“The Cause of Autism: Its Footprint Tells”

Inaugural Autism Symposium

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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.

Convergence of Clinical With Anatomic
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Group mean HC 60-70%; megalencephaly in 15%
Onset accelerated growth 9-12 months w/ 15-20% macrocephaly by 4-5 years
Growth decelerates and plateaus so that brain volume “normalizes” in childhood, though subset remain macrocephalic throughout life
Important to recognize that HC>HT is not universal in autism and HC=HT and HC<HT growth trajectories also compatible with autism
Major role for white matter but without accompanying long tract signs and thus the difference between acquired and devel. disorders

Disturbance in connectivity

Increased white matter volume associated with dysfunction, not increased function

Inter-hemispheric white matter e.g. corpus callosum not involved in the same process

Minshew & Williams, Arch Neurol 2007
Minicolumn Abnormalities in Autism: Evidence of Cortical Involvement

- First substantive abnormalities of cerebral cortex
- Radially oriented arrays of pyramidal neurons, interneurons, axons and dendrites
- Smallest radial unit of information processing; then macrocolumns and receptive fields?
- Bilateral abnormalities in areas 3, 4, 9, 17, 21, 22
- Increased #, narrower, reduced neuropil space (inhibitory neurons), neurons small

Autism is a disorder of the neuron.

It is not a white matter or gray matter disorder or rather it is both but it is fundamentally a disorder of the neuron.
Autism is a dysconnectivity syndrome—both increased & decreased connectivity.”
Superior to age-, IQ-, gender- matched controls on word & non-word decoding, spelling, vocabulary, fluency

Inferior to controls on comprehension of sentences, idioms, metaphors, stories
Cortical activation & synchronization during sentence comprehension in HFA subjects

Marcel Just
Vlad Cherkassky
Tim Keller
Nancy Minshew

Just et al. 2004, Brain 127: 1811-1821
Sentence reading task and comprehension probe

The player was followed by the parent

Who was following? player parent
Brain activation during sentence comprehension in autism

Autism group has less activation in **Broca’s area**
- *(a sentence integration area)*
than the control group and more in **Wernicke’s area**
- *(a word processing area)*

Results are consistent with poorer comprehension of complex sentences, coupled with good word reading *(spelling bee champs)*
Example of less synchronized activation across two areas (upper panel, participant with autism) or more synchronized (lower panel, control participant) in comprehension task
Reliably lower functional connectivity for autism participants between pairs of key areas during sentence comprehension (red end of scale denotes lower connectivity)
Reliable differences in functional connectivity: autism group has lower functional connectivity but same rank order.
Functional Underconnectivity: 
fMRI of the Tower of London

Marcel Just
Nancy Minshew
Tim Keller
Vlad Cherkassky
Rajesh Kana

Just et al., 2006 [Epub ahead of print], Cereb Cortex
Two systems-level characteristics of cortical function

1. It is always a set of cortical areas, not just one area, that activates in any thinking task, identifying the multiple neural centers involved.
2. The activation is synchronized across subsets of participating areas
   (Broca’s and DLPFC, in this example)

   Synchronization implies that the areas are collaborating and communicating with each other, and are not acting as independent agents.

   - Technical jargon: the measure of synchronization is referred to as “functional connectivity”
Other Brain Networks Affected in ASD: Innate Specialization Disturbed

- Theory of Mind
- Mirror Neuron
- Motion Processing (Gaze & Biologic Motion)
- Face Processing
- Emotion Processing
- Motivation, Incentive, Disincentive
- Language- left and right hemisphere
- Concept formation
What are the brain systems involved in representing the actions and intentions of other people?

Pelphrey et al. (2003) *Journal of Neuroscience*
Carter & Pelphrey (2007) *Social Neuroscience*
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At this point, clear that typical brain development results in pre-fab circuitry & systems that predispose human infant to automatically orient and prefer human contact over objects, experience emotions and perceive them in others, acquire language, make sense of the world, play with toys symbolically and with others.
Is autism a synapse-opathy?
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Genetic Advances

Discovery of rare families with SHANK3 gene mutations added further evidence to synaptic dysfunction hypothesis.

Codes for synapse formation & maintenance. It also interacts with neuroligins and neurolexins.
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Potential reversal of Neurodevelopmental Disorders (in Fragile X, Rett & Angelman Syndromes) in adult mice;

Proof of concept that delineating neurobiologic and genetic mechanism would lead to treatment
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**Mouse models** of genes associated with autism in humans: neuroligin-3 gene mouse model:

mouse has deficits in social behaviors and an increased ability for spatial learning.
The Loop From Clinical Syndrome to Genes is Completed: Widespread disturbance in integrative processing, neural systems development, and genes related to development of connectivity
Many non-traumatic child neurologic disorders present “out of the blue”. They are divided by age groups, gray or white matter, and then regions.

A recent example at CNS meeting-, neuronal ceroid lipofuscinosis, uniformly fatal, not responsive to bone marrow transplant, thus a candidate for stem cell therapy. Three forms: neonatal, infantile, juvenile.

DNA as the day to day director of life; may come with faults with different decay rates-time bombs present from birth

Clarification of Onset & Genetic For Public
Research Studies

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

Through July 2012; no cost; participant payment; we pay airfare & hotel