Important Developments In Autism

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June 5, 2008

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Key Features of Autism

1. Impaired social reciprocity
2. Impaired social communication
3. Repetitive, stereotyped interests & behavior
4. Onset in first 2-3 years of life

Q: Is the constellation inherent in a cohesive syndrome or is it an artifact of diagnostic practice?

Courtesy of Michael Rutter “Autism: Clinical features and research challenges”
Some Key Clinical Features of Autism

1. Marked male preponderance (3-4:1) BUT this applies to most neurodevelopmental disorders
2. Association with intellectual impairment BUT IQ range extends from severely impaired to superior
3. Association with epilepsy in 25-33% with onset in adolescence
4. Association with increased head circumference

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

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

The Top 10 of 2007 (cont’d.)

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

Some Biological Features of Autism

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

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

Courtesy of Michael Rutter “Autism: Clinical features and research challenges”
Some Genetic & Related Features

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

Courtesy of Michael Rutter “Autism: Clinical features and research challenges”
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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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
Brain Developmental Processes

- Organogenesis
- Neuronal proliferation
- Glial proliferation, migration
- Neuronal migration
- Neuronal organization
- Myelination
Autism Speaks
Top 10 Autism Research Events of 2007

Courtesy of:
The Top 10 of 2007

1. 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 the 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.

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

4. First drug approved by FDA 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.
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 instability in replication of DNA.

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The Top 10 of 2007 (cont’d)

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.
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.
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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Transforming Findings

1. Autism as a disorder of complex information processing
2. Autism as a disorder of connectivity
3. Autism as a disorder of dysregulated growth of the cerebral hemispheres-gray and white matter but not cc
4. CNV in simplex; synapse-related genes in simplex & multiplex families
The Profile of Intact & Impaired Abilities in High Functioning Autistic Individuals

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

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

Inference: higher order circuitry is under developed-they are reliant on lower order circuitry & basic cognitive abilities to function.
fMRI Activation During a Spatial Working Memory Task  (Courtesy John Sweeney)
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 stomachache. 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.
Effect of dual task on memory span and tracking performance

<table>
<thead>
<tr>
<th>People with autism (n = 16)</th>
<th>Digit recall</th>
<th>Tracking performance</th>
<th>Mu score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>single</td>
<td>dual</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>86.19</td>
<td>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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<th>Controls (n = 16)</th>
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<td></td>
<td>single</td>
<td>dual</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>87.25</td>
<td>86.88</td>
<td>54.06</td>
</tr>
<tr>
<td>SD</td>
<td>4.81</td>
<td>7.58</td>
<td>14.61</td>
</tr>
</tbody>
</table>

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
- Group mean 60-70%
- Onset accelerated growth at 12 months w/ 15-20% macrocephaly 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
Increased Brain Volume in Autism: What does it Mean?

- Group TBV paralleled group HC findings; increase related to intracerebral white matter, and cortical gray matter depending on parcellation.
- Herbert et al. parcellated white matter into inner and outer radiate white matter: increased volume of outer intra-hemispheric short and medium range cortico-cortical connections; no increase in inter-hemispheric or cortical-subcortical connections.

Herbert et al. Brain 2003; 126: 1182-92
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 in press
Why does WM damage from other causes not result in autism?

Because autism is a disorder of neurons, not axons, myelin, or glia.

And because autism is a disorder of early brain development not of damage to already developed structures.
Minicolumn Abnormalities in Autism: Evidence of Cortical Involvement

- First substantive abnormalities of cerebral cortex
- Radially oriented arrays of pyramidal neurons, interneurons, axons and dendrites
- Smallest radial unit of information processing; then macrocolumns and receptive fields?
- Bilateral abnormalities in areas 3, 4, 9, 17, 21, 22
- Increased #, narrower, reduced neuropil space (inhibitory neurons), neurons small

Proton MRS study of 3-4 yr olds with autism, DD, TD: reduced choline compound concentrations and transverse relaxation, suggesting decreased cellularity or density in ASD but not DD or TD.

T2 relaxation in same children prolonged in GM but not WM in ASD but in both GM and WM in DD. Selective involvement of GM interpreted as abnormal developmental process in ASD.

Friedman et al. Arch Gen Psych 2006; 63:786—794;
Petropoulous et al. Neurology 2006; 67:632-636
26 males 6-17 years IQ>70 w/ autism & 26 controls
Proton MRs revealed significantly lower levels of cortical gray matter NAA and glutamate-glutamine that were widespread in cerebral lobes and cerebellum
Conclusion: widespread reduction in gray matter neuronal integrity and dysfunction of cortical and cerebellar glutamatergic neurons

Cortical activation & synchronization during sentence comprehension in HFA subjects

Marcel Just
Vlad Cherkassky
Tim Keller
Nancy Minshew

Just et al. 2004, Brain 127: 1811-1821
Superior to age-, IQ-, gender- matched controls on word & non-word decoding, spelling, vocabulary, fluency

Inferior to controls on comprehension of sentences, idioms, metaphors, stories
The player was followed by the parent.

Who was following?  
player  parent
fMRI Activation During a Spatial Working Memory Task (Courtesy John Sweeney)
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
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*
Incongruent > Congruent

Neurotypical

Typically Developing - Right Superior Temporal Sulcus

Autism - Right Superior Temporal Sulcus

Pelphrey et al. (2005) *Brain*
Pelphrey et al. (2002); Journal of Autism and Developmental Disorders
Mirror Neuron System

• 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.
Second Hit: Frontal Systems Don’t Mature

- Oculomotor studies have demonstrated a delay and incomplete maturation of the frontal lobe in the second decade of life in HFA.
- This accounts for the apparent worsening of function in the second decade as the skills needed to cope with more challenging problems fail to emerge.
- It also explains the poorer than expected outcomes and poorer adaptive behavior in adults.
Cognitively the problem is with prototype formation and automatic processes as opposed to conscious, verbally mediated reasoning.
Concept Formation Impairments Global: All Rely On Prototype Formation & Frontal Connections

- Motor concept learning
- Memory dependent on strategies
- Story creation or theme identification
- Face recognition
- Face affect recognition
- Strategy formation, problem solving
Abilities that adults take for granted that normally develop in infancy and toddlerhood:

For example:

- Our abilities to recognize faces and emotional expressions
- Our abilities to understand the difference between basic categories in the world—cats, dogs, lions …
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?