The Evolution of Autism Research: 
A Child Neurologist’s Perspective

March 2, 2012

Cleveland Autism Consortium

Nancy J. Minshew, M.D.
Child Neurologist & Professor of Psychiatry & Neurology
Director of U. Pittsburgh-Carnegie Mellon ACE

minshewnj@upmc.edu; www.pittautismresearch.org
Progress Comes From Participation

We wish to honor those individuals and families who have believed in research and been committed to participating, again and again.
A Mission Statement For Autism Research

- Significantly advance our understanding of the causes of ASD to enable significant advances in treatment and services.
- To be effective in these roles, an autism center requires close and synergistic interactions between scientists in many fields & clinicians.
- Translational efforts require adaptations specifically for community professionals, educators, parents/families & affected individuals into team.
What Does ‘cause’ Mean?

Etiology
Pathophysiology
Functional analysis of behavior
Disconnection between behavior & brain
Why Is Cause Important?

Defining Mechanisms That Lead To More efficacious treatments
Targeting mechanisms that are increasingly proximal to originating events
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.

Potential reversal of Neurodevelopmental Disorders (in Fragile X, Rett & Angelman Syndromes) in adult mice.

In 2007:
- Abnormalities in Genetic Code for Brain Development
- Abnormal Mechanisms of Brain Development
- Structural and Functional Abnormalities of Brain
- Cognitive & Neurological Abnormalities
- Behavioral Syndrome

From DNA to Behavior: A Complex Sequence of Mechanisms
Where Are We Coming From

Autistic Disorder: DSM IV

- 3 Core Symptoms
- Associated symptoms: sensory, motor
- Co-morbid Conditions: intellectual disability, ADHD, seizures, mood problems, long list of behavior issues (Pg. 71-72 TR version)

Not a valid conceptualization and no longer functional. Do we wonder why families & clinicians are confused?
Q: Is the constellation inherent in a cohesive syndrome or is it an artifact of diagnostic practice?

What causes these signs and symptoms to co-occur?
Brain disturbances produce a constellation of neurologic signs & symptoms: symptoms/signs equally important.

The constellation & mode of presentation reflect the underlying brain mechanism and its location.

Impairments present when the time in brain development comes for that skill to appear.
Child Neurologists Differential Diagnosis For De Novo Neurodevelopmental Disorders

- Organogenesis
- Neuronal proliferation*
- Glial proliferation, migration
- Neuronal migration** \textit{CNTNP2}
- Neuronal organization***
- Myelination

*Implicated in ASD
Abnormalities in complex behavior, cognition, language, intellectual disability, seizures

- No primary sensory deficit
- No long tract signs
- No focal findings (dyslexia, visuospatial deficits)
- De novo developmental disorder

Association cortices

Distributed neural network disorder

Disorder of neuronal organization
## Discriminant Function Analysis\(^1\): Domains With Deficits

<table>
<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)
## Discriminant Function Analysis: Domains Without Deficits

<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>0.42²</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>

¹Kappa below .40 indicates poor agreement beyond chance
²Significant Kappa reflects superior performance by autistic subjects
³Based on 33 individually age, IQ, gender matched pairs of subjects
<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 is the pattern? A Two-Part Disturbance in Information Processing

- Elementary abilities intact or enhanced

- Information processing capacity constrained-integrative processing disproportionately impaired

Inference: higher order brain circuitry is underdeveloped-over-reliance or over-development of lower order visual circuitry for functioning; neuronal organizational events disrupted
fMRI Activation During a Spatial Working Memory Task  (Courtesy John Sweeney)

Neuroimaging of the functional and structural networks underlying visuospatial vs. linguistic reasoning in high-functioning autism.

Sahyoun CP, Belliveau JW, Soulières I, Schwartz S, Mody M.

MGH/MIT/HMS Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA 02129-2060, USA. cherif@mit.edu

High-functioning individuals with autism have been found to favor visuospatial processing in the face of typically poor language abilities. We aimed to examine the neurobiological basis of this difference using functional magnetic resonance imaging and diffusion tensor imaging. We compared 12 children with high functioning autism (HFA) to 12 age- and IQ-matched typically developing controls (CTRL) on a pictorial reasoning paradigm under three conditions: V, requiring visuospatial processing; S, requiring language (i.e., semantic) processing; and V+S, a hybrid condition in which language use could facilitate visuospatial transformations. Activated areas in the brain were chosen as endpoints for probabilistic diffusion tractography to examine tract integrity (FA) within the structural network underlying the activation patterns. The two groups showed similar networks, with linguistic processing activating inferior frontal, superior and middle temporal, ventral visual, and temporo-parietal areas, whereas visuospatial processing activated occipital and inferior parietal cortices. However, HFA appeared to activate occipito-parietal and ventral temporal areas, whereas CTRL relied more on frontal and temporal language regions. The increased reliance on visuospatial abilities in HFA was supported by intact connections between the inferior parietal and the ventral temporal ROIs. In contrast, the inferior frontal region showed reduced connectivity to ventral temporal and middle temporal areas in this group, reflecting impaired activation of frontal language areas in autism. The HFA group's engagement of posterior brain regions along with its weak connections to frontal language areas suggest support for a reliance on visual mediation in autism, even in tasks of higher cognition.

PMID: 19698726 [PubMed - in process]
How altered is information processing in autism? What is the neural basis of this?

Details:
- elementary perception at its most elementary

Facts:
- meaning associated with details

Knowledge:
- connecting related details; understanding

Wisdom:
- capacity to use knowledge to negotiate life
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
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
Decreased connectivity and cerebellar activity in autism during motor task performance.

Mostofsky SH, Powell SK, Simmonds DJ, Goldberg MC, Caffo B, Pekar JJ.

Kennedy Krieger Institute, Baltimore, MD 21205, USA. mostofsky@kennedykrieger.org

Although motor deficits are common in autism, the neural correlates underlying the disruption of even basic motor execution are unknown. Motor deficits may be some of the earliest identifiable signs of abnormal development and increased understanding of their neural underpinnings may provide insight into autism-associated differences in parallel systems critical for control of more complex behaviour necessary for social and communicative development. Functional magnetic resonance imaging was used to examine neural activation and connectivity during sequential, appositional finger tapping in 13 children, ages 8-12 years, with high-functioning autism (HFA) and 13 typically developing (TD), age- and sex-matched peers. Both groups showed expected primary activations in cortical and subcortical regions associated with motor execution [contralateral primary sensorimotor cortex, contralateral thalamus, ipsilateral cerebellum, supplementary motor area (SMA)]; however, the TD group showed greater activation in the ipsilateral anterior cerebellum, while the HFA group showed greater activation in the SMA. Although activation differences were limited to a subset of regions, children with HFA demonstrated diffusely decreased connectivity across the motor execution network relative to control children. The between-group dissociation of cerebral and cerebellar motor activation represents the first neuroimaging data of motor dysfunction in children with autism, providing insight into potentially abnormal circuits impacting development. Decreased cerebellar activation in the HFA group may reflect difficulty shifting motor execution from cortical regions associated with effortful control to regions associated with habitual execution. Additionally, diffusely decreased connectivity may reflect poor coordination within the circuit necessary for automating patterned motor behaviour. The findings might explain impairments in motor development in autism, as well as abnormal and delayed acquisition of gestures important for socialization and communication.

PMID: 19389870 [PubMed - indexed for MEDLINE]
Encoding by the brain is distributed- involves multiple brain regions- leads to flexibility

Each word encoded according to four attributes in adults:

- Eating
- Shelter
- Manipulation
- Number of characters in word

Vital to design of early interventions
Brain Affected Broadly But Selectively

Cortical-Cortical Connections
Cortical-amygdala
Cortical-striate
Figure 2. 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).
Home movies showed signs of autism long before diagnosis

Key Q: What are the first behavioral characteristics that predict the development of autism?

Method: study of infants with an older sibling diagnosed with autism—“infant sibs”
“First Signs”:
Visual Regard-Sensory-Motor

- Socially normal at 6 months
- Unusual visual regard at 9-12 mos
- Repetitive waving of arms and hands at 9-12 mos
- Sensory-related behaviors: under and over responsiveness at 9-12 months
- Temperament: no differences at 6 mos, over time temperamentally more difficult with more intense distress and more time fixating on objects; accompanies- does not predate- sx
Delays in verbal and nonverbal language at 12 months but not earlier
Developmental differences at 12 mos on standardized tests
Exhibit faster or slower deceleration in developing
Gap widens between 12 & 24 months and beyond
At 24 months, emotional and behavioral dysregulation distinguish infant sibs dx with ASD
Lack of behavioral markers at 6 months;
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 aspects of ASD - irritability, sensory reactivity, hyperactivity, inattention, mood lability, 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
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
Is autism a synapse-opathy?
Dendrite Morphology/Function
- SHANK3/SHANK2
- Reelin
- DLGAP2

Synaptic CAMs
- Neurexins/Neuroligins
- Cadherins
- CNTN4
- CNTNAP2
- SYNGAP1

Axonal Outgrowth/Pathfinding
- Slit/LRRs
- Reelin
- Tau Kinases
- Cadherins
- SYNGAP1
Autism is the result of alterations in how the brain processes information, which alters how the mind sees the world.

Alterating cortical connectivity: remediation-induced changes in the white matter of poor readers.

Keller TA, Just MA.
Center for Cognitive Brain Imaging, Department of Psychology, Carnegie Mellon University, Pittsburgh, PA 15213, USA.
tk37@andrew.cmu.edu

Neuroimaging studies using diffusion tensor imaging (DTI) have revealed regions of cerebral white matter with decreased microstructural organization (lower fractional anisotropy or FA) among poor readers. We examined whether 100 hr of intensive remedial instruction affected the white matter of 8- to 10-year-old poor readers. Prior to instruction, poor readers had significantly lower FA than good readers in a region of the left anterior centrum semiovale. The instruction resulted in a change in white matter (significantly increased FA), and in the very same region. The FA increase was correlated with a decrease in radial diffusivity (but not with a change in axial diffusivity), suggesting that myelination had increased. Furthermore, the FA increase was correlated with improvement in phonological decoding ability, clarifying the cognitive locus of the effect. The results demonstrate the capability of a behavioral intervention to bring about a positive change in cortico-cortical white matter tracts.

PMID: 20005820 [PubMed - indexed for MEDLINE]
Interventions To Promote Connectivity

Many in progress
Change thinking to change circuitry
Categorization and Perceptual Expertise in Autism

Mark S. Strauss, Ph.D.
Holly Gastgeb, Ph.D.
Nancy Minshew, M.D.
Desiree Wilkinson, M.S.
Sarah Hannigen, M.S.
Catherine Best, Ph.D. (Ohio State)
Keiran Rump, Ph.D. (University of Pennsylvania)

Supported by grants from the National Institutes of Health, Autism Science Foundation and Autism Speaks
Categorization & Perceptual Expertise

- We are all experts at faces
- It is an implicit skill— even experts are unable to explain how they “do it”
- These learning mechanisms start in infancy
- Individuals with autism have deficits in these implicit (domain general) mechanisms
Categorizing Prototypical Gender Faces (Percent Correct)

- Control
- Autism

5 to 7 yrs  8 to 12 yrs  Adolescents  Adults
Categorizing Less Typical Gender Faces
(Percent Correct)

Control
Autism

* * *

5 to 7 yrs 8 to 12 yrs Adolescents Adults
Proportion of Looking to LVF and EYES

**Proportion of Looking**

- **Left Visual Field Bias (LVF)**
- **Eye/Mouth Bias**

**Comparison Groups**
- **Control**
- **Autism**

*Note: The * symbol indicates a significant difference.*

*Dundas, Best, Minshew & Strauss (under review)*
Is it domain specific – dot category study

Gastgeb (2010)
Prototype
Novel
Exemplar
Test Pair
Infant Dot Prototype Study
6, 11, 16 month old high and low risk infants
Proportion of Looking to Exemplar vs. Prototype

Error Bars: 95% CI

Risk Status

\( H \)
\( L \)

\( P < .05 \)
Percent Looking to Left Visual Field: 6- and 11- month old infant siblings at High and Low Risk for Autism: Delayed Cortical Specialization
Deciphering Altered Brain Connectivity in ASD to Improve Intervention

Nancy Minshew
Bernard Devlin
Kathryn McFadden
Suzy Scherf
Marlene Behrmann
Shaun Eack
A Neurological Disorder: Searching for Underlying Brain Mechanisms

Convergence Among Genetic, Neuroimaging, and Behavioral findings
Disruption of Connectivity within Neural Systems

Neuronal Level

Structural Connections

Functional Connections

Multiple Levels of Analysis
Big Questions

• How does aberrant neuronal connectivity arise?

• Can we induce plasticity in developing (and even mature) neural system to modify profile of aberrant connectivity?
Aberrant Connectivity: Neuronal Level

• Dysregulated axonal growth and pathfinding

• Process linking implicated genes to clinical manifestation of ASD

• Genome-wide association studies implicate Leucine Rich Repeats (LRR) genes
**LRR Candidate Genes - Expression**

- Expressed in frontal cortical neurons of mouse embryos in neuronal processes (dendrites and axons)

- Expressed prenatally in human cortical neurons (neuronal processes)

- Higher expression rates in frontal compared to posterior regions for most part
LRR Candidate Genes - Modulation

- Growing neural stem cells
- Modulate expression and observe effects on neural maturation and behavior

Differentiated Neurons – Day 1
Process staining

Differentiated Neurons – Day 4
Synaptic staining pattern

- Looking at axonal behavior in neurons derived from a mouse model of syndromic ASD (Tuberous Sclerosis)
Disruption of Connectivity within Neural Systems

Neuronal Level

Structural Connections

Functional Connections

Inducing Plasticity
Evidence-Based Cognitive Rehabilitation to Improve Functional Outcomes for Adults with Autism Spectrum Disorders

Shaun M. Eack, Ph.D.
Nancy J. Minshew, M.D.
University of Pittsburgh
Background

- Autism spectrum disorders are characterized by core brain-based impairments in information processing.
- Cognitive impairments make the transition to adulthood particularly challenging.
- Few interventions exist that successfully target core information processing deficits, and even fewer in adults.
- Cognitive rehabilitation has repeatedly shown success at addressing brain-based cognitive impairments:
  - Stroke
  - TBI
  - Alzheimer’s
  - Schizophrenia
  - Autism Spectrum Disorder?
Cognitive Enhancement Therapy

- **Aim:** To help improve thinking and social wisdom (social cognition)

- **Two parts:**
  - **Neurocognitive Training** – Computer-based training in attention, memory, and problem-solving
  - **Social-Cognitive Groups** – Training in perspective-taking, gistfulness, non-verbal communication, emotion perception, and more

- Conducted in a small group (6-8) individuals with a skilled CET therapist/coach
Enriched Supportive Therapy

- **Aim:** To help prevent the meltdown

- **Teaches individuals:**
  - About autism spectrum disorders
  - How to manage emotions and stress
  - How to improve social skills
  - Cope with everyday problems and changes

- **Individual therapy approach with a skilled EST therapist**
CET Effects in Schizophrenia

Hogarty et al., 2004. *Arch Gen Psychiatry*. 61:866-876.
CET Effects in Schizophrenia

Eack et al., 2010. *Arch Gen Psychiatry* 67:674-682.
Recommendations/Implications

- Provide targeted interventions to improve quality of life and adaptive function in adults with ASD
- Likely to reduce a significant amount of disability in this population
- Will contribute to increased work, and reduced reliance on social insurance
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.
Or—Which of these is the best example of a dog?
Which of the following two faces looks more familiar to you?
Attractiveness Ratings

- Correlation of ratings by Controls vs. Autistics: $r = -.06$