Production
Myelination
Majority of Cells
Mostly Cortical Cells
ID genes - non-specific involvement throughout development
C
Neocortical Layers Increased for ASD Genetic Risk
Fetal
MZ
CPo/ CPi
SP
IZ
SZi/ SZi
VZ
SFARI ASD, M13
SFARI ASD, M13
M2
asdM12, M16, M17
M3
Adult
L2/ L3
L4
L5
L6
asdM12[a,b], M2[b], M13, M16, M17
M2[b], M3[b]
Correlated to markers of:
[a]general glutamatergic neurons
[b]upper layer glutamatergic neurons


A
Gene Lists
Autism genes from SFARI (SFARI ASD)
Differential co-expression in autism from Voineagu et al., 2011 (asdM12)
Intellectual disability genes (ID genes)
Genes with rare de novo variants in autistic probands (RDNV genes)
Map Genes to Developmental and Anatomical Relationships
Developmental Dynamics
Neocortical development gene expression (BrainSpan)
Gene co-expression networks
Module-level characterization
- Reproducibility
- List over-representation
- Co-regulation
Laminar Specificity
Cortical laminar gene expression
- Human fetal, adult primate
Laminar differential expression
Laminar-level analyses
- List enrichment
- Module enrichment
- Cell-type marker enrichment


Autism Spectrum Disorder (ASD)
Intellectual Disability (ID)
Genes
Rare de novo exome variants
Siblings
ASD
No ASD
Differential coexpression
Candidate genes
Candidate genes
Molecular Networks
Gene modules sharing:
-Function
-Expression pattern
-Protein interactions
-Regulation
Transcriptional regulation
Synaptic development
Age (prenatal to infancy)
Anatomical Circuits
Cortical layers
L2-3
L4
L5
L6
ASD genes converge to disrupt neural development and cortical-cortical connectivity
ID genes show less specificity

Epilepsy in Autism Spectrum Disorder: The Clinical Picture

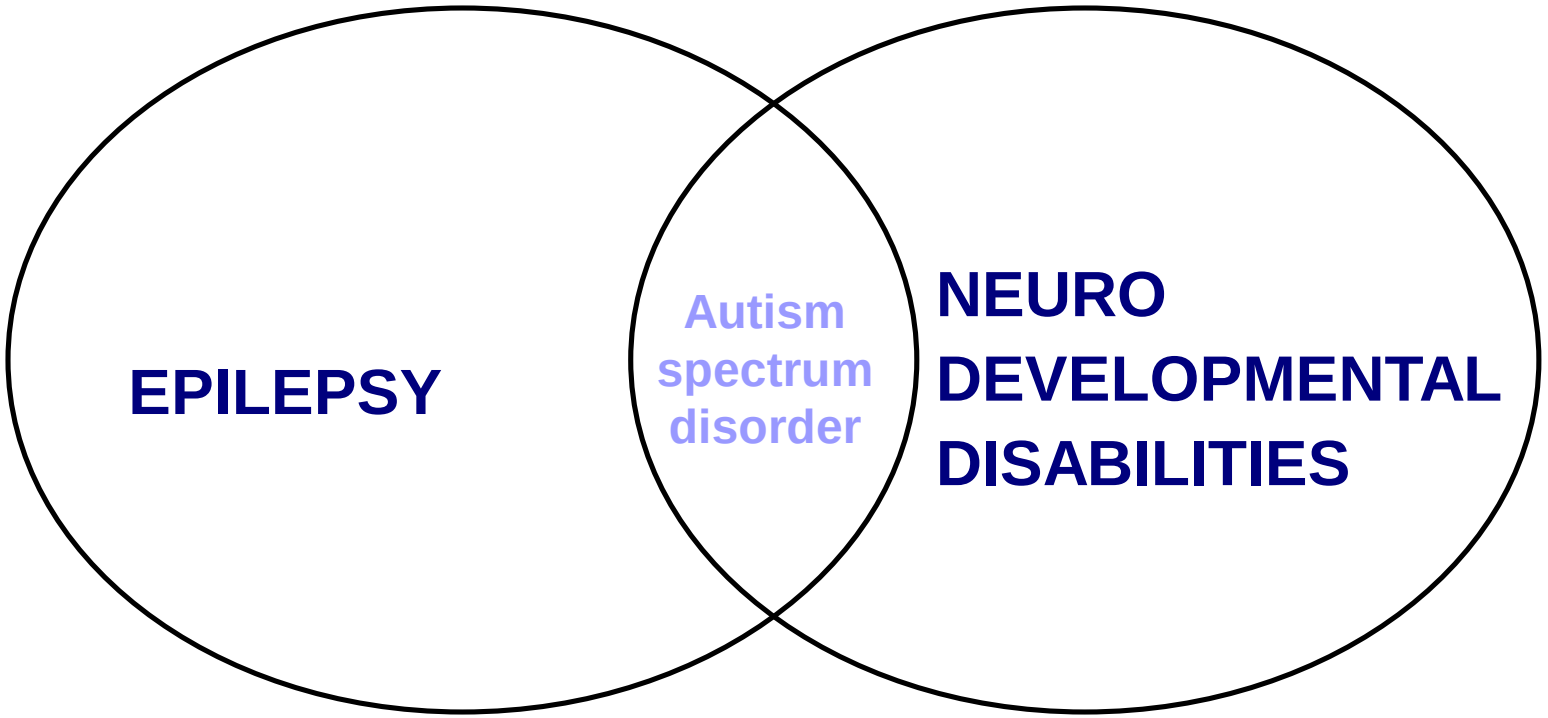
Sarah J Spence MD PhD
Boston Children's Autism Spectrum Center

Boston Children's Hospital
Until every child is well℠

Disclosures

- No relevant financial relationships
- Past and present grant funding from NIH, Simons Foundation, Nancy Lurie Marks Foundation, Autism Speaks, Cure Autism Now, MIND Institute
- Member of DSM 5 Neurodevelopmental Disabilities workgroup.
- Current Co-Investigator in Roche trial for ASD (not epilepsy)
- Consultant to Yamo pharmaceuticals for new compound (not epilepsy)

- *Apologies in advance for using "person first" language*

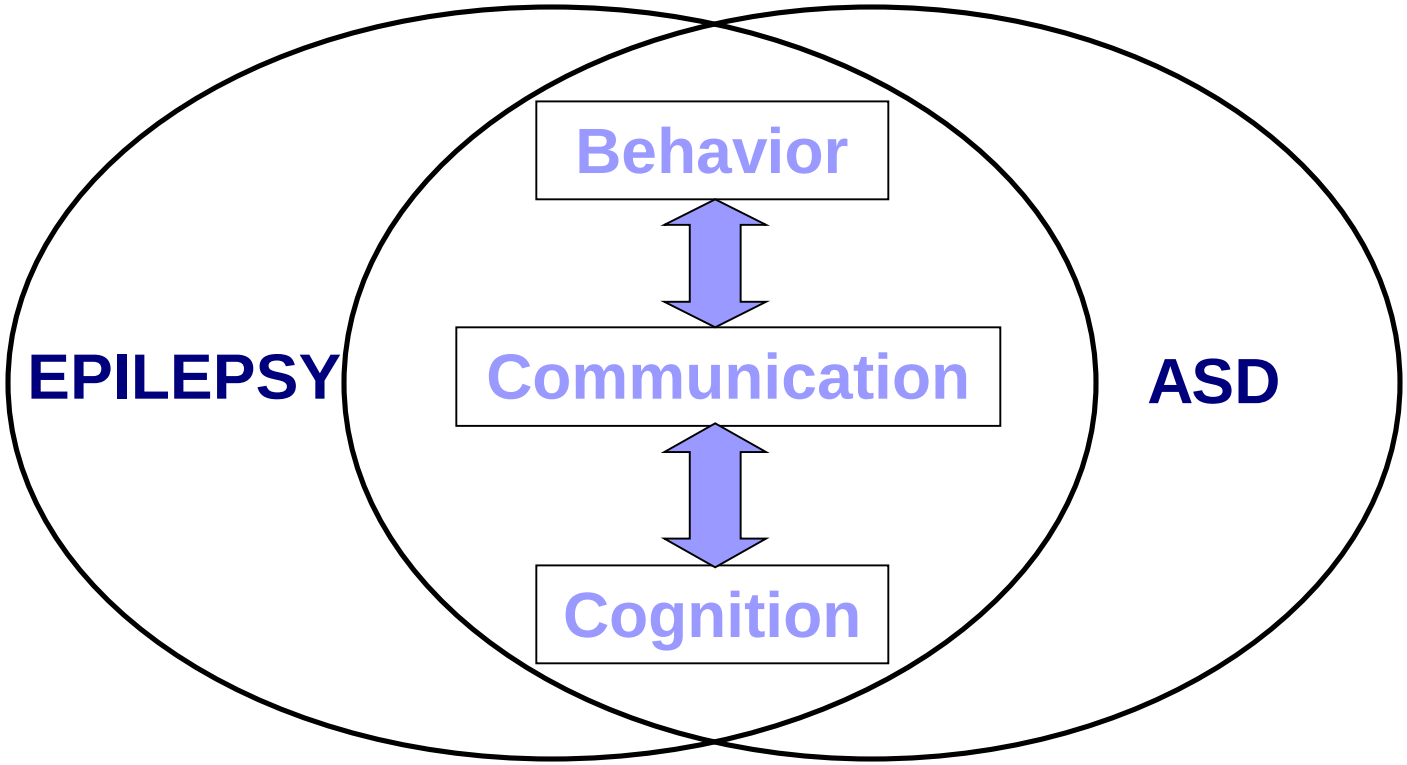


Association is frequent

Major impact on patient quality of life

Could represent common neural mechanisms

Overlapping phenotypes



Is there any causal relationship or is this epiphenomenon?

Epilepsy is increased in ASD

- But - rates very variable (5-45%)
- Probably dependent on sample characteristics:
  - SAMPLE ASCERTAINMENT
    - Population based samples have lower rates than clinic based
  - AGE
    - bimodal age of onset (early childhood & adolescence).
    - Bolton (2011) found >50% had seizure onset after age 10
  - NON-IDIOPATHIC or SYNDROMIC AUTISM
    - Neurogenetic syndromes or brain injury have more epilepsy.
  - IQ and LANGUAGE skills
    - Most studies show that lower IQ associated with epilepsy.
    - Some studies show language regression and poorer language skills predict epilepsy.

Variability in published reports

Citation	Sample size	Age	Ascertainment	Diagnosis	Syndromic	Epilepsy rate
Amiet 2008	2112		Mixed	Autism, PDD	yes	With intellectual disability: 21.4 % Without intellectual disability: 8%
Miles et al . 2005	233		Clinic based	Autism, Asperger's	yes	17% "essential" 39% "complex"
Canitano 2005	46	Mean 7.8 yrs	Clinic based	Autism, PDD	no	13%
Danie		Mean 25.5 yrs	Population Based	Autistic or "Autistic Like"	yes	38%
Hughes 2005	59	0.5-21 yrs	Clinic based	Autism	yes	46%
Gianotti 2008	104	30mo. -8 yrs	Clinic based	Autism or ASD	yes	19.4%
Hara 2007	130	18-35 yrs	Clinic based	Autism, PDD	no	17% (25% when 1 seizure included)
Bolton 2011	150	All adult	Prospective research cohort	ASD	yes	22%
Mouridsen 2011	118	All adult	Clinic/ population	ASD	no	25%
Kohane 2012	14,381 (2,393,778)	0-35 yrs	Hospital EMR	ASD	yes	19.4%
Suren 2012	1726 (731,318)	0-11 yrs	Population based	ASD	yes	11.2%

Effect of comorbidity (syndrome, ID)

Effect of age

Effect of ascertainment

Overlap between epilepsy syndromes and autism

Infantile Spasms

- High rates of intellectual disability with social communication deficits >> expected for IQ
- 10-15% of kids develop autism
- IS history in 6% of all ASD and up to 30% of ASD patients with epilepsy

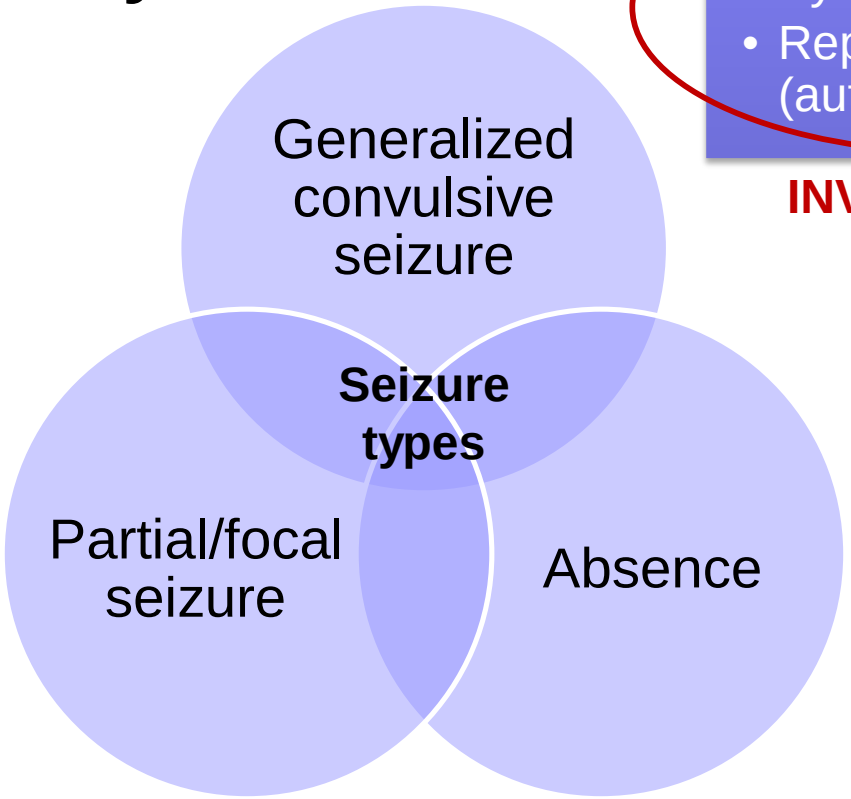
Tuberous Sclerosis Complex

- Very high rates of epilepsy and high rates of ASD (~40%)
- ASD higher in those with intellectual disability

Landau Kleffner Syndrome

- Language and behavioral regression
- EEG abnormalities

No single epilepsy syndrome



Seizure Behavior

- Unresponsiveness
- Eye deviation
- Repetitive behavior (automatisms)

INVOLUNTARY

Autism Behavior

- Not responding to name
- Peering from the corner of eyes
- Stereotypies

VOLUNTARY

Sometimes hard for even expert epileptologists to tell the difference between seizure and behavior

Epilepsy in ASD

- Treatment refractory epilepsy may be common *(Sansa et al., 2011)*
  - 34% treatment refractory
    - significantly earlier age of seizure onset
  - 39% with infrequent or difficult to categorize
  - 27% seizure free
- Epilepsy may increase mortality in ASD

  (Pickett et al., 2011)
  - data from California DDS
  - 5-6x higher mortality in those with ASD plus epilepsy than ASD alone
- Epilepsy may impact outcome of early intervention *(Eriksson et al, 2013)*
  - Epilepsy (among other medical problems) associated with lower adaptive function scores

Risk factors

Intellectual disability	• Most (but not all) show epilepsy associated with intellectual disability • Meta-analysis of 10 studies epilepsy in 21% with ID vs 8% without *(Amiet et al., 2008)*
Co-morbid conditions: syndromic or non-idiopathic autism	• 2-5 x increased risk *(Pavone et al., 2004; Miles et al., 2005; Parmegianni et al., 2010)*
Female gender	• Most studies (but not all) show higher epilepsy in females • Meta-analysis epilepsy in 34% of females vs 18% of males *(Amiet et al., 2008)*
?? Developmental regression	• Several studies suggest an association (*Kobayashi & Murita, 1998; Hrdlicka et al., 2004; Giannotti et al., 2004; Parmeginanni et al., 2010)* • Other studies show no association (*Tuchman & Rapin, 1997; Canitano et al., 2005; Hara, 2007)*
Pre and perinatal factors	• Finish birth cohort study n=4705 • Prematurity, birth weight, low APGARS *(Jokiranta et al,. 2014)*

Relationship between epilepsy and ASD clinical profile

- Less is known
  - Hara 2007 retrospective clinical review
    - lower social scores and more medication use
  - Turk et al 2009 age and IQ matched sample
    - Increased motor & adaptive behavior deficits
    - One item in nonverbal communication: “stares too long and too hard”
    - Several items on social interaction scale: difficulties with peers, psychological barriers, and socially shocking behaviors.
  - Smith & Matson 2011
    - Epilepsy makes everything worse – in ASD and non-ASD developmental delay.

But are these associations independent?

- Viscidi et al., 2013 PLOS-ONE
  - Large study designed to examine the clinical characteristics of epilepsy and ASD
  - Sample of convenience
    - Large data sets available from genetic studies
      - AGRE, Boston Autism Consortium, Simons Simplex Collection
    - Strengths
      - Good ASD diagnostic data
      - Detailed ASD and related behavioral phenotyping data
    - Weaknesses
      - Turns out mediocre epilepsy data
  - Initial analysis showed significant effects of:
    - Regression, Language, IQ, Adaptive function, ASD severity

BUT … Most effects disappear after adjusting for IQ

	Model 1: Unadjusted		Model 2: Adjusted for FSIQ		Model 3: Fully Adjusted	
Characteristic	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Age						
9 years and younger	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
10 years and older	3.05 (2.29–4.06)	<.001	2.40 (1.51–3.82)	<.001	2.35 (1.42–3.88)	<.001
Gender						
Male	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
Female	1.86 (1.35–2.56)	<.001	1.43 (0.82–2.49)	0.21	1.36 (0.77–2.43)	0.29
Cognitive Ability						
Full Scale IQ Score	0.51 (0.4 1–0.63)	<.001	0.51 (0.41–0.63)	<.001	0.53 (0.39–0.73)	<.001
Adaptive Functioning						
Adaptive Behavior Composite Score	0.52 (0.45–0.61)	<.001	0.80 (0.58–1.10)	0.17	0.98 (0.70–1.37)	0.89
Language						
Meaningful Use of Single Words, Two-Word Phrases, or Three-Word Phrases	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
Fewer than 5 Words	2.00 (1.39–2.87)	<.001	0.75 (0.27–2.05)	0.57	0.75 (0.27–2.13)	0.59
Developmental Regression						
No Loss of Language or Skills	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
Loss of any Language or Skills	1.93 (1.45–2.57)	<.001	1.05 (0.64–1.72)	0.86	1.14 (0.69–1.89)	0.60

Abbreviations: OR, odds ratio; CI, confidence interval; FSIQ, full scale IQ score.
[a]Genetic Collaborative Samples (AGRE, SSC, and AC) combined.
Model 1: Individual models for each variable.
Model 2: Individual models for each variable, adjusted for full scale IQ score only.
Model 3: Single model adjusted for all variables.
Odds ratios for full scale IQ score and adaptive behavior composite score represent the odds of epilepsy for a one standard deviation increase.
doi:10.1371/journal.pone.0067797.t006

Treatment

- Anti-Seizure drugs dependent on:
  - seizure type
  - side effect profile
  - practicalities
    - formulation, dosing schedule, need for blood draws in monitoring, etc
- All seizure medications can have behavioral and cognitive effects … so practitioners need to be careful in children who already show impairment.
- New cannabis data is sparking a lot of interest
  - GWPharma Epidiolex trial in severe epilepsy *(Devinsky et al. 2017)*
    - Lots of interest in using CBD in autism for behavior
    - Safety and Tolerability of GWT42006 (cannabidivarin) in subjects with drug resistant epilepsy and autism *(U of Louisville, G Barnes PI)*
      - Measuring both behavioral and seizure outcomes

In reality: Probably multiple kinds of epilepsy in autism

When early onset seizures actually contribute to autism

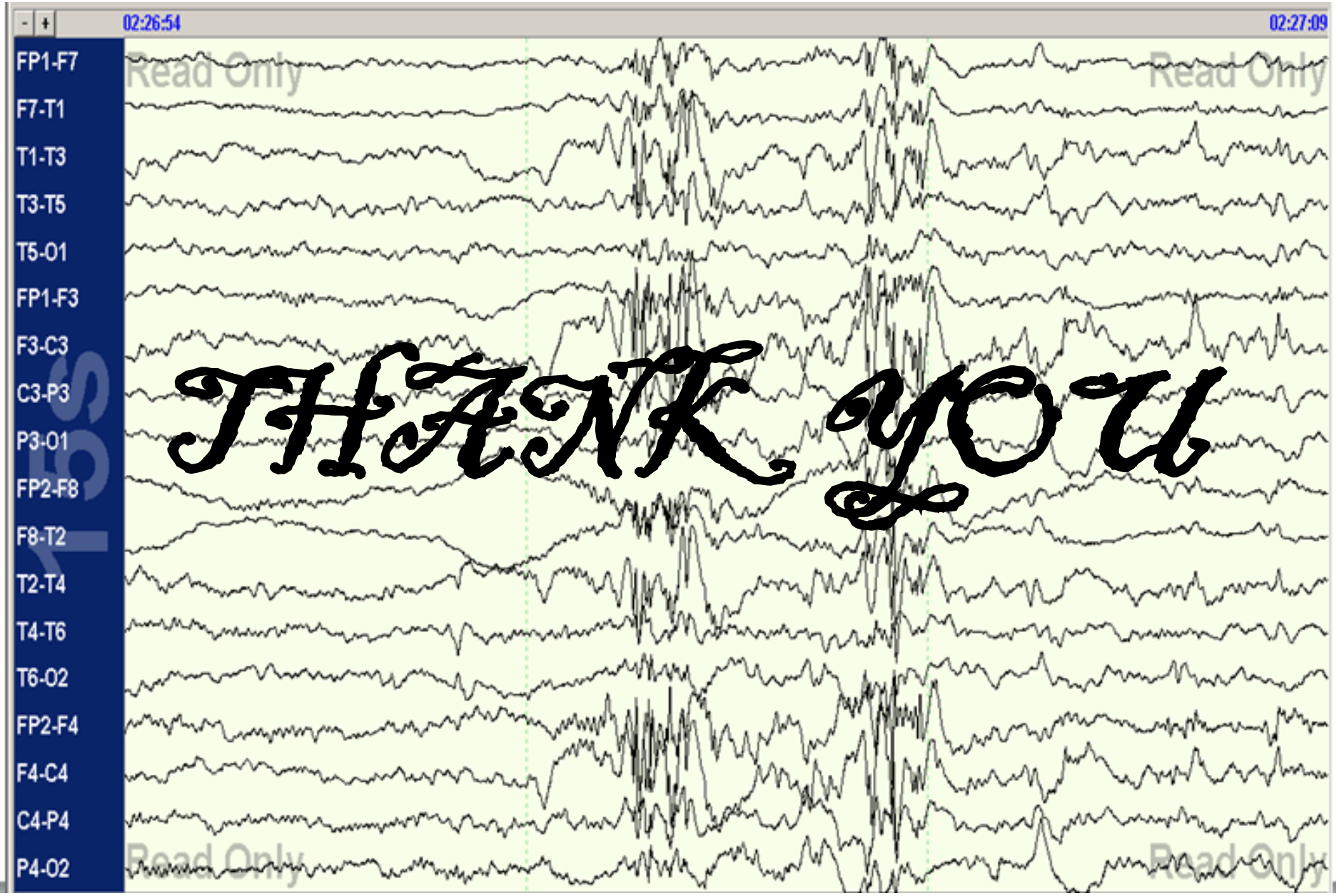
- infantile spasms

When other disorders co-exist

- neurogenetic syndromes (eg Tuberous Sclerosis, Fragile X, 15q duplication)
- neurologic injury (eg CNS malformation or stroke)
- severe intellectual disability

True idiopathic autism

- whatever that means…


02:26:54
02:27:09
FP1-F7
F7-T1
T1-T3
T3-T5
T5-O1
FP1-F3
F3-C3
C3-P3
P3-O1
FP2-F8
F8-T2
T2-T4
T4-T6
T6-O2
FP2-F4
F4-C4
C4-P4
P4-O2
Read Only
Read Only
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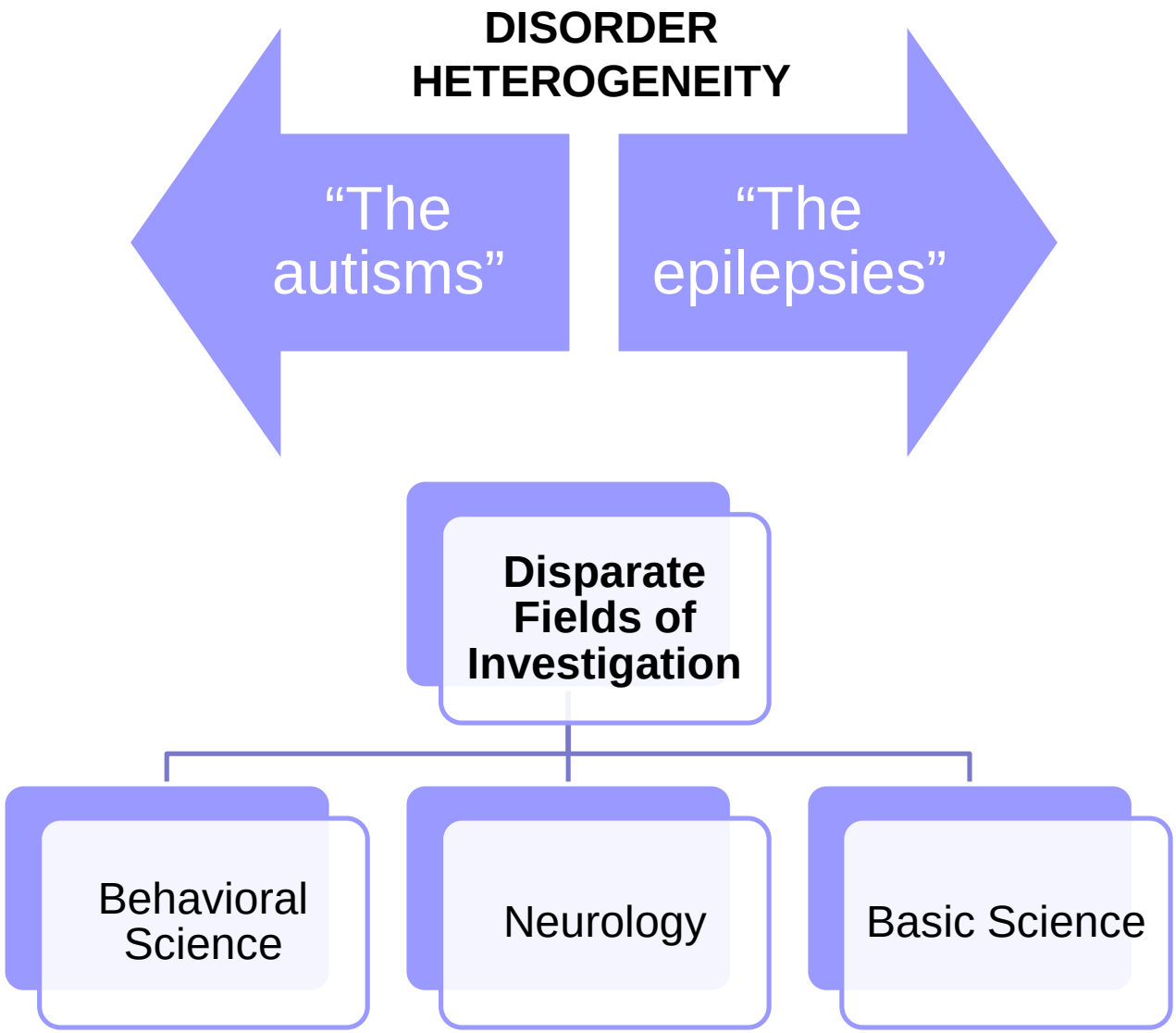
THANK YOU

SOME WAYS TO INTRODUCE DISCUSSION

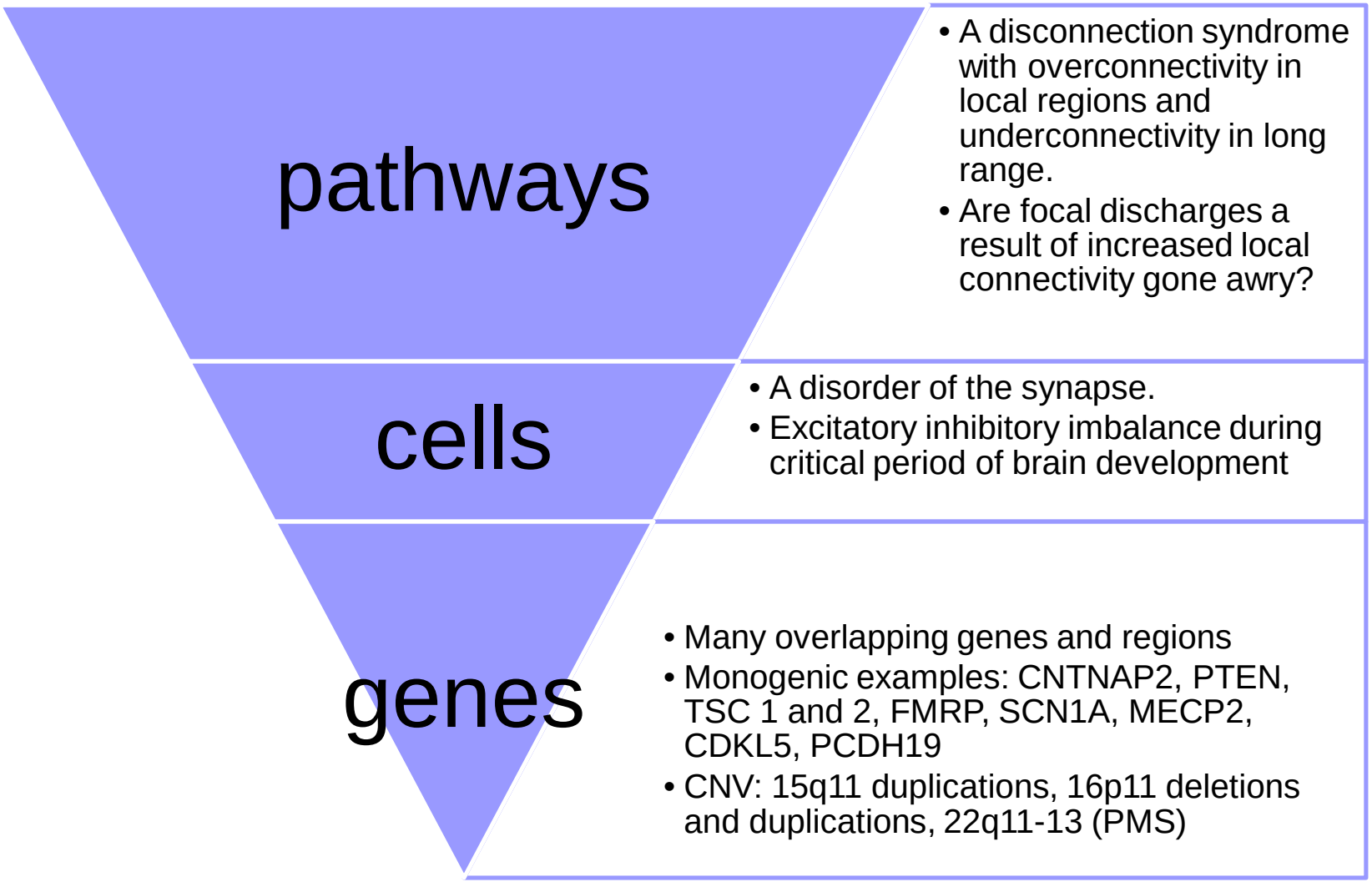
Challenges to research



Bedside to Bench and Back Translational Research

- Bedside -- Clinical research questions:
  - Effects of
    - Severity (of both autism and epilepsy)
    - Development (which comes first – the autism or the epilepsy?)
  - Relationship specifically to ASD symptoms?
    - Is there a causal relationship or is this epiphenomenon?
    - What is the role for intervention?

Translational Research: Are there common mechanisms?



Translational Research: Data from animal models

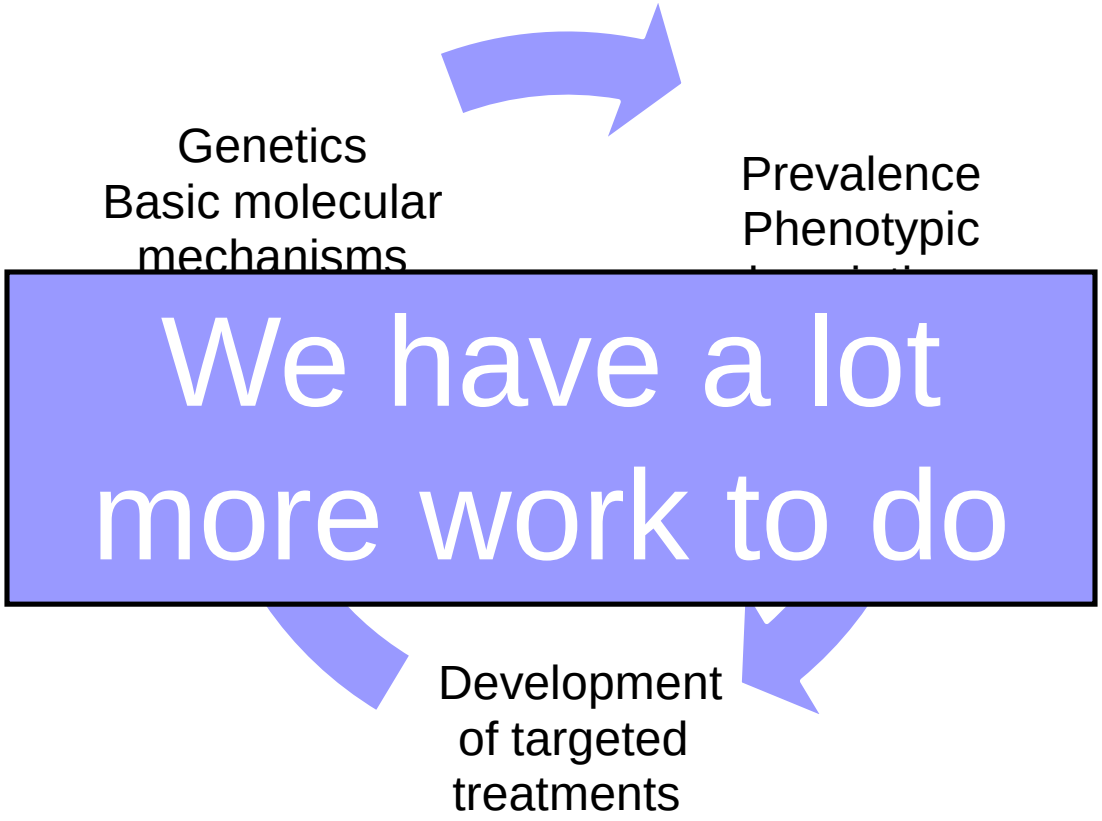
TSC Alert

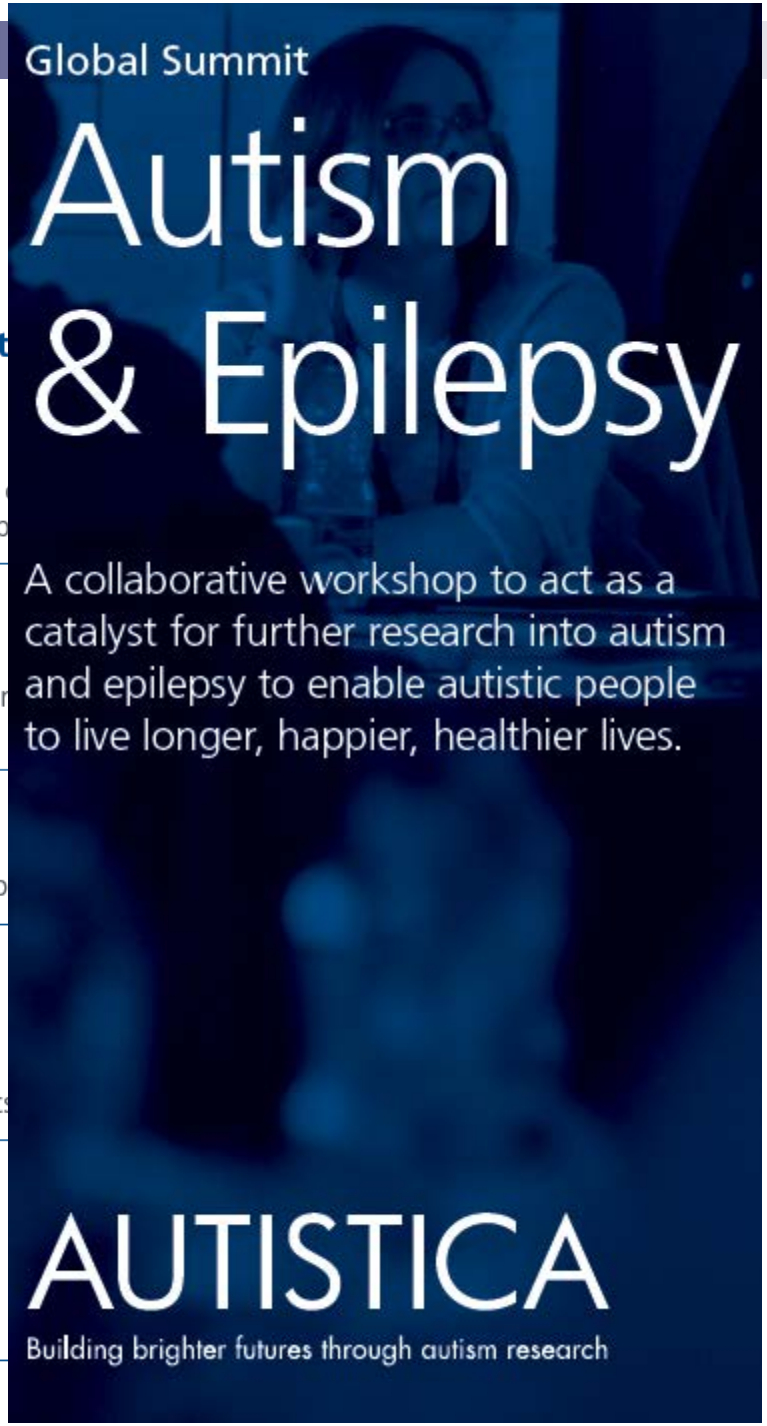
PREVeNT Trial Enrolling Participants

The Preventing Epilepsy Using Vigabatrin in Infants with Tuberous Sclerosis Complex (PREVeNT) trial, led by Martina Bebin at the University of Alabama Birmingham, is continuing to enroll participants at seven sites across the country.

The central hypothesis of this Phase IIb trial, supported by a $7 million grant from NINDS, is that early identification of electroencephalography (EEG) biomarkers and early treatment versus delayed treatment with vigabatrin in infants with tuberous sclerosis complex (TSC) will have a positive impact on developmental outcomes at 24 months of age. It would also prevent or lower the risk of developing infantile spasms and refractory seizures. This preventative approach would be expected to result in more favorable long-term cognitive, behavioral, developmental and psychiatric outcomes and significantly improve overall quality of life.

Autism & Epilepsy:
Moving forward





Research themes generated at

1. Distribution and determinants autism and co-occurring epilep
2. Understanding epilepsy onset i autism
3. Medication and onset of epilep
4. Epilepsy medication side effect
5. Autism characteristics versus epilepsy seizures
11. Genetics – understanding seizures
12. Risk factors for premature death
13. Premature death education

Discussion

Lunch

Meeting of the IACC

Afternoon Agenda

1:30 **Autism and Gastrointestinal Disorders**

Timothy Buie, M.D.,
Attending Physician, Division of Gastroenterology, Hepatology and Nutrition, Boston Children's Hospital, and Assistant Professor of Pediatrics, Harvard Medical School

2:15 **Autism Spectrum Disorder and Sleep – Identifying Challenges and Finding Solutions**

Beth Ann Malow, M.D., M.S.,
Burry Chair in Cognitive Childhood Development, Professor of Neurology and Pediatrics, Vanderbilt Kennedy Center, and Director, Vanderbilt Sleep Disorders Division

3:00 **Break**

Meeting of the IACC

Afternoon Agenda

3:10 **Patient – Provider Interactions**

Healthcare Experiences of Children with Autism: Opportunities for Improvement

Micah Mazurek, Ph.D.
Associate Professor of Education, Curry School of Education, University of Virginia

Meeting of the IACC

Afternoon Agenda

3:25 **Healthcare Experiences of Adults on the Autism Spectrum: Challenges and Solutions**

Christina Nicolaidis, M.D., M.P.H.
Professor and Senior Scholar in Social Determinants of Health, School of Social Work, Portland State University, and Adjunct Associate Professor, Division of General Internal Medicine, Oregon Health and Science University

Dora Raymaker, Ph.D.
Research Assistant Professor, Portland State University; Co-Director, Academic Autism Spectrum Partnership in Research and Education (AASPIRE)

Meeting of the IACC

Afternoon Agenda

4:20	**Working Group Discussion**
5:00	**Adjournment**

Gastrointestinal Problems in Autism

NIH/IACC 09/27/2018

Timothy Buie MD
Boston Children's Hospital/
Harvard Medical School

GI/Autism Issues: 1998

- Prior to 20 years ago there was sparse research into GI or dietary problems in autism
- In 1998, papers discussing possible GI links were published including discussion about colitis, possible dietary factors, intestinal permeability issues and even possible treatments
- GI clinics were filled with individuals with autism but few GI providers had training or experience with autism and there wasn't guidance available for them to help

2018

- We accept GI problems are common and may be more common than the general pediatric population. Our findings didn't find significant differences in the kind of problems seen but we were looking…
- Although Pediatricians and GI doctors are aware of these issues it is not clear if providers are confident in evaluating these individuals or confident who to work up if lacking obvious symptoms

GI/Autism Issues: How prevalent?

Studies quote an **8-90%** prevalence of GI issues in autism. That is useless data Why?

- Early studies had enrollment bias identifying far too few or too frequent cases. Good writers need to stop quoting bad studies

Prevalence of GI issues in autism

- Cross-sectional study; 3 groups-50 per group
  - GI issues identified in each group:
    70% children with ASD
    42% children with developmental disorder
    28% children with typical development

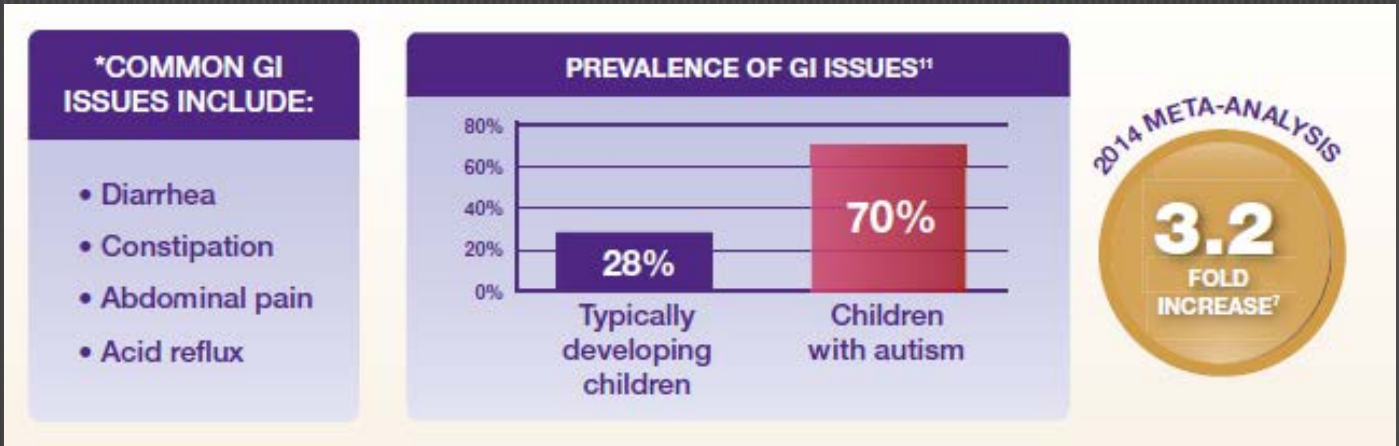
Valicenti-McDermott et al. *J Dev Behav Pediatr*. 2006 Apr;27(2 Suppl):S128-36.

Thoughts on the GI Literature

- In May 2008, a consensus meeting of experts was brought to Boston in an attempt to review and vet the quality of the literature and research regarding Autism and GI issues Sponsored by Easter Seals of Oregon, The Autism Society (of America), The Autism Research Institute
- The resulting consensus papers have been published in Pediatrics, 23 consensus statements issued by 27 experts
- http://pediatrics.aappublications.org/cgi/content/full/125/Supplement_1/S1
- http://pediatrics.aappublications.org/cgi/content/full/125/Supplement_1/S19

Prevalence of GI issues in autism

- Meta-analysis (1980-2012) of 15 qualified studies
- Number of pooled patients = 961



McElhanon BO et al. Pediatrics. 2014 May;133(5):872-83

So, newer data support a more consistent prevalence of **45-70%** of children with autism have GI issues.

Autism and GI Issues: Historical Review

Early dietary or GI discussions in autism were **hypotheses** of causation:

Opioid Peptide Theory: Peptides from milk (casein) and wheat (gluten) caused childhood schizophrenia (autism).

Reichelt KL. 2002. *Biol Psychiatry*. 1991 Mar 1;29(5):515-7.
Shattock P et al. 2002. *Expert Opin Ther Targets*. 2002 Apr;6(2):175-83.

Autistic Enterocolitis: Intestinal inflammation caused intestinal permeability problems and immune disruption.

Wakefield AJ. *Lancet.* 1999 Sept 11;354(9182):949-50.
Wakefield AJ et al. Am J Gastroenterol. 2000 Sep;95(9):2285-95.
Retraction in: *Am J Gastroenterol*. 2010 May;105(5):1214.

GI Findings in Children with Autism

Others have built on the suggestion that many children with autism suffering GI symptoms have a variety of GI findings including:

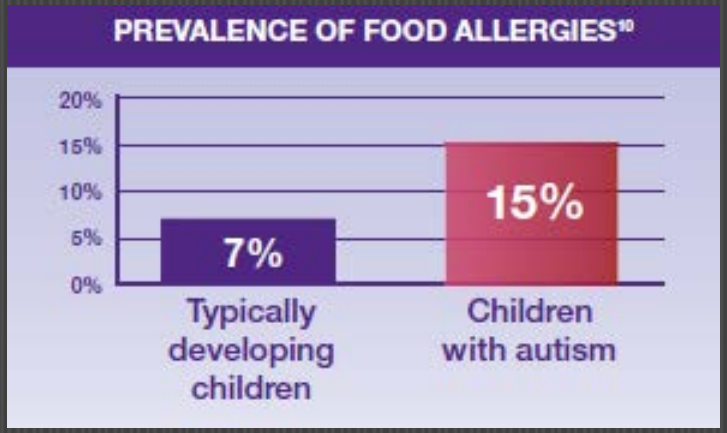
Inflammation	▪ Horvath K et al. Curr Gastroenterol Rep 2002 Jun; 4(3): 251-8.
Increased intestinal permeability	▪ D'Eufemia P et al. Acta Paediatr 1996 Sep;85(9):1076-9.
Impaired digestion of carbohydrates	▪ Horvath K et al. Curr Gastroenterol Rep 2002 Jun;4(3):251 -8. ▪ Kushak RI et al. Autism. 2011 May;15(3):285-94. ▪ Williams BL. PLoS ONE 2011 6(9): e24585.
Disruption of typical microbiota	▪ Finegold SM et al. Anaerobe. 2010 Aug;16(4):444-53. ▪ Williams BL. PLoS ONE 2011 6(9): e24585. ▪ Kang DW, el al. PLoS One. 2013 Jul 3;8(7):e68322.
Altered immune response to inflammation	▪ Ashwood P et al. Clin Dev Immunol. 2004 Jun;11(2):165-74

Food Allergy/Sensitivity

Findings	References
5-8% pediatric food allergy prevalence	Gupta RS, et al. J Pediatr.2011; 128.
Food allergy was reported in 36% of 36 children with ASD	Lucarelli S et al. Panminerva Med. 1995 Sep;37(3):137-41.
Families report their children with ASD had a food allergy or sensitivity in over 40%	Horvath K et al. Curr Gastroenterol Rep. 2002 Jun;4(3):251-8.
Higher frequency of IgE mediated food allergy in children with ASD compared to unaffected siblings	Trajkovski V et al. Focus Autism Other Dev Disabl. 2008;23: 176–185.

Food Allergy in Autism

- Large, population-based case-control study (CHARGE); maternal reporting of asthma and allergies



Lyall K et al. *Autism Res*. 2015 Oct;8(5):567-74.

Feeding Disorders

- Multi-factorial issues well described:
  - 1) Rigid, perseverative behavior could be a core autism component
  - 2) Textural sensitivity could be related but often occurs associated with GE Reflux and can be seen with oral allergy response.
  - 3) Avoidant restrictive food intake disorder (ARFID) is a DSM V diagnosis seen commonly in children with autism

Nutritional Deficiencies in Autism

- Reviews are inconsistent but include concern for inadequate intake of key nutrients:

RECOGNIZED NUTRIENT DEFICIENCIES IN CHILDREN WITH AUTISM	
Protein	Fiber
Iron	Calcium
Zinc	Vitamin A
Vitamin B_{12}	Vitamin C
Vitamin D	Niacin

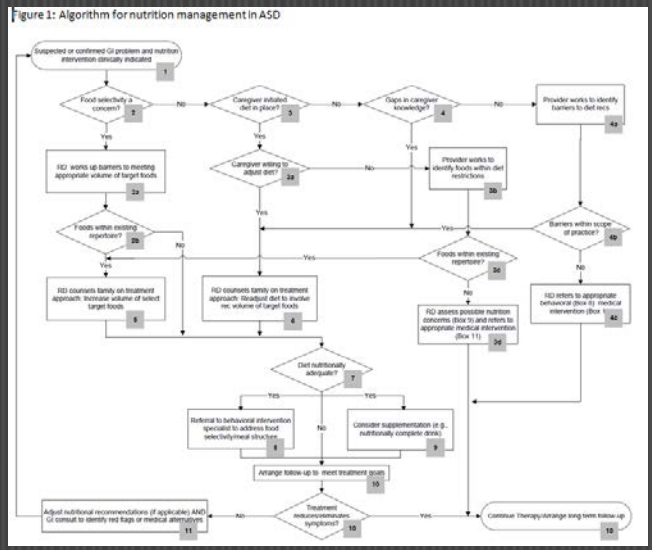
Bandini LG et al. *J Pediatr.* 2010 Aug; 157(2):259.
Hyman SL et al. Pediatrics. 2012 Nov;130 S2:S145.
Sharp WG et al. *J Autism Dev Disord.* 2013 43:2159.

Article in Press

Nutrition Management of Gastrointestinal Symptoms in Children with Autism Spectrum Disorder: Guideline from an Expert Panel *J Acad Nutr Diet 2015*

Rashelle C. Berry, MPH, MS, RD, CSP, Patricia Novak, MPH, RD, Nicole Withrow, PhD, RD, Brianne Schmidt, RD, Sheah Rarback, MS, RD, Sharon Feucht, MA, RD, Kristen K. Criado, PhD, William G. Sharp, PhD

Published Online: July 09, 2015



Comparative GI Findings

- **Evaluation of Intestinal Function in Children With Autism and Gastrointestinal Symptoms** Kushak, Rafail I.; Buie, Timothy M. et al Journal of Pediatric Gastroenterology & Nutrition: May 2016 - Volume 62 - Issue 5 - p 687–691
- **No difference in GI findings of 61 children with autism compared to 50 unaffected children undergoing endoscopy.**
- **This included evaluation of inflammation, intestinal permeability and disaccharide activity**

Autism and Causation?

Could GI issues CAUSE autism?

- Environmental/nutritional/microbiome associated factors modulating genetically predisposed individuals

- An inflammation model where an inflammatory process (colitis, allergy, infection) releases chemical or immune mediators that affect brain function (Vargas 2005, Welch 2005)

Gut/Brain Connections

- Intestinal microbiome disruptions may alter behavior, immune responses, intestinal permeability, metabolic by products which may affect nervous system communication
- Intestinal microbiome disruptions exist in the autism population
- Diet change and early exposure to antibiotics may alter microflora and metabolome

Abnormal Microbiome in Autism

- A growing number of studies point to altered microbiome in populations of children with autism.
- Potential Etiologic Factors of Microbiome Disruption in Autism, Clinical Therapeutics, Buie, T Volume 37 Number 5, 2015
- Analysis of the Duodenal Microbiome in Autistic Individuals: Association With Carbohydrate Digestion Rafail I. Kushak, Harland S. Winter, Timothy M. Buie, et al JPGN 2017;64: e110–e116)

Probiotics Affect Brain Function

Consumption of fermented milk product with probiotic modulates brain activity.

- (Bifidobacterium Lactis, Streptococcus thermophiles, Lactobacillus bulgaricus, and Lactococcus lactis)

Gastroenterology. 2013 Jun;144(7):1394-401, 1401.e1-4. doi: 10.1053/j.gastro.2013.02.043. Epub 2013 Mar 6. Tillisch K[1], Labus J, Kilpatrick L, Jiang Z, Stains J, Ebrat B, Guyonnet D, Legrain-Raspaud S, Trotin B, Naliboff B, Mayer EA

Mouse Models

Microbiota Modulate Behavioral and Physiological Abnormalities Associated with Neurodevelopmental Disorders

Elaine Y. Hsiao,[1,2,*] Sara W. McBride,[1] Sophia Hsien,[1] Gil Sharon,[1] Embriette R. Hyde,[3] Tyler McCue,[3] Julian A. Codelli,[2] Janet Chow,[1] Sarah E. Reisman,[2] Joseph F. Petrosino,[3] Paul H. Patterson,[1,4,*] and Sarkis K. Mazmanian[1,4,*]

Cell 2013

Microbiome 2017 5:10 DOI: 10.1186/s40168-016-0225-7

Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study

- Dae-Wook Kang1†, James B. Adams2†, Ann C. Gregory3,15†, Thomas Borody4, Lauren Chittick5,15, Alessio Fasano6,
- Alexander Khoruts7,8,9, Elizabeth Geis2, Juan Maldonado1, Sharon McDonough-Means10, Elena L. Pollard2,
- Simon Roux5,15, Michael J. Sadowsky8,11, Karen Schwarzberg Lipson12, Matthew B. Sullivan3,5,15,16*,
- J. Gregory Caporaso12,13* and Rosa Krajmalnik-Brown1,14*

Autism Consensus Statements

- **Key Statement (Statement 1)**: Individuals with ASDs who present with GI symptoms **warrant a thorough evaluation**, as would be undertaken in individuals without ASDs who have the same symptoms or signs.
- **Statement 6:** Individuals with ASDs and GI symptoms are at risk for **problem behaviors**. When patients with GI disorders present with behavioral manifestations, the diagnostic evaluation can be complex.

Evaluation, Diagnosis, and Treatment of Gastrointestinal Disorders in Individuals With ASDs: A Consensus Report
T. Buie et al, Pediatrics 2010; 125: S1-S18

Recommendations for the Diagnostic Evaluation and Treatment of Selected Gastrointestinal Problems in Children with Autism Spectrum Disorders

- Discussion of presentation of several common GI problems in children with autism including abdominal pain, constipation, diarrhea and gastro-esophageal reflux
- Some basic suggestions for evaluation and treatment are offered holding mostly to established guidelines for pediatric patients in general, until better data is available to guide evaluation and treatment

Recommendations for Evaluation and Treatment of Common Gastrointestinal Problems in Children With ASDs T Buie et al, Pediatrics 2010; 125: S19-S29

http://pediatrics.aappublications.org/cgi/content/full/125/Supplement_1/S19

Conclusions

- GI issues are common in autism although a unique entity has not been identified
- Diet therapy may have a place in a subgroup of individuals but data are still debated and being gathered
- Problem behaviors can be medically based, behavior is communication in non-verbal individuals
- Profound or self-injurious behaviors may require pharmacological management, but a response to this should not replace proper medical evaluation.

Resource Information

- Office Hours recently launched video series on AutismSpeaks website discussing medical issues and autism. Topics discussed included reflux, sleep, probiotics
  www.autismspeaks.org/site-wide/office-hours
- Food for Thought: recurring blog, Autism Speaks
- A series of Cleveland Clinic CME sessions discussing medical co-morbidity in autism
  www.clevelandclinicmeded.com/online/webcasts/autism-spectrum-disorders/medical-comorbidities/

Thanks to:

MGH Team: Harland Winter, Margaret Bauman, Katherine Murray, Rafail Kushak, Aeri Moon, Sarah Kadzielski, Alessio Fasano

Boston Children's Hospital Team: Sonia Ballal, Athos Bousvaros, Elana Bern, Fiona Paul

My Support: Newman Foundation, Autism Research Institute, AutismSpeaks, The Buie Family

Discussion

Meeting of the IACC

Afternoon Agenda

2:15 **Autism Spectrum Disorder and Sleep – Identifying Challenges and Finding Solutions**

Beth Ann Malow, M.D., M.S.,
Burry Chair in Cognitive Childhood Development, Professor of Neurology and Pediatrics, Vanderbilt Kennedy Center, and Director, Vanderbilt Sleep Disorders Division

2:30 **Discussion**

3:00 **Break**

Autism Spectrum Disorder and Sleep-- Identifying Challenges and Finding Solutions

Beth A. Malow, M.D., M.S.
Burry Chair in Cognitive Childhood Development
Professor of Neurology and Pediatrics
Director, Sleep Disorders Division
Vanderbilt University Medical Center

Disclosures

- Grant support from Neurim Pharmaceuticals and Autism Treatment Network
- Consultant for Janssen and Vanda Pharmaceuticals
- Royalties from Woodbine House for “Solving Sleep Problems in Children with Autism Spectrum Disorders: A Guide for Frazzled Families” (with Dr. Terry Katz)
- I will discuss off-label uses of medications for sleep in autism (there are no approved FDA medications indicated for sleep in this population!)

Questions to Consider

- What kinds of sleep problems do individuals on the autism spectrum experience?
- What are the causes and contributors to these problems?
- What are the consequences on the individual and family?
- What are the latest treatments and guidelines?
- What areas are most in need of future research to move the field forward?

Alex

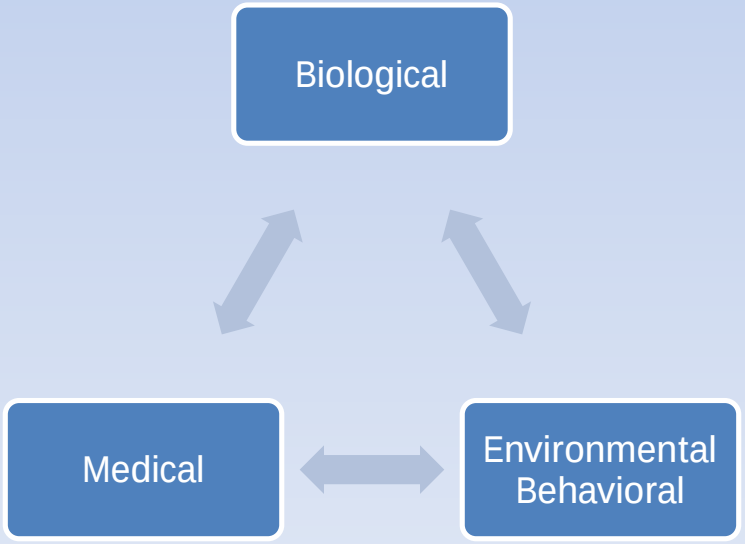
- Alex is a 10-year-old boy with autism spectrum disorder. Bedtime is 8 pm. He takes hours to fall asleep. His parents state that “he can’t shut his brain down.” He takes methylphenidate (Ritalin) in the afternoon for ADHD symptoms, drinks sweet ice tea with dinner, and plays video games after dinner. He can’t settle down to go to sleep and leaves his room repeatedly to find his parents. They rub his back to help him fall asleep.
- Once asleep, he awakens multiple times during the night. Sometimes he sleepwalks and sometimes he comes to his parents’ bedroom and falls asleep there (they are too exhausted to move). He snores in his sleep, and is very restless with frequent leg kicks.
- It is “nearly impossible” to awaken Alex in the morning for school. Alex’s teacher describes him as being sleepy as well as hyperactive and “disruptive” in class. His parents are exhausted and very overwhelmed.

Unpacking Alex's sleep problems

Insomnia
Hypersomnia
Parasomnia

Sleep study
Eliminate tea at dinner
Methylphenidate earlier
Turn off screens
Teach Alex to fall asleep on his own
Later bedtime

- Snoring
- Leg movements
- Sleepwalking
- Tea
- Methylphenidate
- Video Games (light/content)
- Parent interactions
- Bedtime of 8 pm ("forbidden zone")



Journal of Intellectual Disability Research
VOLUME 46 PART 4 pp 352–358 MAY 2002

commentary

Social timing, clock genes and autism: a new hypothesis

The Possible Interplay of Synaptic and Clock Genes in Autism Spectrum Disorders

T. BOURGERON
Human Genetics and Cognitive Functions Unit, Department of Neuroscience, Institut Pasteur, Paris, France, and Université Denis Diderot Paris 7, Paris, France

Cold Spring Harbor Symposia on Quantitative Biology,2007

International Journal of *Molecular Sciences*

MDPI

Article

Clock Genes and Altered Sleep–Wake Rhythms: Their Role in the Development of Psychiatric Disorders

Annaëlle Charrier [1,*], Bertrand Olliac [2,3], Pierre Roubertoux [4] and Sylvie Tordjman [1,5]

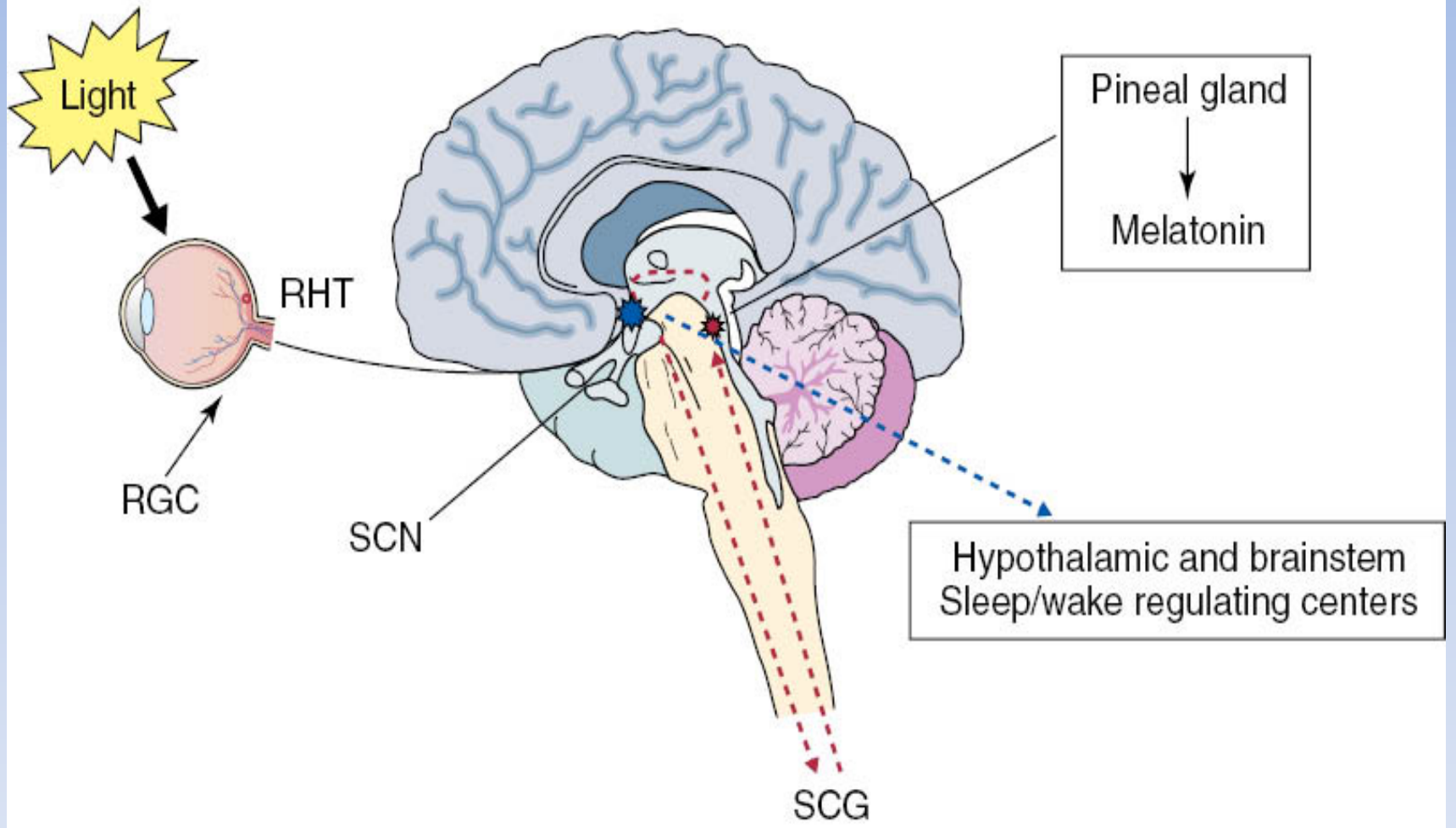
2017

Table 5

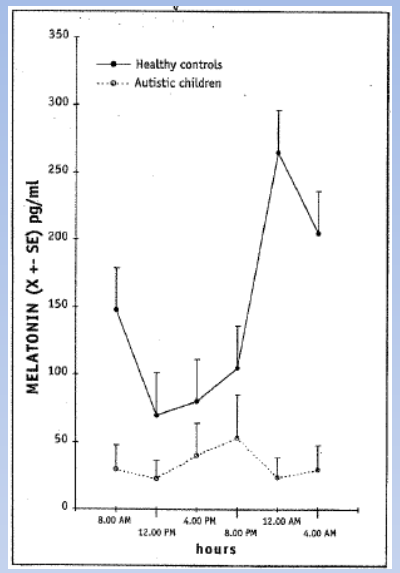
Clock genes and autism spectrum disorder (ASD).

Studies	Measure	Individuals with Psychiatric Disorder (*n*)	Controls (*n*)	Results
Nicholas et al. [89]	Screening of eleven clock/clock-related genes	High-functioning ASD individuals (*n* = 110)	Healthy parents (*n* = 220)	Significant association for two single-nucleotide polymorphisms in *Per1* and in *Npas2*.
Yang et al. [168]	Direct sequencing analysis of the coding regions of 18 canonical clock genes and clock-controlled genes	ASD individuals with sleep disorders (*n* = 14); ASD individuals without sleep disorders (*n* = 14)	Healthy individuals (*n* = 23)	Mutations in circadian-relevant genes (specifically *Per1*, *Per2*, *Per3*, *Clock*, *Npas2*, *Bmal1*, *Tim*, *Cry1*, *Cry2*, *Dbp* and *Ck1ε*) affecting gene function are more frequent in individuals with ASD than in controls.

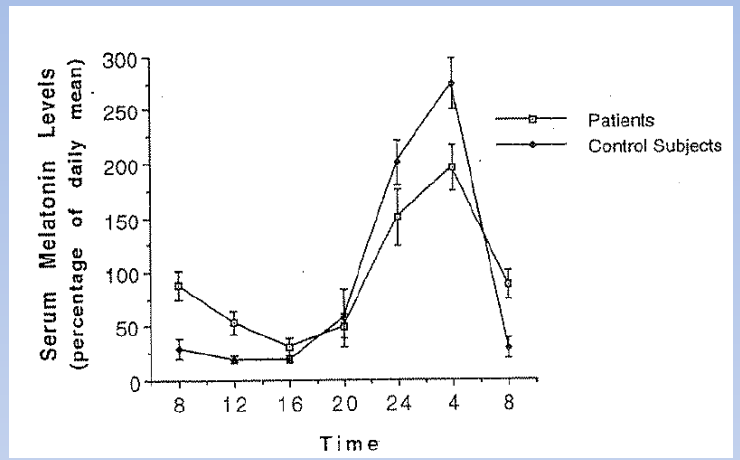
Circadian rhythms regulation



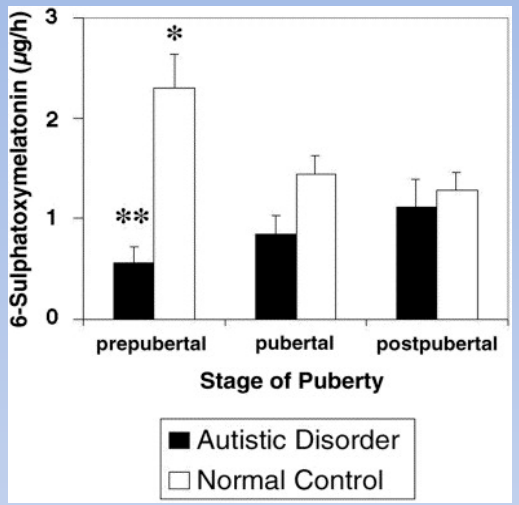
Melatonin is abnormally processed in ASD



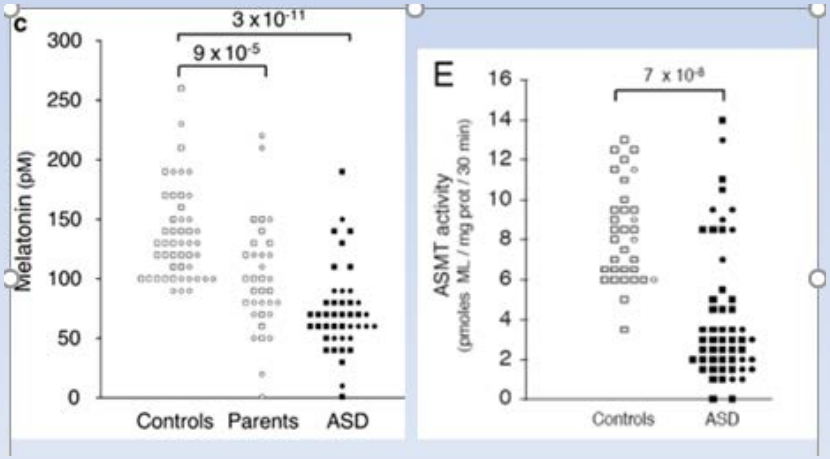
Kulman, Neuro Endocrine Letters 2000



Nir, JADD, 1995



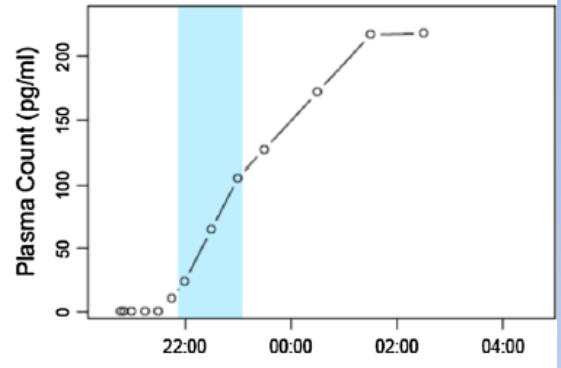
Tordjman, Bio Psych, 2005



Melke, Mol Psych, 2008

Tryptophan
↓
serotonin
↓ AA-NAT
N-acetylserotonin
↓ ASMT
Melatonin
↓ CYP1A2
6-sulfoxymelatonin
(major metabolite)

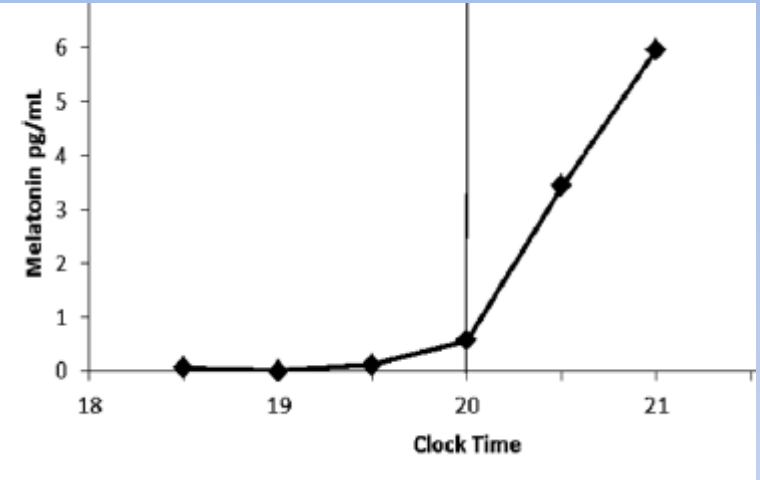
Melatonin levels may be normal in ASD



Overnight blood sampling in 3-10 year olds with ASD and sleep-onset insomnia whose insomnia responded to melatonin supplements had documented normal endogenous melatonin profiles prior to treatment. (representative child's profile shown above)

Goldman & Malow, JADD, 2014

NICHD–funded R01



Evening saliva sampling in adolescents with ASD, including those with sleep-onset insomnia, documented normal endogenous melatonin profiles (representative teen's profile shown above)

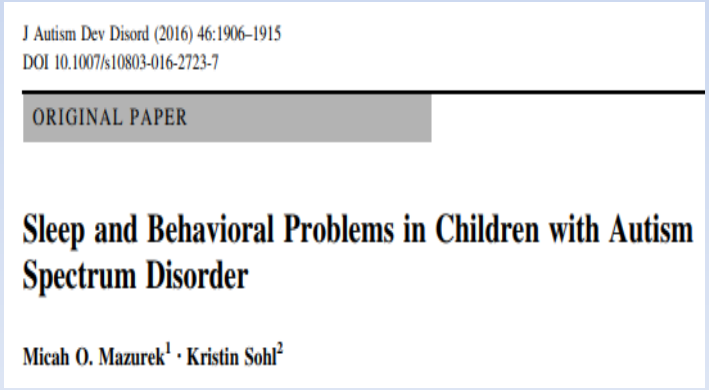
Goldman & Malow, JADD, 2017

Autism Speaks Grant

Sleep Deprivation Affects Emotional Regulation, Behavior, and Core Symptoms

fMRI studies have shown increased amygdala activation and decreased connectivity between prefrontal cortex and amygdala after sleep deprivation (Yoo, Curr Biol, 2007; Reidy, Neuropsychologia, 2016).

In > 2,714 children with ASD in the Simons Simplex Collection, severity scores for social/communication impairment and restricted and repetitive behaviors were increased for children reported to sleep ≤ 7 hours per night (lower 5th percentile) compared to children sleeping ≥ 11 hours per night (upper 95th percentile).
(Veatch, Autism Research, 2017)


J Autism Dev Disord (2016) 46:1906–1915
DOI 10.1007/s10803-016-2723-7

ORIGINAL PAPER

Sleep and Behavioral Problems in Children with Autism Spectrum Disorder

Micah O. Mazurek[1] · Kristin Sohl[2]

- 81 children with autism, ages 3-19 years
- Sleep problems were significantly associated with physical aggression, irritability, inattention, and hyperactivity.
- Night wakings was most strongly related to behavioral problems, even after controlling for the effects of age and sex.

Research Article

Support Needs and Coping Strategies as Predictors of Stress Level among Mothers of Children with Autism Spectrum Disorder

Autism Research and Treatment, 2017

Sheri R. Kiami[1] and Shelley Goodgold[2]

Table 3

Family needs questionnaire percentages ranked by important unmet needs.

"I need" statement[a]	% important unmet needs	% important needs
Financial support in order to provide my child with therapies, treatments, and care. (n/a)	87%	89%
To get a break from my responsibilities. (P)	86%	94%
To have the other children in my child's after-school program understand my child's special needs. (n/a)	79%	100%
To get enough rest or sleep. (P)	79%	96%
Help remaining hopeful about my child's future. (P)	79%	85%
To have counseling for myself and my spouse/partner/child's father. (P)	78%	69%
To have other family members understand my child's problems. (n/a)	77%	94%
To have time to care for my own health needs (Note: additional question added to Modified FNQ. (P)	76%	90%

Back to Alex (and the future teenage and adult Alex)

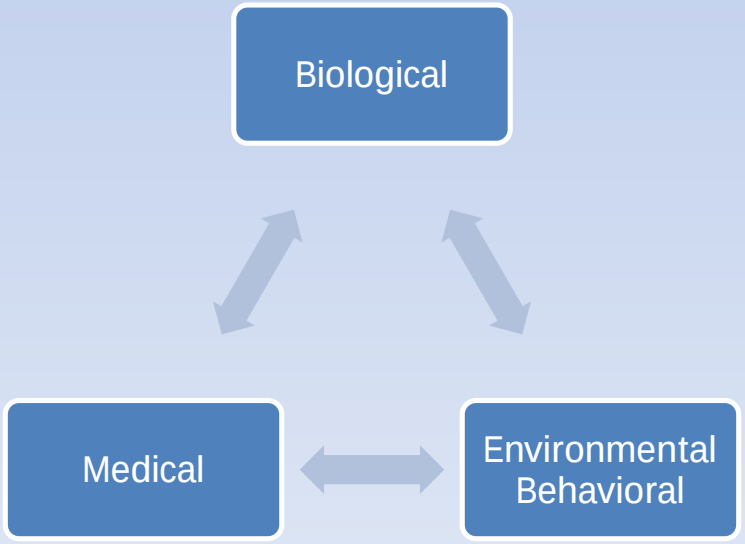
Pediatrics
November 2012, VOLUME 130 / ISSUE Supplement 2
SUPPLEMENT ARTICLE

A Practice Pathway for the Identification, Evaluation, and Management of Insomnia in Children and Adolescents With Autism Spectrum Disorders

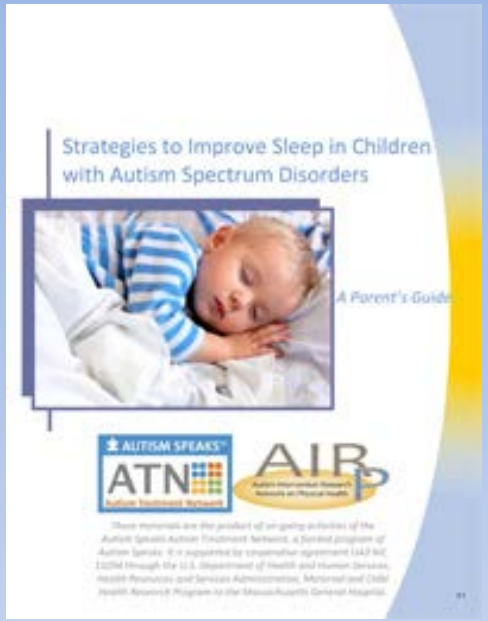
Beth A. Malow, Kelly Byars, Kyle Johnson, Shelly Weiss, Pilar Bernal, Suzanne E. Goldman, Rebecca Panzer, Daniel L. Coury, Dan G. Glaze

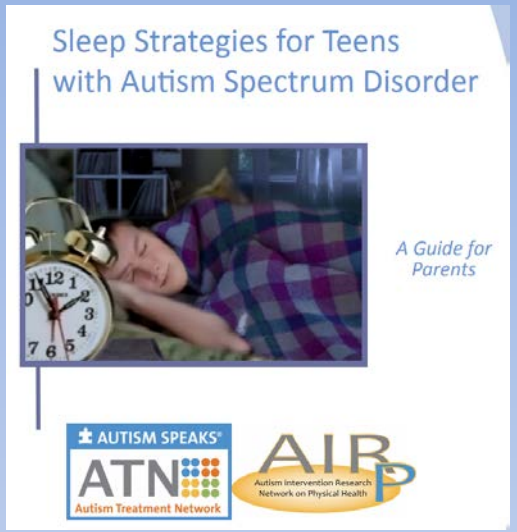
- #1 Hunt hard for medical co-occurring conditions that affect sleep
- #2 Behavioral approaches work if you can implement them (Malow, JADD, 2014)
- #3 Consider medications for overwhelmed individuals and families but also do #1 and #2

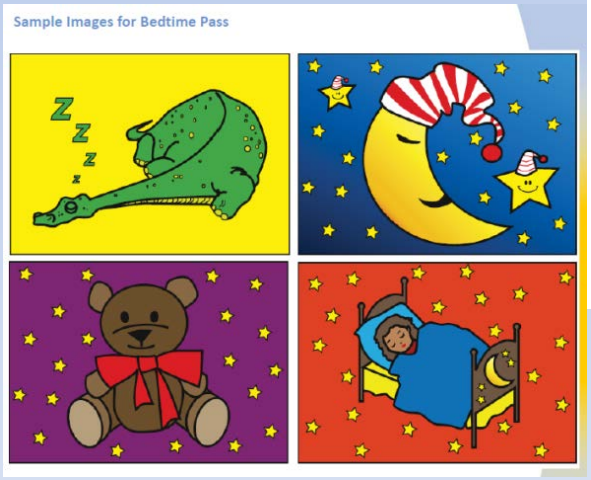
Sleep study
Eliminate tea at dinner*
Methylphenidate earlier
Turn off screens*
Teach Alex to fall asleep on his own*
Later bedtime*

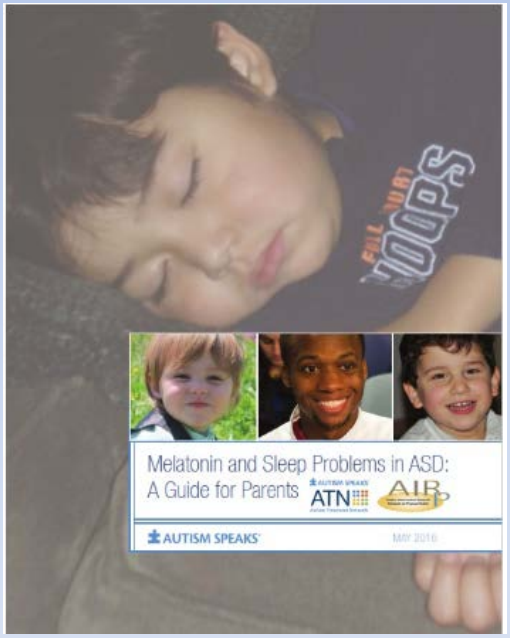


ATN/AIR-P Toolkits









Autism Speaks, on line materials

http://www.autismspeaks.org/science/resources-programs/autism-treatment-network/tools-you-can-use/sleep-tool-kit

Children with Limited Verbal Skills

Schedule Boards:

Some children are not able to use a visual schedule that uses words, photos, or icons. It may help to use objects instead.

Here's an example: If your child's bedtime routine consists of using the toilet, taking a bath, washing hair, brushing hair, having a massage, and listening to music, you might have a place near the bathroom or bedroom with the following items: a roll of toilet paper, a bar of soap, a bottle of shampoo, a hairbrush, a bottle of lotion, and a CD. Your child would get each object before the start of an activity and use this to guide his or her actions. Save a special object just for bedtime. This might be a special blanket, pillow, or stuffed animal. Once your child has this object, he or she should go into his or her bed. Even if you do not use objects, write down your child's schedule so that you are going through the same steps each night. Use single words or two-word phrases to label what you are doing.

The Rocking Chair Method (parental presence with fading)

- Rocking and Swinging
- Snuggling
- Massaging
- Music
- White noise
- Night lights
- Calming scents
- Weighted blankets

(Mostly Understudied) Medication Options for Insomnia in Autism

- Melatonin and melatonin agonists (most studied, safe/well tolerated)
  - Several meta-analyses and reviews (Rossignol, Dev Med Child Neuro, 2011)
  - Prolonged release preparations improve sleep duration (Gringras, Am Acad Child Adol Psych 2017)
  - Melatonin + behavioral therapy most effective (Cortesi, J Sleep Res, 2012)
- Gabapentin (Robinson and Malow, J Child Neuro, 2013)
- Alpha-adrenergic agonists (Ming, Brain Dev, 2008; Ingrassia, Eur Child Adol Psych, 2005)
- Trazadone
- Mitazapine (Posey, J Child Adol Psychopharm, 2001)
- Benzodiazepines– works in NREM arousal disorders like sleepwalking
- Non-benzodiazepine receptor agonists (zolpidem, eszopiclone)
- Tricyclic antidepressants
- Other OTCs besides melatonin
  - ✓ Valerian, Tryptophan/5-Hydroxytryptophan

Future Directions

- Are any of the old or new medications for insomnia effective in autism and what are the side effects (across the lifespan)
- How do these medications compare in terms of effectiveness and side effects? (as to melatonin)
- Can medications and behavioral treatment work synergistically?
- How do we get overwhelmed parents of children with autism to use behavioral strategies?
- What about teens and adults with autism? How do we motivate them?
- Can genetic or biomarker studies guide our treatment plans?

Discussion

Break

Meeting of the IACC

Afternoon Agenda

3:10 **Patient – Provider Interactions**

Healthcare Experiences of Children with Autism: Opportunities for Improvement

Micah Mazurek, Ph.D.
Associate Professor of Education, Curry School of Education, University of Virginia

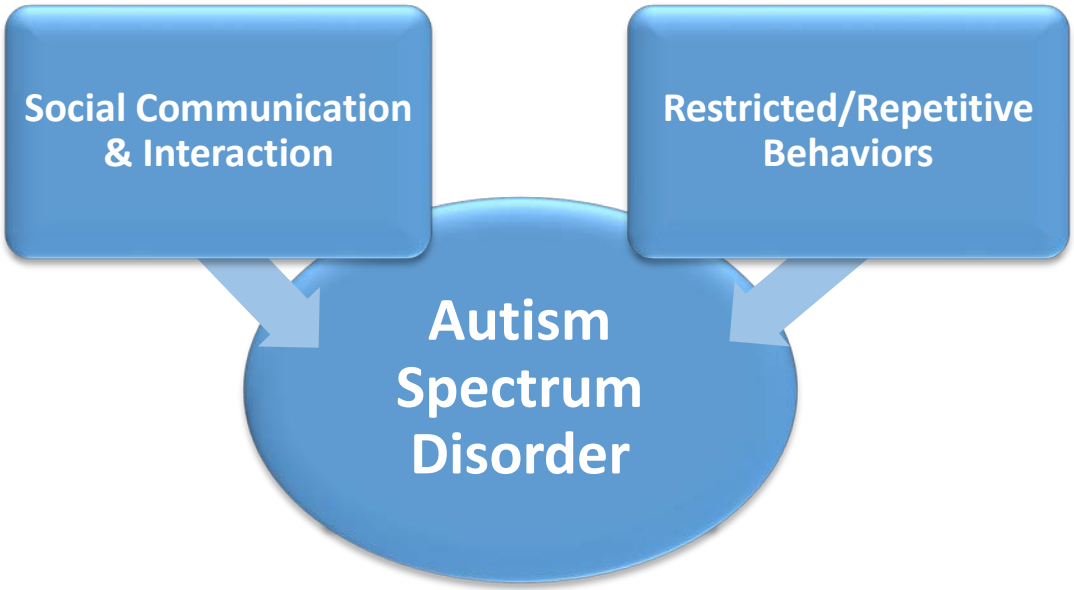
Healthcare Experiences of Children with Autism: Opportunities for Improvement

Micah Mazurek, PhD
Associate Professor

University of Virginia

ASD: Complex Healthcare Needs

- "Core" Diagnostic Features:



Co-Occurring Conditions

- Cognitive Problems
  - Intellectual disability
  - Executive functioning problems
- Medical Conditions
  - Seizures
  - Gastrointestinal problems
  - Sleep disturbance
  - Feeding problems
- Emotional/Behavioral Problems
  - Anxiety
  - Depression
  - ADHD symptoms
  - Aggression
  - Self-Injurious behaviors
- Others…
  - Language disorders
  - Sensory processing difficulties
  - Many others…

Co-Occurring Conditions

- Co-occurring conditions are common
  - More than 95% of 8- and 4-year old children with ASD in the 2010 ADDM Network study had at least one co-occurring condition/symptom
  - Many children with ASD have *multiple* co-occurring conditions
  - Many conditions appear to be inter-related
  - Some symptoms overlap and/or mask core symptoms of ASD

(Aldinger et al., 2015; Doshi-Velez, Ge, & Kohane, 2014; Kohane, et al., 2012; Mazurek et al., 2013; Mazurek et al., 2014; Mazurek & Petroski, 2015; Soke et al., 2018)

Impact of Co-Occurring Conditions

- The impact of co-occurring conditions in children with ASD may include:
  - Interference with daily life
  - Greater family stress and burden
  - Worse health care experiences
  - Greater financial strain
  - Higher healthcare costs

(Benson & Karlof, 2008; Estes et al., 2009; Lecavalier et al., 2006; Zablotsky et al., 2014)

Healthcare Needs

- *Despite their need for care,* compared to children with other special healthcare conditions, children with ASD have:
  - **Greater unmet** healthcare needs
  - **Worse access** to medical home
  - Less coordinated, family-centered care

- Children with ASD and comorbid conditions have **even worse** health care experiences and greater financial strain

(Brachlow, Ness, McPheeters & Gurney, 2007; Kogan et al., 2008; Krauss et al, 2003; Zablotsky et al., 2014)

Barriers: Access to Care

- Few providers with autism expertise
  - Shortages of autism specialists in most communities
  - Long wait-lists at specialty centers
- Geographic/transportation barriers
  - Remote and rural areas
- Financial barriers
- Cultural or linguistic barriers

(Chiri et al., 2012; Doshi et al., 2017; Krauss et al, 2003; Magaña et al., 2015, Zablotsky et al., 2014; Zhang et al. 2017)

Barriers: Clinic Environment

- Challenges for Children with ASD
  - Noisy and unpredictable clinic environment
  - Discomfort with unfamiliar providers
  - Difficulty with communication
    - Trouble understanding verbal cues and prompts
    - Trouble expressing thoughts, feelings, or experiences
  - Painful or uncomfortable procedures
    - Discomfort being touched by providers
    - Sensory differences

Barriers: Accurate Assessment

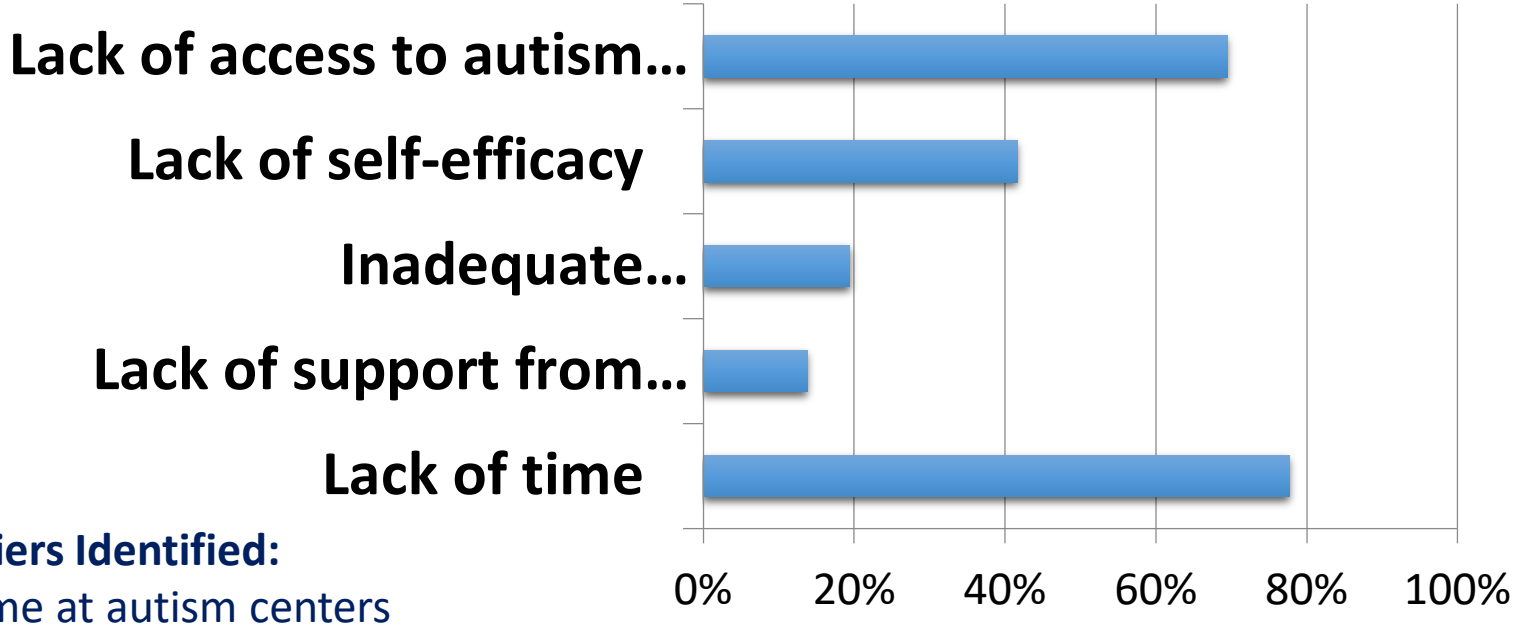
- Challenges to accurate assessment of co-occurring symptoms
  - Atypical symptom presentation
    - Overlapping symptoms
    - Atypical displays of discomfort
  - Lack of validated tools for children with ASD
  - Self-report is not always possible
    - Difficulties recognizing or reporting pain or emotional experiences
  - Parent-report may miss internally experienced symptoms

Barriers: Provider Knowledge

- Healthcare providers:
  - Report feeling unprepared to manage complex needs of children with ASD
  - Report a lack of knowledge and confidence in identifying ASD symptoms and in treating comorbid conditions
- Parents of children with ASD
  - Are dissatisfied with healthcare experiences
  - Lack confidence in provider knowledge of ASD

(Boreman et al., 2007; Carbone et al., 2013; Self, Parham, & Rajagopalan, 2015; Bruder, et al., 2012; Golnik, Ireland, & Borowsky, 2009; Liptak et al., 2006; Shah, 2001; Wilkinson et al., 2012)

Perceived Barriers: Primary Care Providers



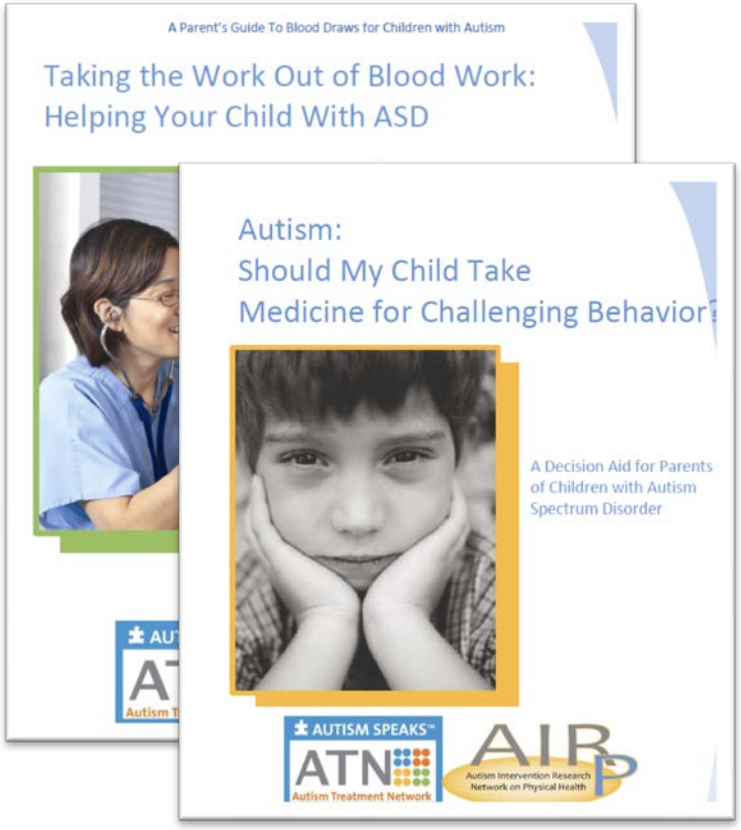
Other Barriers Identified:

- Wait time at autism centers
- Limited knowledge of community resources
- The office "flow" is difficult to adjust/make accommodations
- Lack of assessment tools

(Mazurek et al., 2017; Mazurek et al., 2018)

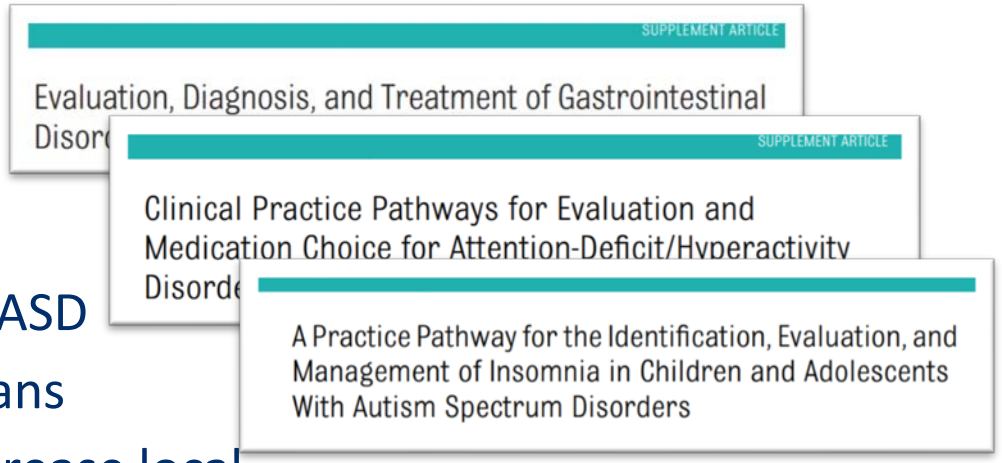
Opportunities for Improvement

- Healthcare Environment & Family Empowerment
  - Toolkits for children & families
  - Resources to improve patient-provider communication/partnership
  - Autism-friendly clinic spaces
  - Family-centered practices



Opportunities for Improvement

- Evidence-based tools & guidelines
- Psychometrically sound screening/assessment tools
- Provider Training
  - Pre-professional training on ASD
  - Training for practicing clinicians
  - Leveraging technology to increase local capacity



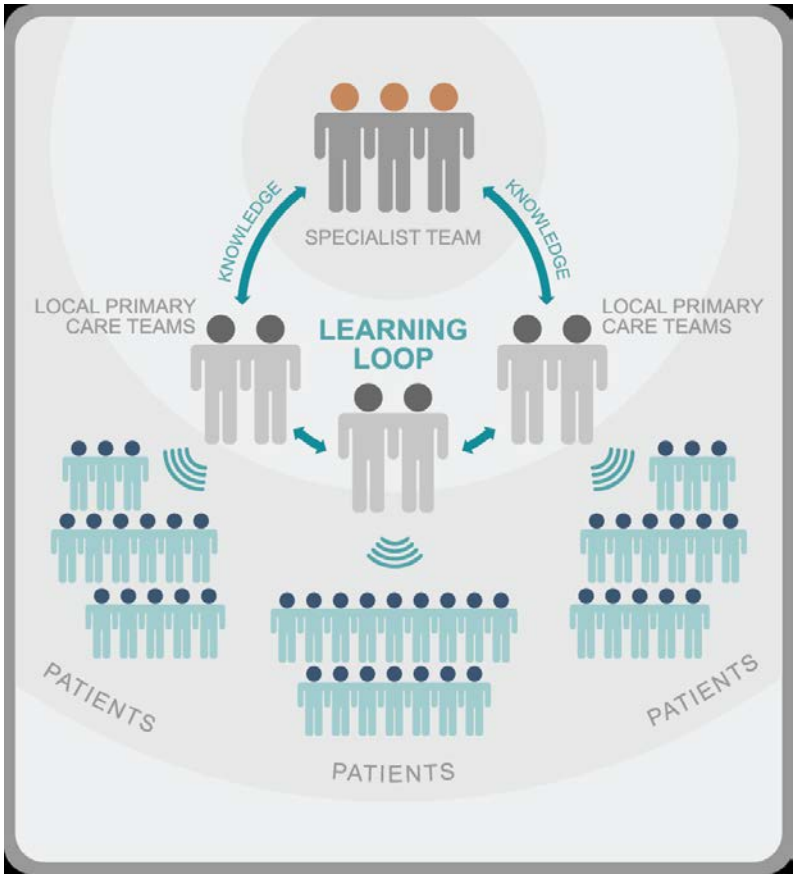
Model Program: Project ECHO

- **E**xtension for **C**ommunity **H**ealthcare **O**utcomes
- Developed at the University of New Mexico to improve outcomes for adults with hepatitis C
- Purpose:
  - Expand **local capacity** for treatment of common and complex conditions
  - **Improve access** for rural and underserved populations
  - **Train community-based** providers in best-practice care

(Arora et al., 2010; Arora et al., 2011)

Project ECHO Framework

- Using Multipoint Videoconferencing
- Expert “Hub” Connecting to PCP “Spokes”
- Case-Based Learning
- Didactics
- Learning Network



ECHO Autism Pilot

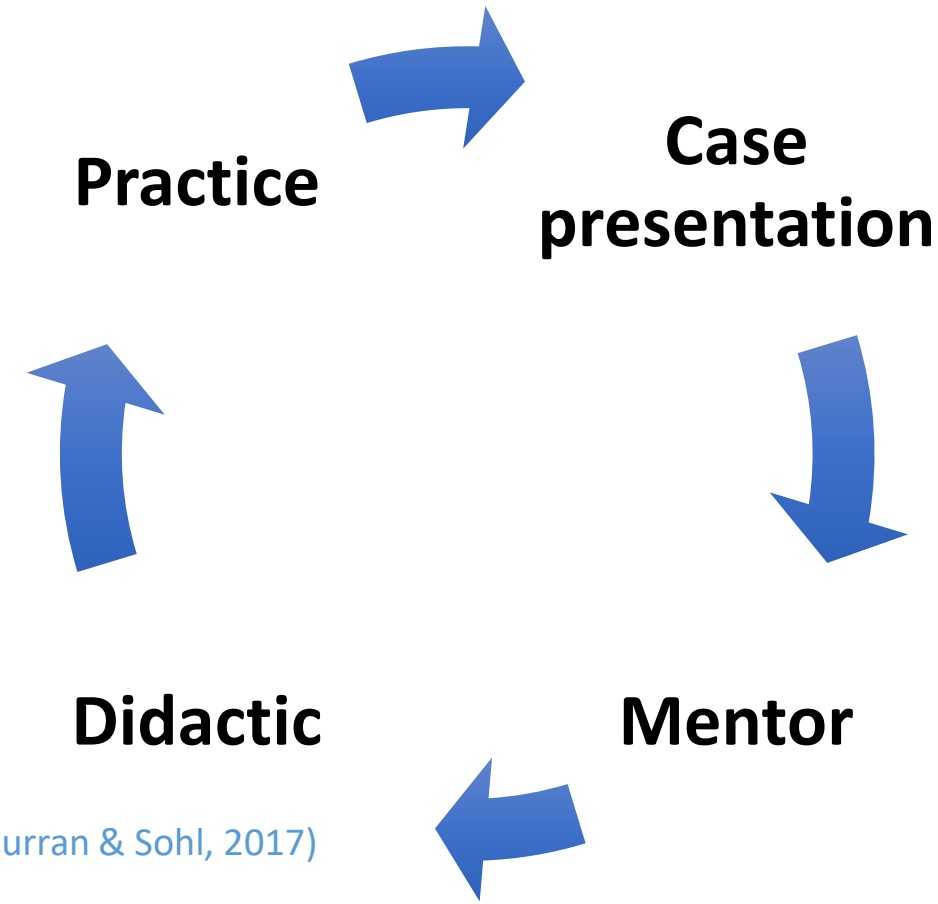
- **Interdisciplinary Expert Hub:**
  - Pediatrician specializing in ASD
  - Clinical Psychologist
  - Child & Adolescent Psychiatrist
  - Parent of Child with ASD
  - Dietician
  - Social Worker
- **Spokes:**
  - Primary Care Providers
  - Underserved areas

(Mazurek, Brown, Curran & Sohl, 2017)

Learning Loop

ECHO Autism Clinic Format

- Introductions 10 minutes
- Case #1 35 minutes
- Didactic 20 minutes
- Case #2 35 minutes
- Wrap Up 20 minutes



(Mazurek, Brown, Curran & Sohl, 2017)

ECHO Autism Pilot

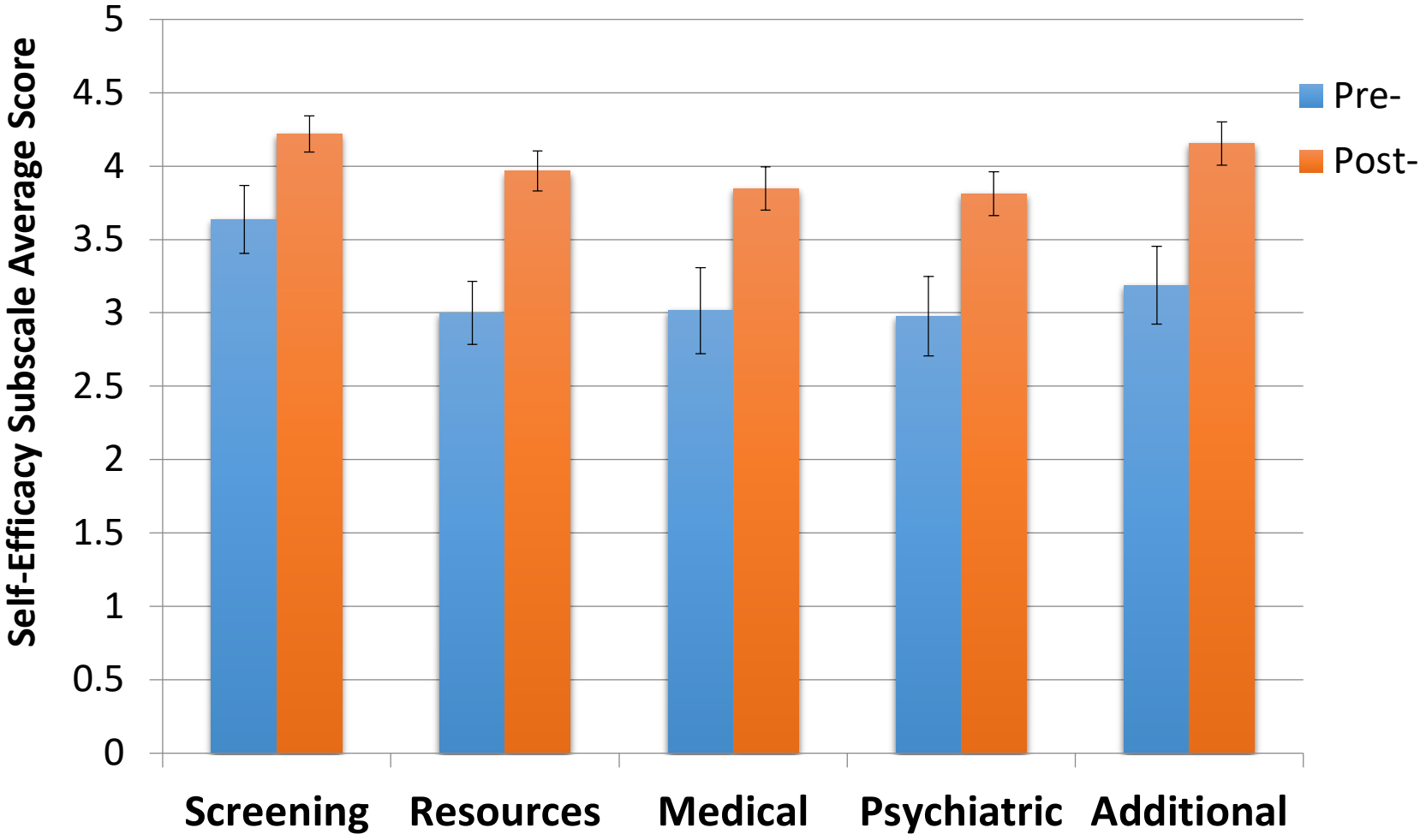
- 6-month pilot
  - Twelve 2-hour ECHO Autism clinics
  - 2 clinics per month
  - 14 PCP participants (79% practicing in underserved area)

Specific focus on:

- **Screening & identification** of ASD symptoms
- Managing common **medical** & **psychiatric comorbidities**

(Mazurek, Brown, Curran & Sohl, 2017)

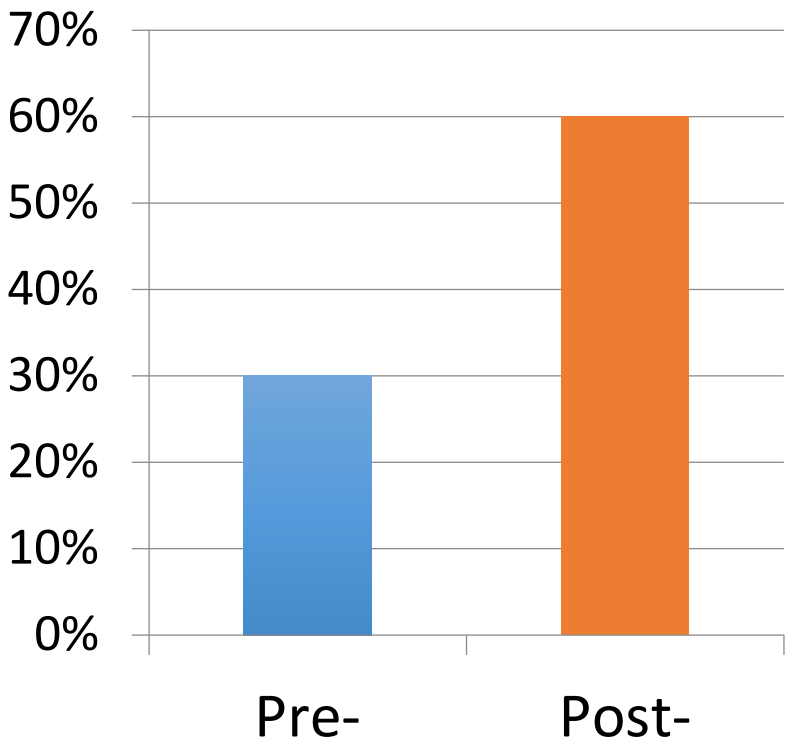
Improvements in Self-Efficacy



(Mazurek, Brown, Curran & Sohl, 2017)

Adherence to Autism Screening Guidelines

Percentage Administering ASD Screenings at all 18- and 24-month Well-Child Visits



Pilot Study Conclusions

- Implementation of ECHO Autism was **feasible**
- PCP participants reported **high satisfaction** with the program
- PCPs demonstrated improvements in:
  - **Self-efficacy** in ASD screening and management
  - Adherence to AAP **autism screening** guidelines
  - Use of ASD-specific **resources**

(Mazurek, Brown, Curran & Sohl, 2017)

ECHO Autism Replication Study

Multi-Site Replication Study

- 10 Collaborating Sites
  - n =150 PCP participants
    - University of Arkansas for Medical Sciences
    - Children's Hospital of Philadelphia
    - Cincinnati Children's Hospital Medical Center
    - Lurie Center for Autism
    - Nationwide Children's Hospital
    - University of Pittsburgh
    - University of Rochester
    - University of Toronto/Holland Bloorview Kids Rehab Hospital
    - University of California Irvine
    - Vanderbilt University Medical Center

AIRP Autism Intervention Research Network on Physical Health

AUTISM SPEAKS ATN Autism Treatment Network

Procedures Overview

Each replication site:

- Recruit 15 primary care providers
  - Patient population >50% underserved
- Conduct 12 ECHO Autism clinics over a 6 month period
- Complete assessments at 4 time points
  - Knowledge Test
  - Chart Review
  - Self-Efficacy

Study Design

- Cluster-randomized design
  - Sequential, staggered roll-out
  - 5 Cohorts
    - 2 Sites & 30 PCPs per cohort
    - Sites are randomized

	12/1/16	3/1/17	6/1/17	9/1/17	12/1/17	3/1/18	6/1/18	9/1/18
Cohort 1: Arkansas CHOP	T1: ECHO Launch	T2: 3 mo Assessment	T3: 6 mo Assessment	T4: Final Assessment				
Cohort 2: Rochester Toronto		T1: ECHO Launch	T2: 3 mo Assessment	T3: 6 mo Assessment	T4: Final Assessment			
Cohort 3: Lurie Ctr Vanderbilt			T1: ECHO Launch	T2: 3 mo Assessment	T3: 6 mo Assessment	T4: Final Assessment		
Cohort 4: Pittsburgh UC Irvine				T1: ECHO Launch	T2: 3 mo Assessment	T3: 6 mo Assessment	T4: Final Assessment	
Cohort 5: Cincinnati Nationwide					T1: ECHO Launch	T2: 3 mo Assessment	T3: 6 mo Assessment	T4: Final Assessment

Future Directions

- Application of ECHO and other technology-based models for increasing access to best-practice care
  - Early Diagnosis (e.g., ECHO Autism STAT; Mazurek, Curran, Burnette, & Sohl 2018)
  - Adult Healthcare/Transition
  - Crisis Care
  - Education
  - Mental Health
  - Family Support

Thank you!

Discussion

Meeting of the IACC

Afternoon Agenda

3:25 **Healthcare Experiences of Adults on the Autism Spectrum: Challenges and Solutions**

Christina Nicolaidis, M.D., M.P.H.
Professor and Senior Scholar in Social Determinants of Health, School of Social Work, Portland State University, and Adjunct Associate Professor, Division of General Internal Medicine, Oregon Health and Science University

Dora Raymaker, Ph.D.
Research Assistant Professor, Portland State University; Co-Director, Academic Autism Spectrum Partnership in Research and Education (AASPIRE)

Healthcare for Autistic Adults: Challenges and Solutions

Christina Nicolaidis, MD, MPH

Professor, Portland State University

Co-Director, Academic Autism Spectrum Partnership in Research and Education

Dora Raymaker, PhD

Research Assistant Professor, Portland State University

Co-Director, Academic Autism Spectrum Partnership in Research and Education

AASPIRE

- Academic Autism Spectrum Partnership in Research and Education (www.aaspire.org)
- Co-Founded in 2006 by Christina Nicolaidis and Dora Raymaker
- Autistic adults, academics, family members, disability services and healthcare providers
- Community Based Participatory Research
  - Autistic adults serve as equal partners throughout all phases of our research projects.

Nicolaidis et al, *PCHP*, 2011

A Brief Note About Language

- Ongoing language debate
  - Preference among self-advocates for identity-first (e.g. autistic adult) vs. person-first (e.g. adult with autism)
  - Similar to Deaf community

Gernsbacher, 2017; Kapp et al, 2013; Kenny et al 2016; Sinclair, 1999; Nicolaidis 2012

Healthcare Disparities

Healthcare Disparities

- AASPIRE online survey comparing autistic adults (N=209) to non-autistic adults (N=228)
- Greater unmet healthcare needs
  - Physical health needs (aOR 1.9)
  - Mental health needs (aOR 2.2)
  - Prescription medication needs (aOR 2.8)
- Greater Emergency Department use (aOR 2.1)
- Lower use of Pap Smears (aOR 0.5)
- Lower satisfaction with patient-provider communication and healthcare self-efficacy

Nicolaidis et al, *JGIM* 2013

Healthcare Disparities

- Large Kaiser Permanente case-control study
- Compared to adults with ADHD, autistic adults had:
  - ↑ primary care visits (74% VS 67%)
  - ↑ outpt mental health visits (43% vs 33%)
  - ↑ hospitalizations for ambulatory care sensitive diagnoses (5.4% vs. 2.3%)
  - ↓ gynecology visits and cervical cancer screening (35% vs 50%)
- Differences even greater when compared with general population

Zerbo et al, *Autism in Adulthood*, 2018

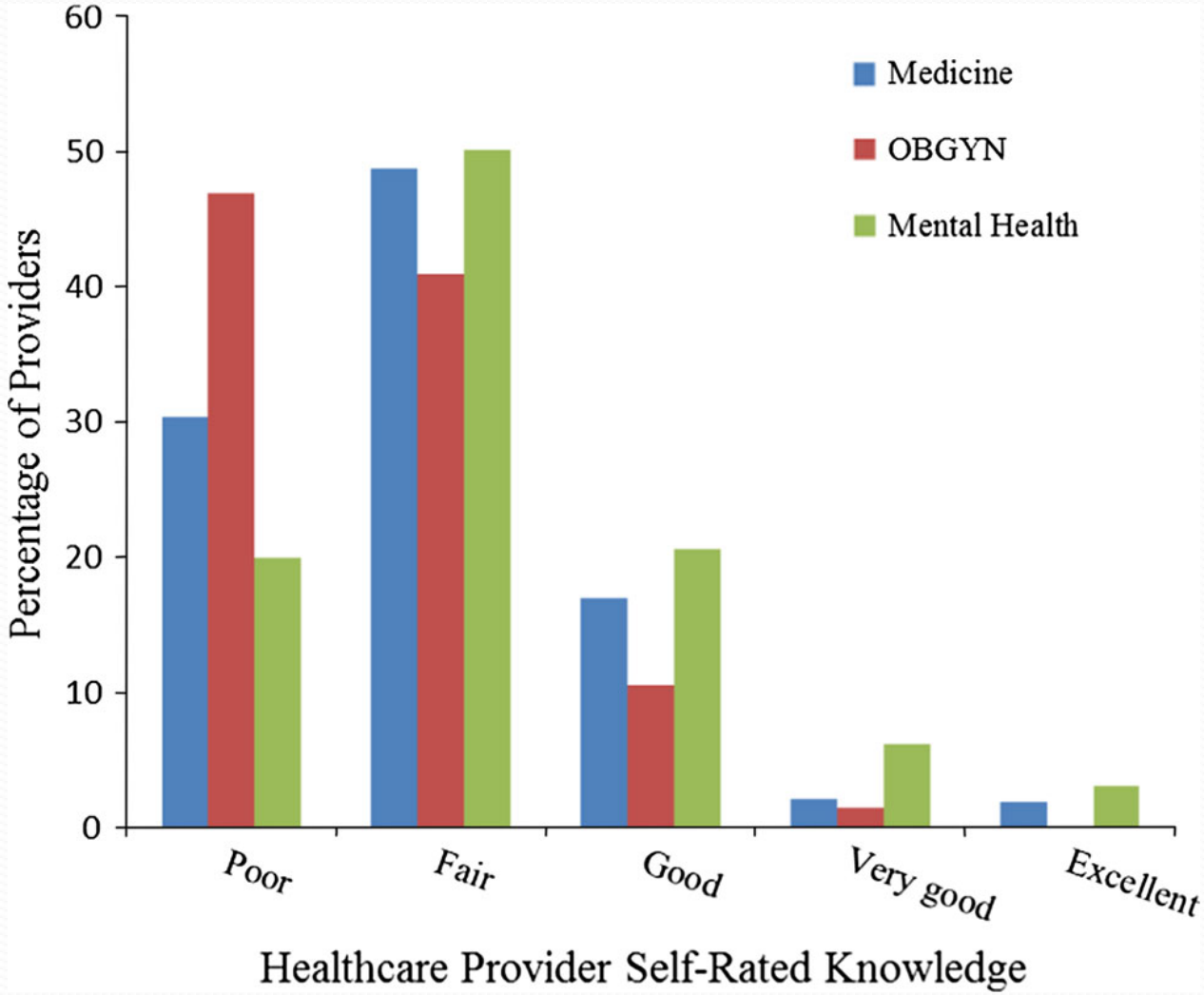
Provider Knowledge and Self-Efficacy

AASPIRE Survey of 129 PCPs

- Brief online survey of internal Medicine and Family Practice Providers who care for adults
- 73% felt uncomfortable in their ability to provide quality care for adults on the spectrum
- 84% no plans to seek additional training on ASD
- 88% would accept autistic adult in their practice
  - If new autistic pt, <50% would attend CME
  - 82% would search information on the Internet
  - 98% would read customized report about pt needs

Nicolaidis et al, *JGIM* 2016

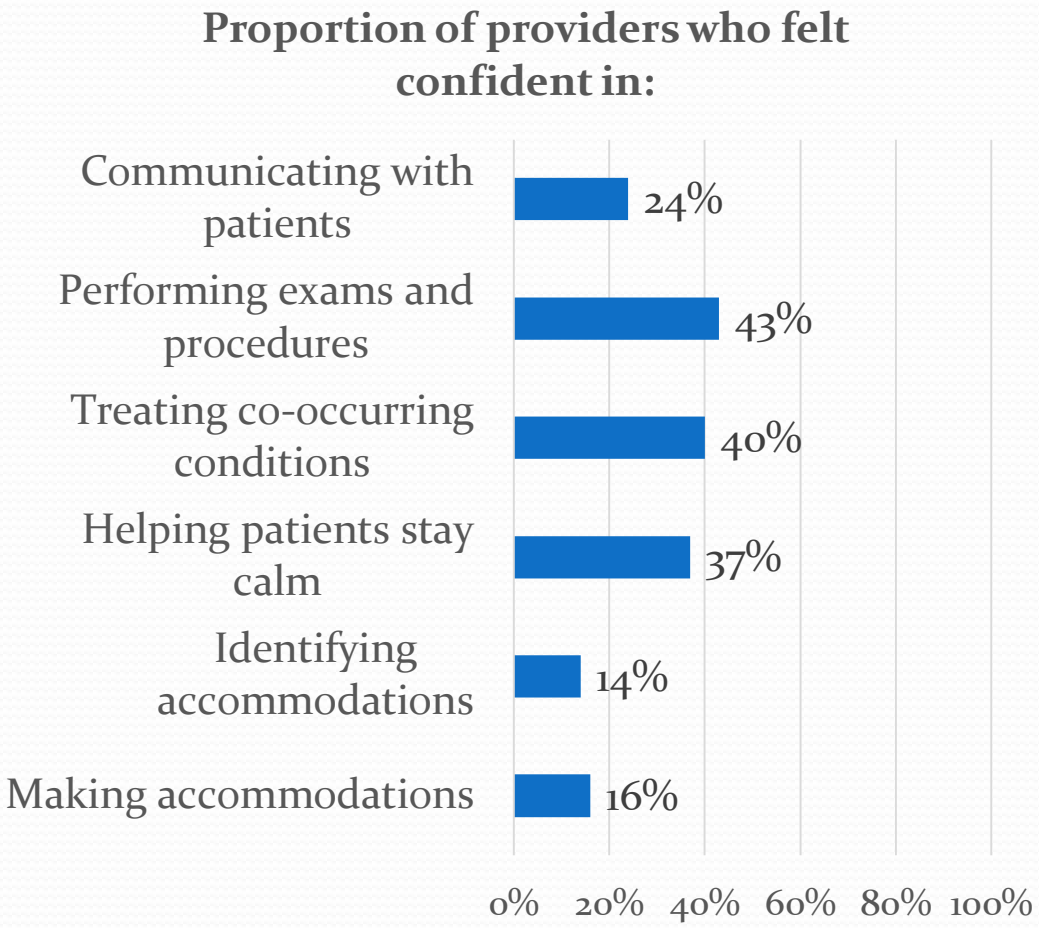
Kaiser Survey of 922 Healthcare Providers



Zerbo et al, *JADD*, 2015

Provider Self-Efficacy in Caring for Autistic Adults

- Baseline survey data from current AASPIRE intervention
- 143 PCPs in 3 health systems in Northern California and Oregon



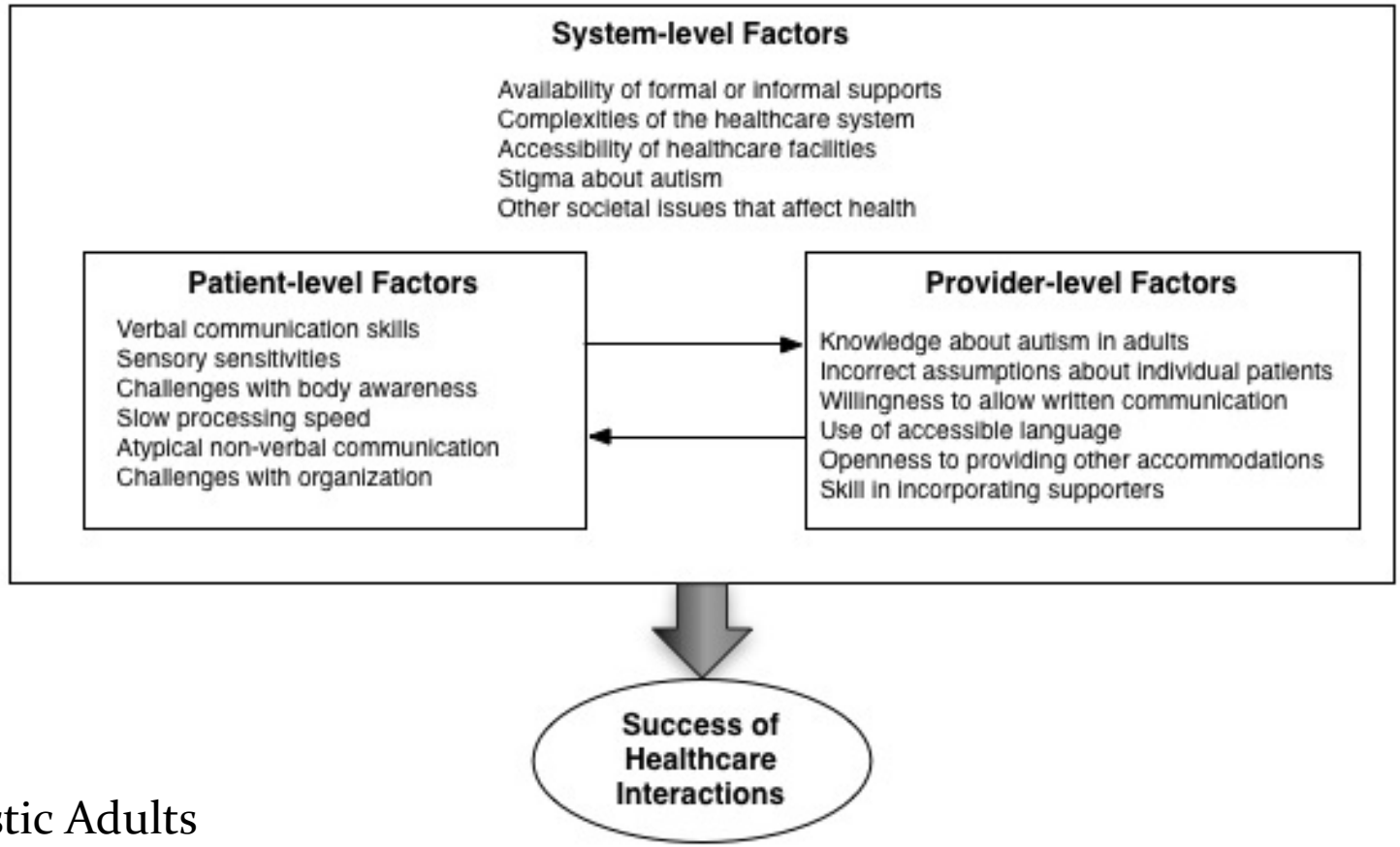
Patient Experiences with Healthcare

Barriers to Healthcare

- Data from AASPIRE online healthcare survey
- People without disabilities experienced far fewer barriers to healthcare than autistic or other disability groups.
- Autistic group reported more barriers to healthcare than people with other disabilities, plus different pattern.
- Top barriers:
  - Fear or anxiety (35%)
  - Can't process information fast enough in real-time (32%)
  - Concern about cost (30%)
  - Facilities cause sensory issues (30%)
  - Difficulty communicating with providers (29)

Raymaker et al, Autism, 2017

Healthcare Experiences



39 Autistic Adults
16 Supporters

Nicolaidis et al, *JGIM* 2015

Sensory Sensitivities

"The lights in the office are very bright and that is exacerbated by the white walls. Sometimes the waiting rooms are crowded and I cannot filter out the background of people talking or shuffling magazines. I feel disoriented by being led down long hallways to different rooms … I am not able to bring up my concerns because it is all I can manage to figure out what the doctor is saying so I can respond to his questions. But he refills my usual meds and I go on my way."

Challenges with Body Awareness

- "Like when they ask if pain is shooting or stabbing or burning, it's like, I don't know, it just feels funny."

- "The problem is it is difficult for me to isolate specific sources of pain and identify duration and intensity. It's sort of like the equivalent to white noise."

Providers' Incorrect Assumptions

- "I have used my Alphasmart [portable communication device] when my speech is too slow or difficult to understand for medical appointments. Some of the doctors have been really great, but others have acted really condescending when I used it, also immediately assuming I couldn't be alone, had to have had parents there too … So I try to go without, even when my speech is in a poorer shape."

- "Usually when I demonstrate a large vocabulary or some fundamentals, my needs especially around communication are then ignored. My choice is then to pretend to be less intelligent and accept their infantilism, or to be confused, frustrated, and stressed out."

Communication and Openness to Accommodations

- "I prefer and find it easier to communicate in text … But with every doctor I speak to, they wave away the note-card and look at me to ask the same question I have just answered and interpret my confusion as my being non-compliant with the medicine. I wish health care providers would read the notes I make for them."

- "But they talk to him in the same words that they'd use if they were talking to me… If they're gonna talk to him … they need to say it how he can understand it."

Decreased patient autonomy

- “Just because I might need more information to understand things, it doesn’t mean they can or should just talk to me like a child or leave me without knowledge of my own health. My body is my body, and my experiences and wishes about my body are MINE TO MAKE!”

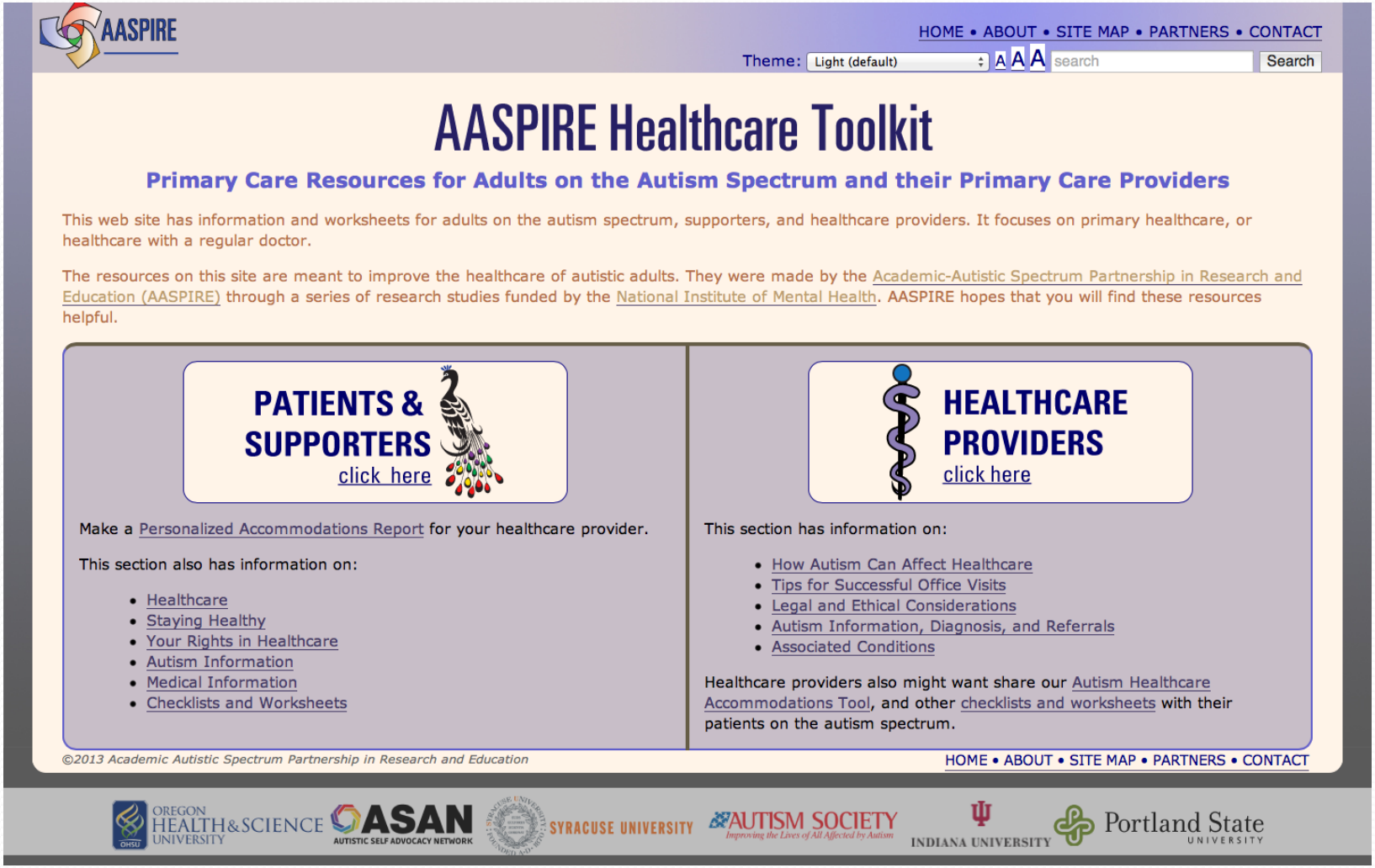
Very Heterogeneous Condition

"When you have met one autistic person, you have met one autistic person"

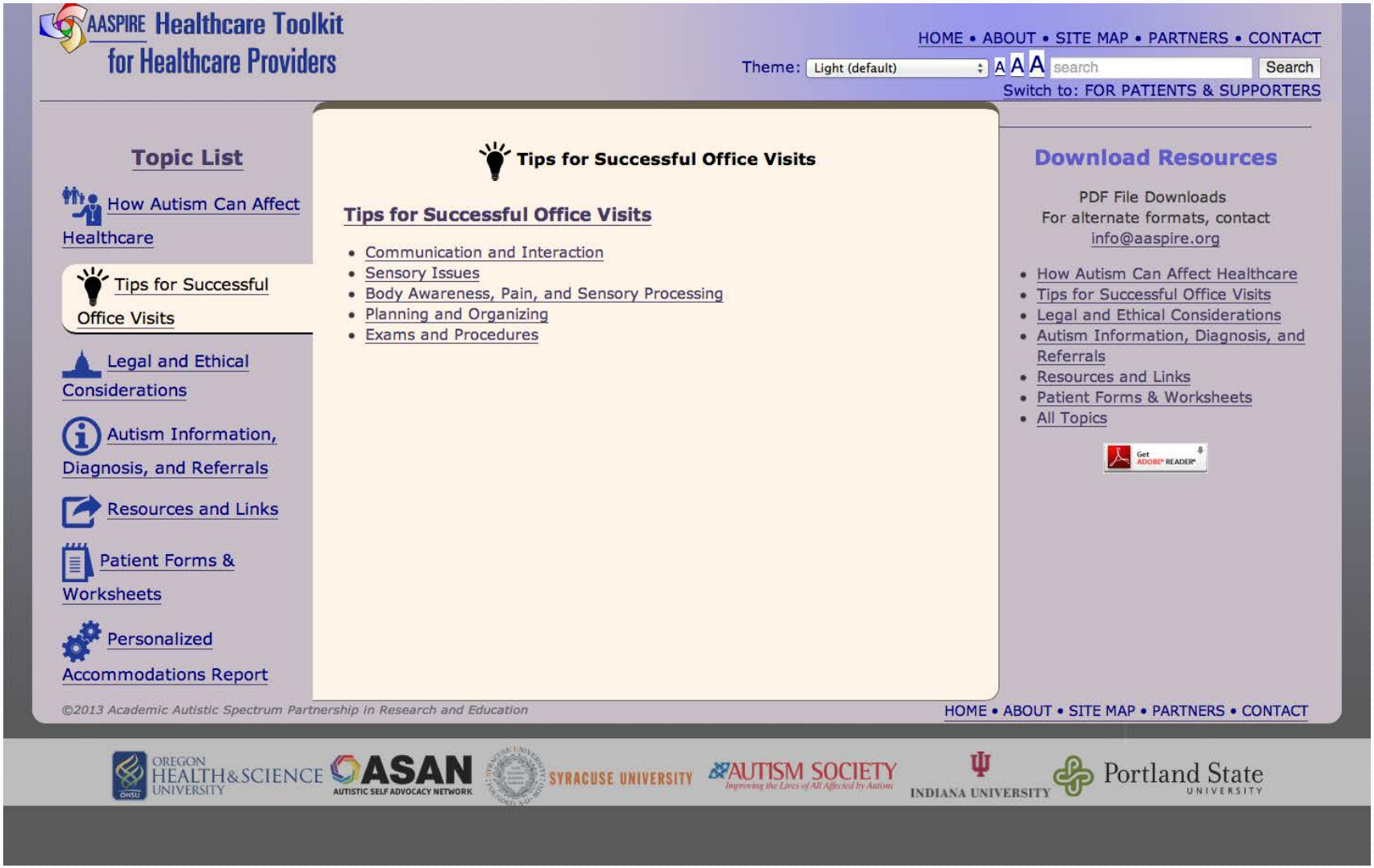
Need for individualized tools!

Potential Solutions I: The AASPIRE Healthcare Toolkit

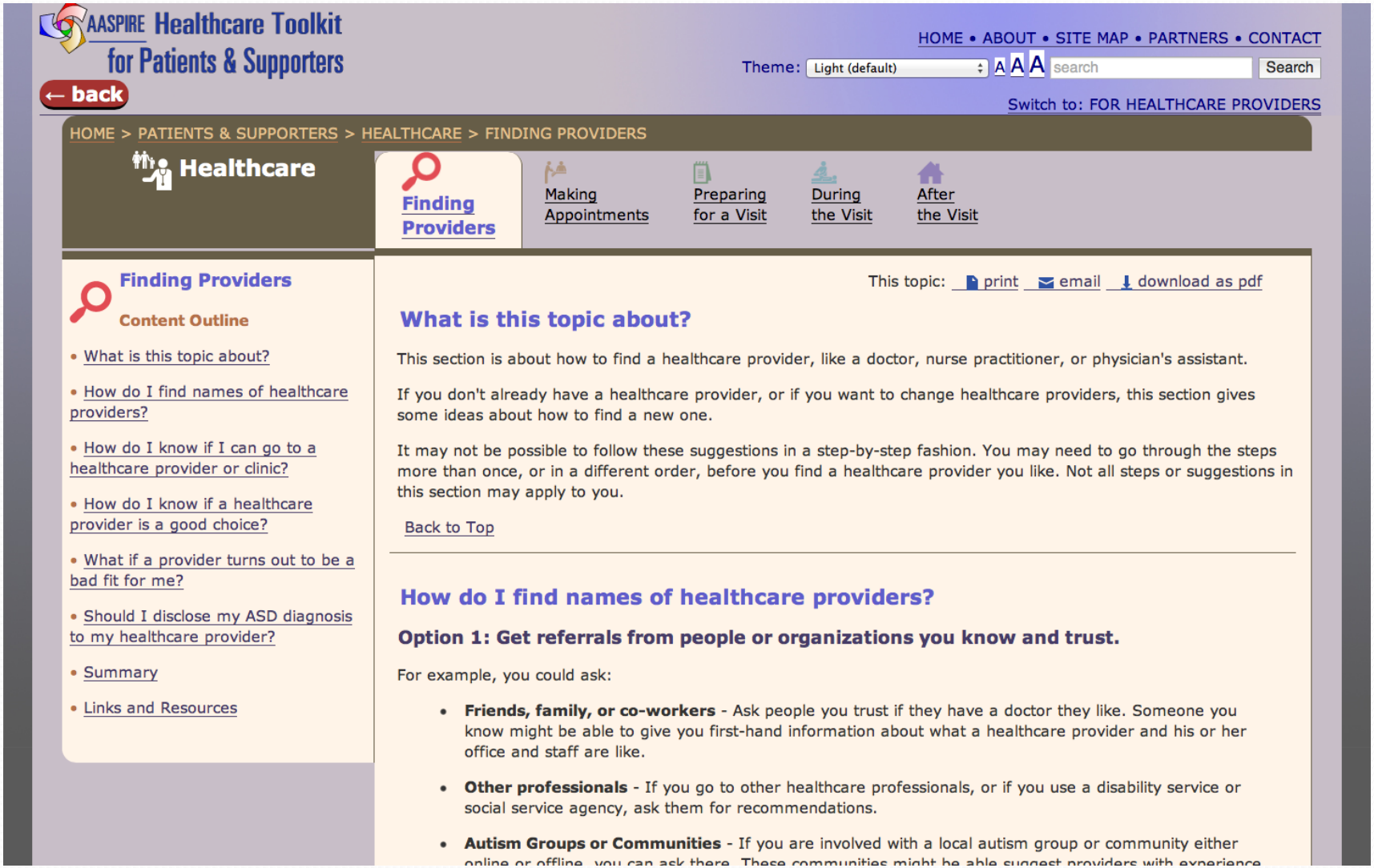
AASPIRE Healthcare Toolkit – www.autismandhealth.org



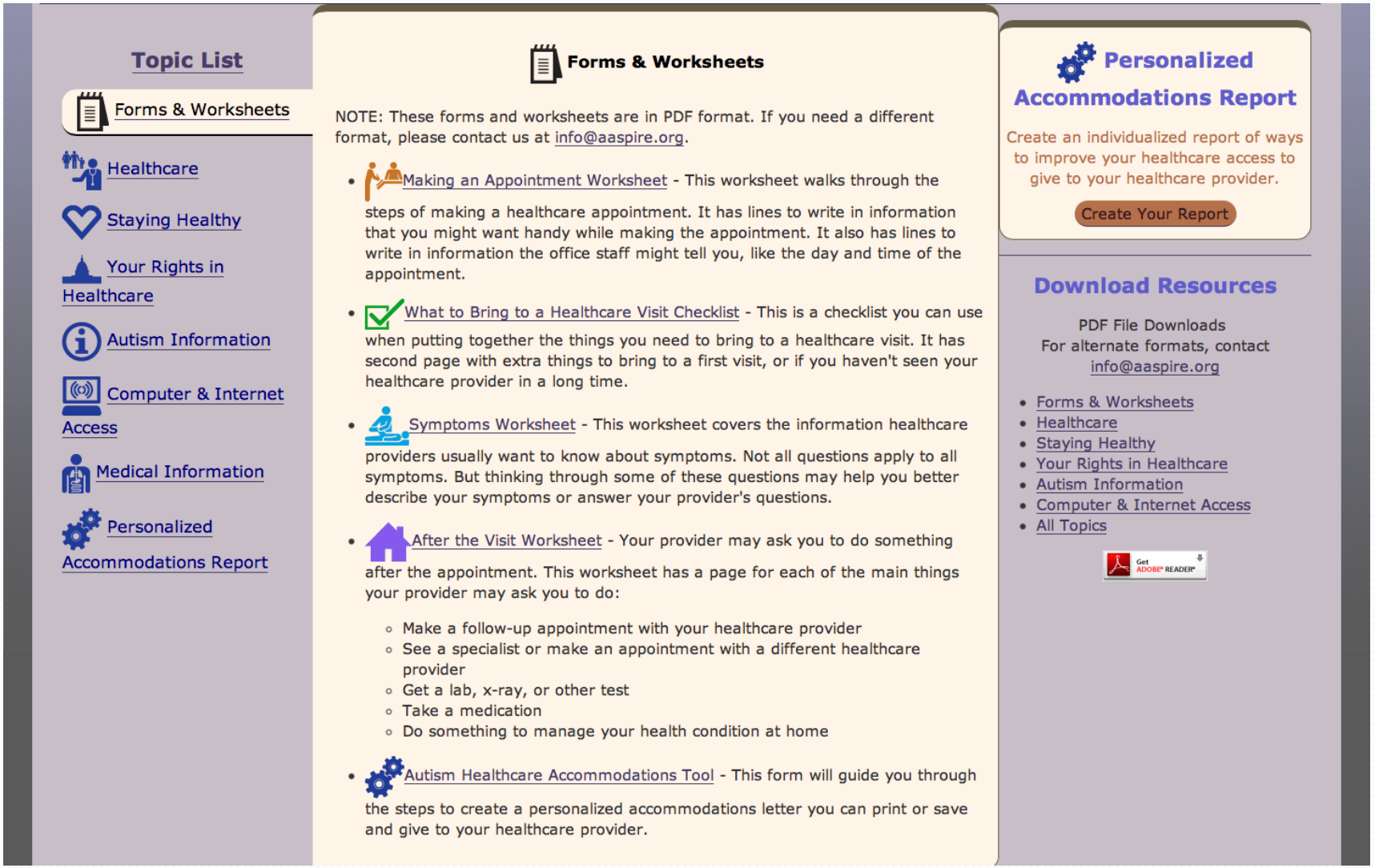
Provider Information



Patient Information



Forms and Worksheets



Topic List

- Forms & Worksheets
- Healthcare
- Staying Healthy
- Your Rights in Healthcare
- Autism Information
- Computer & Internet Access
- Medical Information
- Personalized Accommodations Report

Forms & Worksheets

NOTE: These forms and worksheets are in PDF format. If you need a different format, please contact us at info@aaspire.org.

- Making an Appointment Worksheet - This worksheet walks through the steps of making a healthcare appointment. It has lines to write in information that you might want handy while making the appointment. It also has lines to write in information the office staff might tell you, like the day and time of the appointment.
- What to Bring to a Healthcare Visit Checklist - This is a checklist you can use when putting together the things you need to bring to a healthcare visit. It has second page with extra things to bring to a first visit, or if you haven't seen your healthcare provider in a long time.
- Symptoms Worksheet - This worksheet covers the information healthcare providers usually want to know about symptoms. Not all questions apply to all symptoms. But thinking through some of these questions may help you better describe your symptoms or answer your provider's questions.
- After the Visit Worksheet - Your provider may ask you to do something after the appointment. This worksheet has a page for each of the main things your provider may ask you to do:
  - Make a follow-up appointment with your healthcare provider
  - See a specialist or make an appointment with a different healthcare provider
  - Get a lab, x-ray, or other test
  - Take a medication
  - Do something to manage your health condition at home
- Autism Healthcare Accommodations Tool - This form will guide you through the steps to create a personalized accommodations letter you can print or save and give to your healthcare provider.

Personalized Accommodations Report

Create an individualized report of ways to improve your healthcare access to give to your healthcare provider.

Create Your Report

Download Resources

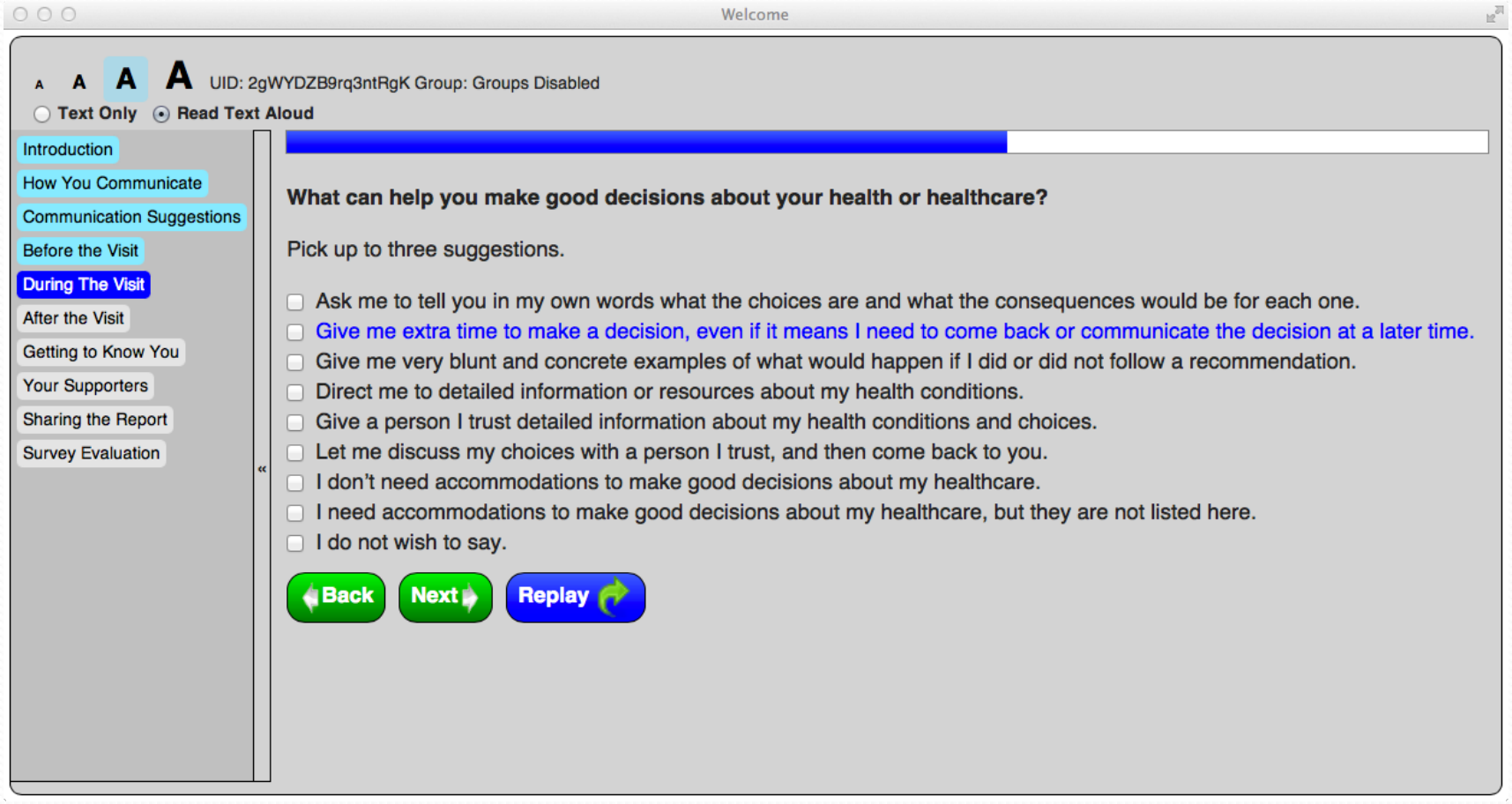
PDF File Downloads
For alternate formats, contact info@aaspire.org

- Forms & Worksheets
- Healthcare
- Staying Healthy
- Your Rights in Healthcare
- Autism Information
- Computer & Internet Access
- All Topics

Autism Healthcare Accommodations Tool (AHAT)

- Fill out a survey
- Computer uses answers to create a personalized and healthcare provider-friendly report of accommodations

Sample AHAT Item



Sample Provider Report

Patient: Dora Raymaker

IV. Recommendations to Assist with Shared Decision Making

- Allow her extra time for making decisions (might involve communicating decision at a later time).
- Be very blunt and give concrete examples of what would happen if a recommendation was or wasn't followed.
- Give a trusted person detailed information about health conditions and choices.
- Allow time for her to discuss choices with a trusted person.

V. Recommendations to Help Ms. Raymaker Comply with Recommendations

- Write out your impressions and the plan for next steps or treatments.
- Write out detailed step-by-step instructions.
- Show pictures as much as possible.
- Show her what to do while she is still in the office.
- Have staff help with scheduling follow-up visits, referrals, or tests.

(just part of the full report)

Initial Toolkit Evaluation

- Mixed-methods, single arm, 1-month pre-post intervention study design in real-life setting.
- 170 autistic participants; 41 PCPs
- 95-97% found it easy to understand, important, & useful.
- Significant changes between pre- and post-test in
  - Number of barriers to healthcare
  - Healthcare self-efficacy
  - Patient Provider communication
- Strong qualitative themes around toolkit utility
  - Means to clarify and communicate needs
  - Validation of experience and empowerment re self-advocacy
  - Improved self-efficacy; better able to prepare for visits
  - Examples of changes in provider behaviors

Nicolaidis et el, *Journal of General Internal Medicine,* 2016

Integrating the Toolkit into Healthcare Systems

- Current NIH grant to integrate AASPIRE Healthcare Toolkit into 3 diverse health systems
  - Kaiser Permanente Northern California, Oregon Health & Science University, and Legacy Health System
- Worked with 7 intervention clinics to find processes that work for their workflows and settings
- Comparing 6-month patient and provider outcomes with those from control clinics

Next Steps

- Need help with dissemination of Toolkit – Available for free at www.autismandhealth.org
- Working with Dr. Parr and collaborators to adapt toolkit for use in the National Health System in the UK.
- Fulbright Scholar, Dr. Urbanowicz, will be adapting toolkit for use in inpatient settings.
- Looking for collaborators for multi-site randomized controlled trial.
- With appropriate resources, would like to:
  - Expand to mental health care, dental care, emergency care
  - Add multi-media training segments
  - Connect directly to EMRs

Other Potential Solutions

Healthcare Provider Training

- Medical / nursing school / residency curricula
  - No current training requirements
  - Crowded curricula
  - Potential for collaborations with accreditation councils?
  - A few model programs – need to be expanded
- CME / CEU trainings for practicing providers
  - Many competing priorities
  - Low number of patients for any one provider
  - Need for creative recruitment strategies and novel formats
  - Possible collaborations with professional societies
- Decision Support Tools / Referral Resources
- Must include perspective of autistic patients and supporters

Healthcare Workforce / Systems

- Consult services / specialized clinics
  - Challenges with access for large parts of the population
- Developmental Medicine as a new field?
  - Equivalent of Developmental Pediatrics for adults
  - Some interest in med/peds community and family practice
- Annual Health Check model in UK
- Peer navigators
- Other ???

Patient Activation and Self-Advocacy / Self-Management

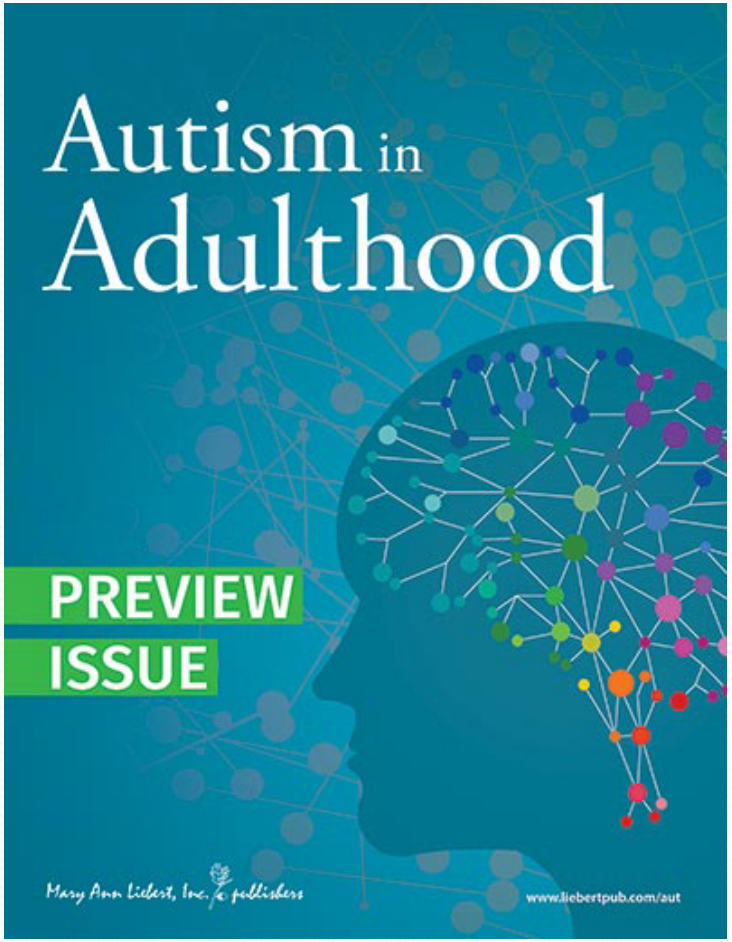
- mHealth Tools
  - Most currently not very accessible
  - If done correctly, could capitalize on autistic characteristics and strengths
- Patient Advocacy Trainings for Supporters
- Other ???

Final Thoughts

Take Home Points

- Autistic adults currently experience significant healthcare disparities
- Adult healthcare system is currently not equipped to manage autistic adults' needs
  - Gaps in provider knowledge and skills
  - Many barriers to care
  - Successful interactions depend on addressing patient, provider, and health system factors
- AASPIRE Healthcare Toolkit is a first step to improving care
- Many more solutions are needed at patient, provider, and system levels!

A New Home for Research on Autism in Adulthood



- Focuses on the most pressing issues affecting autistic adults, from emerging adulthood to late life.
- Includes autistic adults as editorial board members, reviewers, and authors
- www.liebertpub.com/aut

Funding

AASPIRE

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- Portland State University
- The Burton Blatt Institute and Michael Morris

AASPIRE Collaborations (violence, pregnancy)

- Centers for Disease Control
- National Institute of Child Health and Development R21HD078830

Discussion and Questions

- Thank you to all our AASPIRE partners
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  - www.libertpub.com/aut

Discussion

Working Group Discussion

Adjournment

Thank You OARC Staff

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Next IACC Meeting

Wednesday, October 17th 2018