

Mapping Early Brain Development in Autism

Courchesne et al. 2007

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What is Autism?

- A relative common genetic disorder of neural development (1/150 individuals)
- Severe developmental delay and impairment occur in higher-order social, emotional, language and communication functions
- First behavioral signs may appear when children are between 1 and 2 years old, however children usually aren't diagnosed until they are 2-4 yrs.
- Significant abnormalities in social attention, language development, and emotional reactivity

Autism Research

- While 2-4 is the critical age for early intervention therapies, there are very few studies of neural and anatomical development at this age
- Autism studies tend to focus on 10-20 years after the onset of the disorder
- These studies neglect to address the question of what neural structural abnormalities underlie the emergence of autistic behavior in the beginning stages

Anatomic Evidence on the Autistic Brain 10-20 or More Years after Clinical Onset

- The largest postmortem study of autism to use stereological methods for quantify neuron number (10-44 yrs old)
- Findings:
 - Fewer neurons in the amygdala
 - Reduced Purkinje neurons in the cerebellum
 - Neurons in the deep cerebellar nuclei were reported to be abnormally small and pale in adolescence and adult autistic cases

Anatomic Evidence on the Autistic Brain 10-20 or More Years after Clinical Onset

- Findings Con' t
 - Increases in proapoptotic (pro-cell death) and decrease in antiapoptotic (anti-cell death) in the frontal cortex
 - Cortical MRI study reported cortical thinning, sulcal widening and occasionally ventricular enlargement in the superior parietal and frontal regions
 - Reduced corpus callosum

Anatomic Evidence on the Autistic Brain 10-20 or More Years after Clinical Onset

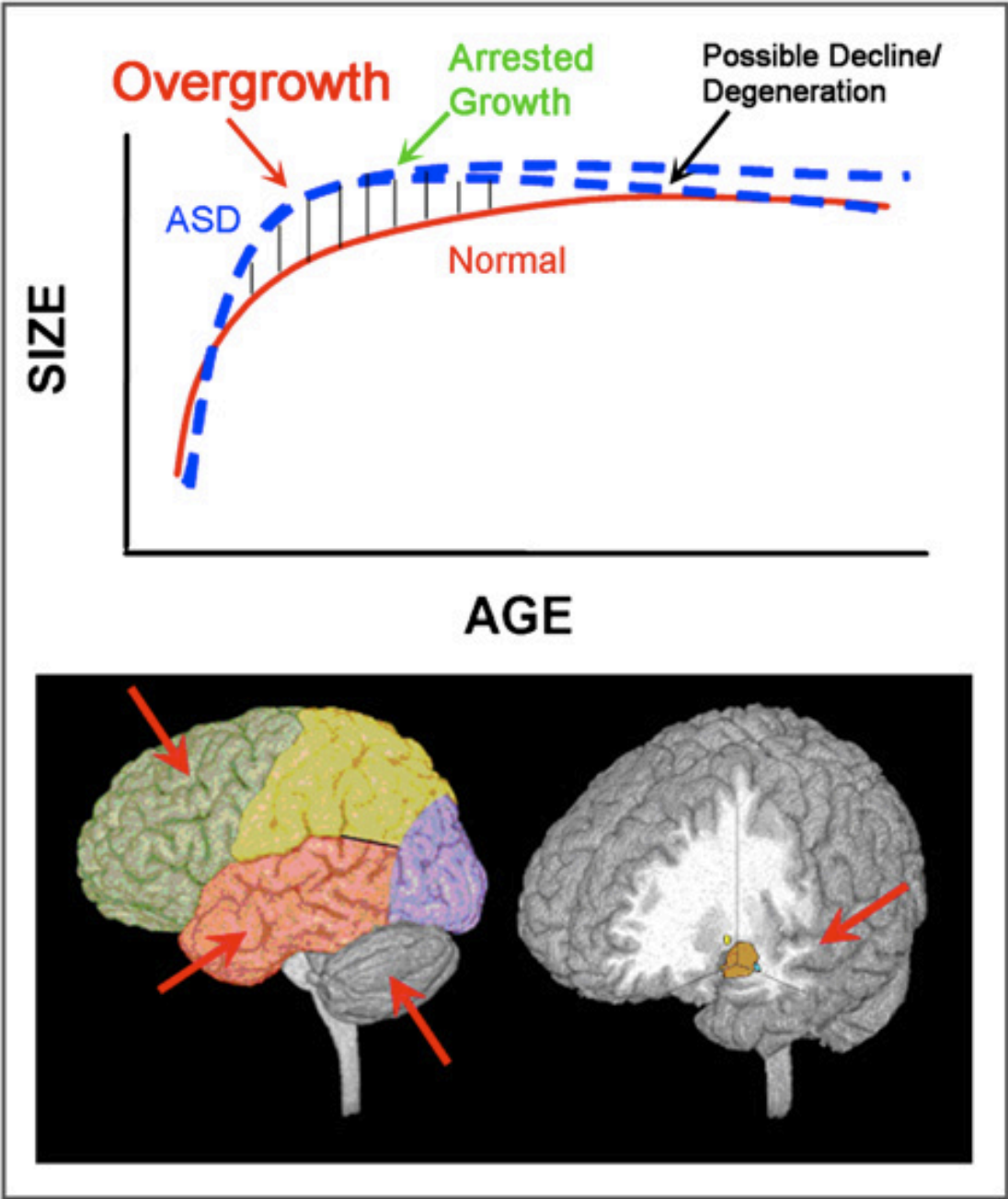
- Head circumference (HC) studies:
 - Imprecise measure
 - In older autistic adolescence, the brain size is near average of typical developing (TD) population
 - Therefore, this measurement may not give an accurate description of the brain size in the head
- Most common finding in general, is average to smaller than normal brain volume

Mature Compared to Developing Brain in Autism

- MRI and single case studies on 2-4 yr olds do NOT show loss of neurons or reduction in size of minicolumns, but rather and excess growth in size
- Brain volume is 5-12% greater than normal controls
- Larger amygdala
- No Purkinje neuron loss
- More spindle neurons

Mature Compared to Developing Brain in Autism

- New Hypothesis:
 - Early brain development in autism is characterized by TWO phases of brain growth pathology
 - Early brain *overgrowth* at the beginning of life
 - And *slowing or arrest of growth* during childhood
 - In some individuals, a third *degenerative* phase make take place in some brain regions by preadolescence



Early Brain Overgrowth in Autism: *Evidence from Head Circumference and MRI Studies*

- At birth, HC is typically near/ slightly below normal in infants who go on to develop autism
- During the first years of life, HC does correlate well with brain size in TD and autistic children
- However, Courchesne et al. (2003) suggested that by 1 or 2 yrs. in autism, HC becomes abnormally enlarged
- By the time a child with autism reaches 2-4, the MRI will show an enlarged brain

Regions Showing Early Anatomic Overgrowth

- By the age of 2-4, some brain regions and structures display overgrowth, while others do not
- The timing of overgrowth/ regional-specific genetic mechanism involved could be an explanation for this
- MRI studies show that the *frontal lobes, temporal lobes, and amygdala* are sites of peak overgrowth in brains of 2-4 yr olds with autism
- Frontal and temporal sulci are abnormally shifted anterior and/or superior in older autistic children

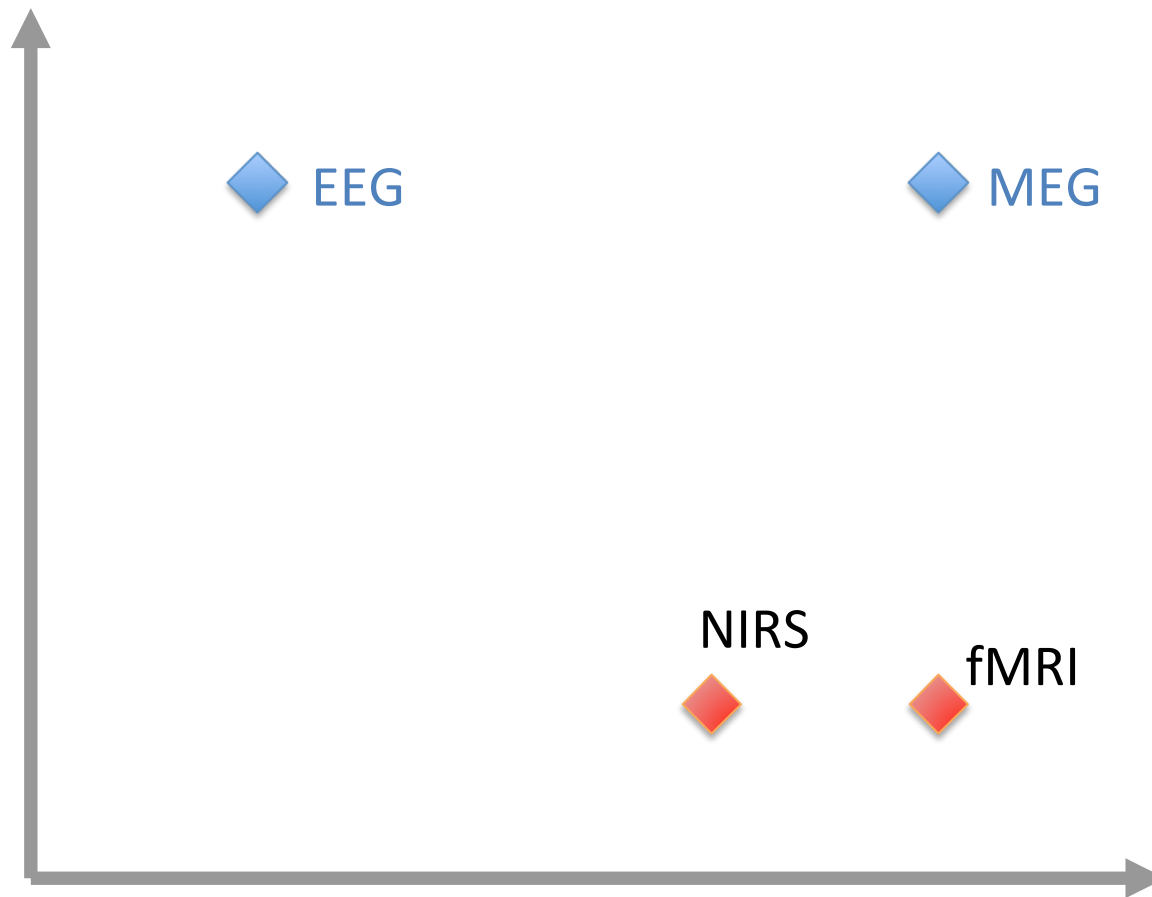
Regions Showing Early Anatomic Overgrowth

- Cerebral regions that experience the greatest amount of early overgrowth may also show the greatest white matter aberrations
- Autism might involve abnormal increases in short-distance connectivity, especially in brain regions that mediate higher-order language, cognitive, social, and emotional functions
- Peak overgrowth in the cerebellum in autism appears to be in the frontal and temporal lobe regions that mediate the above functions, as well as the amygdala

Early Brain Overgrowth and Abnormal Functional Connectivity

- Can we relate abnormal brain overgrowth to abnormal behavioral development?
- Dawson, 2002:
 - TD: increased ERP response to familiar vs unfamiliar stimuli (both social and non-social)
 - ASD: same response for non-social, but not for social
- Kuhl et al, 2005
 - Preference for motherese: $ASD < TD$
 - ERP response to phoneme mismatches (ba/wa): $ASD < TD$
- Neural systems mediating social information more abnormal than systems mediating non-social information

Neurophysiological Measures



Neurophysiological Measures

- ERP doesn't have such good spatial resolution
 - Can't tell WHERE dysfunction is
- fMRI would help with spatially localizing
 - Hard to do with toddlers while awake
- Can do fMRI scans while SLEEPING
 - Integration and processing occur during sleep
 - Lauren's work with rats

www.autismsandiego.org

Cellular and Molecular Bases of Overgrowth: Unknown

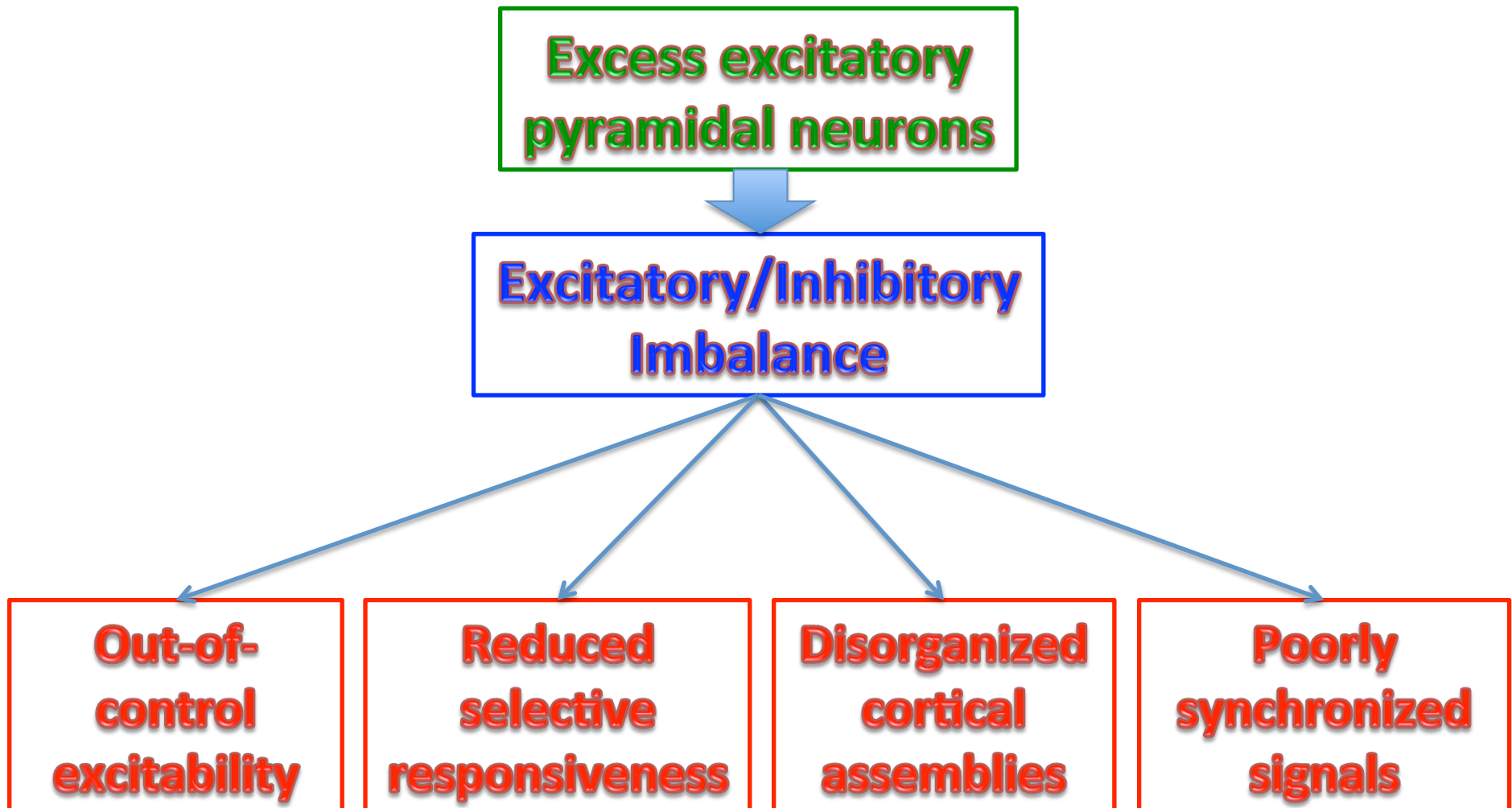
- Inverted U-shaped pattern of development
 - Overgrowth in the developing brain
 - Smaller brain volumes in adults
- Speculations:
 - Increased microcolumns
 - Synapse abnormalities
 - Neuroglien and neurexin gene mutations
 - Copy number variants
 - Reduced MET expression
- No phenotype-genotype association studies of early autism development

Genotype-phenotype associations

Need to be careful about making these associations

- Phenotype results from cascade of developmental processes
- Genes and gene expression have individual variation
- Example:
 - Problem: excess neurogenesis
 - Person A: results in over-compensatory apoptosis
 - Person B: less over-compensatory apoptosis
 - Same initial cause leading to different phenotypes

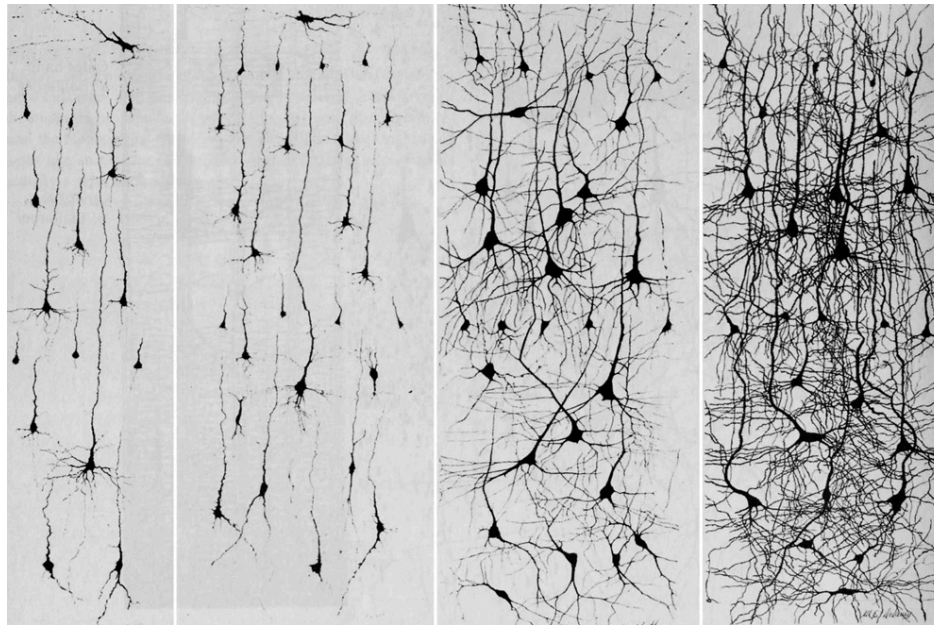
What If: Excess Neurons and the Foundation of Neural Connections



****Later arrested growth and degeneration would also makes sense within this context****

More What-Ifs

- Why do we see signs of autism appearing between 9-24 mos?
- Excess neurons in *frontal and temporal cortices*
 - 9-24 mos: critical period for synaptogenesis
 - Also critical period of vulnerability for these regions



Newborn

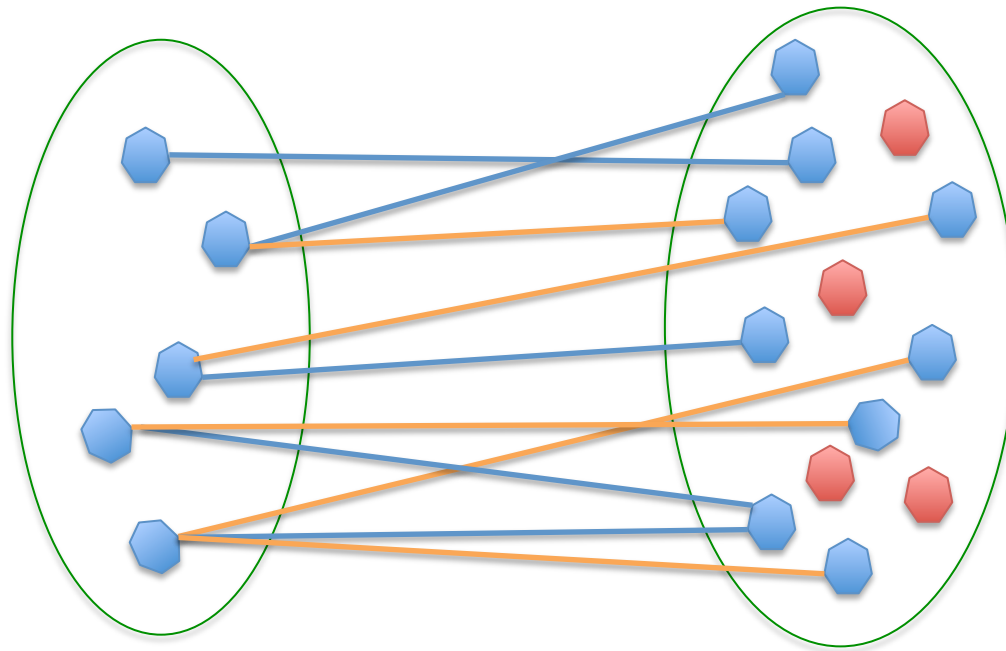
1 month

6 months

2 years

Excess neurons means what?

- “Disparate connectivity”



- Results:
 - weak/inefficient functional cx
 - Short-distance cx > long-distance (# and strength)
 - Large-scale networks have reduced functionality

Large-Scale Network Disruptions

- Mirror/resting systems help with relation of self to others
 - Children with autism have trouble with:
 - social, emotional connections
 - ToM (understanding others' thoughts and intentions)
- fMRI with TD kids show language acquisition also activates these networks
- Behavioral intervention could help
 - Via activity-dependent mechanisms

Behavioral Interventions

- If model of excess pyramidal neurons correct:
 - Networks present in kids w/ASD, just inefficient
- Behavioral interventions could enhance functionality of networks
 - Evidence from face-processing work
- Need to find the right way to incite the right kind of activity

Conclusions

- 2 (3) phases of pathology in autism
 - Overgrowth, slowing/arrest of growth, degeneration
- First few years of development crucial in the development of this pathology
- Likely more than one “major underlying neural defect”
- Authors’ hypothesis: excess neurons in cortical and frontal cortices
- Neurobiological studies in 1st year of life can help us identify cases as early as possible
- Behavioral intervention may be possible