"Neurologic Basis of Autism"

Autism Course for PGY 2 Child and Adolescent Psychiatry Fellows

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1943-1980

- Described as a syndrome in 1943, 1944
- Thought to be psychogenic in etiology until 1970
- Originally described as a broad range of severity with emphasis on high functioning: 60/40 split
- By 1970, syndrome constricted to mild to moderate MR w/ echolalia & self-stim. behavior
- Originally distinguished from schizophrenia, then classified under childhood psychoses until 1980
Where We Were In 1980

- Autism introduced as a category in DSM/ICD
- No diagnostic instruments
- All cases thought to be caused by other disorders
- Focal brain dysfunction
- Single primary cognitive or sensory deficit
- Very rare disorder: 2/10,000
- Mental disorder
Pervasive Developmental Disorders (DSM)  
*Autism Spectrum Disorders (Informal)  

<table>
<thead>
<tr>
<th>DSM-III (1980)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infantile autism</td>
</tr>
<tr>
<td>Childhood onset pervasive development disorder</td>
</tr>
<tr>
<td>Childhood onset PDD NOS</td>
</tr>
</tbody>
</table>
| DSM-III-R (1987):  
| Autistic Disorder |  
| PDDNOS |  
| DSM-IV (1994): Pervasive Developmental Disorders  
| *Autistic Disorder |  
| *Asperger’s Disorder |  
| *Pervasive Developmental Disorder NOS |  
| Childhood Disintegrative Disorder |  
| Rett’s Disorder |
Diagnostic Instruments

- Autism Diagnostic Interview-Revised
- Autism Diagnostic Observation Schedule
- Expert clinical opinion for confirmation
- Research reliability of administration & scoring of instruments- initial & ongoing
- Expert clinical opinion rules out cases but does not over-ride instruments to include cases
How Research Findings Changed The Disorder: Autism 1990

- Diagnostic methods resulted in recognition that 90-95% of cases idiopathic e.g. autism existed as a disorder in its own right & genetic in origin
- Dawning recognition of neural systems origin
- Increasing documentation of much higher prevalence 1-2/10,000 to 1/100 for ASD
- Recognition that cognitive & neurologic deficits involved higher order abilities in HFAs, not basic abilities, e.g. cerebral hemispheres and cortical systems in particular
## Prevalence 1/166 2002-2006

<table>
<thead>
<tr>
<th>Description</th>
<th>Baird et al(^1)</th>
<th>Chakrabarti &amp; Fombonne(^2)</th>
<th>Brick Township, NJ(^3)</th>
<th>Chakrabarti &amp; Fombonne(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism</td>
<td>30.8/10,000</td>
<td>16.8/10,000</td>
<td>40.5/10,000</td>
<td>22.0/10,000</td>
</tr>
<tr>
<td>Other ASDs</td>
<td>27.1/10,000</td>
<td>45.8/10,000</td>
<td>26.9/10,000</td>
<td>36.7/10,000</td>
</tr>
<tr>
<td>Total for ASDs</td>
<td>57.9/10,000</td>
<td>62.6/10,000</td>
<td>67.4/10,000</td>
<td>58.7/10,000</td>
</tr>
<tr>
<td>Total for ASDs</td>
<td>1/170</td>
<td>1/170</td>
<td>1/150</td>
<td>1/170</td>
</tr>
</tbody>
</table>

- \(^1\) Baird et al, 2000
- \(^2\) Chakrabarti & Fombonne, 2001
- \(^3\) Bertrand et al, 2001
- \(^4\) Chakrabarti & Fombonne et al, 2001
Prevalence 1/150 or 1/100
February 2007

<table>
<thead>
<tr>
<th>Description</th>
<th>Kadesjo, et al(^1) 1999</th>
<th>Baird, et al(^2) 2006</th>
<th>CDC(^3) 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism</td>
<td>60/10,000</td>
<td>38.9/10,000</td>
<td></td>
</tr>
<tr>
<td>Other ASDs</td>
<td>48/10,000</td>
<td>77.2/10,000</td>
<td></td>
</tr>
<tr>
<td>Total for ASDs(^4)</td>
<td>108/10,000</td>
<td>116.1/10,000</td>
<td>66/10,000</td>
</tr>
<tr>
<td>Total for ASDs</td>
<td>1/100</td>
<td>1/100</td>
<td>1/150</td>
</tr>
</tbody>
</table>

\(^1\)Kadesjo et al, JADD, 29:4, 327-331  
\(^2\)Baird et al, The Lancet 368, 210-215 206  
\(^3\)ADDM Network, MMWR 02-09-07; 12-28  
\(^4\)This number was 20/10,000 in 1980
# Estimates of Expressive Language Level at Age 9

151 Autism Participants

*Lord et al* Arch Gen Psych 2006; 63: 694-701

<table>
<thead>
<tr>
<th>Description</th>
<th>Chicago</th>
<th>North Carolina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex sentences (ADOS Module 3)</td>
<td>40.9%</td>
<td>39.6%</td>
</tr>
<tr>
<td>Sentences but not fluent (ADOS Module 2)</td>
<td>35.3</td>
<td>28.9</td>
</tr>
<tr>
<td>Words but not sentences (ADOS Module 1; ADI-R = 1)</td>
<td>10.5</td>
<td>16.8</td>
</tr>
<tr>
<td>No or few consistent words (ADI-R=2)</td>
<td>14.3</td>
<td>14.4</td>
</tr>
</tbody>
</table>
Complex behavior abnormalities
Cognitive impairments w/ MR in 50-60%
Seizures in 30%
Absence of blindness, deafness, long tract signs

Synthesis: association cortex with sparing of primary sensori-motor cortices and white matter
Caveat: no focal signs- distributed neural systems disorder
Neurologists’ approach to understanding disease is therefore to examine all impaired AND intact abilities to define common principles or characteristics of the underlying disease process.
Disease Processes

- 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
## Discriminant Function Analysis: Domains Without Deficits

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tests Passing Tolerance</th>
<th>Percent Correct</th>
<th>Kappa&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Letter Cancellation; Number Cancellation</td>
<td>66.70</td>
<td>0.33</td>
</tr>
<tr>
<td>Sensory Perception</td>
<td>Finger Tip Writing; Luria-Nebraska Sharp/Dull Tactile Scale item</td>
<td>64.40</td>
<td>0.29</td>
</tr>
<tr>
<td>Simple Language</td>
<td>K-TEA Reading; K-TEA Spelling WRMT-R Attack; Controlled Oral Word Association</td>
<td>71.20</td>
<td>0.42&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Simple Memory</td>
<td>CVLT Trial 1</td>
<td>65.20</td>
<td>0.30</td>
</tr>
<tr>
<td>Visuo-Spatial</td>
<td>WAIS-R Block Design</td>
<td>56.10</td>
<td>0.12</td>
</tr>
</tbody>
</table>

<sup>1</sup>Kappa below .40 indicates poor agreement beyond chance
<sup>2</sup>Significant *Kappa* reflects superior performance by autistic subjects
<sup>3</sup>Based on 33 individually age, IQ, gender matched pairs of subjects
**Discriminant Function Analysis\(^1\): Domains With Deficits**

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<th>Percent Correct</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor</td>
<td>Grooved Pegboard; Trail Making A</td>
<td>75.80</td>
<td>0.52</td>
</tr>
<tr>
<td>Complex Language</td>
<td>K-TEA Reading Comprehension; Verbal Absurdities; Token Test</td>
<td>72.70</td>
<td>0.45</td>
</tr>
<tr>
<td>Complex Memory</td>
<td>Nonverbal Selective Reminding-Consistent Long Term Retrieval; WMS-R Story Recall-Delayed Recall; Rey-Osterrieth Figure-Delayed Recall</td>
<td>77.30</td>
<td>0.55</td>
</tr>
<tr>
<td>Reasoning</td>
<td>20 Questions; Picture Absurdities; Trail Making B</td>
<td>75.80</td>
<td>0.52</td>
</tr>
</tbody>
</table>

\(^1\text{Based on 33 individually matched pairs of autistic & control subjects (Neuropsychologic Functioning in Autism: Profile of a Complex Information Processing Disorder, JINS, 3:303-316, 1997)}\)
### 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
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 going to hell. He carried and read from the Bible constantly. The psychiatrists attempted daily to convince 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 lithium. 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 and he became disorganized but not manic. Socially-emotionally he was three.

In the last three panels, SC4-SC6, the difficulty emerges as platform motion is introduced. These panels demonstrate delayed development and a failure of the autism group to achieve adult levels.

Measures for autistic subjects (circles) and control subjects (crosses) and locally smoothed curves (solid line for autistic subjects, broken line for control subjects). R-square for fits: 0.198 (SC3), 0.164 (SC4), 0.175 (SC5), and 0.170 (SC6).
Autism is defined on the basis of abnormalities in social, communication and imaginative play, and restricted interests-repetitive behavior.

The neuropsychologic and postural findings define deficits considerably beyond this triad, suggesting a more brain-wide disturbance in information processing.

Williams et al. 2006, 12: 279-298
The New Neurobiology of Autism

- Distributed or focal?
- Neocortical or subcortical?
- White matter or gray matter?
- Intra- and inter- hemispheric?
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
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
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 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, suggestion 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

Theories have proposed that gastrointestinal or immune dysfunction caused CNS dysfunction. However, neurologic disorders are typically multi-organ disorders. Scientific evidence is required before hypotheses become tentative fact. No evidence of environmental cause of vast majority of cases of autism. Compelling evidence of genetic role.
2.27 relative risk of autism diagnosis conferred by the CC genotype 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.

Campbell et al. PNAS 2006, 45: 16834-16839
mRNA levels reduced in autism postmortem brain

In particular, comparing temporal (language) region from Autism and Asperger brain, the mRNA was reduced in the first but not the second, corresponding to the impaired language development in autism and its sparing in Asperger’s disorder.

This represents the first connection from gene to mRNA to brain structure to behavior in autism.
Neural Basis of Clinical Symptoms

- fMRI studies have been the window on the mind and the path to understanding of complex behavior and higher order cognition

- Extensive studies- social cognition system, emotion system, mirror neuron system, gaze processing, motion processing, face processing, …
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
Sentence reading task and comprehension probe

The player was followed by the parent

Who was following? player parent
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 Cherkasskky
Rajesh Kana

Just et al., 2006 [Epub ahead of print], Cereb Cortex
fMRI of N-back Letter Task in Autism

Hideya Koshino
Patricia Carpenter
Nancy Minshew
Vlad Cherkassky
Tim Keller
Marcel Just

NeuroImage 2005; 24:810-821
Autism group used visually oriented processing of letters as visual-graphical codes
Controls converted letter to verbal-phonological codes
Autism group relied on lower level visuospatial analysis, and the large scale brain network has different organization from normals (see factor analysis)
Common Features of fMRI Studies of Brain Connectivity in Autism

- General underconnectivity of cortices with frontal cortex
- Increased right posterior activation-compensatory
- Reduced inter-regional connectivity
Mirror Neuron System

- MNS (pars opercularis in IFG) is active during observation, imitation, and performance of motor acts
- When acting in conjunction with the limbic system, it is thought to mediate the understanding of actions, emotions and 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. (2005) *Brain*
Motor concept learning
Memory dependent on strategies
Story creation or theme identification
Face recognition
Face affect recognition
Strategy formation, problem solving
How the mind organizes information,
Or not in the case of autism

Cognitively the problem is with prototype formation and *automatic processes* as opposed to conscious, verbally mediated reasoning.
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 ...
Which of these is the best example of a dog?
Which of the following two faces looks more familiar to you?
Cognitive Research in 5-50 year old HFAs

- The way individuals with autism come to learn about both the world and people is different from individuals who do not have autism.
- There are core differences in the way they learn categorical information and acquire “expertise”

Gasgeb, Strauss, & Minshew. Child Dev 2006; 77: 1717-1729
TYPICAL                      SOMEWHAT TYPICAL                   ATYPICAL
Top 10 Autism Research Events of 2007

Courtesy of:
The Top 10 of 2007

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.
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 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 - instability in replication of DNA.

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.
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.

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

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 corpus callosum
4. CNV in simplex; synapse-related genes in simplex & multiplex families
5. Selective gene expression will explain pattern of brain involvement and variability