Autism Awareness Night

Understanding Causes & Treatments of ASD
In the Next 25 Years

Nancy Minshew, MD
Professor of Psychiatry & Neurology
Director NIH Autism Center of Excellence
We wish to honor those individuals and families who have believed in research and been committed to participating again and again.
ASD: Behaviorally Defined Syndromes

3 Core Symptoms
Associated Symptoms: sensory, motor
Co-morbid Conditions: intellectual disability, ADHD, seizures, regulation disorders
Behaviorally Based Autism Theories Dominated the 20th Century

- Social impairment: pathognomonic, inferred to be the cause of syndrome - social primacy
- Alternative: No unifying core deficits found - each independent (dimensional approach) & genes independent
- Pitfall: expectation that human behavior predicts brain function; failure to seek out neurological mechanisms & principles that govern presentation & expression of neurodevelopmental disorders
Developmental Neurobiologic Events

- Organogenesis
- Neuronal proliferation*
- Glial proliferation, migration
- Neuronal migration**
- Neuronal organization***
- Myelination
## Organization

<table>
<thead>
<tr>
<th>TABLE 2-24</th>
<th>Organization</th>
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</thead>
<tbody>
<tr>
<td><strong>Peak Time Period</strong></td>
<td>5 months’ gestation–years postnatal</td>
</tr>
<tr>
<td><strong>Major Events</strong></td>
<td></td>
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<tr>
<td>Subplate neurons: establishment and differentiation</td>
<td></td>
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<tr>
<td>Lamination: alignment, orientation, and layering of cortical plate neurons</td>
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<td>Neurite outgrowth: dendritic and axonal ramifications</td>
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<td></td>
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<td></td>
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<td>Glial proliferation and differentiation</td>
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</tbody>
</table>
How the Brain Develops

- 15-1/2 wks
- 22 wks
- 23 wks
- ~25 wks

- 27 weeks
- Full term brain
- Adult
Camera Lucida composite drawings of neurons in the visual (calcarine) cortex of human infants indicated gestational ages. Note the appearance and elaboration of basilar dendrites and the tangential spread of apical dendrites, as well as the accompanying maturation of the visual evoked response (top). (Courtesy of Dr. Dominick Purpura).
How the Brain Develops

A  One month old
B  Six month old
C  24 month old
Clues To Underlying Brain Events in Autism

- Age of onset
- Selective involvement of higher cortical functions
- Golgi stain: truncated dendritic tree development
- Whole brain: too big- HC, weights, total volume
- Cortical Under-connectivity
Reliably lower functional connectivity for autism participants between pairs of key areas during sentence comprehension (red end of scale denotes lower connectivity)
Reliable differences in functional connectivity: autism group has lower functional connectivity but same rank order
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Developmental Neurobiologic Events

- Organogenesis
- Neuronal proliferation*
- Glial proliferation, migration
- Neuronal migration**
- Neuronal organization***
- Myelination
1. Spontaneous Mutations: Increased rate of “de novo” copy number variations: submicroscopic deletions or duplications of DNA sequences. More common in simplex than multiplex families. Opened door to two genetic mechanisms: inherited gene mutations and spontaneous copy number mutations—instability in replication of DNA.

2. Potential reversal of Neurodevelopmental Disorders (in Fragile X, Rett & Angelman Syndromes) in adult mice.

Abnormalities in Genetic Code for Brain Development

Abnormal Mechanisms of Brain Development

Structural and Functional Abnormalities of Brain

Cognitive & Neurological Abnormalities

Behavioral Syndrome

Define A Pathophysiologic Sequence For ASD
Brain disturbances produce a constellation of cognitive & neurologic deficits, not a single deficit.

The constellation & mode of presentation reflect the underlying brain mechanism and its location.

Vascular, infectious, traumatic, autoimmune, developmental-maturational-degenerative are types of mechanisms.
Brain Affected Broadly in ASD

From the beginning
Many domains, not one
Began with: home video movies showed symptoms of autism long before diagnosis

Key Q: What are the first behavioral characteristics that predict the development of autism?

Method: study of infants with an older sibling diagnosed with autism

This strategy is proving invaluable in bringing new insights to autism
Developmental Characteristics of Infant Sibs: Onset > 6 mos; Motor & Balance

- No developmental differences at 6 mos
- Differences in fine and gross motor- early
- Less mouthing of objects-less vocalizations
- Truncal instability when sitting- early
- Developmental differences at 12 mos on standardized tests- a developmental deceleration
- Gap widens between 12 & 24 months and beyond
Developmental Characteristics of Infant Sibs: Sensory-Repellitive-Visual Regard

- Repetitive behaviors: unusual visual regard and waving of arms and hands at 12 and 18 mos
- Sensory-related behaviors: under and over responsiveness at 12 months but not 6 mos
- Social emotional: no temperamental differences at 6 mos, over time temperamentally more difficult with more intense distress and more time fixating on objects; accompany- don’t predate- sx
- At 24 months, emotional and behavioral self-dysregulation distinguished infant sibs dx ASD
No social signs at 6 months don’t predate other sx
Delays in verbal and nonverbal language at 12 months but not earlier
Best predictor of response to name at 14 mos-child’s self initiated and spontaneous gaze shifts from toy to parent- joint attention
Social-communication impairments evolve 12-24 months
Lack of behavioral markers at 6 months; earliest differences are subtle, involve a few behaviors or small differences

Socially normal at 6 months

Onset: not early or regressive but rather slower or faster mounting of symptoms- a deceleration of development: core symptoms present at 12 mos and grow more severe over time

“Associated symptoms” are integral-irritability, sensory responsivity, activity level, poor gross motor development
Developmental Characteristics of Infant Sibs: Conclusions

- “These findings do not support the view that autism is primarily a social-communicative disorder and instead suggest that autism disrupts multiple aspects of development rather simultaneously.”

- “Children’s developmental rates are decelerating markedly in a 12 month period, with IQs dropping from average to below 50 for some children.”

   Sally Rogers, 2009
What is happening in the BRAIN in infant sibs?

- Onset of acceleration of brain growth at 9-12 months - coincident with or before onset of symptoms.

- Brain growth in ASD is inverse of Retts syndrome.
Figure 2. Occipital–frontal (OFC) Z score measurements ($N = 195$) with mean estimated growth trajectory for 28 children with autism spectrum disorder (hierarchical linear model two-piece linear model centered at 12 months).
Reliably lower functional connectivity for autism participants between pairs of key areas during sentence comprehension (red end of scale denotes lower connectivity)
fMRI Activation During a Spatial Working Memory Task  (Courtesy John Sweeney)
BRAIN AFFECTED BROADLY in ASD

Cortical-Cortical Connections
Cortical-amygdala
Cortical-striate
Growth dysregulation at other critical ages
### The Profile of Intact & Impaired Abilities in High Functioning Autistic Individuals

#### Intact or Enhanced
- Attention
- Sensory Perception
- Elementary Motor
- Simple Memory
- Formal Language
- Rule-learning
- Visuospatial processing

#### Cognitive Weaknesses
- Complex Sensory
- Complex Motor
- Complex Memory
- Complex Language
- Concept-formation
- Face Recognition
20-25 Genes Identified So Far
More As We Speak

Share common signaling pathways involved in connecting neurons together
Mechanisms are basis of new intervention
No single or even few genes implicated. Rather, numerous candidates with a modest at best increased risk for autism.

Tend to have one thing in common: are involved in determining where and how brain cells (neurons) are connected and talk to each other.
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s) associated with the syndrome</th>
<th>Proportion of patients with the syndrome that have an ASD</th>
<th>Proportion of patients with an ASD that have the syndrome</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>15q duplication — Angelman syndrome</td>
<td>UBE3A (and others)</td>
<td>&gt;40%</td>
<td>1–2%</td>
<td>101–103</td>
</tr>
<tr>
<td>16p11 deletion</td>
<td>Unknown</td>
<td>High</td>
<td>~1%</td>
<td>20, 35, 44</td>
</tr>
<tr>
<td>22q deletion</td>
<td>SHANK3</td>
<td>High</td>
<td>~1%</td>
<td>21, 22, 104</td>
</tr>
<tr>
<td>Cortical dysplasia-focal epilepsy syndrome</td>
<td>CNTNAP2</td>
<td>~70%</td>
<td>Rare</td>
<td>37</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>FMR1</td>
<td>25% of males; 6% of females</td>
<td>1–2%</td>
<td>105</td>
</tr>
<tr>
<td>Joubert syndrome</td>
<td>Several loci</td>
<td>25%</td>
<td>Rare</td>
<td>106</td>
</tr>
<tr>
<td>Potocki–Lupski syndrome</td>
<td>Chromosome position 17p11</td>
<td>~90%</td>
<td>Unknown</td>
<td>107</td>
</tr>
<tr>
<td>Smith–Lemli–Optiz syndrome</td>
<td>DHCR7</td>
<td>50%</td>
<td>Rare</td>
<td>108</td>
</tr>
<tr>
<td>Rett syndrome</td>
<td>MECP2</td>
<td>All individuals have Rett syndrome</td>
<td>~0.5%</td>
<td>109</td>
</tr>
<tr>
<td>Timothy syndrome</td>
<td>CACNA1C</td>
<td>60–80%</td>
<td>Unknown</td>
<td>24</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC1 and TSC2</td>
<td>20%</td>
<td>~1%</td>
<td>110</td>
</tr>
</tbody>
</table>

The rates quoted in the table depend on the population that is being evaluated. For example, rates are higher in individuals from simplex families compared with multiplex families, and are higher in dysmorphic and mental retardation populations compared with idiopathic populations. ‘High’ is used for syndromes in which no good estimates exist (that is, only a handful of individuals with the syndrome in question have been identified). It should also be noted that none of the studies cited here indicates that assessment for the autism spectrum disorder (ASD) was performed blind to a patient’s primary diagnosis. An expanded version of the table with additional variables can be found in Supplementary Information S1 (table). CACNA1C, calcium channel voltage-dependent L type alpha 1C subunit; CNTNAP2, contactin associated protein-like 2; DHCR7, 7-dehydrocholesterol reductase; FMR1, fragile X mental retardation 1; MECP2, methyl CpG binding protein 2; SHANK3, SH3 and multiple ankyrin repeat domains 3; TSC1, tuberous sclerosis 1; TSC2, tuberous sclerosis 2; UBE3A, ubiquitin protein ligase E3A.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome or mutation(s)</th>
<th>Replicated association</th>
<th>Analysis of variant</th>
<th>Mouse model</th>
<th>Other evidence</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Promising</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AVPR1A</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
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<tr>
<td>DISC1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
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<tr>
<td>ITGB3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>AHI1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
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<tr>
<td>EN2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
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<tr>
<td>GRIK2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1; homozygous mutation results in non-syndromic mental retardation</td>
<td>2</td>
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<tr>
<td>NRXN1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
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<tr>
<td>SLC25A12</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1; associated with neurite outgrowth, expression is upregulated in ASD brain</td>
<td>2</td>
</tr>
<tr>
<td><strong>Probable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CACNA1C</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>CNTNAP2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>MET</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1; expression reduced in brains of cases versus controls</td>
<td>3</td>
</tr>
<tr>
<td>OXTR</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1; expression reduced in blood of cases versus controls</td>
<td>3</td>
</tr>
<tr>
<td>SHANK3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1; modulates glutamate-dependent reconfiguration of dendritic spines</td>
<td>3</td>
</tr>
<tr>
<td>SLC6A4</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1; clinical benefit from inhibitors, variation linked to gray-matter volume</td>
<td>3</td>
</tr>
<tr>
<td>CADPS2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>DHCRT7</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1; hypocholesterolaemia in a proportion of probands</td>
<td>4</td>
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<tr>
<td>FMR1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>NLGN3</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>NLGN4X</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>PTEN</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1; mutations result in abnormal structure and function of the synapse</td>
<td>4</td>
</tr>
<tr>
<td>TSC2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1; regulates dendrite morphology and function of glutamatergic synapses</td>
<td>4</td>
</tr>
<tr>
<td>GABRB3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1; expression is dysregulated in pervasive developmental disorders</td>
<td>4</td>
</tr>
<tr>
<td>MECP2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1; MECP2 deficiency causes reduced expression of UBE3A and GABRB3</td>
<td>5</td>
</tr>
<tr>
<td>TSC1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1; regulates dendrite morphology and function of glutamatergic synapses</td>
<td>5</td>
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<tr>
<td>UBE3A</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1; expression is dysregulated in pervasive developmental disorders</td>
<td>5</td>
</tr>
<tr>
<td>RELN</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1; levels reduced in brains of cases versus controls</td>
<td>6</td>
</tr>
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</table>
Axonal Pathfinding & Targeting:
-- Cadherins
-- LRRs

Synaptic Targeting & Function:
-- Neurexins/Neuroligins

Dendritic Morphology/Function:
-- SHANKs

Adapted from www.morphonix.com
1. Genes whose products affect **axonal targeting and pathfinding** i.e. getting neurons connected in the right way. **Cadherins** and **leucine-rich repeat proteins** which are cell surface proteins expressed in neuronal processes - thought to be important for establishing connections between cells in the developing brain.
2. Those that affect **synaptic functioning**: 

**Neurexins and neuroligins** bind each other across the synapse (i.e. glue neurons together) and mediate signaling across the synapse, and affect the properties of neural networks by specifying synaptic functions (i.e. excitatory versus inhibitory)
3. Those that appear to affect **dendritic function**:

   Shank family of synaptic proteins function as molecular scaffolds at the post synaptic density and promote the maturation and enlargement of dendritic spines.
Axonal Pathfinding & Targeting:
-- Cadherins
-- LRRs

Synaptic Targeting & Function:
-- Neurexins/Neuroligins

Dendritic Morphology/Function:
-- SHANKs

Adapted from www.morphonix.com
A Molecular Pathophysiology Emerges

- Defining molecular mechanisms empowers a new world of interventions
- mTor inhibitor Rapamycin to prevent development of seizures, intellectual disability and ASD in infants and toddlers diagnosed with TSC gene tuberous sclerosis; clinical trials in progress
Rapamycin treatment reduces anxiety, improves social activity, and controls seizures. In the open-field test, rapamycin (Rapa)-treated Pten mutant mice showed no significant difference from rapamycin-treated controls, whereas vehicle-treated Pten mutants showed statistically significant decrease in center time compared with vehicle-treated control mice.
Rapamycin injection progressively reduces seizure duration and frequency of *Pten* mutant mice. *n* = 6 mice per group. *p* < 0.05 compared between vehicle- and rapamycin-treated mutants. Data are mean ± SEM and were analyzed by ANOVA, followed by post hoc *t* test.
The “Cognitive” Profile in Autism

- Simpler abilities intact or enhanced
- Information processing capacity limited—integrative processing & higher order cognitive abilities disproportionately impaired

Inference: higher order brain circuitry is under developed- over-reliance on lower order visual circuitry to function.
Cognitive Enhancement Therapy

- A cognitive rehabilitation intervention for remediating neurocognitive and social-cognitive deficits developed by Hogarty and colleagues (2004, 2006).

- **Neurocognitive Training: processing speed**
  - Computer-based training in attention, memory, and problem-solving.
  - 1 hour/week
  - 60 hours total

- **Social-Cognitive Group Therapy: perspective taking**
  - Training in perspective-taking, gistfulness, non-verbal communication, emotion perception, and much, much more.
  - 1.5 hours/week
  - 45 sessions

Process of CET

- Starts with basic socialization and attention training in pairs (3mo to 6mo)
- Moves to small group-based social-cognitive training (6mo to 18mo)
- Simultaneously moves to executive function and problem-solving training (6mo to 18mo)
- All provided in the context of meaningful functional goals (e.g., work, school, girlfriend)
We wish to honor those individuals and families who have believed in research and been committed to participating again and again.