“From Behavioral Neurology to Neurobiology of Autism”

Robert Wood Johnson Medical School
Neurology Grand Rounds

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Is autism a synapse-opathy?
Autism is a dysconnection syndrome.
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
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.
Neurobehavioral Approach

Neurologists’ characterize all impaired AND all intact abilities to identify their common characteristics that will delineate key features of the underlying neurobiology.

This approach turned out to be particularly appropriate in autism.
Strange or odd, reflecting social impairment
Monotone voice, little to no facial expression
Upset by change, rituals for doing things in set ways; scripts; evolves into obsessive interests
Obsessions w/ facts or collections; memory for detail superb
Clumsy, awkward
Typical Signs & Symptoms of ASD in Minimally Verbal or Nonverbal Individuals

- Intermediate severity: socially isolated; approach for needs only; echolalia, few scripted stereotyped sentences; no imaginative play-odd play; difficulty with change; sensory issues; self-stimulatory behavior

- Most severe: largely mute, no comprehension, no prosody, no adaptive behavior, still attends to details. Direct care staff know who has autism vs non-autism MR because skill deficits are disproportionate for IQ
Behavioral Neurology of Autism

- Abnormalities in complex behavior
- Verbal & nonverbal language impairments
- 60% intellectual disability (aka mental retardation)
- 30% seizures
- Not deaf or blind (elementary sensory spared)
- Subtle alterations in tone & reflexes (WM spared)
- Not dysmorphic, normal growth

Interpretation: diffuse association cortex, bilateral
No dyslexia or visuospatial deficits—actually the opposite—no focal deficits

Language development: capacity to repeat without abilities to use words originally or comprehend

Know names for objects but not meanings

Make requests or speak when no one present

Revision: distributed neural network disorder—underdevelopment of cortical connectivity
Primary sensory & motor cortex
Unimodal association cortex
Heteromodal association cortex
Intra- and inter-hemispheric connections
INFORMATION PROCESSING

- Acquisition abilities
- Processing of simple information
- Processing of complex information
- Auditory & visual domains
Disease Processes

- Infectious disease
- Vascular disease
- Tumor or mass
- Toxins
- Developmental processes
Developmental Processes

- Organogenesis
- Neuronal proliferation
- Glial proliferation, migration
- Neuronal migration
- Neuronal organization
- Myelination
Neuronal organization refers to the events in brain development that result in the abilities that are most unique to humans.

Neuronal organizational events include the development of neuronal processes, dendritic arborizations, synaptogenesis, and the rich interconnections between neurons.
## 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>
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<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 Analysis¹: Domains With Deficits

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<tr>
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<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>
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<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>
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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><strong>Intact or Enhanced</strong></th>
<th><strong>Cognitive Weaknesses</strong></th>
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<tr>
<td>Attention</td>
<td>Complex Sensory</td>
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<tr>
<td>Sensory Perception</td>
<td>Complex Motor</td>
</tr>
<tr>
<td>Elementary Motor</td>
<td>Complex Memory</td>
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<tr>
<td>Simple Memory</td>
<td>Complex Language</td>
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<tr>
<td>Formal Language</td>
<td>Concept-formation</td>
</tr>
<tr>
<td>Rule-learning</td>
<td>Face Recognition</td>
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<td>Visuospatial processing</td>
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What Does The Profile Mean?

- Simpler abilities are intact or enhanced
- Information processing capacity is limited- & integrative processing & higher order cognitive abilities are disproportionately impaired

Inference: higher order brain circuitry is under developed- they are reliant on lower order circuitry particularly visual circuitry to function.
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 stomachache. 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.
Within each domain, there was a pattern of intact and impaired abilities. The dissociation was characteristic and was exemplified by the abstraction-EF domain. The result has a marked impact on behavior, and also on adaptive function. Along with social ineptness, the hallmark of autism in verbal individuals is their reliance on rules despite failure and generally slow processing speed.
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.”
Solid line for autistic subjects, broken line for control subjects. In the last three panels, difficulty emerges as platform motion is introduced and demand placed on multi-sensory integration; development delayed and failure to achieve adult levels.
Lessons of First Chapter

- Happe & colleagues: no cognitive explanation for deficits; reverted to deficit triad in theory of mind, executive dysfunction, and central coherence. But: omits sensory, motor, postural deficits.

- Minshew, Goldstein & Williams: no single primary deficit but there is a multiple primary deficit pattern in which all deficits characterized by disturbances in integrative or high level processing.
A Major Omission From All Cognitive Theories
Autism: A Disorder of Affective Contact

Capacity to experience, understand & regulate emotions also fundamentally altered and not appreciated, despite frequent imaging studies of amygdala.

Many verbal ASD individuals socially-emotionally as young as 12-18 months to 3-5 years of age- causes major symptoms.

Studies of amygdala-cortical interactions, social motivation, tolerance of frustration ongoing.

Social Emotional Immaturity: Also Not in Diagnosis.
Convergence of Cognitive With Anatomic

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
fMRI Activation During a Spatial Working Memory Task  (Courtesy John Sweeney)
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.

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The Top 10 of 2007 (cont’d.)

From Entrenched, Focal Brain Dysfunction Models

Getting To A Neural Systems Perspective
- Group mean HC 60-70%; megalencephaly in 15%
- Onset accelerated growth 9-12 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 also compatible with autism
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Emergence of Connectivity Model

Technology and Attitudes As Huge Obstacles
Implications 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 associated with dysfunction, not increased function
- Inter-hemispheric white matter e.g. corpus callosum not involved in the same process

Minshew & Williams, Arch Neurol 2007
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
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
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

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
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.

The Top 10 of 2007 (cont’d.)

- Broad strokes in place - regional connectivity with frontal lobe a major tenet; detail compensation
- Intra-hemispheric but probably not inter-hemispheric
- Much detail at inter-regional and local level remains to be defined but
- Where does word or concept meaning live? How is it represented?

Continuing Story: Just & Mitchell


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<thead>
<tr>
<th></th>
<th>Authors</th>
<th>Title</th>
<th>Journal</th>
<th>Volume</th>
<th>Pages</th>
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</table>


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*
Convergence of Imaging With Genetics

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
Autism Genome Project (AGP): largest genetics consortium, launched in 2004, 50 institutions from 19 countries, used DNA microarray to scan the human genome for genetic causes of autism; first analyses made public in 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.
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

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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 raise rescue possibilities.
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
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.
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
Neuronal Organization


Is autism a synapse-opathy?
Many non-traumatic child neurologic disorders present “out of the blue”. They are divided by age groups, gray or white matter, and then regions.

A recent example at CNS meeting neuronal ceroid lipofuscinosis because it is uniformly fatal, not responsive to bone marrow transplant and thus a candidate for stem cell therapy. Three forms: neonatal, infantile, juvenile.

DNA as the day to day architect of life; it may come with faults with different decay rates-time bombs present from birth.
A Mechanism For Rapid Automatic Processing

- Non-conscious
- Not verbally mediated
- Flexible
Concept Formation Deficits: Search for More Fundamental Cognitive 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?
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)
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
### Effect of dual task on memory span and tracking performance

<table>
<thead>
<tr>
<th></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></td>
</tr>
<tr>
<td>People with autism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 16)</td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>86.19</td>
<td>&gt; 48.13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.55</td>
<td>16.77</td>
<td></td>
</tr>
<tr>
<td>Controls (n = 16)</td>
<td>Mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>87.25</td>
<td>= 86.88</td>
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<tr>
<td></td>
<td>4.81</td>
<td>7.58</td>
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</table>

Digit recall is expressed as a percentage of correct sequences.

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

Garcia-Villamisar & Della Sala, 2002 Cognitive Neuropsychiatry