

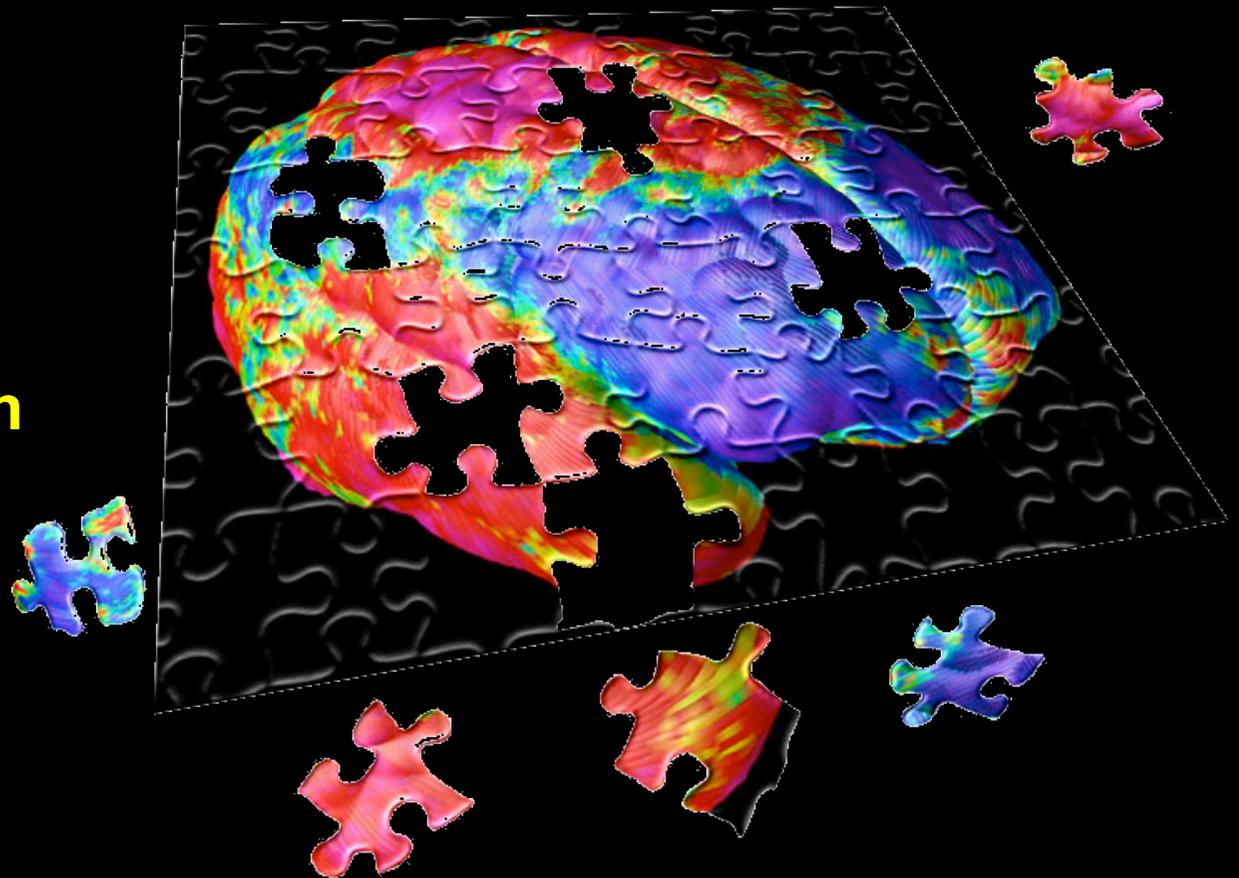
Teen Brain Maturation and Vulnerability to Drug Use: New Views from Neuroimaging

Jay N. Giedd, MD
Child and Adolescent
Psychiatry, NIMH

Addiction: new evidences
from Neuroimaging and Brain

Session 1–Neuroimaging of
addiction in diagnostic and
clinical

Verona, Italy
November 13, 2012



BUSH AND GORE: IN THEIR FATHERS' FOOTSTEPS

**Behind
the Atlanta
Rampage**

**Parched
Nation**

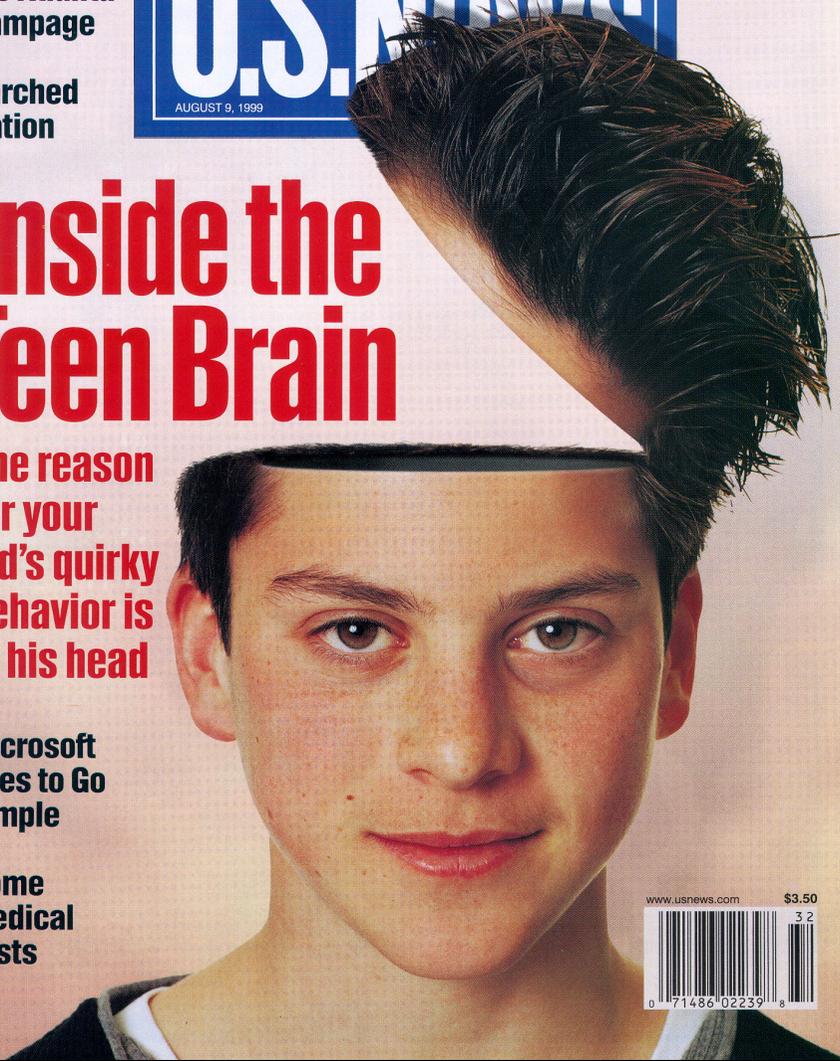


Inside the Teen Brain

**The reason
for your
kid's quirky
behavior is
in his head**

**Microsoft
Tries to Go
Simple**

**Home
Medical
Tests**

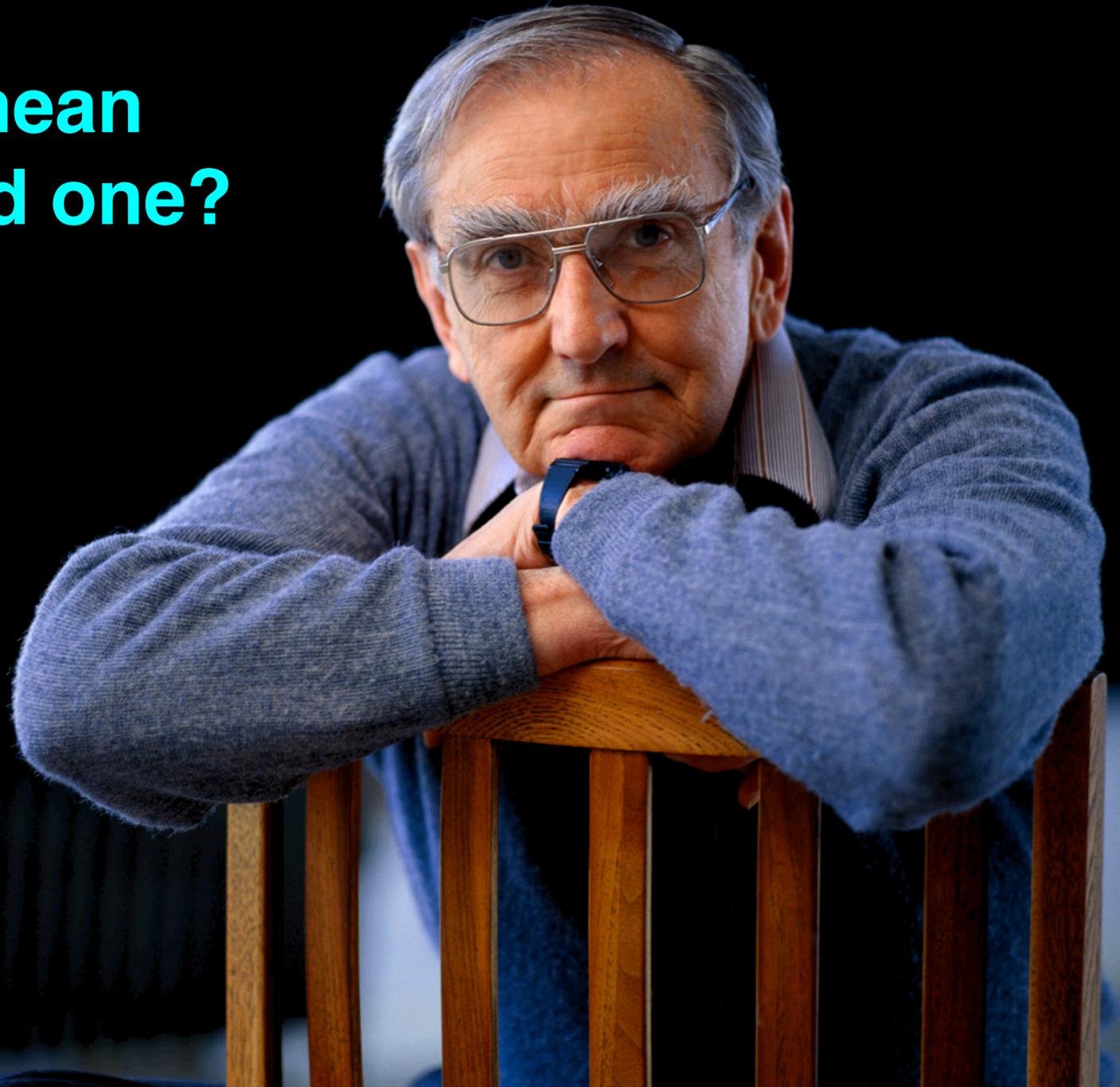


www.usnews.com \$3.50
3 2
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Short talk, huh?



**Oh, you mean
they found one?**





**Isn't that a
contradiction
of terms?**

**What is your next talk on –
the Loch Ness Monster?**



The adolescent brain is not a broken or defective adult brain!

It is exquisitely forged by the forces of our evolutionary history to have different features compared to children or adults.

Adolescent Behavioral Changes in Social Mammals

- Increased risk taking
- Increased sensation seeking
- Greater peer affiliation

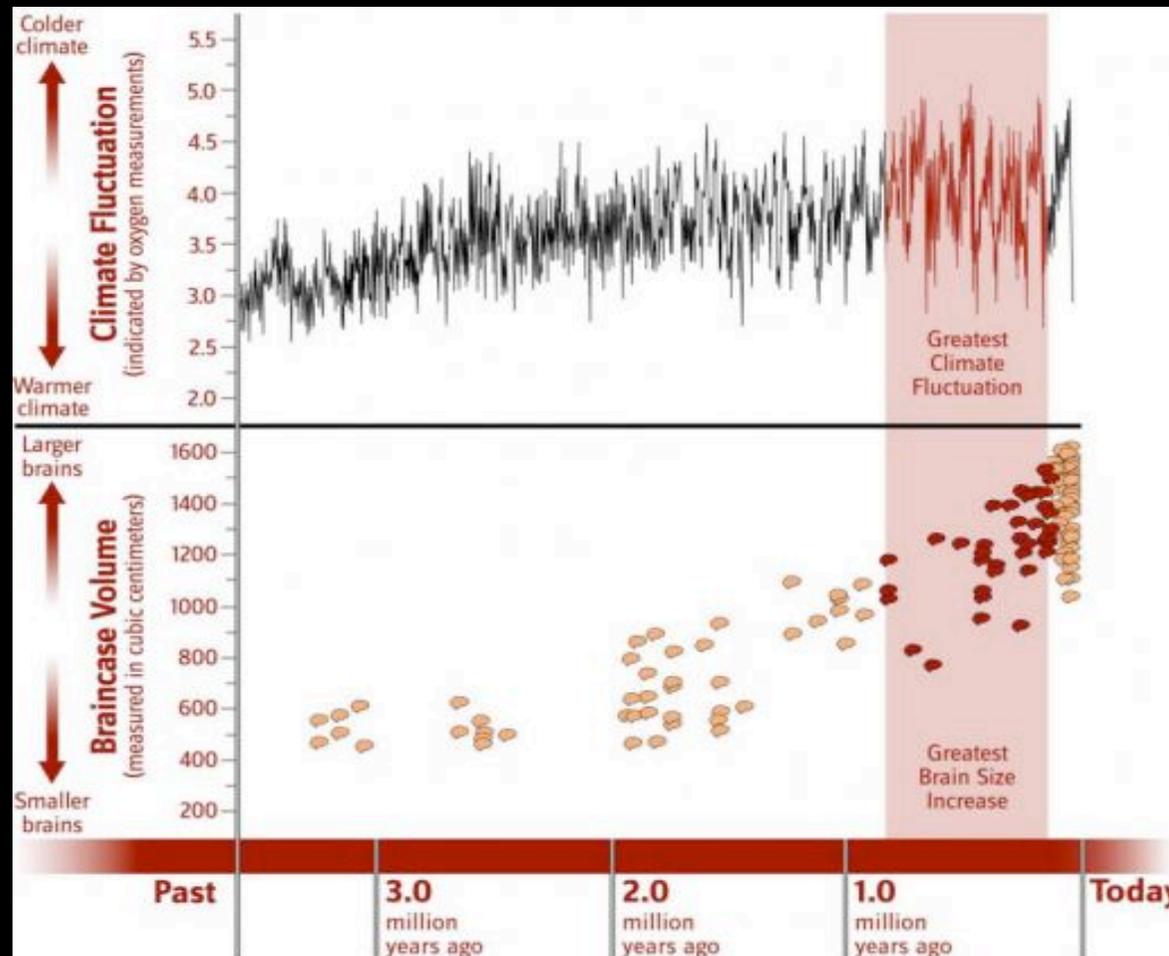
Facilitate separation from natal family?

Less inbreeding = evolutionary advantage?

Hall of Human Origins Smithsonian Museum, Washington DC



Brain volume increase driven by *change* in environment



The Digital Revolution

The way we **learn**, **play**, and **interact** with each other has changed more in the last 15 years than in the previous 570 years since Gutenberg's popularization of the printing press.



ELSEVIER

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Commentary

The Digital Revolution and Adolescent Brain Evolution

Jay N. Giedd, M.D.

Brain Imaging Section, Child Psychiatry Branch, National Institute of Mental Health, Bethesda, Maryland

Keywords: Digital technology; Neurodevelopment; Adolescent; Computer; Internet; Social networking sites

Adolescents

Young enough to embrace change

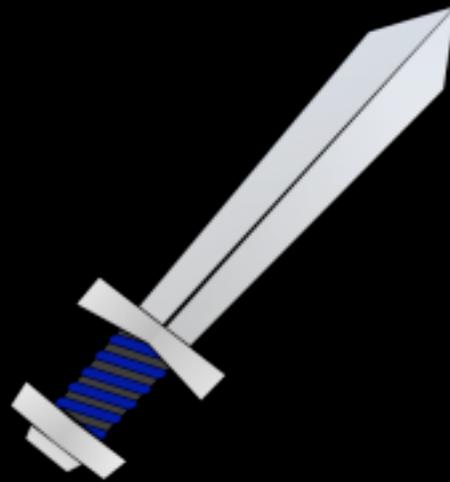
Old enough to master the technology

It aint natural!



The Double Edged Sword of Adolescent Brain Plasticity

Opportunity



Vulnerability

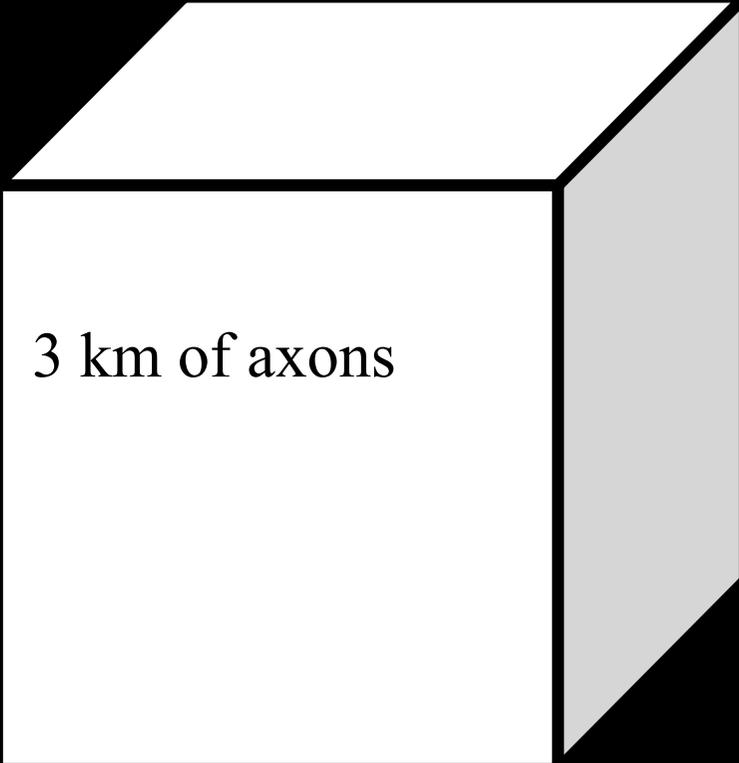
NIMH Child Psychiatry Data Base

- Longitudinal Assessment (~ 2 year intervals)
 - Imaging (sMRI, fMRI, MEG, DTI, MTI)
 - Genetics
 - Neuropsychological / Clinical
- 9000+ Scans from 4000+ Subjects (ages 0 to 97)
 - ~ 1/2 Typically-Developing
 - ~ 1/2 Twins (NIDA TWING Project?)
 - 25 Clinical Populations
 - ADHD, Autism Spectrum, Autism Savants,, Bipolar Disorder, Childhood Onset Schizophrenia, Depression, OCD, PANDAS, Sex Chromosome Variations (XXY, XXX, XXY, XXYY, XXXXY), Tourette's Syndrome, ...

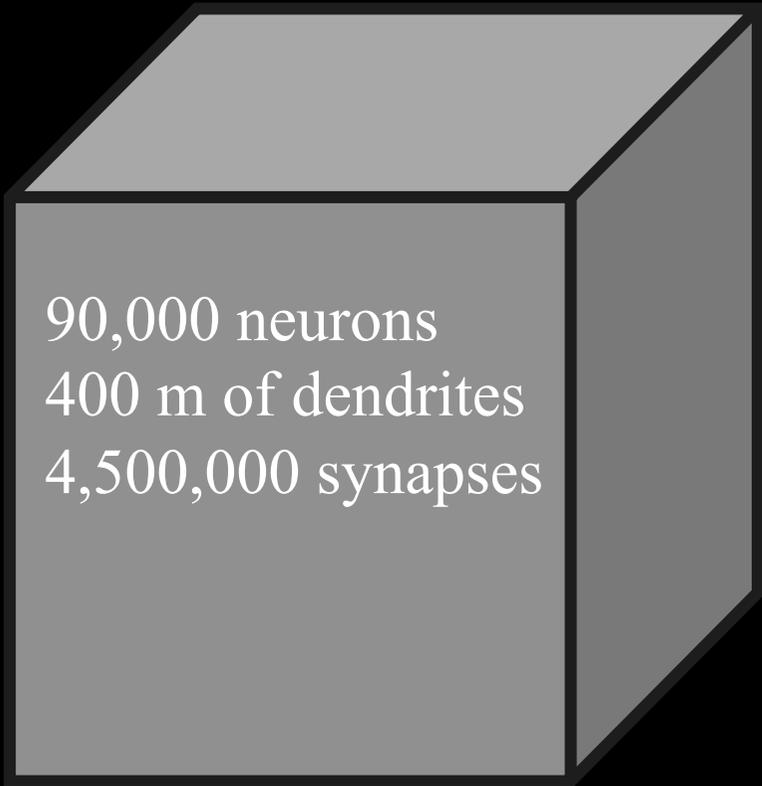




How the Brain Looks to MRI

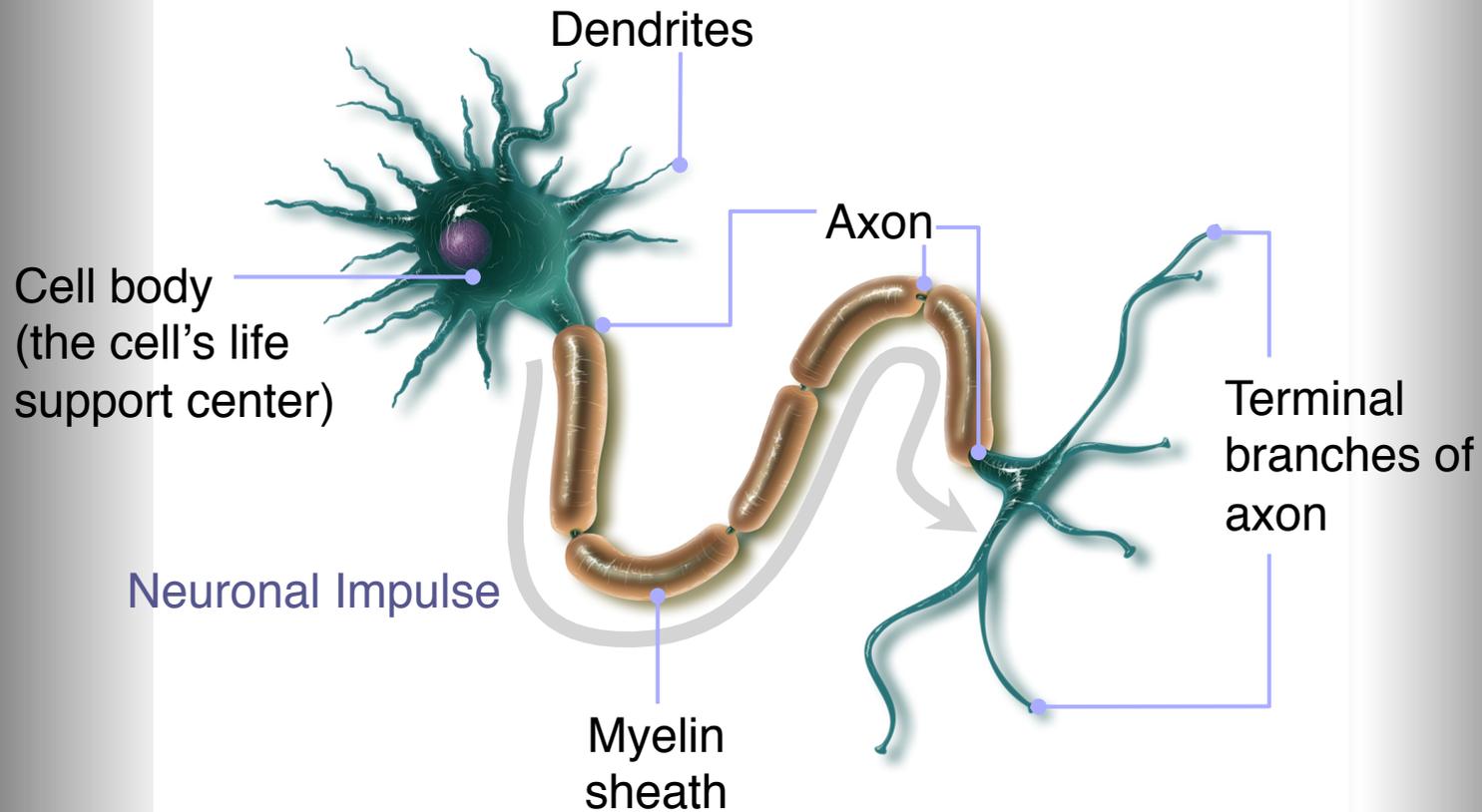


3 km of axons



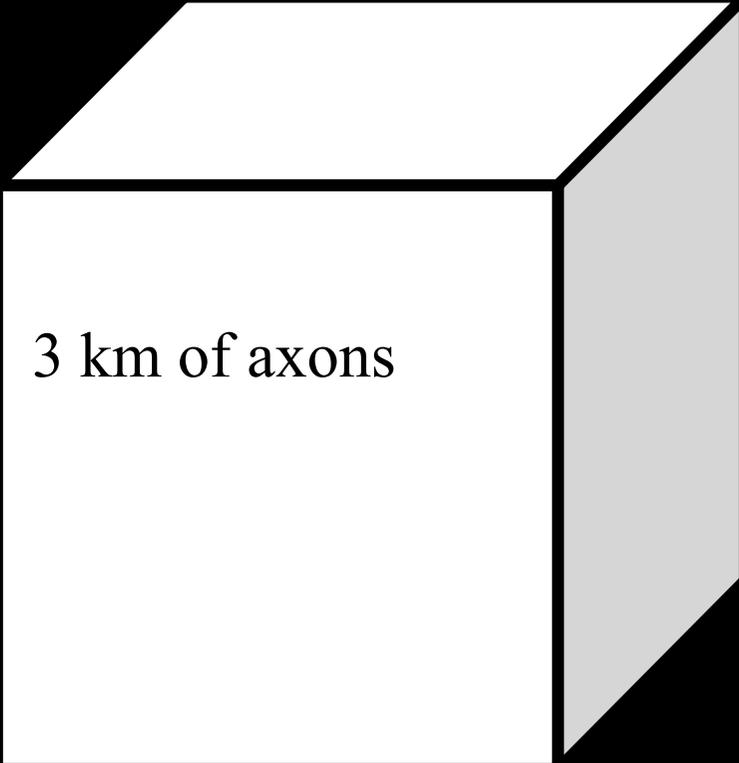
90,000 neurons
400 m of dendrites
4,500,000 synapses

The Neuron

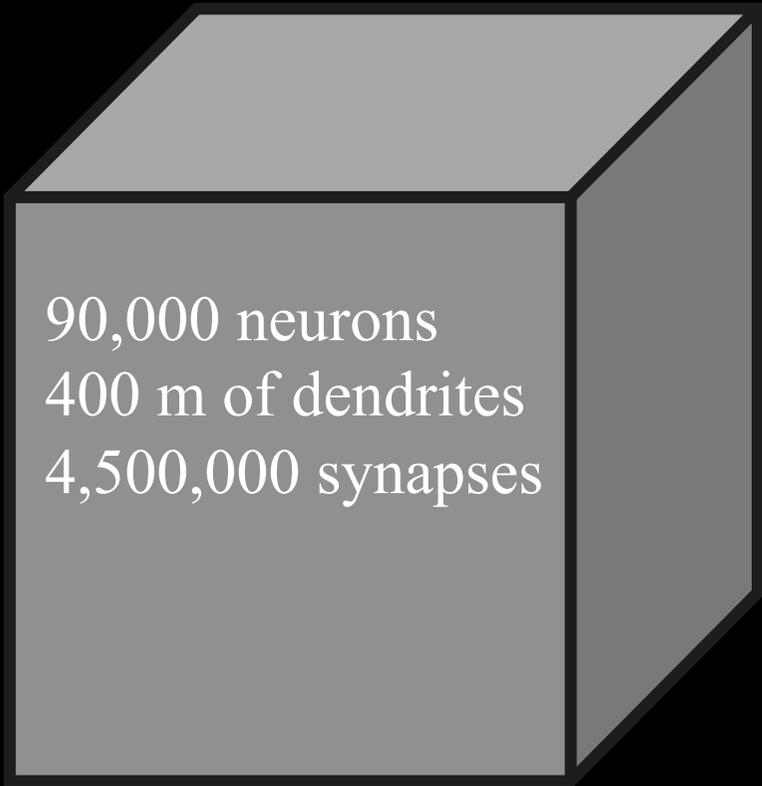


Donald Bliss, MAPB, Medical Illustration

How the Brain Looks to MRI



3 km of axons



90,000 neurons
400 m of dendrites
4,500,000 synapses

How do we bridge gaps across disciplines?



- Non human primate / mouse/ other species studies
- Higher resolution imaging

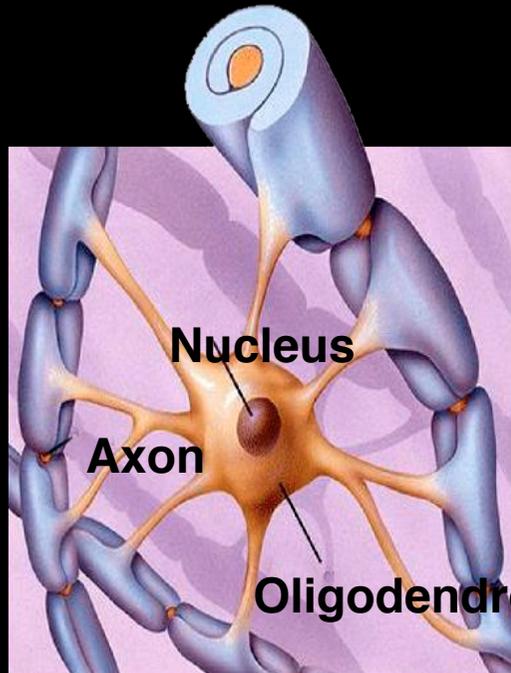
Key Points of Brain Maturation

- The brain matures by becoming more “connected” (white matter) and more specialized (gray matter)
- A changing prefrontal/limbic balance affects reward circuitry, hot vs cold cognition, temporal discounting, and decision making relevant to the issue of substance abuse

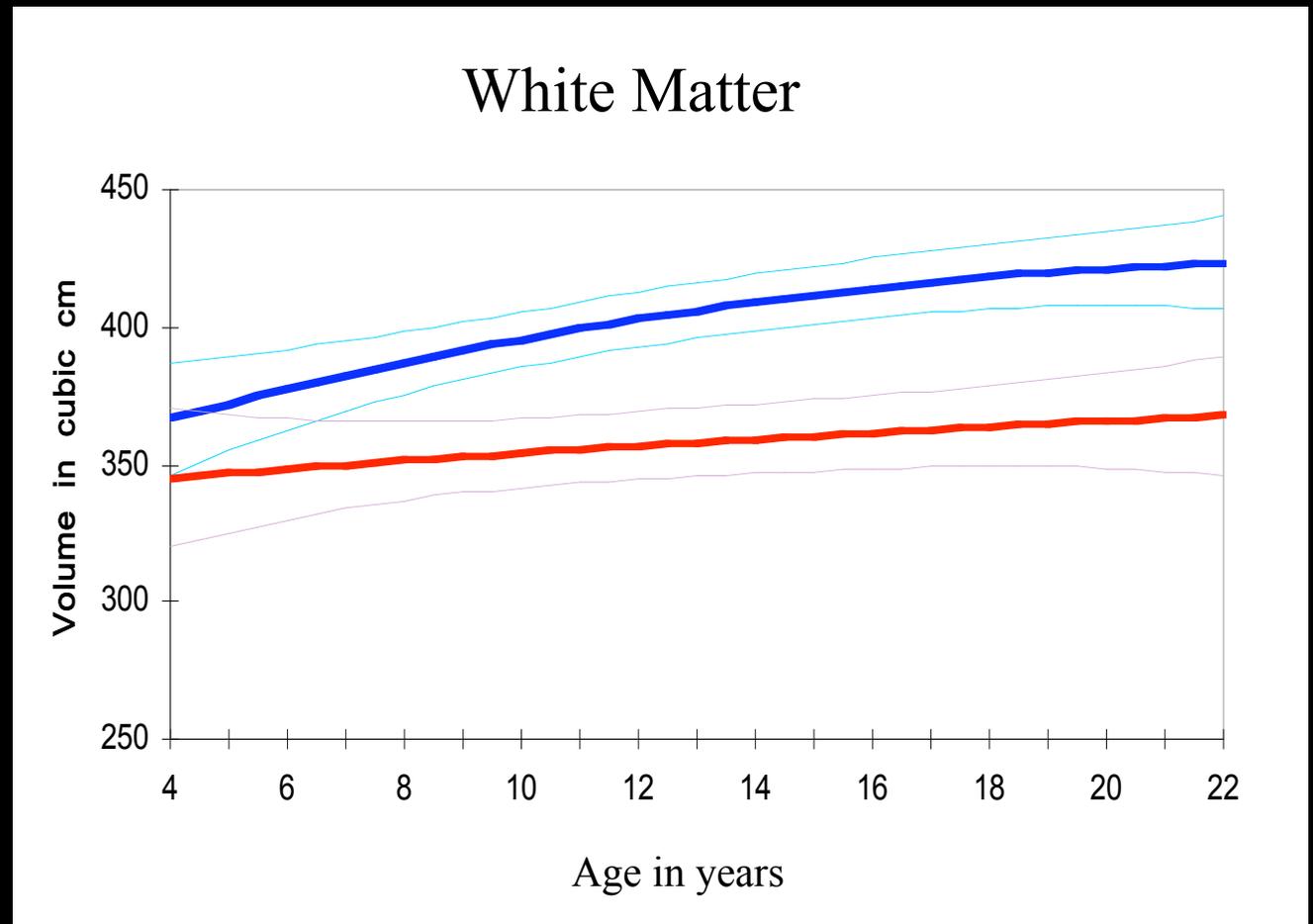
“Connectivity”

- White Matter
- Gray Matter

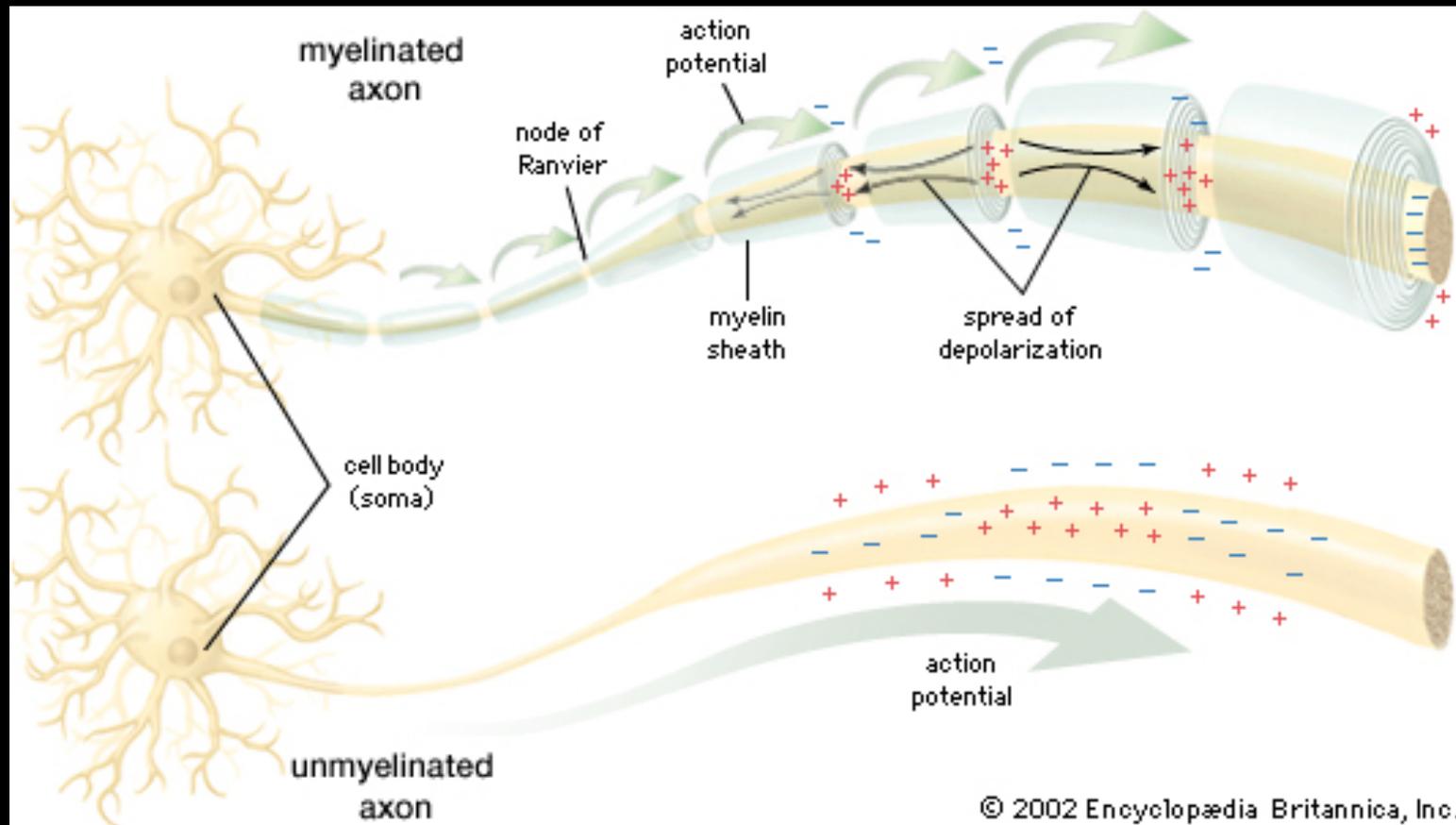
White Matter



- Male (152 scans from 90 subjects)
- Female (91 scans from 55 subjects)
- 95% Confidence Intervals



Myelin → Increased Bandwidth Speed 100x, Refractory Period 1/30x



Signal “hops” between nodes of Ranvier

More than just maximizing speed ...

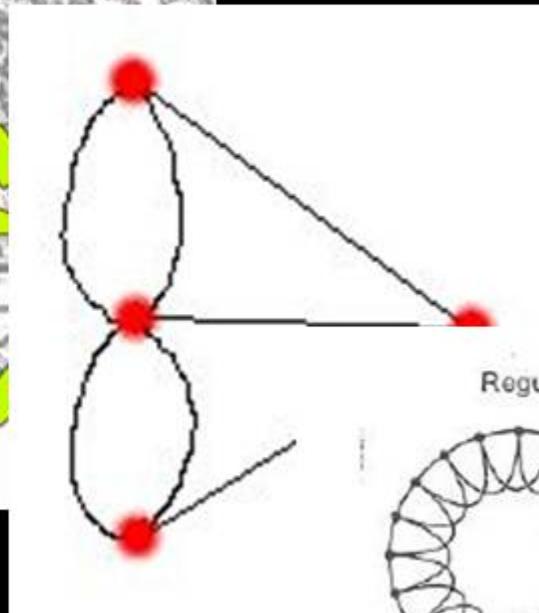
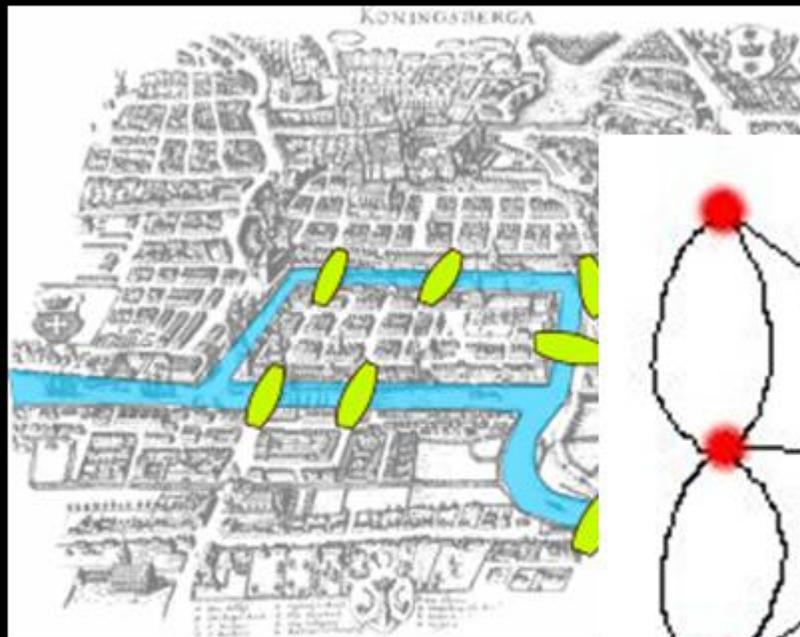


- Synchrony
- Plasticity
- Sensitive Periods
- Integration

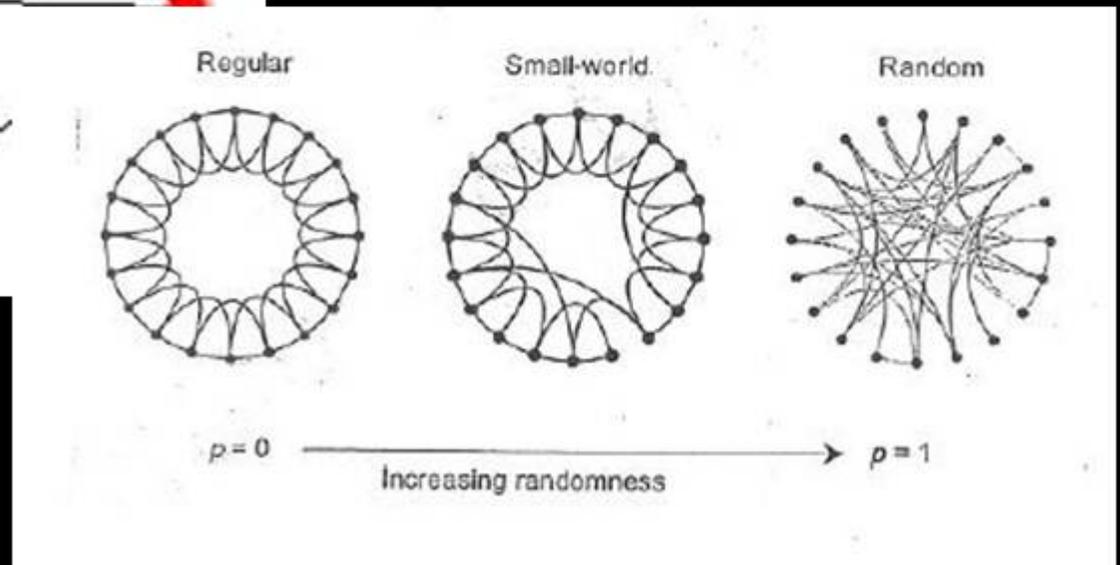
Facets of “Connectivity”

- Long Term Potentiation (LTP)
- White Matter
- EEG coherence
- fMRI coactivation
- Temporally coupled developmental trajectories
 - fire together → wire together → grow together?
- Similarly affected by same genetic/environmental factors
- Graph Theory (nodes and edges)

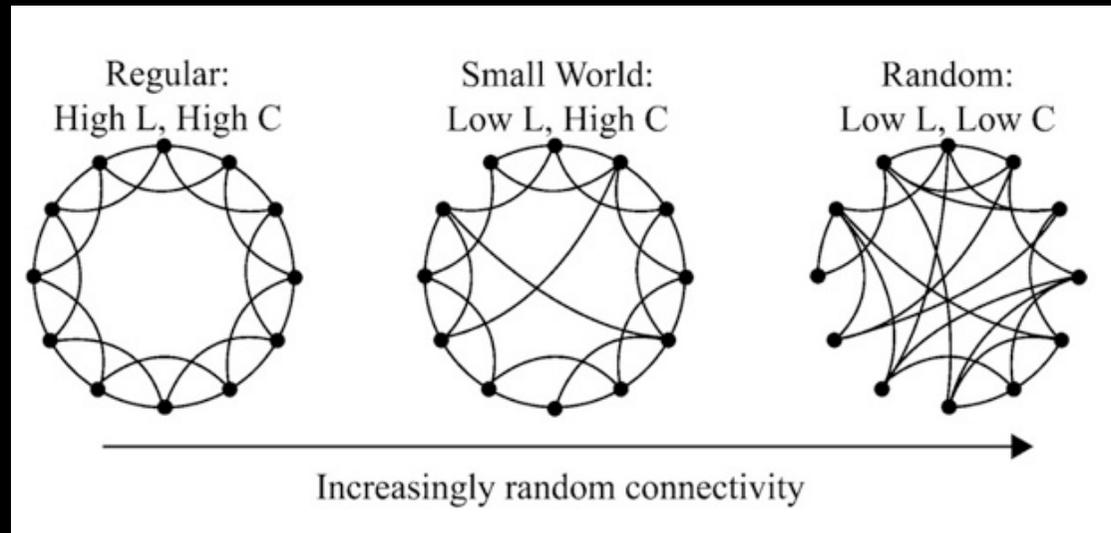
Graph Theory: Is it a small world after all? (strangers linked by mutual acquaintance)



Nodes and Edges

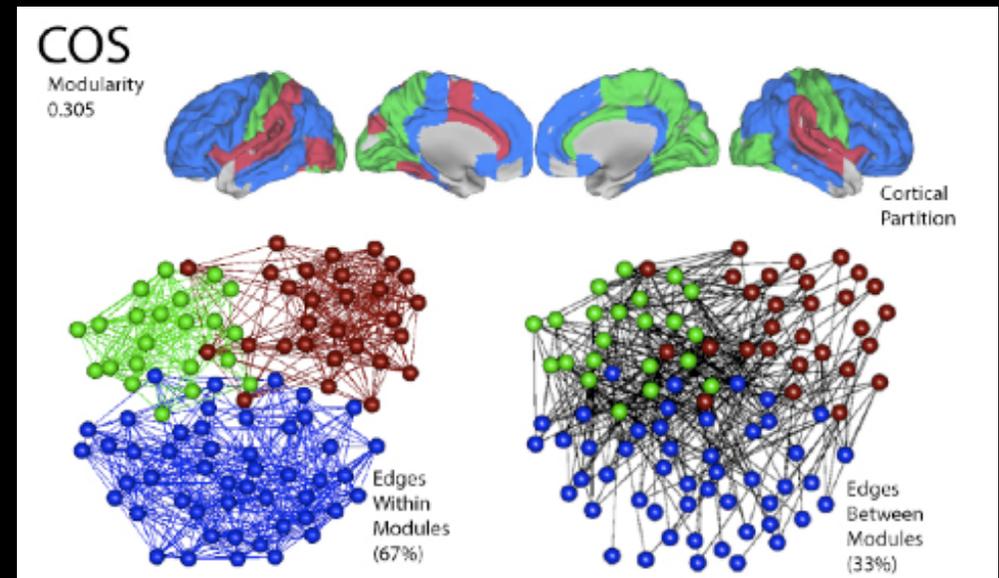
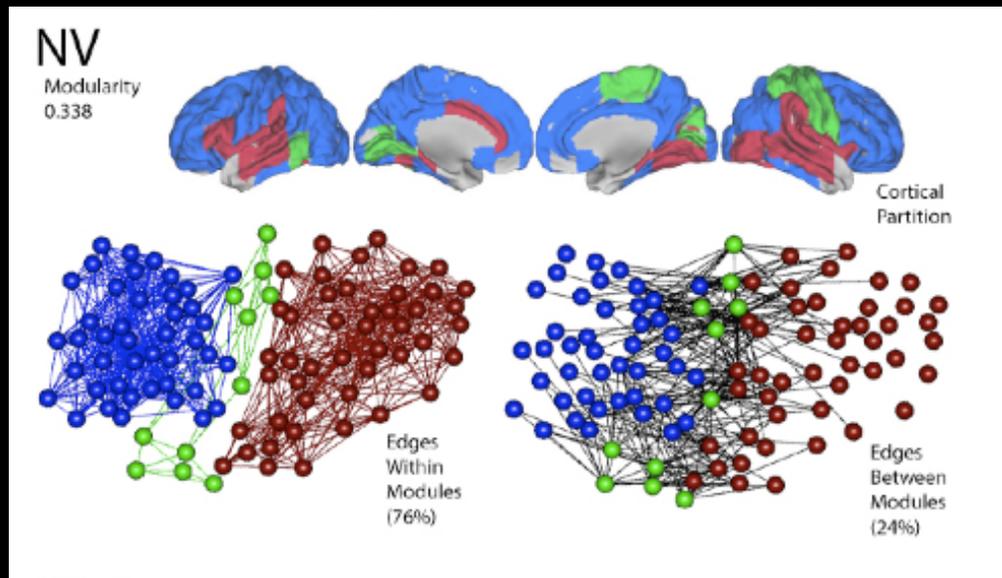


Collective dynamics of 'small-world' networks (Nature, June 1998)



- Small world networks
 - Many beneficial properties
 - Surprisingly often seen in natural systems
 - A whole field of mathematics developing to quantify aspects of “connectivity”

Disrupted modularity and local connectivity in childhood onset schizophrenia



Alexander-Bloch, Bulmore, Giedd 2010

Specialization

- White Matter
- Gray Matter

Bizarro | *Dan Piraro*



White Matter vs Gray Matter

White Matter

- Linear increase
- Not different by region

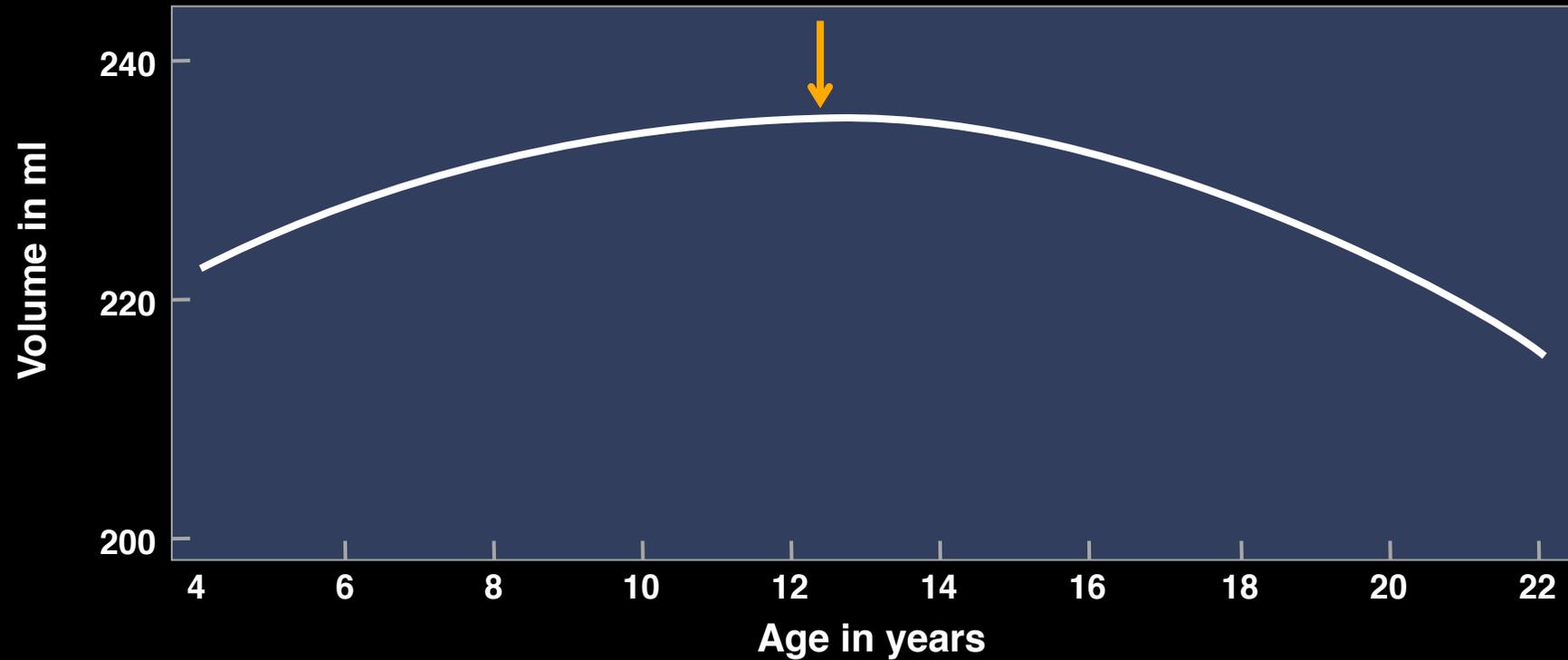
Gray Matter

- Inverted “U”
- Regionally specific

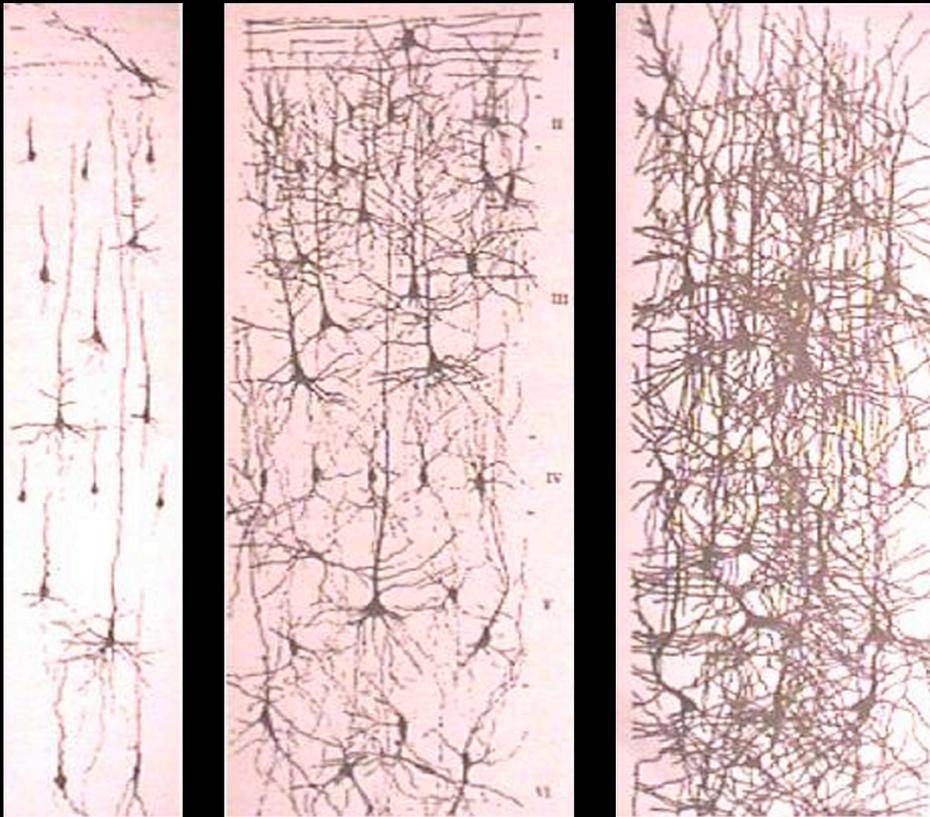
Gray Matter Development in Healthy Children & Adolescents

(1412 Scans from 540 Subjects)

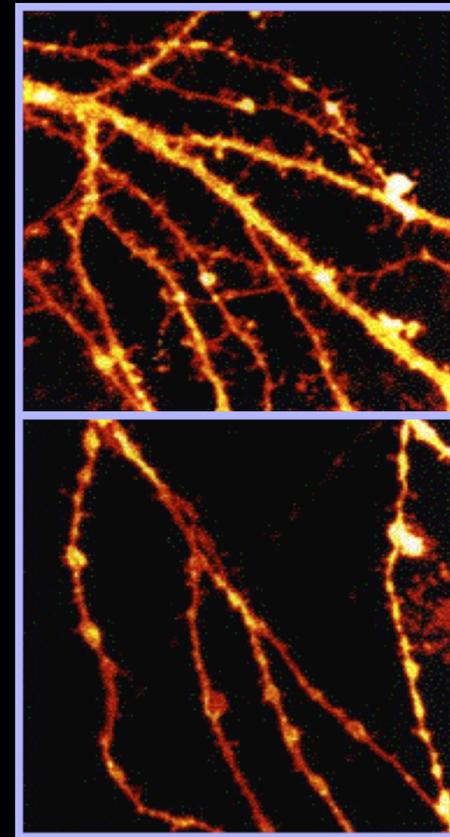
Frontal Lobe Gray Matter



Overproduction / Selective Elimination

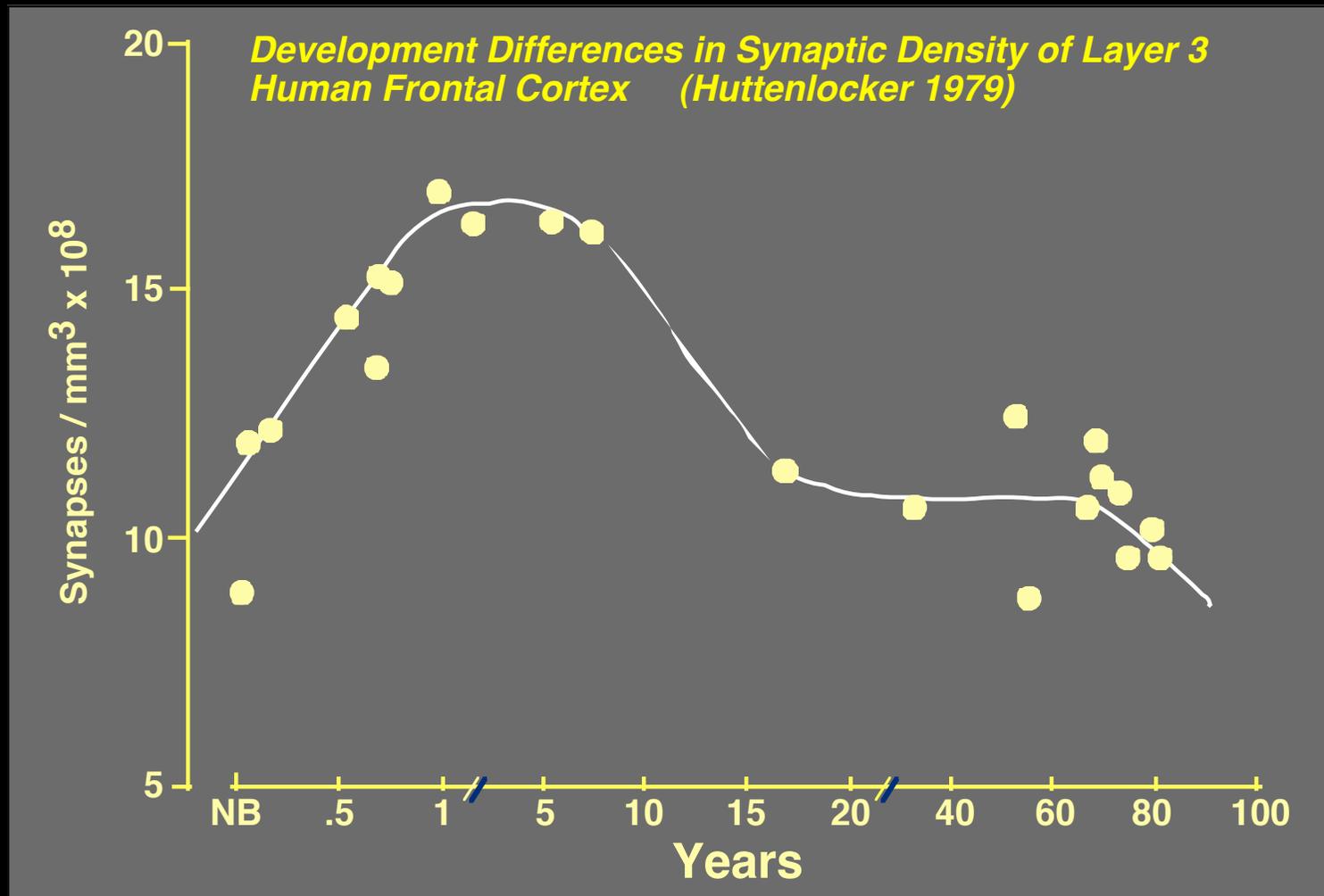


Diamond, Hopson, Scheibel, 1998

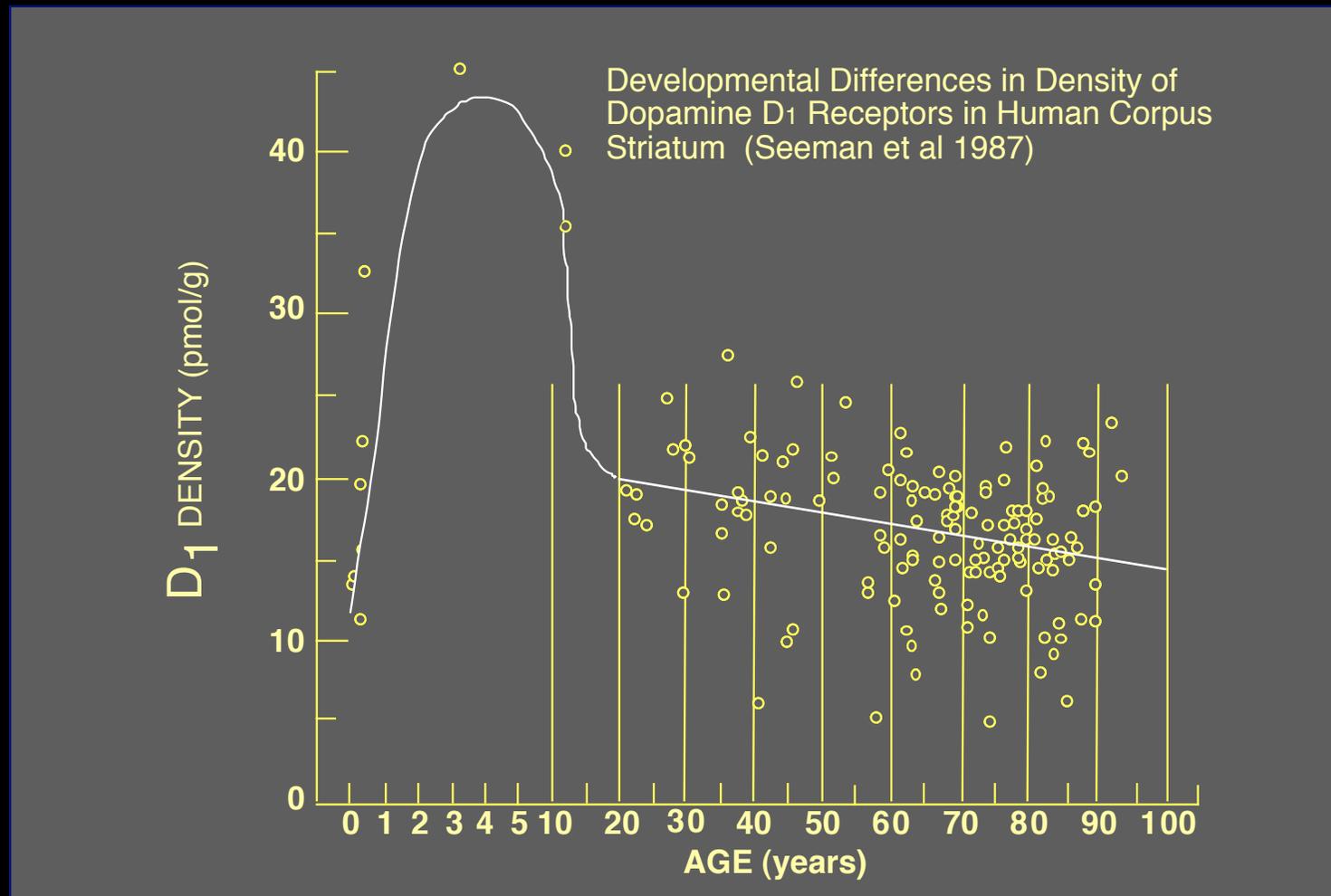


Images by Diane Murphy, PhD, NIH

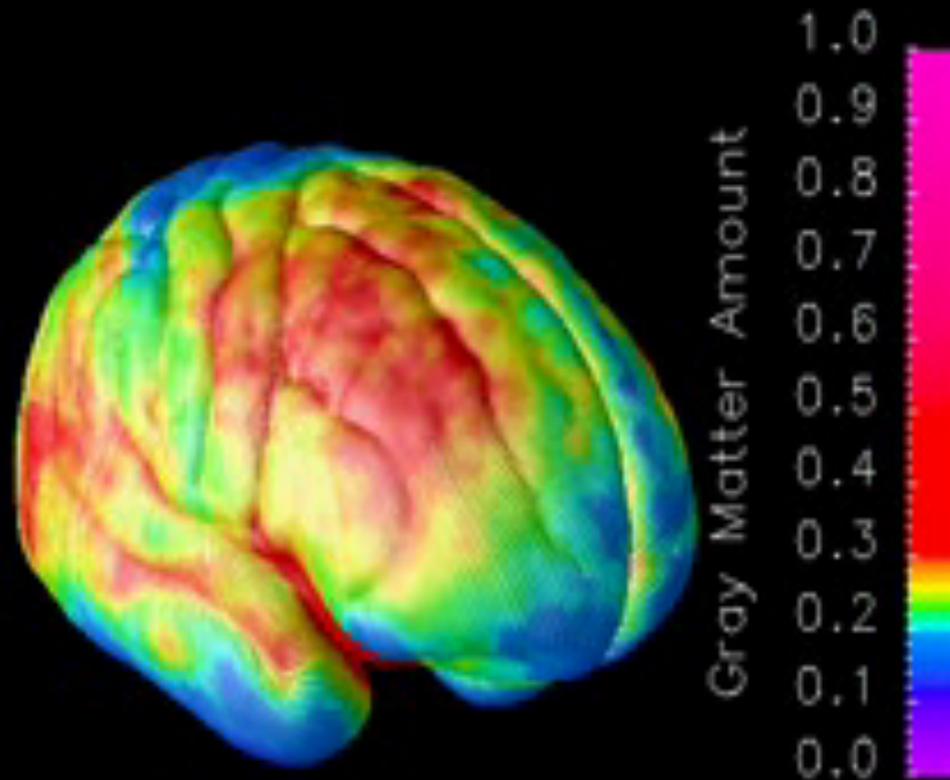
Similar Pattern for Synaptic Density



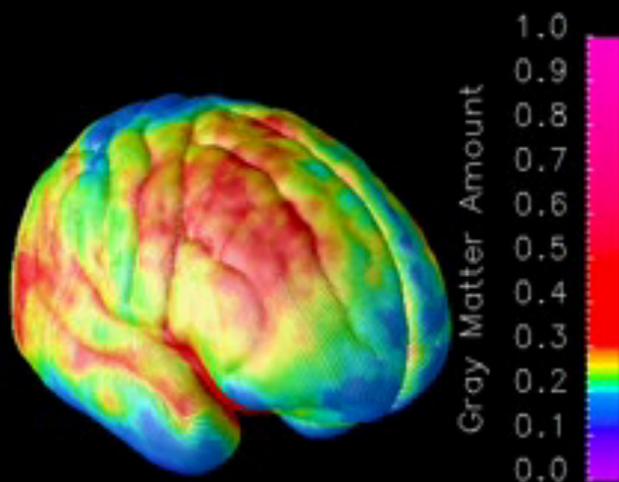
And for D1 Receptor Density in Striatum



Gray Matter Thickness: Ages 4 to 25 years

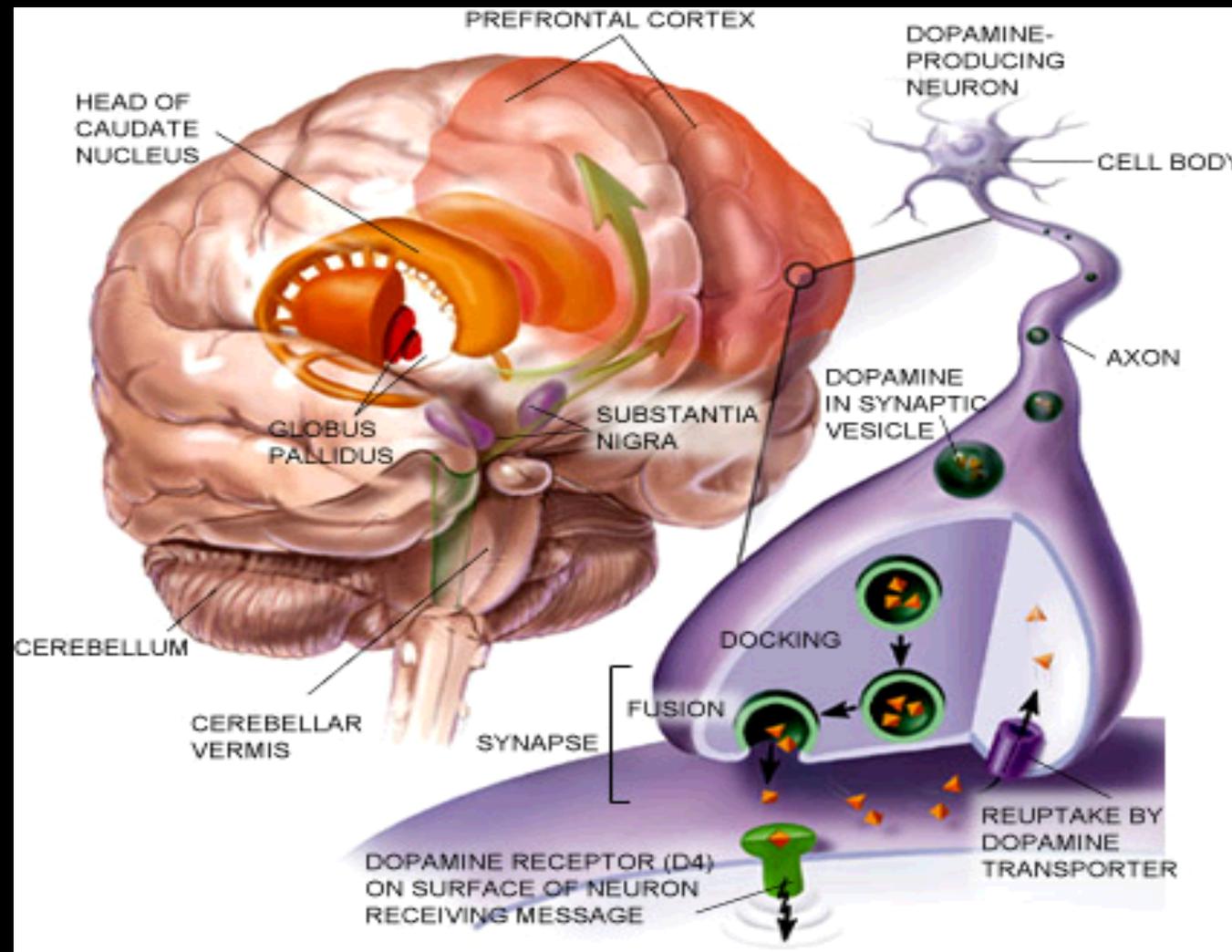


Prefrontal Cortex



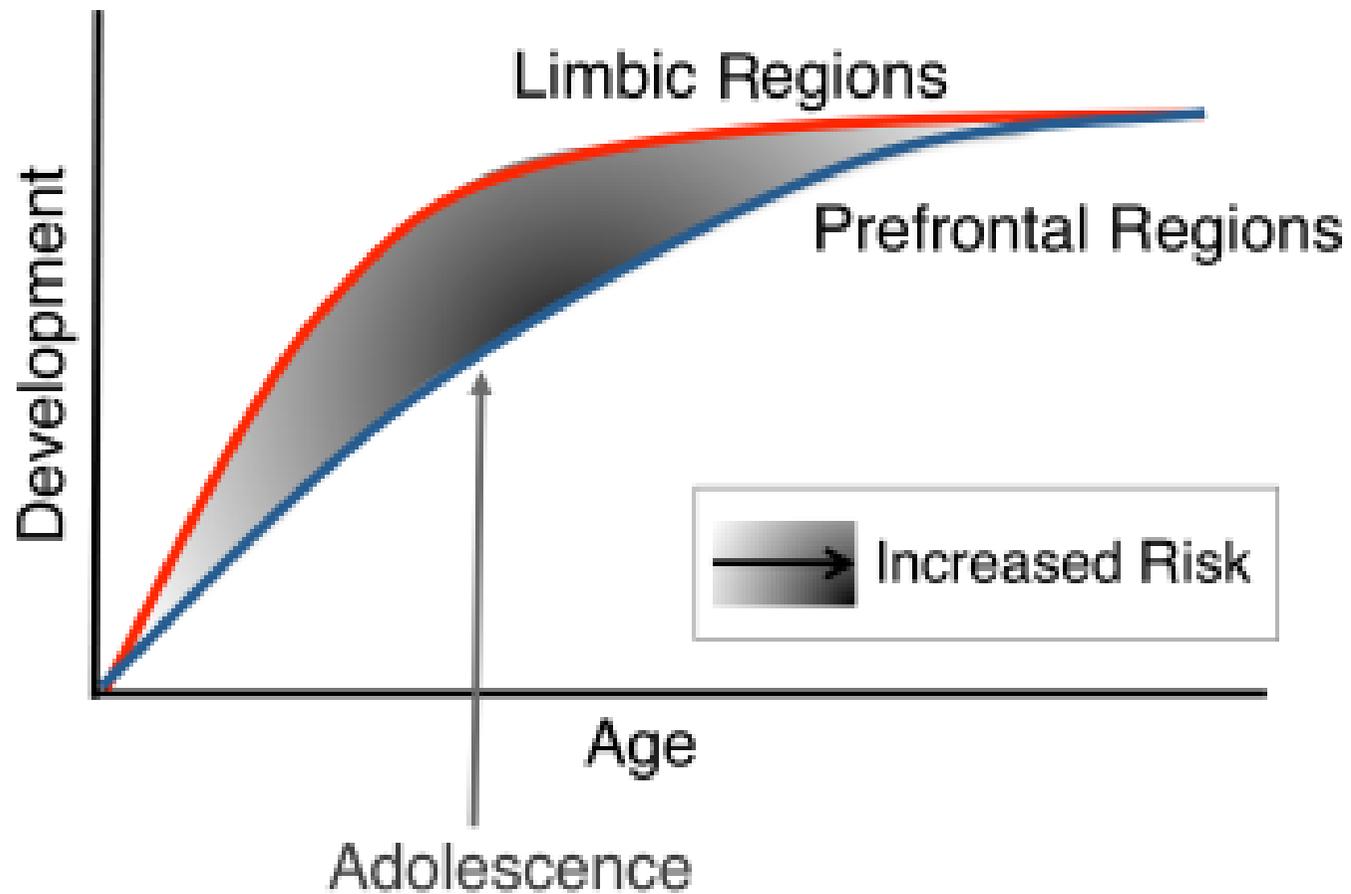
- “Executive” functions
 - Long term strategy
 - Planning
 - Organization
 - Impulse control
- Integrates input from rest of the brain (“top down”)
- social brain circuitry
- Time Travel
- Multi tasking bottle neck?

Limbic circuitry – ignites at puberty



Braking and Accelerating of the Adolescent Brain

B. J. Casey, Rebecca M. Jones, and Leah H. Somerville



Frontal Limbic Balance Shift During Adolescence

- In general ...
 - Increase in reward sensitivity
 - Decrease in avoidance
 - Temporal discounting
 - Delay aversion
- ... but many exceptions to these rules.
 - All are very context dependent, malleable, and vary by gender, genetics, and from person to person.

Summary

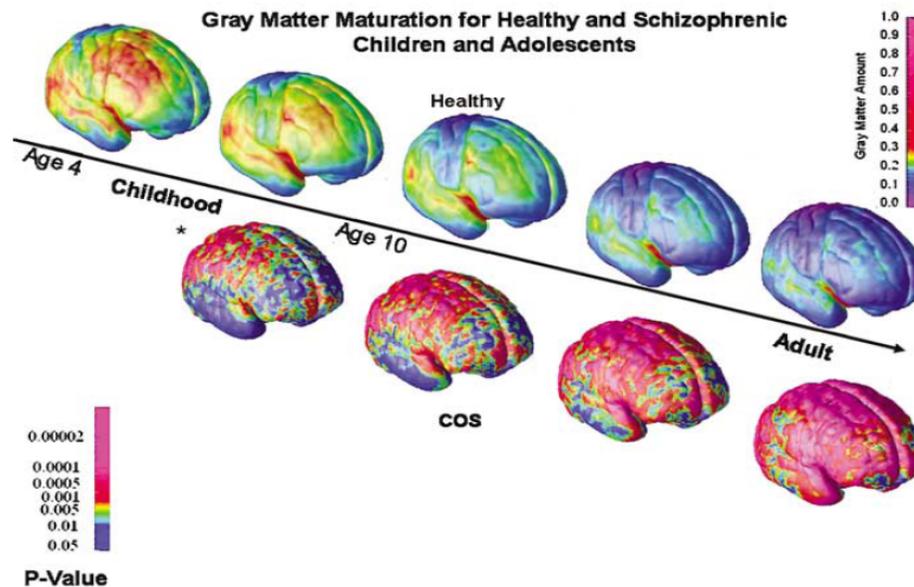
- The adolescent brain is developing not defective
- **Enormous plasticity confers both vulnerability and opportunity**
- Journey not just destination
- Differences in prefrontal/limbic balance affect temporal discounting, reward circuitry, hot vs cold cognition, and decision making that may be relevant to the issues of substance abuse

Why do so many brain disorders emerge during adolescence?

- Time of dramatic change in brain, body, and behavior
- Time of peak emergence of:
 - Schizophrenia
 - Depression
 - Anxiety
 - Substance Abuse
 - Eating Disorders
 - Not Autism, ADHD, Alzheimer's
- Moving parts get broken?

Adolescent Brain Changes

sMRI
WM ↑
GM ∩



EEG
Delta sleep ↓
Cyclic power ↓

PET
↓ glucose utilization

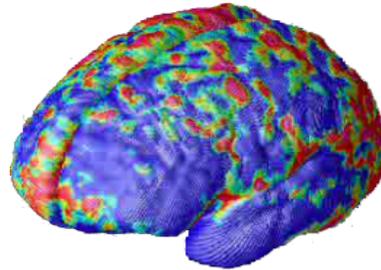
fMRI
Diffuse → focal
↑ “frontalization”
↑ integration

Postmortem
Overproduction/
Selective elimination
Synapses
Neurotransmitters

Risks for psychopathology during adolescence

Typical behavior changes

- ↑ Risk taking
- ↑ Novelty seeking
- ↑ Social priorities



Schizophrenia

Exaggeration of typical regressive changes:

- Delta sleep
- Membrane phospholipids
- Synaptophysin expression
- Synaptic spine density
- Neuropil
- Prefrontal metabolism
- Frontal gray matter

Substance Abuse

- ↓ Sensitivity to hangover, sedation, and motor impairment
- ↑ Hippocampal vulnerability

Depression

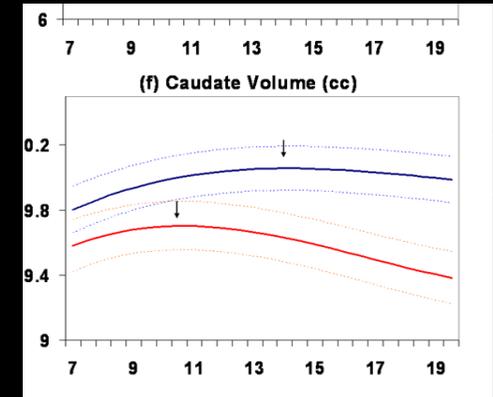
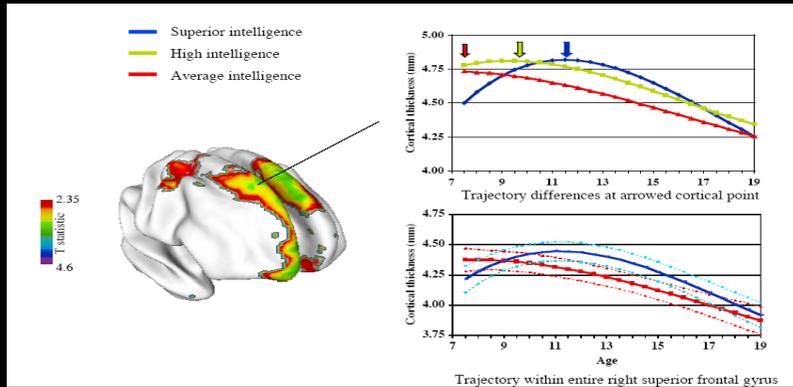
Hormonally mediated limbic effects preceding maturation of cognitive-regulatory system

Why Adolescence: Schizophrenia

- Is schizophrenia related to an exaggeration of typical regressive changes of adolescence?
- Delta sleep (synaptic pruning?) – (Feinberg 1982)
- Membrane phospholipids (Pettegrew et al. 1991)
- Prefrontal metabolism (Andreasen et al. 1992)
- Density of synaptic spines (Garey et al. 1998)
- Neuropil (Selemon et al. 1995)
- Expression of synaptic marker synaptophysin (Eastwood et al. 1995)
- Frontal cortical gray matter (Sporn et al. 2003)

Summary

- The adolescent brain is developing not defective
- Enormous plasticity confers both vulnerability and opportunity
- **Journey not just destination**
- Differences in prefrontal/limbic balance affect temporal discounting, reward circuitry, hot vs cold cognition, and decision making that may be relevant to the issues of substance abuse



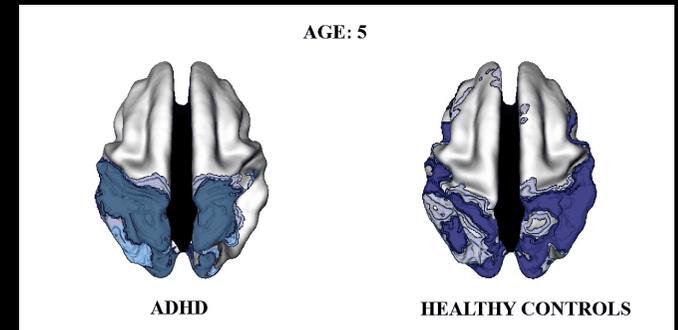
1. Cognitive/Behavioral

2. Male/Female Differences

**Journey not
just Destination**



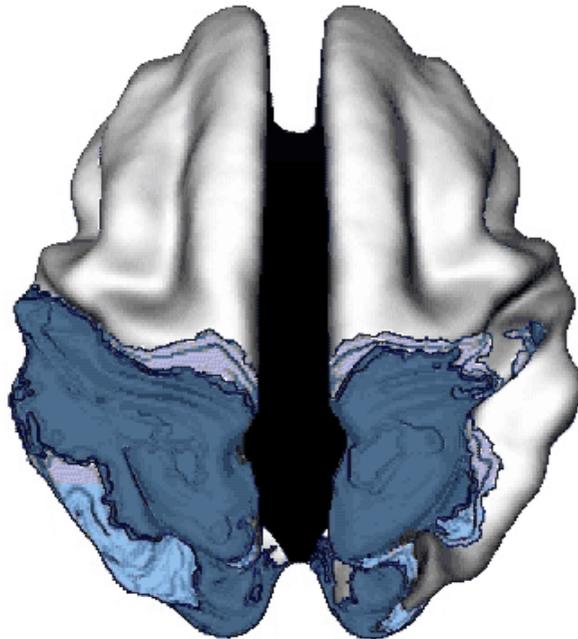
3. Genetic/Environmental



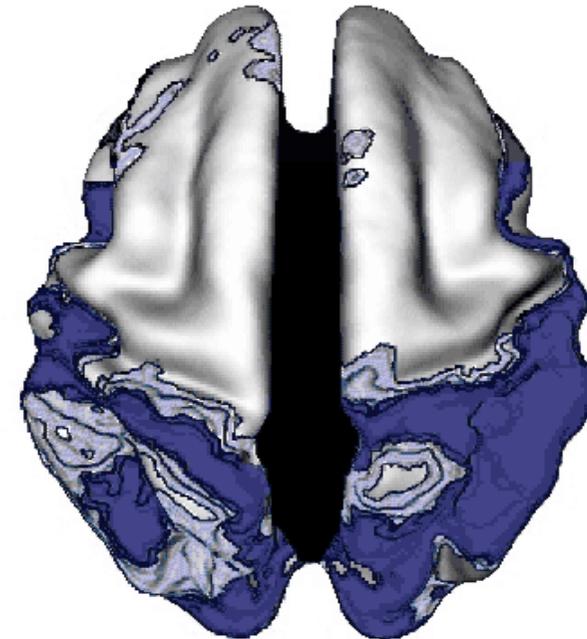
4. Health/Illness

Age of attaining peak cortical thickness for the ADHD and healthy control groups: ADHD has “shift to the right”

AGE: 5



ADHD

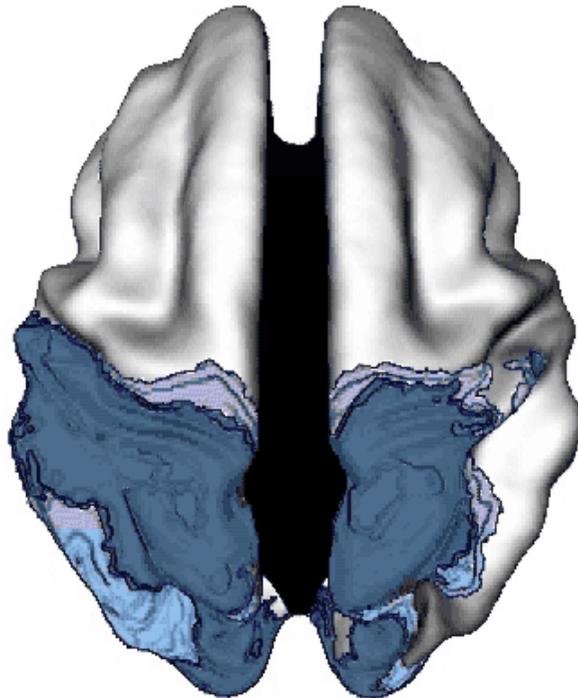


HEALTHY CONTROLS

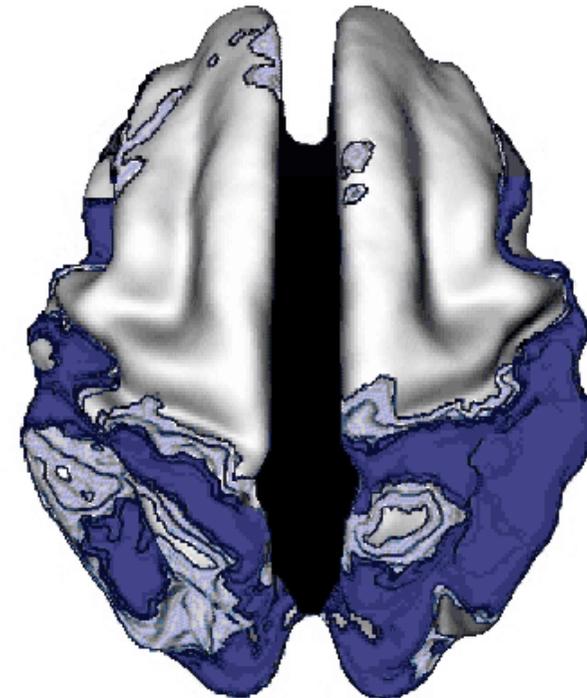
The darker colors indicate regions where a quadratic model was not appropriate and thus a peak age could not be calculated, or that the peak age was estimated to lie outside the age range covered

Age of attaining peak cortical thickness for the ADHD and healthy control groups: ADHD has “shift to the right”

AGE: 5



ADHD



HEALTHY CONTROLS

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They need their parents



They need their parents



just as much as they do.

The Infant From Hell

