The State of Autism Research: What Do We Know?

Pennsylvania Immunization Conference
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University of Pittsburgh
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.
Autism is the result of alterations in how the brain processes information that alters how the mind sees the world.
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.
It is the footprint of the cause.
Most Important Unanswered Question?

My answer: what is the basis of heterogeneity?
My guess: variable genes & variable gene expression
Brain disturbances produce a constellation of cognitive & neurologic deficits, not a single deficit

There is no expectation by neurologists of a single primary deficit that causes all the other deficits—that is a fiction of behaviorists.

Most neurologic disorders are multi-organ system disorder because the genes are present in all cells.
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
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.
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 fortuitous in autism.
# The Profile of Intact & Impaired Abilities in High Functioning Autistic Individuals

<table>
<thead>
<tr>
<th>Intact or Enhanced</th>
<th>Cognitive Weaknesses</th>
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<tbody>
<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>
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<tr>
<td>• Rule-learning</td>
<td>• Face Recognition</td>
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<tr>
<td>• Visuospatial processing</td>
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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 & 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.
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.
Behavioral Example of Cognitive Profile: Rules Override Concepts

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>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>
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<th>Controls (n = 16)</th>
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<tr>
<td></td>
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<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>
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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
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...
The neuropsychologic profile and postural findings define deficits considerably beyond the DSM triad, suggesting a more brain-wide disturbance in information processing and its neuronal architecture—befitting a disorder of neuronal organization.

Williams et al. 2006, 12: 279-298
A Major Omission From All Cognitive Theories
Dr. Temple Grandin

“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.”
“I experience the emotion of love, but it’s not the same that most neurotypical people do. Does that mean my love is less valuable than what other people feel?”

“Some people with autism don’t understand or experience any sort of emotional attachment or romantic love. I would speculate that autism involves an atypical development of the ...reward systems.”
On June 2, 1975, I was very angry. The bottom of my stomach felt as if I had swallowed a dumbbell: I spent much of my childhood and teenage years dealing with that emotion and getting to know it intimately.

My autism brought me much misery and unhappiness, and in essence robbed me of a childhood. I was born with a pervasive fear that never seemed to diminish, so I spent most of my earliest years devising ways to lessen the unrelenting terror, if not get rid of the chronic dread completely. To that end, I tried to find ways to look at and take in the world that would make sense to me and
“..be less overwhelming, while at the same time, provide a measure of comfort, control, balance, and security- all of which were missing from my life. Isolating and manipulating objects while tuning out people; fixating on repetitive motions; asking the same questions over and over; developing stereotypical movements, arbitrary rules and rigid thinking; and focusing to an extreme degree on one item or event to the exclusion of every else were among the ways I found some control and security, while temporarily sidestepping my fears.”
Autism: A Disorder of Affective Contact

- Capacity to experience, understand & regulate emotions fundamentally altered and not appreciated

- 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 and connectivity related to social motivation, frustration management, in progress

Social Emotional Immaturity: Also Not in DSM
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
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?
Correlation of ratings by Controls vs. Autistics: $r = -.06$
TYPICAL  

SOMewhat TYPICAL  

ATYPICAL
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
Research Studies

High functioning individuals 5 - 45 years with autism or “Asperger disorder”
- IQ between 80 – 120
- speak in sentences
- some med exclusions

Through July 2012; no cost; participant payment; we pay airfare & hotel
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
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Getting To A Neural Systems Perspective

Early Brain OverGrowth Shifts Thinking From Entrenched, Focal Brain Dysfunction Models To Developmental Neurobiologic Model
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
Autism is a disorder of the neuron.

It is not a white matter or gray matter disorder or rather it is both but it is fundamentally a disorder of the neuron.
Autism is a dysconnectivity syndrome—both increased & decreased connectivity.”
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 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
Other Brain Networks Affected in ASD: Innate Specialization Disturbed

- Theory of Mind
- Mirror Neuron
- Motion Processing (Gaze & Biologic Motion)
- Face Processing
- Emotion Processing
- Motivation, Incentive, Disincentive
- Language- left and right hemisphere
- Concept formation
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*
At this point, clear that typical brain development results in pre-fab 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.
Is autism a synapse-opathy?
Convergence of Imaging With Genetics

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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**.
Genetic Advances

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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
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**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.
The Loop From Clinical Syndrome to Genes is Completed: Widespread disturbance in integrative processing, neural systems development, and genes related to development of connectivity.

The Footprint is Visible: A Developmental Brain Disorder of Neuronal Organization.
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, uniformly fatal, not responsive to bone marrow transplant, thus a candidate for stem cell therapy. Three forms: neonatal, infantile, juvenile.

DNA as the day to day director of life; may come with faults with different decay rates-time bombs present from birth.
High functioning individuals 5 - 45 years with autism or “Asperger disorder”
  - IQ between 80 – 120
  - speak in sentences
  - some med exclusions

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