Autism: What We Know

Mental Health & Wellness Lecture Series

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Why Do We Hear About Autism So Much?

- Institutionalization very early
- No school or training programs
- Special schools
- Special education, integration in regular ed.
- Sesame Street, Mr. Rogers
- Autism narrow-Autism Spectrum Disorder+
- Incentive to identify increased by EIBI
- Internet provides dissemination & magnification
Augmenting Factors

- Drama: media’s goal is to entertain, keep ratings
- Fear: potentiated
- Concealment of actual scientific findings
- Financing of false science and its promotion
- False allegations of conspiracy by those conspiring
- Poorly informed politicians

What Do We Know About The Cause of Autism?

- A LOT more than we used to
- Difference between pathophysiology & etiology
- Disorder & Disease & Syndrome
Known Environmental Causes

- 1st trimester rubella & cytomegalovirus
- Untreated phenylketonuria (inborn error of metabolism);
- Fetal exposure to thalidomide, depakene
Evidence Cited In Support of An Environmental Cause

- Increase in number of diagnosed cases- interpreted to mean an increase in incidence
- Heterogeneity in symptoms across cases interpreted to mean many causes
- Dizygotic twins not 100% concordant for autism
- Assumption: Dizygotic twins have exactly the same genetic material and it is decoded the same.
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Ingredients to Misleading Science
vs Reliable Science

- Emotion over reason, belief over science
- The plural of anecdotes is not evidence
  - Experts credentialed in the areas of the work
  - Experts working at an academic institution
  - Publications are in society journals w/ good IF
  - Funding source for research is respected and w/o influence on outcome
  - Concept based on solid science foundation
  - Finding replicated by others and other methods
Some Biological Features of Autism

- Raised serum serotonin in 30% but nonspecific
- No consistent or marked response to psychotropics
- Very limited generalization of responses to psychological interventions
- Brain imaging: no localized abnormality, rather an impaired integration across systems
- No consistent neuropathological pattern except findings suggest prenatal origin

Courtesy of Michael Rutter “Autism: Clinical features and research challenges”
Medical Associations

- Association with some diagnosable medical condition in at least 10% of cases
- Strongest association with tuberous sclerosis but largely a function of location of tubers, low IQ and epilepsy
- Definite, but weak association with fragile X anomaly

Some Genetic & Related Features

- Marked increase in familial risk (50x)
- Heritability circa 90%, 3-12 genes involved
- Increased rate of chromosomal anomalies (but diagnostically nonspecific)
- Increased rate of congenital anomalies but apart from ch 15, nonspecific
- Association with increased parental age
- Increase in copy number variations (CNV)

Courtesy of Michael Rutter “Autism: Clinical features and research challenges”
Pathophysiologic Sequence Of A Neurodevelopmental Disorder

Abnormalities in Genetic Code for Brain Development

↓

Abnormal Mechanisms of Brain Development

↓

Structural and Functional Abnormalities of Brain

↓

Cognitive & Neurologic Abnormalities

↓

Behavioral Syndrome
Developmental Neurobiological Events

- Organogenesis (basic form of the brain)
- Neuronal proliferation (increase in neurons)
- Glial proliferation, migration
- Neuronal migration (nerve cells move)
- Neuronal organization (connections)
- Myelination (coated for faster signaling)
Autism Speaks
Top 10 Autism Research Events of 2007

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

2. This is proof of concept, e.g., that the strategy of finding genes and understanding neurobiological mechanisms enables the development of chemical rescues or restorations

3. The adult animal is easier to restore because it is not a moving target among the moving masses.
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.

3. **Autism Genome Project (AGP):** largest genetics consortium, launched in 2004, largest study ever conducted to find genes associated with risk of developing autism. 50 academic and research institutions from 19 countries, pooled resources and used DNA microarray to scan the human genome for genetic causes of autism; first analyses made public in 2007. Nature Genetics 2007. Chromo 2, 7, and 11 plus linkage signals only present in girls, identification of a specific candidate gene neurexin, associated with copy number variation.
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.

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4. First drug FDA-approved to treat symptoms associated w/ autism; Risperdal.

5. PTEN conditional knock-out mice display enlarged brains and social behavioral deficits: PTEN interacts with several proteins in a signaling cascade that are tied to tuberous sclerosis and neurofibromatosis. 17% of individuals with autism & macrocephaly had PTEN gene. KO mice raises rescue possibilities.
6. Mouse models of genes associated with autism in humans: *neuroligin-3* gene mouse model: mouse has deficits in social behaviors and an increased ability for spatial learning.

7. Functional connectivity: neural deficits not in a single structure but in wiring that networks that connect different parts of brain.
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.

8. Discovery of rare families with SHANK3 gene mutations added further evidence to synaptic dysfunction hypothesis. Codes for synapse formation & maintenance. It also interacts with neuroligins and neurolexins.

9. Lack of response to name at one year is one of earliest signs of autism; signs of autism can be identified at 14 mos in half of cases.

10. Parental age (paternal or maternal or both) is related to but not necessarily the cause of increased risk of autism.
Pervasive Developmental Disorders (DSM)  
*Autism Spectrum Disorders (Informal)

DSM-IV (1994): Pervasive Developmental Disorders
- *Autistic Disorder
- *Asperger’s Disorder
- *Pervasive Developmental Disorder NOS
- Childhood Disintegrative Disorder
- Rett’s Disorder

Multiple organ involvement is the rule in neurologic disorders not due to acquired brain damage- because they are caused by faulty genes and these genes are present in every cell in the body.
2.27 relative risk of autism diagnosis conferred by the CC genotype at MET receptor tyrosine kinase. MET signaling is involved in neocortical and cerebellar development, immune function, and gastrointestinal repair, consistent with the multi-organ symptoms reported in autism.

Need not invoke GI or immune disease as causing brain dysfunction; same gene may cause all.

Campbell et al. PNAS 2006, 45: 16834-16839
Neurologists’ approach to understanding brain disorders is to characterize all impaired AND all intact abilities to define the common characteristics that will provide guiding principles that advance intervention.
Disease Processes or Mechanisms

- Infectious disease
- Vascular disease
- Tumor or mass
- Toxins
- Developmental processes
Developmental Processes

- Organogenesis (basic form of the nervous system)
- Neuronal proliferation
- Glial proliferation, migration
- Neuronal migration
- Neuronal organization
- Myelination
# The Profile of Intact & Impaired Abilities in High Functioning Autistic Individuals

<table>
<thead>
<tr>
<th><strong>Intact or Enhanced</strong></th>
<th><strong>Cognitive Weaknesses</strong></th>
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<tbody>
<tr>
<td>Attention</td>
<td>Complex Sensory</td>
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<tr>
<td>Sensory Perception</td>
<td>Complex Motor</td>
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<tr>
<td>Elementary Motor</td>
<td>Complex Memory</td>
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<td>Simple Memory</td>
<td>Complex Language</td>
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<td>Formal Language</td>
<td>Concept-formation</td>
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<td>Rule-learning</td>
<td>Face Recognition</td>
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<td>Visuospatial processing</td>
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What Does The Profile Mean?

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

Inference: higher order brain circuitry is under developed- they are reliant on lower order circuitry particularly visual circuitry to function.
fMRI Activation During a Spatial Working Memory Task  (Courtesy John Sweeney)
Behavioral Example of Cognitive Profile: Using the Profile to Intervene

Jim was admitted for possible mania. He was agitated and had been sending money to television evangelists and became preoccupied with sin and being good, which he talked about constantly. The psychiatrists attempted daily to PERSUADE him to try lithium but he refused. His reason was that he took lithium on June 4, 1978 and he got a stomach ache. He went to the clinic and a scene ensued. Staff yelled at him. No amount of REASONING worked to change his mind, until he was told and SHOWN there were now two forms of lithium - one was pink and one was blue. He took the bad blue before, but this time he would take the good pink. He immediately agreed to the medication. The deterioration in his behavior was the result of losing his job for asking a woman a question about her clothing, which was interpreted as sexual harassment. All structure was gone from his life. Socially-emotionally he was three years old. He was not reciprocal in conversation. He talked, the doctors talked.
Bill is a young adult with autism who decided to take figure skating lessons. His mother drove to the rink several times a week. After a while, she decided to skate while he had his lesson. Bill performed his routine, but people learned to stay out of his way. He went where his program required him to go regardless of others. One day his mother forgot to note where Bill was and he ran her over, knocking her unconscious. The emergency team was called and she was given first aide and taken to the hospital. The next day she asked Bill why he did not come to her assistance, since he was an Eagle Scout with a first aide badge. He replied “It expired.”
### Effect of dual task on memory span and tracking performance

<table>
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<tr>
<th>People with autism (n = 16)</th>
<th>Digit recall</th>
<th>Tracking performance</th>
<th>Mu score</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>single</td>
<td>dual</td>
</tr>
<tr>
<td>Mean</td>
<td>86.19</td>
<td>&gt; 48.13</td>
<td>52.75</td>
</tr>
<tr>
<td>SD</td>
<td>7.55</td>
<td>16.77</td>
<td>10.47</td>
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| Controls (n = 16)           |              | 86.88   | 55.25 | 84.75   |
| Mean                        | 87.25        |         |       |         |
| SD                          | 4.81         | 7.58    | 14.61 | 7.39    | 11.52 |

Digit recall is expressed as a percentage of correct sequences.

**Dual task performance deficit in autism; (but matched performance in single task conditions)**

Garcia-Villamisar & Della Sala, 2002 Cognitive Neuropsychiatry
Within each domain, there was a pattern of intact and impaired abilities. The dissociation was characteristic and was exemplified by the abstraction-EF domain. The result has a marked impact on behavior, and also on adaptive function. Along with social ineptness, the hallmark of autism in verbal individuals is their reliance on rules despite failure and generally slow processing speed.
Social Emotional Immaturity: Disturbance in Affective Contact Not Included in DSM

• Capacity to experience, comprehend, and regulate emotions at a basic and cognitive level is severely impaired and unrecognized despite frequent abnormal imaging abnormalities of the amygdala, an emotion structure of the brain.

• Most verbal ASD adults are socially-emotionally 12-18 months to 4-5 years of age. Failure to recognize this in treatment worsens behavior.
Head Growth in Autism

- Group mean 60-70%
- Onset accelerated growth at 9 months w/ 15-20% macrocephalic by 4-5 years
- Growth decelerates and plateaus so that brain volume “normalizes” in childhood, though subset remain macrocephalic throughout life
- Important to recognize that HC>HT is not universal in autism and HC=HT and HC<HT growth trajectories compatible with autism
Synthesis of Brain Volume Studies

- Major role for white matter but without accompanying long tract signs and thus the difference between acquired and devel. disorders
- Disturbance in connectivity
- Increased white matter volume was associated with dysfunction not increased function
- Inter-hemispheric white matter e.g. corpus callosum was not involved in the same process

Minshew & Williams, Arch Neurol 2007
Brain activation during sentence comprehension in autism in Brain, 2004

Autism group has less activation in **Broca’s area**
- (a sentence integration area)
than the control group and more in **Wernicke’s area**
- (a word processing area)

Results are consistent with poorer comprehension of complex sentences, coupled with good word reading (spelling bee champs)
Reliably lower functional connectivity for autism participants between pairs of key areas during sentence comprehension (red end of scale denotes lower connectivity)
Functional Connectivity
The activation in two cortical areas can be less synchronized (upper panel) or more synchronized (lower panel) for different people.
Reliable differences in functional connectivity: autism group has lower functional connectivity but same rank order.
Functional Underconnectivity: fMRI of the Tower of London

Marcel Just
Nancy Minshew
Tim Keller
Vlad Cherkassky
Rajesh Kana

Just et al., 2006 [Epub ahead of print], Cereb Cortex
Information processing capacity is reduced—dual tasks, speed of processing, and any task relying on strategy.

Functional under-connectivity of neural systems is a general feature of the brain in autism.

Circuitry underlying basic abilities is intact, and these circuits plus visual processing are relied upon to perform tasks that typical individuals perform using integrative circuitry and higher order abilities.
Infants are born with automatic mechanisms that allow them to form Prototypical Representations of Information.
Which of these is the best example of a dog?
Which of the following two faces looks more familiar to you?
Attractiveness Ratings

Correlation of ratings by Controls vs. Autistics: \( r = -0.06 \)
Individuals with autism have difficulty with categorizing atypical exemplars of categories. While categorization improves with development, adults with autism never reach the “expertise” abilities of controls. These deficits are seen with both faces (e.g., gender discrimination) and object categorization. The inability to form prototypical representations of categories also impacts facial recognition skills so that distinctive faces are not remembered better than typical faces. A lack of facial prototypes can also be seen in their not perceiving “average” or protoypical faces as attractive.
Mirror Neuron System: How the Brain Learns What Others Feel

- MNS (pars opercularis in IFG) is active during observation, imitation, and understanding of the intentions of others.
- Thought to provide a mechanism for understanding the actions & intentions of others.
- When acting in conjunction with the limbic system it is thought to mediate the understanding of emotions and the internal experiences of others.
What are the brain systems involved in representing the actions and intentions of other people?

Pelphrey et al. (2003) *Journal of Neuroscience*
Carter & Pelphrey (2007) *Social Neuroscience*
Pelphrey et al. (2002); Journal of Autism and Developmental Disorders
Resources For Families

• Autism Speaks – First 100 Days Kit
  http://www.autismspeaks.org/community/family_services/100_day_kit.php

• Children’s Hospital of Philadelphia: Vaccine Education Center
  http://www.chop.edu/consumer/jsp/division/generic.jsp?id=84662

• American Academy of Pediatrics – Autism and Vaccine Safety for Parents
  http://www.medicalhomeinfo.org/health/autism.html
Resources For Families (con’t)

- **First Signs**  [http://www.firstsigns.org/](http://www.firstsigns.org/)
- **Department of Welfare – Autism Services**  [http://www.dpw.state.pa.us/ServicesPrograms/Autism/](http://www.dpw.state.pa.us/ServicesPrograms/Autism/)
Resources For Families and Physicians

- American Academy of Pediatrics – The National Center of Medical Home Initiatives for Children with Special Needs
Resources for Professionals

- Autism Speaks – Community Toolkit
  http://www.autismspeaks.org/community/family_services/school_kit.php

  https://www.nfaap.org/netforum/eweb/dynamicpage.aspx?site=nf.aap.org&webcode=aapbks_productdetail&key=be7a9f12-f5d9-482b-a289-d299a8b9ac64
Books

- “Emergence Labeled Autistic, A True Story” by Temple Grandin, PhD and Margaret Scariano. ISBN 0-446-67182-7
“Developing Talents, Careers for Individuals with Asperger Syndrome and High-Functioning Autism” by Temple Grandin, PhD and Kate Duffy. ISBN 1-93-1282-56-0


Books (cont’d)

- “Unwritten Rules of Social Relationships, Decoding Social Mysteries Through the Unique Perspectives of Autism”, by Temple Grandin, PhD and Sean Barron  

- “Autism’s False Prophets”, by Paul A. Offit, MD  
Autism Treatment Network (ATN)

- Previous diagnosis of ASD not necessary
- Families with a child age 7 and under call 412-692-5560
- Families with a child age 8 and above call 412-235-5412
- Services completed as part of "routine clinical services" will be billed to your insurance; other services will be completed as part of study participation at no cost to you.
- Families will receive ADOS ADI and other tests not typically available, written report, referrals to Medical Specialists, and support & guidance through the process.
- For general inquiries contact Dana Barvinchak at 412-235-5412 or barvinchakdm@upmc.edu
# Tests Used by the ATN Registry

## Standard Measures
- ADI-R
- ADOS
- Mullen Scales of Early Learning
- Stanford-Binet
- Vineland-II
- CBCL
- PedsQL
- Sensory Profile

## ATN Custom Measures
- DSM-IV Checklist
- Developmental & Medical History
- Diagnosis & Treatment
- Dysmorphology Exam
- Neurological Exam
- GI Symptoms Inventory
- Sleep Habits Questionnaire
Specialists Referrals

• Gastrointestinal
• Sleep
• Genetics
• Metabolic
• Neurology
• Psychiatry
• Speech Therapy
• Nutrition
• Otolaryngology
• Dental
• Cardiology
• Endocrinology
• Occupational Therapy
Autism Center of Excellent - Research

- Are between the ages 5 - 45 with an IQ between 80 - 120.
- Infants between 6 - 16 months, there is another study that starts at 5 months. Parents who are pregnant or have an infant no more than 5 months old may participate. These infants must have an older sibling with or without an autism spectrum diagnosis, who live within a two hour drive from the Pittsburgh area.
- Young children with autism who are not yet speaking in complex sentences.
- Participants are reimbursed for travel costs and compensated for their participant.
Contact Information

- Telephone: 412-246-5485
- Fax: 412-246-5470
- Email: autismrecruiter@upmc.edu
- Website: http://www.pittautismresearch.org/
Research Studies

- If you are interested in participating in our studies, call 412-246-5485 or email: autism
- Through July 2012; no cost; participant payment; we pay airfare & hotel