“How Does The Mind & Brain Think In Autism”

PACT 4 9th Annual Brain Conference

Tuesday, November 16, 2010

Nancy Minshew, MD
Professor Psychiatry & Neurology
University of Pittsburgh USA
We wish to honor those individuals and families who have believed in research and been committed to participating again and again.
A Few of the Many Scientists

Nancy Minshew, MD  William Eddy, PhD  Marcel Just, PhD  Marlene Behrmann, PhD
John Sweeney, PhD  Beatriz Luna, PhD  Mark Strauss, PhD  Tom Mitchell, PhD
A Few of the Many Scientists (cont’d)

Diane Williams, PhD
Suzy Scherf, PhD
Carla Mazefsky, PhD
Kate McFadden, MD
Shaun Eack, PhD
Tim Keller, PhD
Ilan Dinsein, PhD
Uri Hasson, PhD
Research Studies

Verbal individuals 5 - 45 years with autism, Asperger disorder or PDDNOS with:
  – IQ between 80 – 120
  – speak in sentences
  – some med exclusions

Through July 2012; no cost; participant payment; we pay airfare & hotel
Impact of Diagnostic Criteria and Methods On the Severity of ASD & Thus Results of Studies

DSM-IV (1994): Pervasive Developmental Disorders
- *Autistic Disorder
- *Asperger’s Disorder
- *Pervasive Developmental Disorder NOS
- Childhood Disintegrative Disorder
- Rett’s Disorder

Composition of group may vary widely depending on diagnostic instruments used-ADI-R &/or ADOS- & other exclusions; such differences can result in wide variations in ASD severity and differences in findings.
Operationalization of Diagnostic Criteria To Achieve Accuracy & Reliability

Research instruments (current gold standards): Autism Diagnostic Interview-R (ADI) & Autism Diagnostic Observation Schedule-Generic (ADOS):

1. A. Highest reliability and validity with combination
2. B. Further improved by expert opinion that excludes cases that aren’t autism despite scores in the autism or ASD range either because disorder has different quality of signs or because the scores reflect other primary symptoms like anxiety disorder and or depression

Questionnaires:
A. Social Reciprocity Scale (SRS) (Constantino)
B. Asperger Questionnaire (AQ) (Baron Cohen)
C. Social Communication Questionnaire (SCQ) (Lord)
Autism is the result of alterations in how the brain processes information that alter how the mind sees, thinks and feels about the world.
Autism is the result of altered information processing and integration by the brain and mind.
These alterations are the result of altered development of the connections among brain cells that form cortical systems.
15-20 genes account for about 20% of ASD cases. These genes direct brain development of connectivity among cortical neurons.
These events occur during three phases of brain development:

- Neuronal organization
- Neuronal migration
- Neuronal proliferation
Discovery of these genes led to definition of molecular events, which led to use of a drug (biologic) treatment to prevent the development of intellectual disability, seizures, & ASD in tuberous sclerosis.
Understanding the basis of alterations in thinking and feeling has led to new neurocognitive interventions designed to promote secondary growth of brain connections.
Understanding the basis of alterations in thinking and feeling and in the brain has led to more accurate functional analysis of behavior and in turn to more effective clinical approaches.
All human disease could be considered a disorder of the genome.
Autism is a synapse-opathy?

State of science hypothesis, 2006
Autism results from altered brain connectivity that alters higher order information processing.

Autism begins with altered genetic guidance of brain development—specifically cortical connections.
Why that is important to you

It is the cornerstone of treatment.
It is the footprint of the cause.
Most Important Unanswered Question?

Q: What is the basis of heterogeneity?
A: genetic variability of the disorder & variability in familial inheritance
How the search began

Behavioral psychology approach: looking for explanations in the behavior

Neurology approach: looking for explanations of behavior in the brain
What does ‘cause’ mean?

Etiology
Pathophysiology
Functional analysis of behavior
Brain Affected Broadly in ASD

From the beginning
Many domains, not one
Developmental Characteristics of Infant Sibs: Onset > 6 mos; Motor & Balance First

- No developmental differences at 6 mos
- Developmental differences at 12 mos on standardized tests- a developmental deceleration
- Gap widens between 12 & 24 months and beyond
- Differences in fine and gross motor- early
- Less mouthing of objects-less vocalizations
- Truncal instability when sitting- early
Developmental Characteristics of Infant Sibs: Sensory-Repellitive-Visual Regard

- Unusual visual regard & Repetitive waving of arms and hands at 12 and 18 mos
- Sensory-related behaviors: under and over responsiveness at 12 months but not 6 mos
- Social emotional: no temperamental differences at 6 mos, over time temperamentally more difficult with more intense distress and more time fixating on objects; accompany- don’t predate- sx
- At 24 months, emotional and behavioral self-dysregulation distinguished infant sibs dx ASD
No social signs at 6 months don’t predate other sx
Delays in verbal and nonverbal language at 12 months but not earlier
Best predictor of response to name at 14 mos-child’s self initiated and spontaneous gaze shifts from toy to parent- joint attention- this is a social impairment (acts as if deaf)
Lack of behavioral markers at 6 months; earliest differences are subtle, involve a few behaviors or small differences

Socially normal at 6 months

Onset: not early or regressive but rather slower or faster mounting of symptoms - a deceleration of development: core symptoms present at 12 mos and grow more severe over time

“Associated symptoms” are integral - irritability, sensory responsivity, activity level, poor gross motor development
These findings do not support the view that autism is primarily a social-communicative disorder and instead suggest that autism disrupts multiple aspects of development rather simultaneously.

“Children’s developmental rates are decelerating markedly in a 12 month period, with IQs dropping from average to below 50 for some children.”

Sally Rogers, 2009
What is happening in the BRAIN in infant sibs?

- Onset of acceleration of brain growth at 9-12 months - coincident with onset of symptoms.
- Brain growth in ASD is inverse of Retts syndrome.
Figure: Occipital–frontal (OFC) Z score measurements ($N = 195$) with mean estimated growth trajectory for 28 children with autism spectrum disorder (hierarchical linear model two-piece linear model centered at 12 months).
Behaviorally Defined Syndrome With No Known Connection Between “Core”, “Associated” Comorbid”

FROM: 3 Core Symptoms +
Associated Symptoms: sensory, motor
Co-morbid Conditions: intellectual disability, ADHD, seizures, regulation disorders

TO: integrated relationship of all manifestations-whatever mechanism causes one causes all; neurologic or developmental neurobiologic disorders w/ organizing principles at original events
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

- 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: details
- Clumsy, awkward
- Sensory sensitivities or other disturbances
Classical Neurological Assessment of ASD: A Clinical Appraisal Leads to Hypotheses

- 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 of Association Cortex

- Primary sensory & motor cortex
- Unimodal association cortex
- Heteromodal association cortex
- Intra- and inter-hemispheric connections
Information Processing

- Acquisition of information
- Processing of simple or elementary information
- Processing of complex or derivative information
- Auditory & visual domains
Disease Processes

- Infectious disease
- Vascular disease
- Tumor or mass
- Toxins
- Trauma or injury
- Developmental processes
- Degenerative 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.
From the beginning:
Finding the cognitive & brain mechanisms underlying behavior
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.
## 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>
</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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<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>
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\(^1\)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</td>
<td></td>
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</table>
What Does this 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- brain is reliant on lower order circuitry particularly visual circuitry to function.
fMRI Activation During a Spatial Working Memory Task  (Courtesy John Sweeney)

Healthy Group

Autism Group
What Else Did The Profile Demonstrate?

Autism results in disturbances far beyond the classic triad of social, communication and RRBI

And

These disturbances in “non-core” domains exhibited the same differential impact on higher order abilities as seen in “core” deficits
### 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 = 86.88</td>
<td>= 86.88</td>
<td>54.06 = 55.25</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
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.
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.”
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…"

“Neurotypical people have a social sense right from the time they’re born.”

p. 32 Grandin
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 database” to see patterns and use them to improve her behavior and function.

Similar description of mind blindness.
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.)

- 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).

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
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 …
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
A Mechanism For Rapid Automatic Processing

- Non-conscious
- Not verbally mediated
- Flexible
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?
Other Examples of Altered Category Structures in 5-50 year olds With HFA
Most Difficult Faces for Participants with Autism To Classify By Gender
Attractiveness Ratings

Correlation of ratings by Controls vs. Autistics: $r = -.06$
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
A Major Omission From All Cognitive Theories:
Impaired affective contact
(social emotional development)
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.”
Capacity to experience, understand & regulate emotions fundamentally altered and not appreciated

Many verbal ASD individuals are socially-emotionally as young as 12-18 months to 3-5 years of age-critical factor in any intervention

Studies of amygdala-cortical interactions and connectivity related to social motivation, response to reward, risk taking, in progress (studies of specific mechanisms)

Social emotional developmental delays play a critical role in behavior & function: Not in DSM