"Autism As A Widespread Disorder of Neural Connectivity & Information Processing”

Development Disorders Colloquium

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Director NIH Autism Center of Excellence

Boston MA
June 10, 2008
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
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>

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
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
Asperger’s Disorder vs Autism

- 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?
Brain disturbances produce a constellation of cognitive & neurologic deficits, not a single deficit.

Multi-organ involvement is the rule in non-acquired neurologic disorders- because affected genes are in every cell in the body.
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 (signatures like CO)
- Developmental processes
Developmental Processes

- Organogenesis (basic form of the nervous system)
- Neuronal proliferation
- Glial proliferation, migration
- Neuronal migration
- Neuronal organization
- Myelination
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 Analysis\(^1\): Domains With Deficits

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<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>75.80</td>
<td>0.52</td>
</tr>
</tbody>
</table>

\(^1\)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

<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>
<td></td>
</tr>
</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)
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.

Additional Implication of Profile: Triad to Brain-Wide
Genetic Origins of Most Cases

- Documentation that 40% of first degree relatives have broader autism phenotype
- 18-20% of siblings have ASD (see infant sibs)
- Additional siblings have language delays
- Affective and anxiety disorder common in first degree relatives including sibs; “OCD” frequent & ADHD occasional
- Autism heritability .90; polygenetic; considered most likely disorder for genes to be found soon
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 deficits involved higher order abilities not basic abilities e.g. cerebral hemispheres and cortex in particular
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
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
Implications of White Matter Dysfunction

- 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

Additional Evidence of Cortical Involvement

- 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
Additional Evidence of Cortical Involvement

- 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

Implications of White Matter Dysfunction

- 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
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 postmortum 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
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

Who was following?
player          parent

The player was followed by the parent

Cent for Cognitive Brain Imaging
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
Group differences in functional connectivity

Control group

Group with autism

Functional connectivity (z)

ROI pairs

LPOCG:RPOCG
LPOCG:RT
RIFG:RIPL
RPOCG:RST
RDLPC:RIPS
LDDLPC:LSES
LIPL:RIPS
LIPS:RSFG
LIPS:LSFG
RIPS:RSFG
RIPS:RIPS
LDDLPC:RIPS
LIFG:RIPS
RCHL:RIPS
RCEL:RIPS
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
Vлад Cherkassky
Tim Keller
Marcel Just

NeuroImage 2005; 24:810-821
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
Multiple Meanings of 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.
Concept Formation Impairments Present Globally
All rely on prototype formation mechanisms

- 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 …
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?
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
Gender Categorization
5- to 7- Year- Old Children

Typical Hair
Typical Cap
Atypical Hair
Atypical Cap

Control
Autism

*p < .05

Strauss, M.S. et al., Child Development (under revision)
Gender Categorization
8- to 12- Year Old Children

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

* p < .05
Gender Categorization Adults

* p < .05
TYPICAL

SOMewhat TYPICAL

ATYPICAL
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 Autism

Pelphrey et al. (2005) *Brain*
Pelphrey et al. (2002); Journal of Autism and Developmental Disorders
Top 10 Autism Research Events of 2007

Courtesy of:
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
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.

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

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.
Conclusions

- Alterations in information processing
- Alterations in neural connectivity
- Early brain overgrowth
- Cortical gray & white matter disorder: the neuron
- Minicolumns increased, inhibitory cells decreased
- Multiple gene defects related to synapses, fidelity of DNA replication
Future: Now & Tomorrow

- Understand affective contact, emotion
- Search for underlying mechanisms of all findings
- 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
Volunteers Needed For Pittsburgh Research
Minshew, Pelphrey, Just, Strauss & Behrman

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

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

Autismrecruiter@upmc.edu, 1-866-647-3436