Neurologic Basis of Autism

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Director NIH Collaborative Program of Excellence in Autism

Autism course for
PGY4 Child Psychiatry Fellows
University of Pittsburgh, WPIC
March 26, 2009
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
## 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
### 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 Vol. 29 No. 4 327-331
\(^2\) Baird et al, The Lancet 368; 210-215 2006
\(^3\) ADDM Network, MMWR Feb 9, 2007; 12-28
\(^4\) This number was 20/10,000 in 1980
## Estimates of Expressive Language Level at Age 9; 151 Autism Participants

<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>

¹Lord et al Arch Gen Psych 2006; 63: 694-701
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
Other Important Features of Verbal ASDs

- No hallucinations
- Onset in first three years
- Socially emotionally very young
- Very poor perspective taking if any; little empathy
- Poor face & emotion recognition
- Gullible
- Very few strategies for problem solving, no flexibility
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: Beginning with the Right Questions
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 Deficits³

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tests Passing Tolerance</th>
<th>Percent Correct</th>
<th>Kappa¹</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>0.42²</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>

¹Kappa below .40 indicates poor agreement beyond chance
²Significant Kappa reflects superior performance by autistic subjects
³Based 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>
<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)
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.
### 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>single</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>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Controls (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>single</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.

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

Garcia-Villamisar & Della Sala, 2002 Cognitive Neuropsychiatry
Underdevelopment of the postural control system in autism

- 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).

1Minshew et al. 2004 Neurology; 63:2056-2061.
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
Abstract Reasoning: Concept Identification & Concept Formation

- 90 verbal individuals with autism >12 yrs
- 107 control volunteers
- Concept identification
  - Attribute identification
  - Rule-learning
- Concept formation
  - Self-initiated strategy
- Cognitive flexibility
- Extent to which these were dissociable skills
Dissociation Between Concept Identification & Concept Formation in Autism

- **Intact** concept identification:
  - Attribute identification
  - Rule learning

- **Inflexible** in applying rules in changing contexts

- **Impaired** concept and strategy formation

- These two classes of abilities are dissociable in autism: do not develop simultaneously as they do in normal children

Head Growth in Autism

- 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
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

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
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, …
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
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
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
Group differences in functional connectivity

Control group

Group with autism

Functional connectivity (z)

ROI pairs

LPOCG:RPOCG
LPOCG:RT
RIFG:RIPL
RPOCG:RST
RDLFPC:RIPS
LDLFPC:LIPS
LIPS:RSFG
LIPS:LIPG
RIPS:RIFS
RIFG:RIPS
RDLFPC:RIPS
RHESHL:RPH
LIFG:RIPS
RCBEIL:RIPS
Attribution of mental states in high functioning autism: Evidence for cortical underconnectivity

Rajesh Kana
Tim Keller
Diane Williams
Nancy Minshew
Marcel Just
Mental Imagery in Autism

Rajesh Kana
Nancy Minshew
Tim Keller
Vlad Cherkassky
Marcel Just

Kana et al. 2006, Brain, 129(9):2484-2493
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 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)*
The Functional Neural Basis of Autism

- Information processing capacity is reduced-dual task, 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 are relied upon to perform tasks that typical individuals perform using integrative circuitry and higher order abilities

- Both a cortical gray & white matter disorder
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.
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
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

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

Typical Hair
Typical Cap
Atypical Hair
Atypical Cap

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

* 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)
High functioning individuals 12-55 years with autism or “Asperger disorder” IQ 120 or below, speak in sentences, some med exclusions

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