We wish to honor those individuals and families who have believed in research and been committed to participating again and again.
What does ‘cause’ mean?

Etiology
Pathophysiology
Functional analysis of behavior
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.

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 Connected Sequence of Mechanisms At All Levels
Defining Cause Means

Defining Mechanisms

Leads to:

Developing treatments that specifically target mechanisms
What was/is the established view of autism?
What evidence challenged this view?
What evidence pointed the way forward?
What is an integrated view of cause now?
What are the benefits of the above to care?
Where Are We Coming From

Autistic Disorder: DSM

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

- Social primacy theories: pathognomonic & dominant, inferred to be the cause of syndrome, focal brain origin

- Dimensional theories: no unifying core deficits - each sign independent & independent genes
Today’s Trip Tik

- What was/is the established view of autism?
- What evidence challenged this view?
- What evidence pointed the way forward?
- What is an integrated view of cause now?
- What are the benefits of the above to care?
Findings That Required A New View

- Increase in HC & total brain volume
- Stunted dendritic tree development CA1
- Widespread cortical functional underconnectivity
- Gene abnormalities-many & scattered across genome; all coding for development of connections among neurons
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
Group differences in functional connectivity

Control group

Group with autism

Functional connectivity (z)

ROI pairs

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome or mutation(s)</th>
<th>Replicated association</th>
<th>Analysis of variant</th>
<th>Mouse model</th>
<th>Other evidence</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVPR1A</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
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<tr>
<td>DISC1</td>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
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<tr>
<td>ITGB3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>AHI1</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>EN2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>GRIK2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1; homozygous mutation results in non-syndromic mental retardation</td>
<td>2</td>
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<td>NRXN1</td>
<td>2</td>
<td>0</td>
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<tr>
<td>SLC25A12</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1; associated with neurite outgrowth, expression is upregulated in ASD brain</td>
<td>2</td>
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<tr>
<td>Promising</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>CACNA1C</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>CNTNAP2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>MET</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1; expression reduced in brains of cases versus controls</td>
<td>3</td>
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<tr>
<td>OXTR</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1; expression reduced in blood of cases versus controls</td>
<td>3</td>
</tr>
<tr>
<td>SHANK3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1; modulates glutamate-dependent reconfiguration of dendritic spines</td>
<td>3</td>
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<tr>
<td>SLC6A4</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1; clinical benefit from inhibitors, variation linked to gray-matter volume</td>
<td>3</td>
</tr>
<tr>
<td>CADPS2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
<td>4</td>
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<td>DHCR7</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1; hypocholesterolaemia in a proportion of probands</td>
<td>4</td>
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<tr>
<td>FMR1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
<td>4</td>
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<tr>
<td>NLGN3</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<td>NLGN4X</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
<td>4</td>
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<tr>
<td>PTEN</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1; mutations result in abnormal structure and function of the synapse</td>
<td>4</td>
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<tr>
<td>TSC2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1; regulates dendrite morphology and function of glutamatergic synapses</td>
<td>4</td>
</tr>
<tr>
<td>GABRB3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1; expression is dysregulated in pervasive developmental disorders</td>
<td>4</td>
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<tr>
<td>MECP2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1; MECP2 deficiency causes reduced expression of UBE3A and GABRB3</td>
<td>5</td>
</tr>
<tr>
<td>TSC1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1; regulates dendrite morphology and function of glutamatergic synapses</td>
<td>5</td>
</tr>
<tr>
<td>UBE3A</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1; expression is dysregulated in pervasive developmental disorders</td>
<td>5</td>
</tr>
<tr>
<td>RELN</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1; levels reduced in brains of cases versus controls</td>
<td>6</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Gene(s) associated with the syndrome</td>
<td>Proportion of patients with the syndrome that have an ASD</td>
<td>Proportion of patients with an ASD that have the syndrome</td>
<td>Refs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>--------------------------------------</td>
<td>----------------------------------------------------------</td>
<td>----------------------------------------------------------</td>
<td>------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15q duplication — Angelman syndrome</td>
<td>UBE3A (and others)</td>
<td>&gt;40%</td>
<td>1–2%</td>
<td>101–103</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16p11 deletion</td>
<td>Unknown</td>
<td>High</td>
<td>~1%</td>
<td>20, 35, 44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22q deletion</td>
<td>SHANK3</td>
<td>High</td>
<td>~1%</td>
<td>21, 22, 104</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical dysplasia-focal epilepsy syndrome</td>
<td>CNTNAP2</td>
<td>~70%</td>
<td>Rare</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>FMR1</td>
<td>25% of males; 6% of females</td>
<td>1–2%</td>
<td>105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joubert syndrome</td>
<td>Several loci</td>
<td>25%</td>
<td>Rare</td>
<td>106</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potocki–Lupski syndrome</td>
<td>Chromosome position 17p11</td>
<td>~90%</td>
<td>Unknown</td>
<td>107</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith–Lemli–Optiz syndrome</td>
<td>DHCR7</td>
<td>50%</td>
<td>Rare</td>
<td>108</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rett syndrome</td>
<td>MECP2</td>
<td>All individuals have Rett syndrome</td>
<td>~0.5%</td>
<td>109</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timothy syndrome</td>
<td>CACNA1C</td>
<td>60–80%</td>
<td>Unknown</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC1 and TSC2</td>
<td>20%</td>
<td>~1%</td>
<td>110</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The rates quoted in the table depend on the population that is being evaluated. For example, rates are higher in individuals from simplex families compared with multiplex families, and are higher in dysmorphic and mental retardation populations compared with idiopathic populations. ‘High’ is used for syndromes in which no good estimates exist (that is, only a handful of individuals with the syndrome in question have been identified). It should also be noted that none of the studies cited here indicates that assessment for the autism spectrum disorder (ASD) was performed blind to a patient’s primary diagnosis. An expanded version of the table with additional variables can be found in Supplementary Information S1 (table). CACNA1C, calcium channel voltage-dependent L type alpha 1C subunit; CNTNAP2, contactin associated protein-like 2; DHCR7, 7-dehydrocholesterol reductase; FMR1, fragile X mental retardation 1; MECP2, methyl CpG binding protein 2; SHANK3, SH3 and multiple ankyrin repeat domains 3; TSC1, tuberous sclerosis 1; TSC2, tuberous sclerosis 2; UBE3A, ubiquitin protein ligase E3A.
Is autism a synapse-opathy?
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
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.)
- Abnormalities in Genetic Code for Brain Development
- Abnormal Mechanisms of Brain Development
- Structural and Functional Abnormalities of Brain
- Cognitive & Neurological Abnormalities
- Behavioral Syndrome

Define A Pathophysiologic Sequence(s) For ASDs With Absolute Precision
Today’s Trip Tik

What was/is the established view of autism?
What evidence challenged this view?
What evidence pointed the way forward?
What is an integrated view of cause now?
What are the benefits of the above to care?
What Are Infant Siblings Teaching Us About Autism in Infants? Rogers, 2009

- Began with: home video movies showed symptoms 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”
- Unusual visual regard at 12 mos
- Repetitive waving of arms and hands at 12 mos
- Sensory-related behaviors: under and over responsiveness at 12 months
- 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
No social signs at 6 months don’t predate other sx
Delays in verbal and nonverbal language at 12 months but not earlier
Developmental differences at 12 mos on standardized tests- a developmental deceleration
Gap widens between 12 & 24 months and beyond
At 24 months, emotional and behavioral dysregulation distinguished infant sibs dx ASD
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
Developmental Characteristics of Infant Sibs: Conclusions

- “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
Developmental Characteristics of Infant Sibs: 
Onset > 6 mos; Motor & Balance First

- No developmental differences at 6 mos
- Differences in fine and gross motor- early
- Less mouthing of objects-less vocalizations
- Truncal instability when sitting- early
Brain Affected Broadly in ASD

From the beginning
Many domains, not one
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 development comes for that skill to appear
What is happening in the BRAIN in infant sibs?

Onset of acceleration of brain growth at 9-12 months-coincident with onset of symptoms.
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).
Organogenesis
Neuronal proliferation*
Glial proliferation, migration
Neuronal migration** $CNTNP2$
Neuronal organization***
Myelination
<table>
<thead>
<tr>
<th>TABLE 2-24</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peak Time Period</strong></td>
<td>5 months’ gestation–years postnatal</td>
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<tr>
<td><strong>Major Events</strong></td>
<td></td>
</tr>
<tr>
<td>Subplate neurons: establishment and differentiation</td>
<td></td>
</tr>
<tr>
<td>Lamination: alignment, orientation, and layering of cortical plate neurons</td>
<td></td>
</tr>
<tr>
<td>Neurite outgrowth: dendritic and axonal ramifications</td>
<td></td>
</tr>
<tr>
<td>Synaptogenesis</td>
<td></td>
</tr>
<tr>
<td>Cell death and selective elimination of neuronal processes and of synapses</td>
<td></td>
</tr>
<tr>
<td>Glial proliferation and differentiation</td>
<td></td>
</tr>
</tbody>
</table>
How the Brain Develops

15-1/2 wks

22 wks

23 wks

~25 wks

27 weeks

Full term brain

Adult
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
Today’s Trip Tik

- What was/is the established view of autism?
- What evidence challenged this view?
- What evidence pointed the way forward?
- What is an integrated view of cause now?
- What are the benefits of the above to care?
Brain Affected Broadly in ASD

Many domains, not one
Was this a new idea with infant sibs?
**Discriminant Function Analysis: Domains Without Deficits³**

<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

<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>
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<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>75.80</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

<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 Does The Profile Mean?

- Elementary abilities intact or enhanced

- Information processing capacity limited- integrative processing disproportionately impaired

Inference: higher order brain circuitry is under developed- over-reliance or over-development of lower order visual circuitry to function.
fMRI Activation During a Spatial Working Memory Task  (Courtesy John Sweeney)
A Disorder of Cortical Connectivity

Underconnectivity of cortical networks w/ frontal
Excessive local connections posteriorly
Anterior-posterior connectivity gradient
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 temporoparietal 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]
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]  
PMCID: PMC2775929 [Available on 2010/8/1]
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 behaviors 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 behavior. The findings might explain impairments in motor development in autism, as well as abnormal and delayed acquisition of gestures important for socialization and communication.

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How Does the Brain Classify Words? 
Results of Recent fMRI Studies

- 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
Autism is the result of alterations in how the brain processes information, which alters how the mind sees the world.

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

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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.

Today’s Trip Tik

- What was the established view of autism?
- What evidence challenged this view?
- What evidence pointed the way forward?
- **What is an integrated view of cause now?**
- What are the benefits of the above to care?
Axonal Pathfinding & Targeting:
-- Cadherins
-- LRRs

Synaptic Targeting & Function:
-- Neurexins/Neuroligins

Dendritic Morphology/Function:
-- SHANKs

Adapted from www.morphonix.com
1. Genes whose products affect **axonial targeting and pathfinding** i.e. getting neurons connected in the right way  
**Cadherins** and **leucine-rich repeat proteins** which are cell surface proteins expressed in neuronal processes - thought to be important for establishing connections between cells in the developing brain
2. Those that affect synaptic functioning:

Neurexins and neuroligins bind each other across the synapse (i.e. glue neurons together) and mediate signaling across the synapse, and affect the properties of neural networks by specifying synaptic functions (i.e. excitatory versus inhibitory)
3. Those that appear to affect **dendritic function**:  

**Shank** family of synaptic proteins function as molecular scaffolds at the post synaptic density and promote the maturation and enlargement of dendritic spines.
A Molecular Pathophysiology Emerges

- Defining molecular mechanisms empowers a new world of interventions

- mTor inhibitor Rapamycin to prevent development of seizures, intellectual disability and ASD in infants and toddlers diagnosed with TSC gene tuberous sclerosis; clinical trials in progress
A complex series of phosphorylation events and other protein interactions regulate hamartin/tuberin and activity of the mTOR kinase. Initial growth factor binding to transmembrane receptors (not shown) activates PI-3 kinase resulting in increased production of PIP3 with AKT activation that directly phosphorylates and inhibits tuberin. ERK can also phosphorylate and inactivate tuberin. In contrast, AMPK phosphorylation at distinct amino acid residues serves to activate tuberin. Loss of the TSC1 or TSC2 genes leads to constitutive activation of mTOR within mTORC1 with greatly increased levels of phosphorylated ribosomal S6 kinase and phosphorylated ribosomal S6. Rapamycin inhibits mTOR activity within mTORC1 to restore inhibition of this kinase and downstream components within this signaling pathway. ATP indicates phosphorylation events. AKT (proto-oncogene also known as PKB); AMPK, AMP-activated protein kinase; ERK, extracellular signal-regulated kinases; FKBP38, FK506-binding protein 38; LKB1, Peutz–Jeghers syndrome kinase; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; mTORC2, mammalian target of rapamycin complex 2; PI-3, phosphoinositide 3; PIP2, phosphatidylinositol bisphosphate; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PKB, protein kinase B; PTEN, phosphatase and tensin homolog; Rapa, rapamycin; Raptor, regulatory-associated protein of mTOR; Rictor, rapamycin-insensitive companion of mTOR; Rheb, Ras homolog enriched in brain; TSC1, (hamartin); tuberous sclerosis complex gene 1; TSC2, (tuberin) tuberous sclerosis complex gene 2. →, activates; ←, inhibits.
Tuberous sclerosis complex: a brave new world?

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PURPOSE OF REVIEW: Tuberous sclerosis complex (TSC) is a multiorgan genetic disease caused by mutations in the TSC1 or TSC2 genes. TSC has been recognized for many years as an important cause of severe neurological disease with patients suffering from epilepsy, developmental delay, autism, and psychiatric problems. During the last year, there have been enormous advances in basic and translational research pertaining to TSC. RECENT FINDINGS: In this review, I discuss the basic science findings that position the TSC1 and TSC2 genes as critical regulators of the mammalian target of rapamycin kinase within mammalian target of rapamycin complex 1. In addition, I will discuss the development of new animal models, translational data, and recent clinical trials using mammalian target of rapamycin complex 1 inhibitors such as rapamycin. SUMMARY: The past few years have seen spectacular advances that have energized TSC-related research and challenged existing symptomatic treatments. Although it remains to be seen whether use of mammalian target of rapamycin complex 1 inhibitors will revolutionize the care of patients with TSC, the application of basic and translational research towards a specific clinical disorder emphasizes the potential and promise of molecular medicine.

PMID: 20087180 [PubMed - as supplied by publisher]
Rapamycin injection progressively reduces seizure duration and frequency of *Pten* mutant mice. *n = 6 mice per group. *p < 0.05 compared between vehicle- and rapamycin-treated mutants. Data are mean ± SEM and were analyzed by ANOVA, followed by *post hoc* t test.
Deregulation of *EIF4E*: a novel mechanism for autism

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**ABSTRACT**

**BACKGROUND:** Autism is a common childhood onset neurodevelopmental disorder, characterised by severe and sustained impairment of social interaction and social communication, as well as a notably restricted repertoire of activities and interests. Its aetiology is multifactorial with a strong genetic basis. EIF4E is the rate limiting component of eukaryotic translation initiation, and plays a key role in learning and memory through its control of translation within the synapse. EIF4E mediated translation is the final common process modulated by the mammalian target of rapamycin (mTOR), PTEN and fragile X mental retardation protein (FMRP) pathways, which are implicated in autism. Linkage of autism to the EIF4E region on chromosome 4q has been found in genome wide linkage studies.

**CONCLUSIONS:** These observations implicate EIF4E, and more specifically control of EIF4E activity, directly in autism. The findings raise the exciting possibility that pharmacological manipulation of EIF4E may provide therapeutic benefit for those with autism caused by disturbance of the converging pathways controlling EIF4E activity.
Cognitive Enhancement Therapy

- A cognitive rehabilitation intervention for remediating neurocognitive and social-cognitive deficits developed by Hogarty and colleagues (2004, 2006).

- Mechanisms of efficacy: improved speed of processing & capacity to assume perspectives of others and apply this skill to life function.
Process of CET

- Starts with basic socialization and attention training in pairs (3mo to 6mo)
- Moves to small group-based social-cognitive training (6mo to 18mo)
- Simultaneously moves to executive function and problem-solving training (6mo to 18mo)
- All provided in the context of meaningful functional goals (e.g., work, school, girlfriend)
Cognitive Enhancement Therapy

- 18 months; twice per week
- Documented efficacy in double blind trials in schizophrenia
- Improved processing speed leads to improved comprehension, improved performance on almost all cognitive tasks
- Increased frontal and temporal volumes pre-post treatment in schizophrenia
Cognitive Enhancement Therapy

I. Foster Higher Thinking By Becoming:

- Gistful vs. Concrete
- An Active Thinker vs. Passive Receiver of Information
- Cognitively Flexible vs. Following Rigid Rules
- More Spontaneous vs. Rehearsed
- More of an Initiator vs. Doing Nothing
Interventions To Promote Connectivity

Many in progress.
We wish to honor those individuals and families who have believed in research and been committed to participating again and again.
How Does the Typical Brain Classify Words? Results of Recent fMRI Studies

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- Each word encoded according to four attributes in adults:
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  - 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