Autism As A Disorder of Neural Circuitry & Information Processing

Current Trends in Autism 2008

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Director, NIH Autism Center of Excellence
University of Pittsburgh
Research Participants Needed: 1/1/07-6/1/12

- High functioning individuals 8-55 years
- Families with 2 or more children w/ASD
- Through June 2012; no cost; participant payment; free assessment
- Need control volunteers also!
## Epidemiologic Studies

<table>
<thead>
<tr>
<th></th>
<th>Baird et al. 2000¹</th>
<th>Chakrabarti &amp; Fombonne²</th>
<th>Brick Township, NJ³</th>
<th>Chakrabarti &amp; Fombonne⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autism</strong></td>
<td>30.8/10,000</td>
<td>16.8/10,000</td>
<td>40.5/10,000</td>
<td>22/10,000</td>
</tr>
<tr>
<td><strong>Other ASDs</strong></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><strong>Total for ASDs</strong></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><strong>Total for ASDs</strong></td>
<td>1/170</td>
<td>1/160</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., 2005
### Epidemiologic Studies

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<thead>
<tr>
<th></th>
<th>Kadesjo, et al.¹ 1999</th>
<th>Baird et al², 2006</th>
<th>CDC³</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 ASDs⁴</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>

¹Kadesjo et. al. JADD Vol. 29 No. 4 327-331; ²Baird et al, The Lancet 368; 210-215 2006
³ADDM Network, MMWR Feb 9, 2007; 12-28 ⁴This number was 20/10,000 in 1980
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
Identifying the Cognitive & Neurologic Basis of Autism: Beginning with the Right Questions
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
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 and neural mechanisms
 Discriminant Function Analysis: Domains Without Deficits$^3$

<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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<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>

\(^1\)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)
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>&gt; 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>
<tr>
<td>Controls (n = 16)</td>
<td></td>
<td></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.

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

Garcia-Villamisar & Della Sala, 2002 Cognitive Neuropsychiatry

- 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
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

Bill is a young adult with autism who decided to take figure skating lessons. His mother drove to the rink several times a week. After a while, she decided to skate while he had his lesson. Bill performed his routine, but people learned to stay out of his way. He went where his program required him to go regardless of others. One day his mother forgot to note where Bill was and he ran her over, knocking her unconscious. The emergency team was called and she was given first aide and taken to the hospital. The next day she asked Bill why he did not come to her assistance, since he was an Eagle Scout with a first aide badge. He replied “It expired.”
- 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
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

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, …
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
Brain activation during sentence comprehension in high-functioning autistic subjects

Marcel Just
Nancy Minshew
Tim Keller
Vlad Cherkassky
Jennifer Roth
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
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 autistic participants between pairs of key areas during sentence comprehension (red end of scale denotes lower connectivity)
Autism group has lower functional connectivity but same rank order.
Functional & Structural Underconnectivity: fMRI of a Problem Solving Task

Marcel Just
Nancy Minshew
Tim Keller
Vlad Cherkassky
Group differences in functional connectivity
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)
Speak in sentences-think in words & pictures
Brain operates in systems, systems underconnected
Local connections over-developed
Distant connections under-developed
Key Qs:
Does ABA develop local connections?
Can new cognitive paradigms be designed to develop distant ones?
Compensatory strategies obvious: left side of table
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
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
Most Difficult Faces for Participants with Autism To Classify By Gender
Difficult discrimination for 1/3 of people with autism

Dr. Nancy Minshew
Pittsburgh

Dr. Geraldine Dawson
Seattle
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)
TYPICAL
SOMEWHER TYPICAL
ATYPICAL
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

*\( p < .05 \)