What We Don’t Know About Autism or A Child Neurologist’s Perspective

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University of Utah

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We wish to honor those individuals and families who have believed in research and been committed to participating, again and again.
Significantly advance our understanding of the causes of ASD to enable new mechanistically based advances in treatment.

To be effective, a research effort requires close and synergistic interactions between scientists in many fields & clinicians.

Translational efforts require incorporation of community professionals, educators, parents/families & the affected individuals.
Mission Not Fully Realized

- Not a full deck- most teams are missing players
- Not connecting the dots between fields/findings
- Not communicating or listening across fields
- Not fully leveraging what is known or what is discovered

Obstacle: Each discipline has its own terminology & culture w/ little awareness of cultures or knowledge in other disciplines→ rediscovery of discovered, an unfruitful diversion or unnecessary delays in progress
Dissemination of Knowledge & Translation to Interventions

- Not communicating well to providers, families, or public - these people are the ultimate users of information, knowledge, & advances.

- Propagation of premature guesswork to non-critical audience which is then taken seriously and applied idiosyncratically is a problem & distracting.

- Basic scientists and clinical researchers need to place findings in context & take charge of media dissemination of findings.
The Challenge & Responsibility For All

- Every person who talks about the cause of autism, its treatment, its diagnosis or course needs to have an up to date grasp of all findings.

- Each of us must communicate in many forums.

- We all need to be active listeners and learners and alert to constructs outside our fields in order to seam the pieces together & maximally leverage existing knowledge & new findings.
Urban Myths About Research
Forces Against Progress

There is no single finding that will solve autism.
It is far too complex and at many many levels.
It will take a very large disseminated team approach, many many iterations, & far more advances in technology.
Egg and sperm
One cell, its DNA & many omes
Contains all the instructions to make a human
So where does ‘your ‘ discovery fit in?

What do we have to discover yet?
What will ‘the answer’ look like in autism?
Engage in Perspective-Taking

Know what you know.
Know what you don’t know.
Know who your ‘neighbors’ are & what they know.
Integrate it and give it context & meaning.
Remember what made ‘your ‘ discovery possible.
Remember where you came from.
Going beyond your data usually is deleterious.
What Does ‘cause’ Mean?

Etiology
Pathophysiology
Functional analysis of behavior
Disconnect between behavior & brain
Why Do We Care About Cause?

Defining Mechanisms
Leads to more efficacious treatments
That specifically target mechanisms
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.

From DNA to Behavior: Connected Sequence of Mechanisms

Abnormalities in Genetic Code for Brain Development

Abnormal Mechanisms of Brain Development

Structural and Functional Abnormalities of Brain

Cognitive & Neurological Abnormalities

Behavioral Syndrome
Task: Connect All Pieces

Everyone Who Talks About Cause Needs to Do This

Need fewer “nice stories”
Need to rely on science
Communicate: Families & public want to know
Vacuums are dangerous
Integration of knowledge informs each level & maximally improves treatment
Psychological Theories: The Original & Ongoing Search For Cause

- Social motivation theories: pathognomonic & dominant, inferred to cause entire syndrome; focal brain origin & first in time hypothesis
- Dimensional theories: no unifying core deficit or even triad to explain syndrome→each sign independent & arises from independent genes
- Information processing theories: global-local, impaired higher level skills-enhanced local processing; WCC most widely known
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?

Courtesy of Michael Rutter, 2007 “Autism: Clinical features and research challenges”
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
<table>
<thead>
<tr>
<th><strong>TABLE 2-24</strong> Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peak Time Period</strong></td>
</tr>
<tr>
<td>5 months’ gestation–years postnatal</td>
</tr>
<tr>
<td><strong>Major Events</strong></td>
</tr>
<tr>
<td>Subplate neurons: establishment and differentiation</td>
</tr>
<tr>
<td>Lamination: alignment, orientation, and layering of cortical plate neurons</td>
</tr>
<tr>
<td>Neurite outgrowth: dendritic and axonal ramifications</td>
</tr>
<tr>
<td>Synaptogenesis</td>
</tr>
<tr>
<td>Cell death and selective elimination of neuronal processes and of synapses</td>
</tr>
<tr>
<td>Glial proliferation and differentiation</td>
</tr>
</tbody>
</table>
### 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>
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<tr>
<th>Domain</th>
<th>Tests Passing Tolerance</th>
<th>Percent Correct</th>
<th>Kappa</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</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>

1 Kappa below .40 indicates poor agreement beyond chance  
2 Significant *Kappa* reflects superior performance by autistic subjects  
3 Based on 33 individually age, IQ, gender matched pairs of subjects
## Pattern of Abilities in Major Domains in High Functioning Autism

<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>

- Complex Sensory
- Complex Motor
- Complex Memory
- Complex Language
- Concept-formation
- Face Recognition
Elementary abilities intact or enhanced

Information processing capacity constrained - integrative processing disproportionately impaired

Inference: higher order brain circuitry is under developed - over-reliance or over-development of lower order visual circuitry for functioning
fMRI Activation During a Spatial Working Memory Task  (Courtesy John Sweeney)

Neurotypical Group

Autism Group
What Was & Is Missing?
What don’t you know?

What does the pattern look like in severest cases?
What does that imply about the brain?

What does the pattern look like in very youngest and what does that mean?
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
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.
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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.
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]
Shared and idiosyncratic cortical activation patterns in autism revealed under continuous real-life viewing conditions.

Department of Psychology and the Neuroscience Institute, Princeton University, Princeton, New Jersey, USA. hasson@princeton.edu

Although widespread alterations in cortical structure have been documented in individuals with autism, the functional implications of these alterations remain to be determined. Here, we adopted a novel inter-subject correlation (inter-SC) and intra-subject correlation (intra-SC) technique to quantify the reliability of the spatio-temporal responses of functional MR activity in adults with autism during free-viewing of a popular audio-visual movie. Whereas these complex stimuli evoke highly reliable shared response time courses in typical individuals, cortical activity was more variable across individuals with autism (low inter-SC). Interestingly, when we measured the responses within an autistic individual across repeated presentations of the movie, we observed a unique, idiosyncratic response time course that was reliably replicated within each individual (high intra-SC). Encouragingly, after filtering out the idiosyncratic responses from each individual time course, we were able to uncover a more typical response profile, which resembles the shared responses seen in the typical subjects. These findings indicate that, under conditions approximating real-life situations, the neural activity of individuals with autism is characterized by individualistic responses that, although reliable within an autistic individual, are both highly variable across autistic individuals and different from the responses observed within the typical subjects. These idiosyncratic responses may underlie the atypical behaviors observed in autism. At the same time, we are encouraged by the presence of the more typical activation pattern lurking beneath these idiosyncratic fluctuations. Taken together, these findings may pave the way to future research aimed at characterizing the idiosyncratic response profiles, which, in turn, might contribute to a better understanding of the heterogeneity of the autism spectrum and its diagnosis.

PMID: 19708061 [PubMed - indexed for MEDLINE]
Brain Affected Broadly But Selectively

Cortical-Cortical Connections
Cortical-amygdala
Cortical-striate
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.
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 linearmodel 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
Camera Lucida composite drawings of neurons in the visual (calcarine) cortex of human infants indicated gestational ages. Note the appearance and elaboration of basilar dendrites and the tangential spread of apical dendrites, as well as the accompanying maturation of the visual evoked response (top). (Courtesy of Dr. Dominick Purpura)
How the Brain Develops
Is autism a synapse-opathy?

**Dendrite Morphology/Function**
- SHANK3/SHANK2
- Reelin
- DLGAP2

**Axonal Outgrowth/Pathfinding**
- Slit/LRRs
- Reelin
- Tau Kinases
- Cadherins
- SYNGAP1

**Synaptic CAMs**
- Neurexins/Neuroligins
- Cadherings
- CNTN4
- CNTNAP2
- SYNGAP1
Autism is the result of alterations in how the brain processes information, which alters how the mind sees the world.

**Alterning 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]  
PMCID: PMC2796260 [Available on 2010/12/10]
Interventions To Promote Connectivity

Many in progress
Cognitive Enhancement Therapy
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.
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
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)
Categorizing Less Typical Gender Faces (Percent Correct)
Proportion of Looking to LVF and EYES

Dundas, Best, Minshew & Strauss (under revision)
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

Age in Months

Error Bars: 95% CI

Risk Status

H
L

* P < .05

.50
Percent Looking to Left Visual Field: 6- and 11- month old infant siblings at High and Low Risk for Autism