Autism: Where We Were, Where We Are, Where We Are Going

A Neuroscience & Genetics Paradigm For Progress in Medicine

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Director NIH Autism Center of Excellence

Louisville
October 19, 2007
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) 

**DSM-III (1980)**  
Infantile autism  
Childhood onset pervasive development disorder  
Childhood onset PDD NOS  

**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
# 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>

- 1Baird et al, 2000
- 2Chakrabarti & Fombonne, 2001
- 3Bertrand et al, 2001
- 4Chakrabarti & 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
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
## 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>
Quick Diagnosis of Verbal ASD

- Strange or odd, reflecting social impairment
- Monotone voice, little to no facial expression
- Upset by change, rituals for doing things in set ways; little scripts; evolves into #4
- Obsessions w/ focus on facts or collections; memory for detail superb
- Clumsy, awkward
Absence of delayed & disordered language development

Often precocious language development

Fewer symptoms than for Autistic Disorder

Inaccurate distinction between HFA, AS, PDDNOS in clinical practice
Behavioral Neurology Appraisal

- 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
Identifying the Cognitive & Neurologic Basis of Autism: Single or Multiple Primary Deficits? Few or Many?
Studies have always shown an uneven cognitive profile:

- What do their cognitive strengths have in common?
- What do their cognitive weaknesses have in common?
- Answers to these questions provide insight into the underlying cognitive processes and neural mechanisms
**Discriminant Function Analysis: Domains Without Deficits**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tests Passing Tolerance</th>
<th>Percent Correct</th>
<th>Kappa $^1$</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$^2$</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>

$^1$Kappa below .40 indicates poor agreement beyond chance

$^2$Significant *Kappa* reflects superior performance by autistic subjects

$^3$ Based on 33 individually age, IQ, gender matched pairs of subjects
**Discriminant Function Analysis¹:**
**Domains With Deficits**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tests Passing Tolerance</th>
<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>75.8</td>
<td>0.52</td>
</tr>
</tbody>
</table>

¹Based 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

<table>
<thead>
<tr>
<th>Intact or Enhanced</th>
<th>Cognitive Weaknesses</th>
</tr>
</thead>
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<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>
<td></td>
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</tbody>
</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)

Healthy Group

Autism Group

- 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
Genetic Origins of Most Cases

- Documentation that 40% of first degree relatives have broader autism phenotype
- 18-20% of siblings have ASD
- Additional siblings have DLD
- Affective and anxiety disorder common in first degree relatives; “OCD” frequent & ADHD occasional
- Autism heritability .90; polygenetic; considered most likely disorder for genes to be found soon
Diagnostic methods resulted in recognition that 90-95% of cases idiopathic e.g. autism existed as a disorder in its own right & genetic in cause

Dawning recognition of neural systems origin

Increasing documentation of much higher prevalence 1-2/10,000 to 1/100 for ASD

Recognition that cognitive deficits involved higher order abilities not basic abilities e.g. cerebral hemispheres and cortex in particular
Where We Were In 1980

- Autism introduced as a category in DSM/ICD
- No diagnostic instruments
- All cases thought caused by other disorders
- Focal brain dysfunction
- Single primary cognitive or sensory deficit
- Very rare disorder
- Mental disorder
Focal brain disorder or distributed
Neocortical or brainstem-cerebellum
White matter or cortical gray matter
Intra- or inter-hemispheric or both
- 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
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 GI 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.

Campbell et al.
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
Language Profile in HFA

- 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
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
Attribution of mental states in high functioning autism: Evidence for cortical underconnectivity

Rajesh Kana
Tim Keller
Diane Williams
Nancy Minshew
Marcel Just

Kana et al. Brain (2006) on line
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
N-Back Results: Alternate Cognitive & Neural Strategies in Autism

- Autism group used more nonverbal visually oriented processing and retained letters as visual-graphical codes
- Controls converted letter to verbal-phonological codes
- Autism group relied on lower level visuospatial analysis, had less activation in anterior regions and more in posterior regions associated with visual processing, more activation in right than left hemisphere, 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 with frontal cortex
- Increased right posterior activation-compensatory
- Reduced inter-regional connectivity
Intra-cerebral white matter volume (see DTI also)

Is volume synonymous w/ effective connectivity?
  • Functional connectivity
  • Dendrites, synapses, receptors

Intra-cortical, cortico-cortico
  • Uni-modal, hetero-modal cortico-cortico
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.
Mechanisms Underlying fMRI Abnormalities

- imbalance between inhibitory & excitatory mechanisms in cerebral cortex may impact cortical specialization
- glutamate cell reduction may reduce inhibition
Motor concept learning
Memory dependent on strategies
Story creation or theme identification
Face recognition
Face affect recognition
Strategy formation, problem solving

Concept Formation Impairments Present Globally
All rely on prototype formation mechanisms
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 …
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?
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
Difficult discrimination for 1/3 of people with autism

Dr. Nancy Minshew
Pittsburgh

Dr. Geraldine Dawson
Seattle
Most Difficult Faces for Participants with Autism To Classify By Gender
Gender Categorization
5- to 7- Year- Old Children

Control
Autism

*p < .05
Gender Categorization
8- to 12-Year Old Children

* *p < .05
Gender Categorization
13- to 17-Year Old Teenagers

* p < .05
Gender Categorization Adults

![Bar chart showing typical hair and cap comparisons between Control and Autism groups.](image-url)

- *p < .05
Why are less typical faces so difficult?

- Require comparison to prior stored knowledge (e.g., prototypes)
- Require subtle spatial/configural processing
- Require flexible weighting of features and perhaps formation of a holistic representation
- (Note the importance of varying both age and difficulty of task)
Conclusions

- Higher order information processing capacity
- Functional under-connectivity of neural systems
- Early overgrowth disrupts neuronal organization
- Both a cortical gray & white matter disorder
- Overgrowth of WM does not extend to functional dendritic tree development or synaptogenesis
- Minicolumns increased but inhibitory cells decreased
Understand affective contact, emotion
Search for underlying mechanisms
Search for genes
Establish gene to behavior links
Develop interventions based on advances
Implement legislative and public policies
Catch up education
Develop jobs, living opportunities
Improve community attitudes: do no harm, help
Research Studies

High functioning individuals 5 - 45 years with autism or “Asperger disorder”
- IQ between 80 – 120
- speak in sentences
- some med exclusions

Through July 2012; no cost; participant payment; we pay airfare & hotel