“The Cause of Autism: Its Footprint Tells”

Autism Symposium-Part II

May 22, 2009

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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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Head Growth in Autism

- 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
Implications of Brain Volume Studies

- 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
<table>
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<th>TABLE 2-24  Organization</th>
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<tr>
<td><strong>Peak Time Period</strong></td>
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<td>5 months’ gestation–years postnatal</td>
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<td><strong>Major Events</strong></td>
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<td>Subplate neurons: establishment and differentiation</td>
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<td>Lamination: alignment, orientation, and layering of cortical plate neurons</td>
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<td>Neurite outgrowth: dendritic and axonal ramifications</td>
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<td>Synaptogenesis</td>
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<td>Cell death and selective elimination of neuronal processes and of synapses</td>
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<td>Glial proliferation and differentiation</td>
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Figure 2-39  Schematic summary of development of the human prefrontal cortex. At the earliest age studied (10.5 weeks), the preplate zone has been split by the early-arriving neurons of the cortical plate into neurons of the marginal zone (MZ) above and of the subplate zone (SP) below. Note the exuberant neuronal development of the subplate zone into the third trimester of gestation. CP, cortical plate; IZ, intermediate zone; SP_l, subplate zone (lower); SP_p, subplate-preplate zone; SP_u, subplate zone (upper); SV, subventricular zone; V, ventricular zone; WM, white matter.

Figure 2-41. Golgi preparation (×80) of the middle frontal gyrus from a 6-year-old child without known neurological disease. Note the abundant and complex horizontal and tangential dendritic branches. *(From Buchwald NA, Brazier MAB, editors: Brain Mechanisms in Mental Retardation, New York: 1975, Academic Press.)*
Figure 2-45 Measurements of cortical surface area and volume by advanced magnetic resonance imaging (MRI) (upper) and conventional MRI images of gyral development (lower) during the last 14 weeks of gestation. Data were derived from study of 113 preterm infants. (From Kapellou O, Counsell SJ, Kenna NL, Dvet L, et al: Abnormal cortical development after premature birth shown by altered allometric scaling of brain growth, PLoS Med 3:e265, 2006.)
Figure 2-43 Camera lucida composite drawings of neurons in the visual (calcarine) cortex of human infants of 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.)*
Figure 2-47  Synaptic density in layer I and layer II/III of the striate cortex. Open circles represent layer I; closed circles represent layer II/III. Note the striking increase in the first postnatal year and the subsequent decline. (From Huttenlocher PR, de Courten C: The development of synapses in striate cortex of man, Hum Neurobiol 6:1-9, 1987.)
Brodman’s Map & Connectivity

- Primary sensory & motor cortex
- Unimodal association cortex
- Heteromodal association cortex
- Intra- and inter-hemispheric connections
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 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
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 Cherkasskky
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*
Convergence Across Systems

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?
Genetic Advances

Increased rate of “de novo” copy number variations: submicroscopic deletions or duplications of DNA sequences. More common in simplex than multiplex families. Instability in replication of DNA

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

Proof of concept that delineating neurobiologic and genetic mechanisms would lead to treatment
PTEN conditional knock-out mice display enlarged brains and social behavioral deficits: PTEN interacts with several proteins in a signaling cascade that are tied to tuberous sclerosis and neurofibromatosis. 17% of individuals with autism & macrocephaly had PTEN gene. KO mice raises rescue possibilities.
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.

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The Top 10 of 2007 (cont’d.)

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.

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**.
The role of the discovered genes has been defined at a cellular-molecular level to involve common inter-related signaling pathways that regulate development of brain connections.

Emerging concept that two much (autism) and too little (Rett) connectivity both result in brain dysfunction.

Cellular defects are discrete and disorder specific.
The Loop From Clinical Syndrome to Genes is Completed: Widespread disturbance in integrative processing, neural systems development, and genes related to development of connectivity.

The Footprint is Visible: A Developmental Brain Disorder of Neuronal Organization
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“Machine learning analyses of language representation in the brain: words & concepts encoded 5 ways—5 attributes; this enables generalization in typical brain.

Analyses of fMRI in face processing disorders reveals it is not a focal brain function but a distributed brain function.

So What’s Really Really New

- Machine learning analyses of language representation in the brain: words & concepts encoded 5 ways—5 attributes; this enables generalization in typical brain.
- Analyses of fMRI in face processing disorders reveals it is not a focal brain function but a distributed brain function.
So What’s Really Really New: 3 New Interventions

- Cognitive Enhancement Therapy: 18 months, focuses on cognitive, social, and emotional function and life skills
- Multidimensional information integration: training a common brain mechanism needed for a wide range of abilities
- Using animals and related information to train face processing
Implications for Intervention

- Speak in sentences-think in words & or pictures
- Brain operates in systems, systems underconnected
- Local connections over-developed
- Key Qs:
  - Does ABA develop local connections?
  - Can new cognitive paradigms be designed to develop systems connections? Flexibility?
- Use cognition to boot strap behavior later
- Milieu to ingrain automatic good societal behavior
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.