The Investigators

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

And how that came to be known.
Why that is important to you.

It is the cornerstone of treatment.
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  

Group may vary widely depending on diagnostic instruments used-ADI-R &/or ADOS- & other exclusions; therefore findings may vary widely.
Brain disturbances produce a constellation of cognitive & neurologic deficits, not a single deficit. Common denominators of deficits provide clues to cause of constellation.

Multi-organ involvement is the rule in non-acquired neurologic disorders- because affected genes are in every cell in the body
Typical Signs & Symptoms of ASD in Verbal Individuals

- 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
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
Brodman’s Map & Connectivity

- Primary sensory & motor cortex
- Unimodal association cortex
- Heteromodal association cortex
- Intra- and inter-hemispheric connections
Across the Autism Spectrum

- Lowest functioning: no attachment of meaning to information; little to no connections with unimodal association cortex; no adaptive function
- Intermediate: local connections but not systems connections; rote repetition and a few facts but very superficial, one dimensional understanding
- High functioning: increased local connections, under development of systems connections; enhanced recall of facts but reduced comprehension of higher order meanings
No dyslexia or visuospatial deficits—actually the opposite = no focal deficits

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

Know names for objects but not meanings

Revision: distributed neural network disorder—underdevelopment of cortical connectivity
Disease Processes

- Infectious disease
- Vascular disease
- Tumor or mass
- Toxins
- 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.
Cause of Autism: What is its Footprint?

Developmental neurobiologic disorder,
Neuronal organizational disorder

- Dr. Roy Grinker, father and anthropologist
- CDC toxicologist and father
Neurologists’ characterize all impaired AND all intact abilities to identify their common characteristics linked to their shared dependence on a common underlying cause.

This approach turned out to be particularly informative in autism.
## 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><strong>Attention</strong></td>
<td>Letter Cancellation; Number Cancellation</td>
<td>66.70</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Sensory Perception</strong></td>
<td>Finger Tip Writing; Luria-Nebraska Sharp/Dull Tactile Scale item</td>
<td>64.40</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>Simple Language</strong></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><strong>Simple Memory</strong></td>
<td>CVLT Trial 1</td>
<td>65.20</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>Visuo-Spatial</strong></td>
<td>WAIS-R Block Design</td>
<td>56.10</td>
<td>0.12</td>
</tr>
</tbody>
</table>

<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 Analysis\(^1\): Domains With Deficits

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<tr>
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<th>Percent Correct</th>
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</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

**Intact or Enhanced**
- Attention
- Sensory Perception
- Elementary Motor
- Simple Memory
- Formal Language
- Rule-learning
- Visuospatial processing

**Cognitive Weaknesses**
- Complex Sensory
- Complex Motor
- Complex Memory
- Complex Language
- Concept-formation
- Face Recognition
What Does The Profile Mean?

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

Inference: higher order brain circuitry is under developed- they are reliant on lower order circuitry, particularly visual circuitry, 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 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.”
### 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>single</td>
</tr>
<tr>
<td>People with autism</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>((n = 16))</td>
<td>86.19</td>
<td>7.55</td>
<td>52.75</td>
</tr>
<tr>
<td></td>
<td>48.13</td>
<td>16.77</td>
<td>37.81</td>
</tr>
<tr>
<td>Controls ((n = 16))</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>87.25</td>
<td>4.81</td>
<td>54.06</td>
</tr>
<tr>
<td></td>
<td>86.88</td>
<td>7.58</td>
<td>55.25</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
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- befitting a disorder of neuronal organization.

Williams et al. 2006, 12: 279-298
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.

“My ability to function in the world & develop social relationships has been learned solely through my intellect…and use of my visualization skills. I have learned by rote how to act in different situations. Using my visualization ability, I observe myself from a distance in each situation. I call this my “little scientist in the corner”… I take note of the details that make up the situations just like a scientist observes an experiment. All that data gets put on my computer hard drive memory...

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“Neurotypical people have a social sense right from the time they’re born.” p. 32
Social Interactions contd

How I “tackle social situations is very much a scientific approach, based on observation, analysis, conclusions.”

She learned by reading articles and trial and error, keeping what worked and discarding what did not. She was 40 before she had enough data in her data base to improve.
A Major Omission From All Cognitive Theories
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The Top 10 of 2007 (cont'd.)

“For some of us with ASDs, the emotional-relatedness physical or biochemical circuitry is missing—no matter how hard we try, it’s a bridge that may never be built because some of the basic building materials are missing.”

“Romantic relationships have a level of social complexity that I still don’t understand today and I consciously choose not to participate in them. My way of thinking and functioning does not describe everyone on the spectrum.”

Dr. Temple Grandin
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.
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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Convergence of Clinical With Anatomic
Getting To A Neural Systems Perspective

And to the recognition of a developmental neurobiologic origin, e.g., neuronal organization.

From Entrenched, Focal Brain Dysfunction Models
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
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

Autism is a dysconnectivity syndrome.
Autism is a disorder of gray and white matter.

Autism is a disorder of the neuron.
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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Getting To A Connectivity Perspective
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)
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

Functional connectivity (z)

ROI pairs

Control group

Group with autism
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*
Typical brain development results in pre-specialized circuitry & systems that predispose human infant to automatically orient and prefer human contact over objects, experience emotions and perceive them in others, acquire language, make sense of the world, play with toys symbolically and with others.
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.)

Convergence of Imaging With Genetics
Neuronal Organization

Is autism a synapse-opathy?
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

Potential reversal of Neurodevelopmental Disorders (in Fragile X, Rett & Angelman Syndromes) in adult mice; Proof of concept that delineating neurobiologic and genetic mechanism would lead to treatment
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.

PTEN described in humans in association with ASD; 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.
Genetic Advances

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
Genetic Advances

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.

Anatomic expression pattern of gene overlays brain structures involved in autism- different genes will have different expression patterns.

Campbell et al. PNAS 2006, 45: 16834-16839
Many non-traumatic child neurologic disorders present “out of the blue”.

A recent example at CNS meeting-neuronal ceroid lipofuscinosis, uniformly fatal, not responsive to bone marrow transplant, thus a candidate for stem cell therapy.

3 forms: neonatal, infantile, juvenile.

DNA: day to day director of life; may come with faults with different decay rates-faulty light bulbs or time bombs present from birth.
A Mechanism For Rapid Automatic Processing

- Non-conscious
- Not verbally mediated
- Flexible
How the brain organizes information or thinks

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?
TYPICAL                      SOMEWHAT TYPICAL                   ATYPICAL
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
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)