The Teen Brain

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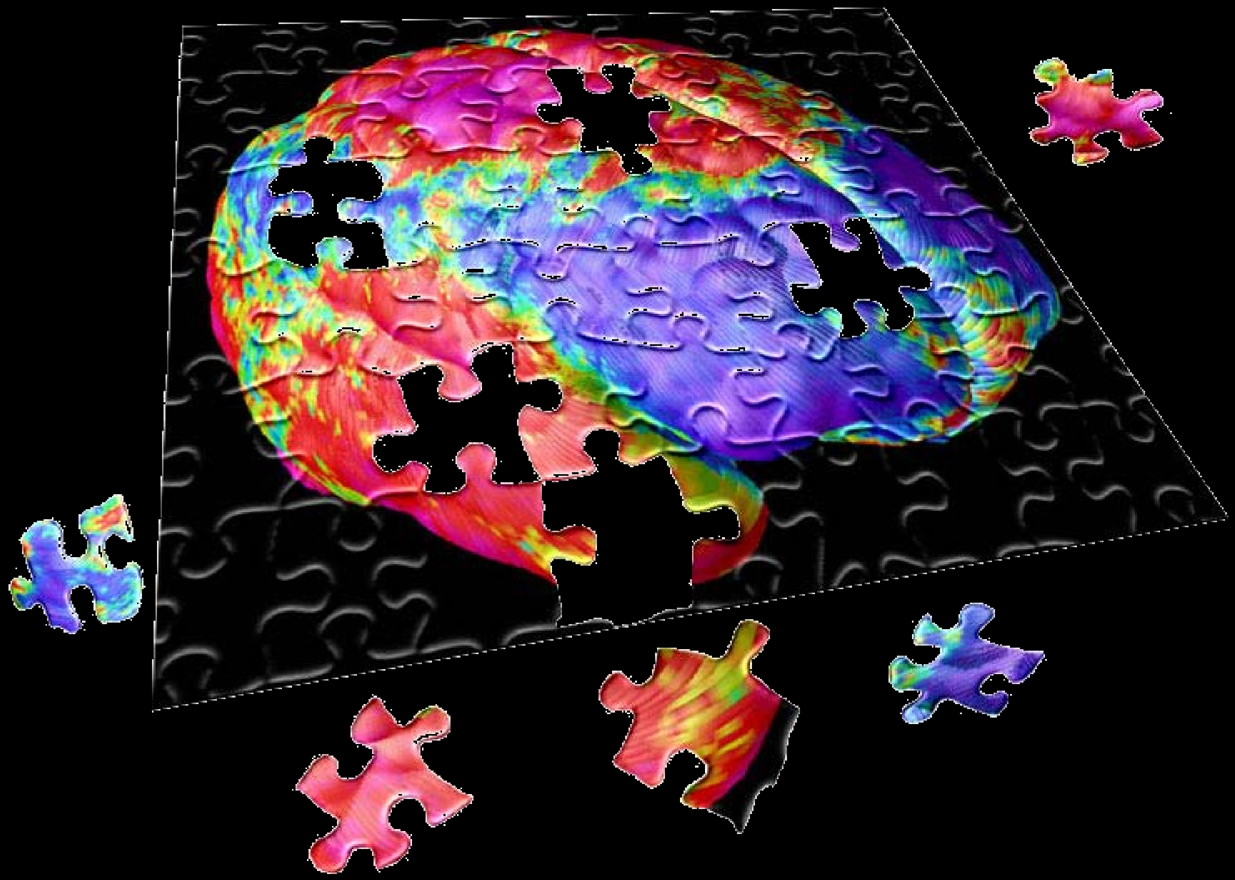
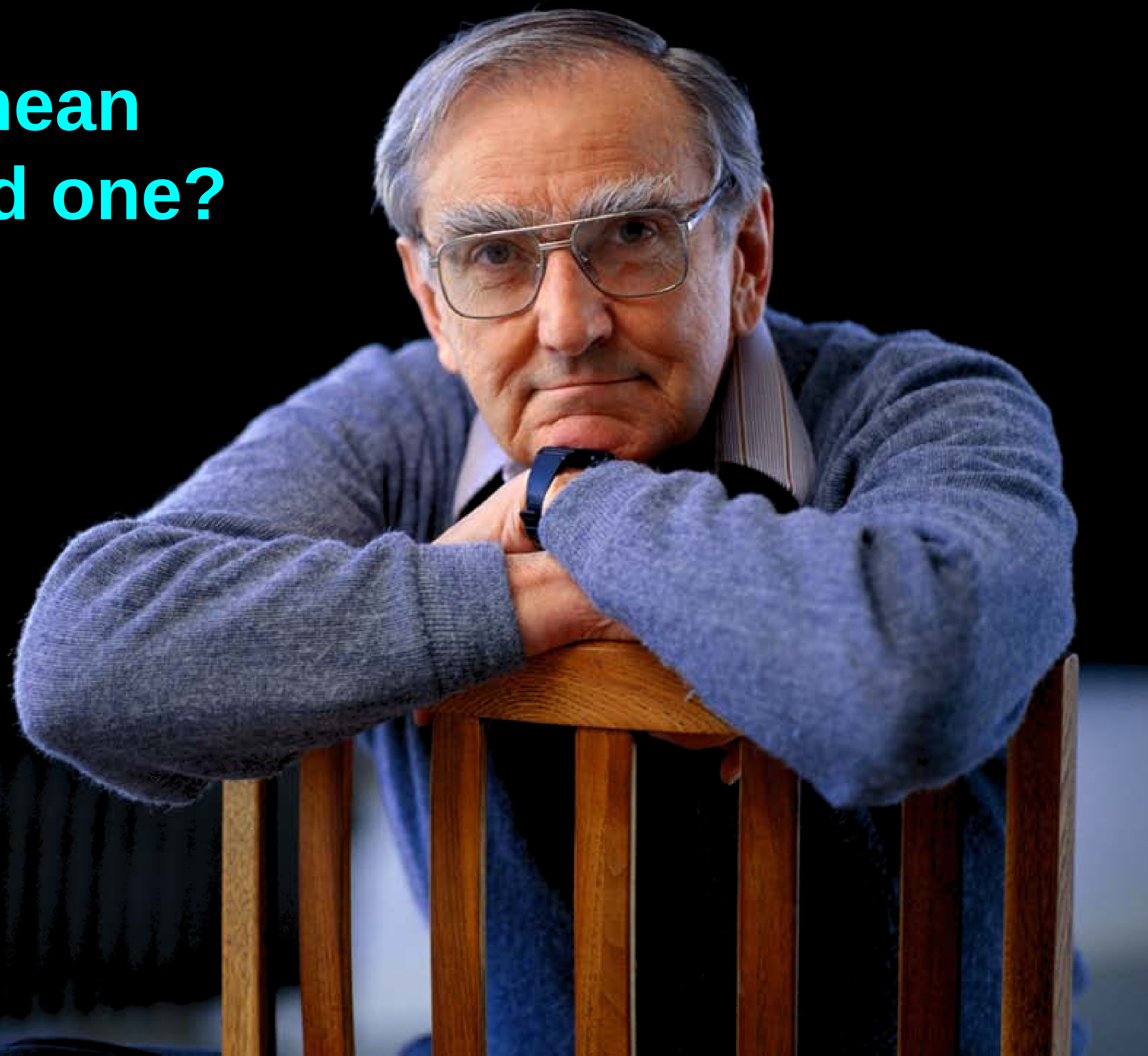
Workshop on the
Mechanism of Brain and
Mind

Kobe, Japan
August 22, 2011




Short talk, huh?

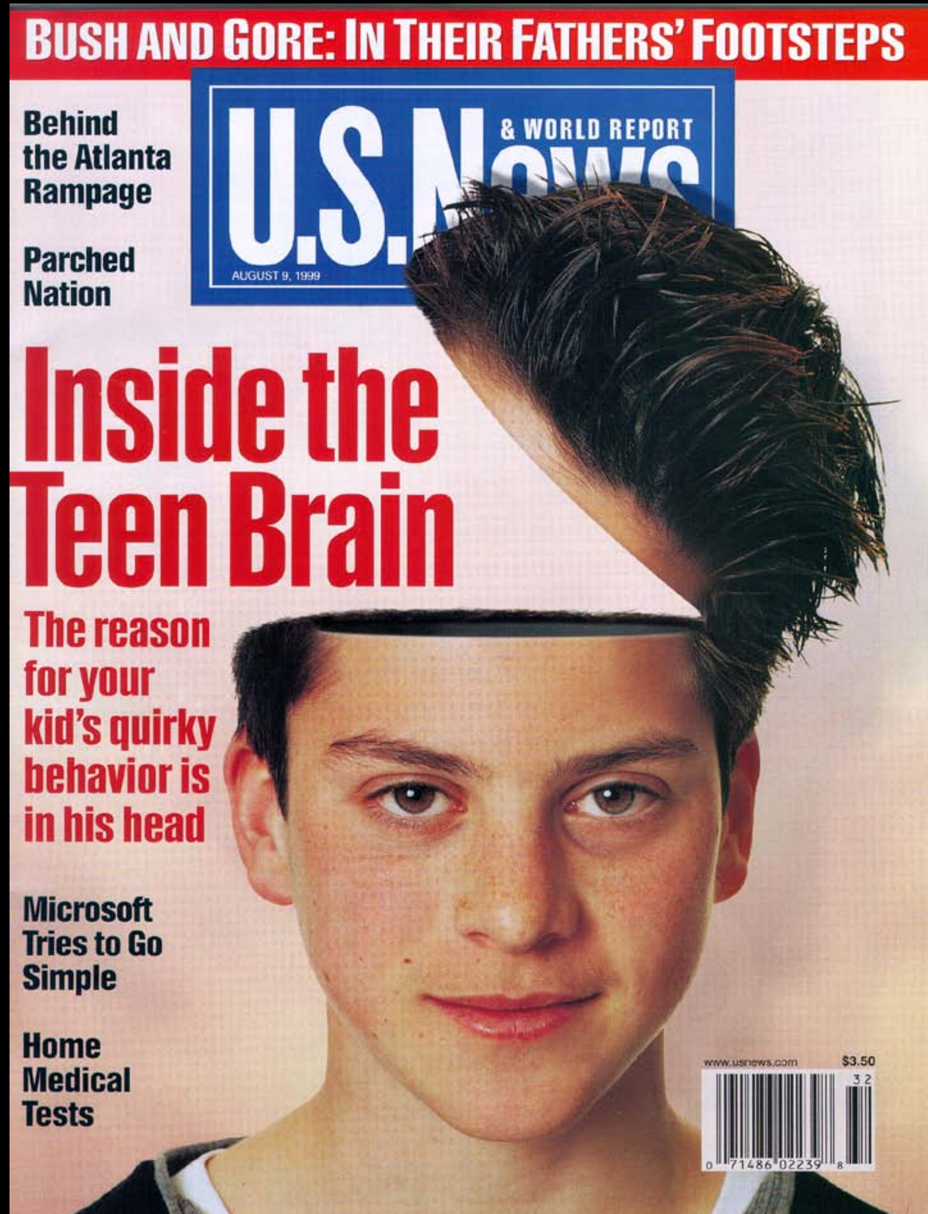
Oh, you mean
they found one?



Isn’t that a contradiction of terms?

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


OXFORD


BUSH AND GORE: IN THEIR FATHERS' FOOTSTEPS
U.S.News & WORLD REPORT
AUGUST 9, 1999
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

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.

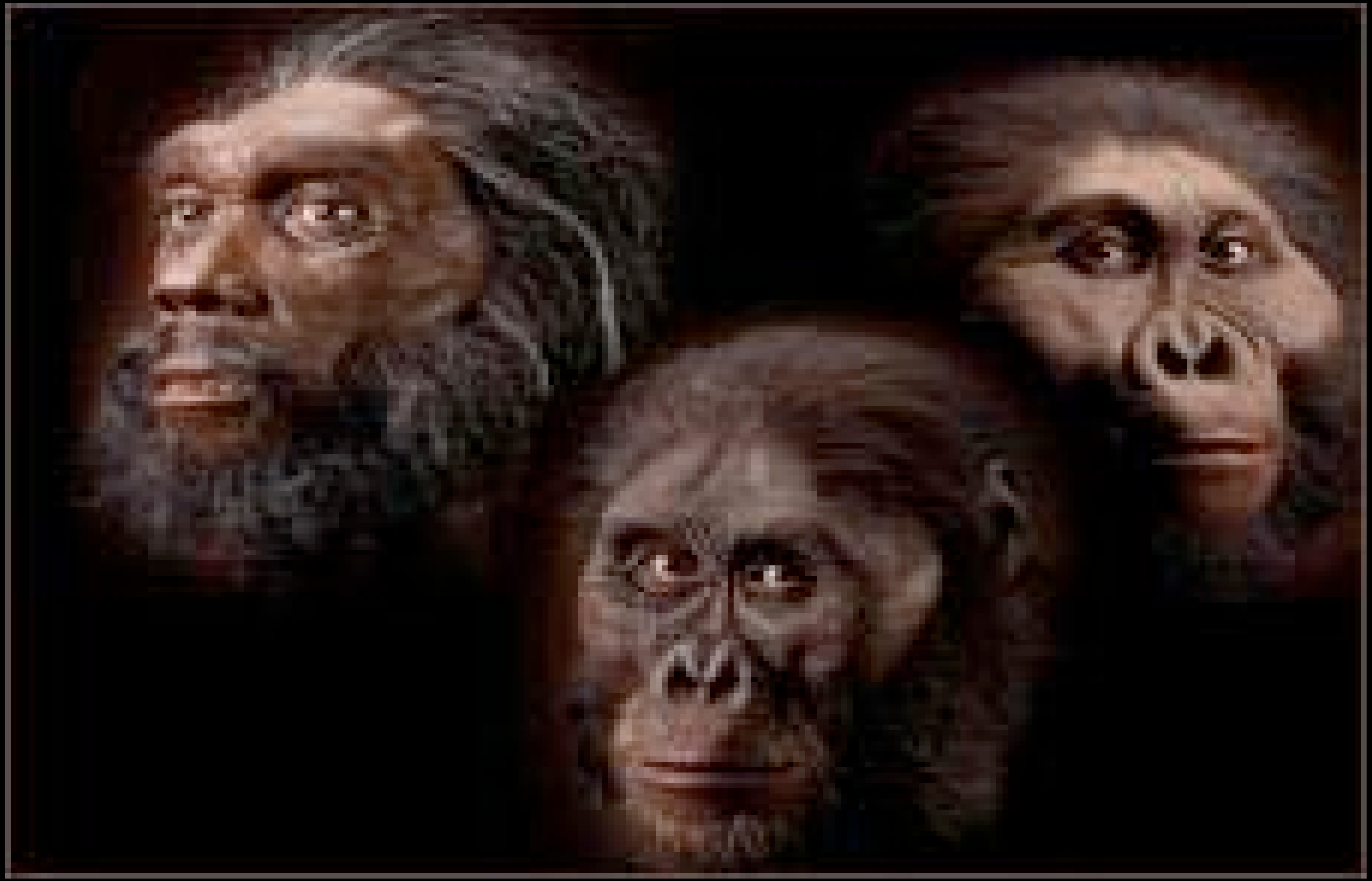
Adolescent Behavioral Changes in Social Mammals

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

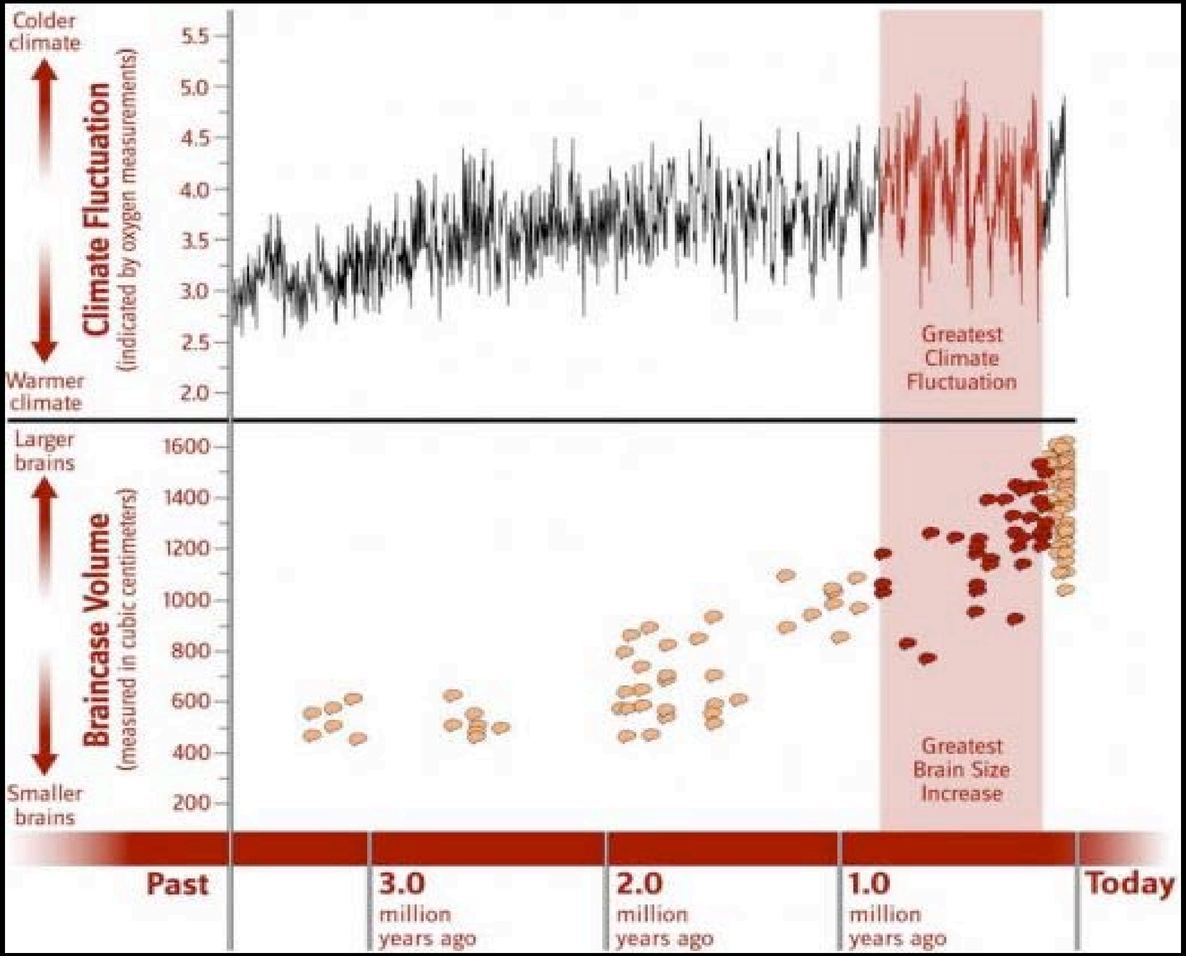
Facilitate separation from natal family?

Less inbreeding = evolutionary advantage?

Hall of Human Origins
(Smithsonian Museum, Washington DC)

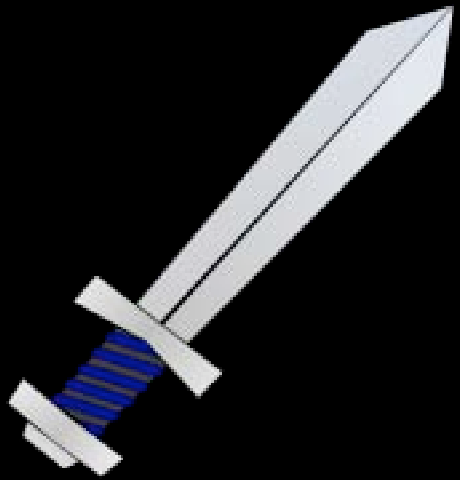


Brain volume increase driven by *change* in environment



The Double Edged Sword of Adolescent Brain Plasticity

Opportunity



Vulnerability

NIMH Child Psychiatry Branch Data Base (1991-present)

- Longitudinal Assessment (~ 2 year intervals)
  - Imaging (sMRI, fMRI, MEG, DTI, MTI)
  - Genetics
  - Neuropsychological / Clinical

- 8000+ Scans from 3000+ Subjects
  - ~ ½ Typically-Developing
    - ~ ½ Twins
  - 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, …

Long Term Strategy

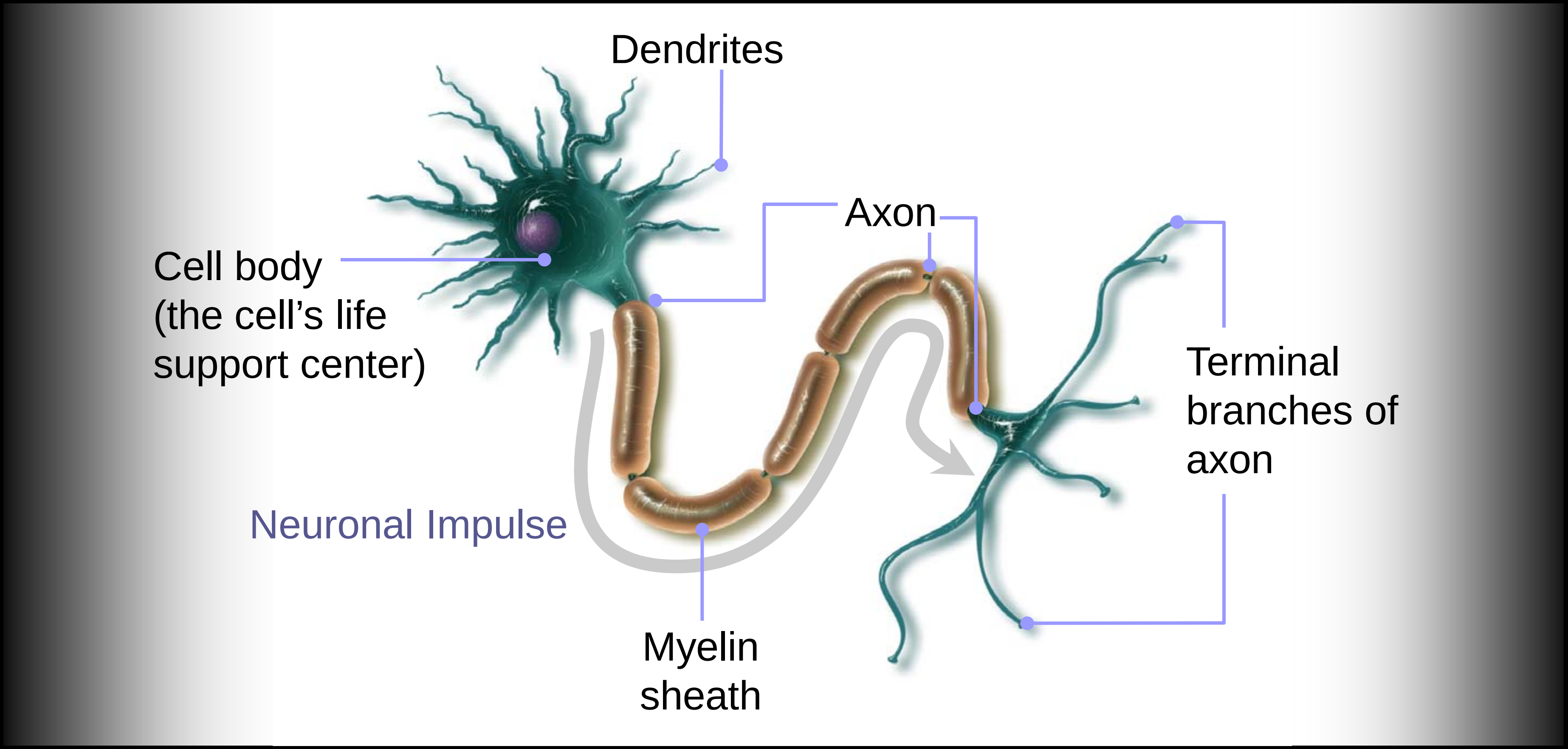
- Map Trajectories
- Discern Influences
- Improve Lives

How the Brain Looks to MRI

Part 1 – Mapping Trajectories of Anatomic Brain Development

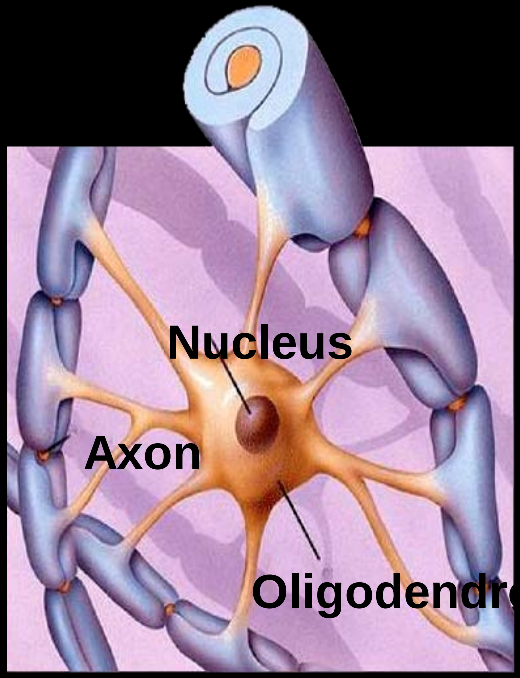
- White Matter
- Gray Matter

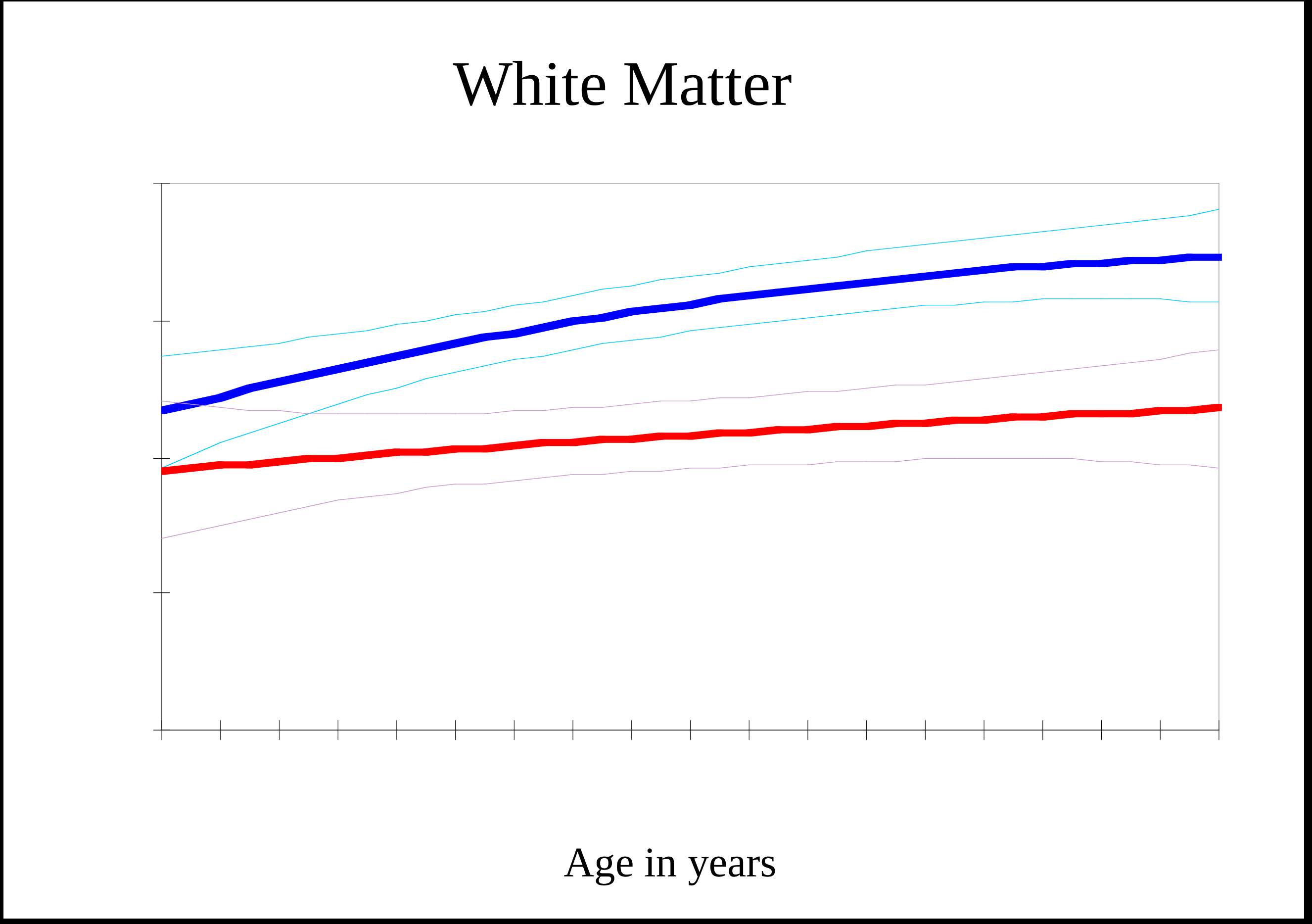
The Neuron



Donald Bliss, MAPB, Medical Illustration

White Matter



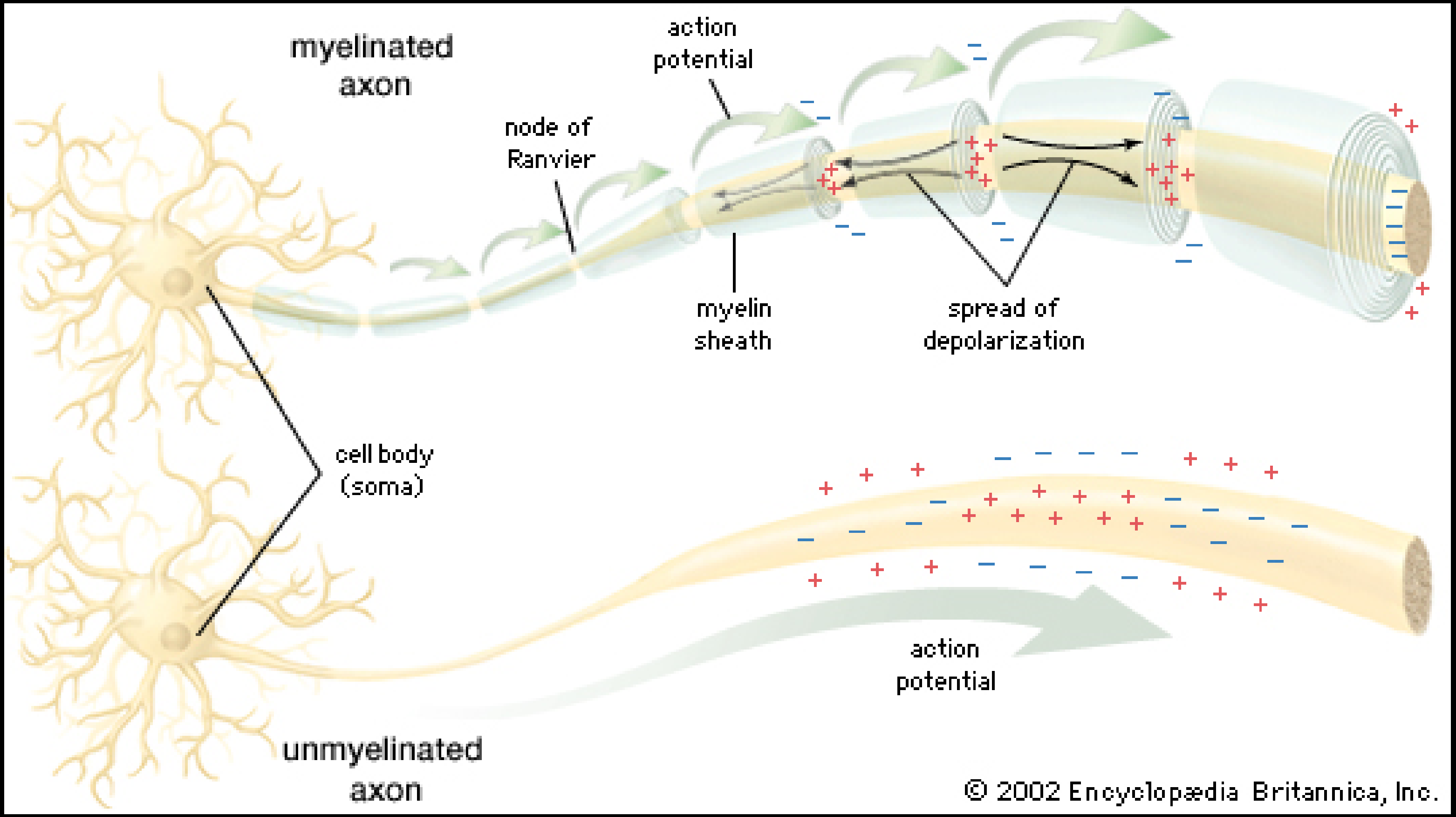


Male (152 scans from 90 subjects)

Female (91 scans from 55 subjects)

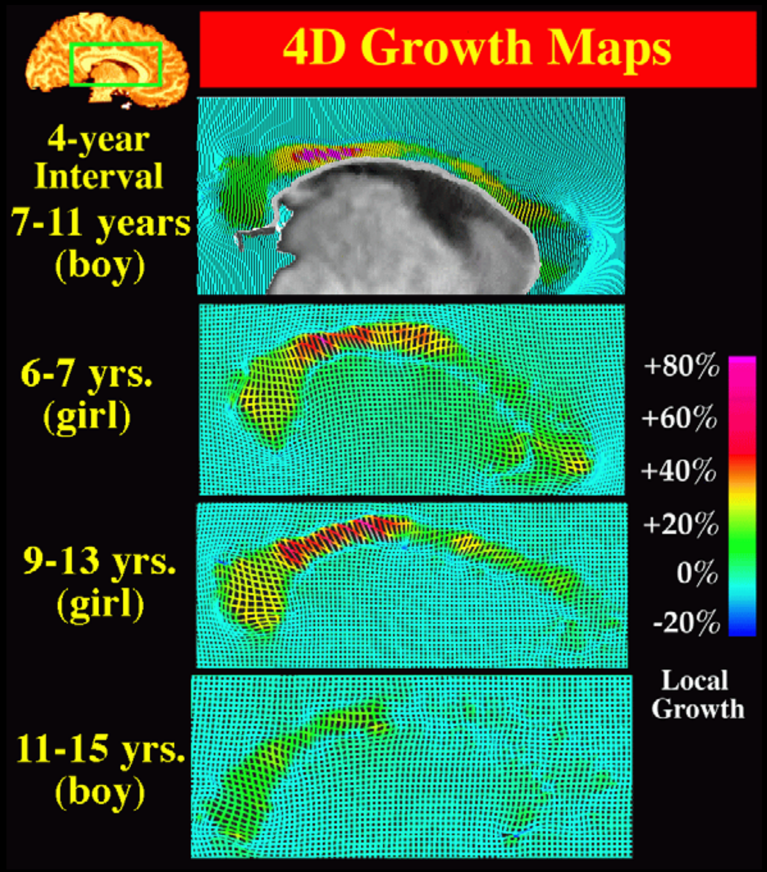
95% Confidence Intervals

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



Signal “hops” between nodes of Ranvier

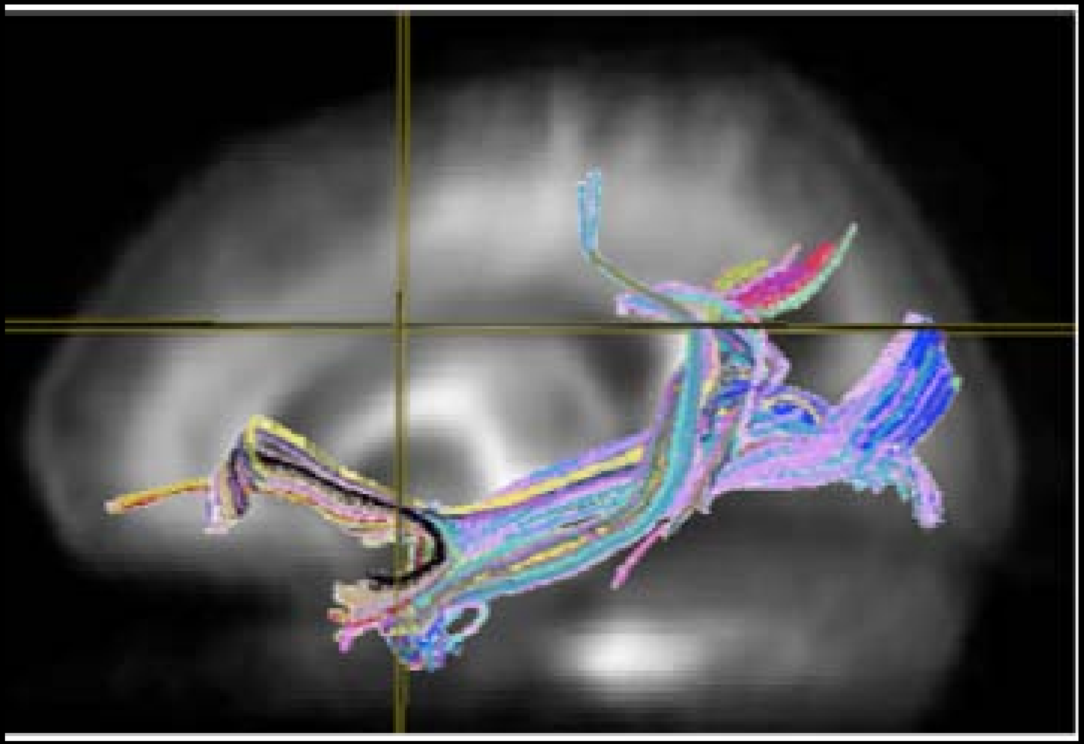
Dynamic White Matter Changes during Pediatric Development



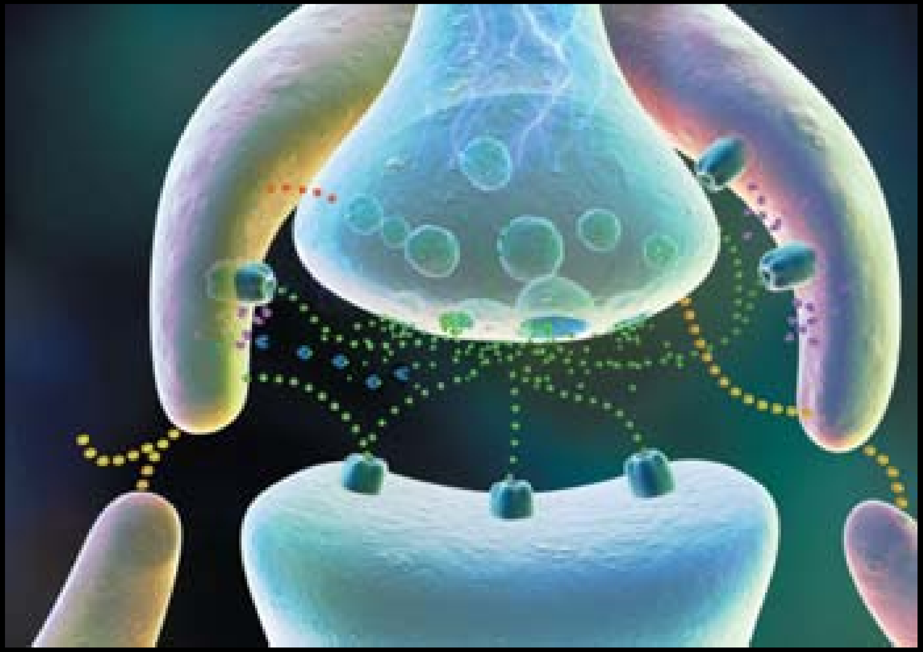
Nature, 2000

- Newborns: few myelinated axons
- Different regions at different ages
  - Wernicke (language comprehension)
  - Broca (speech production) – 6 months later (Need to understand language before producing it)
  - Dramatic CC changes during childhood

Diffusion Tensor Imaging (DTI)
Magnetization Transfer Imaging (MTI)



More than just maximizing speed …



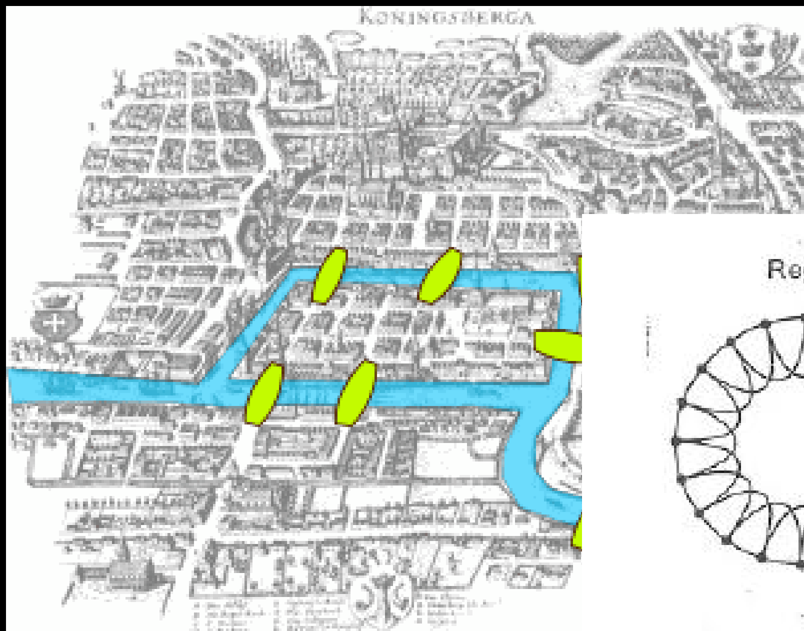
- Synchrony
- Plasticity
- Sensitive Periods
- Integration

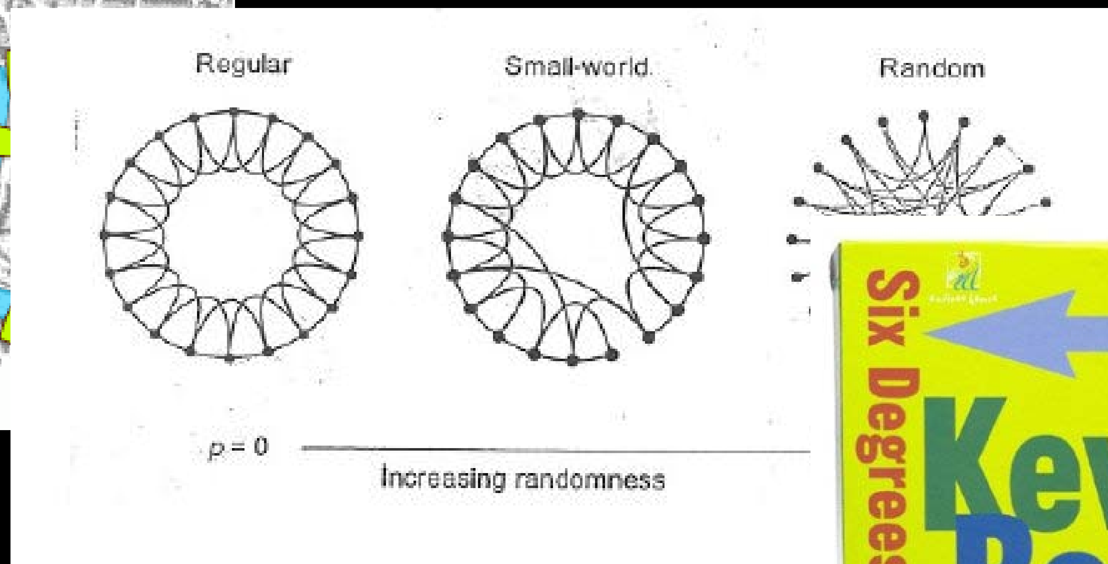
Aspects of "Connectivity"

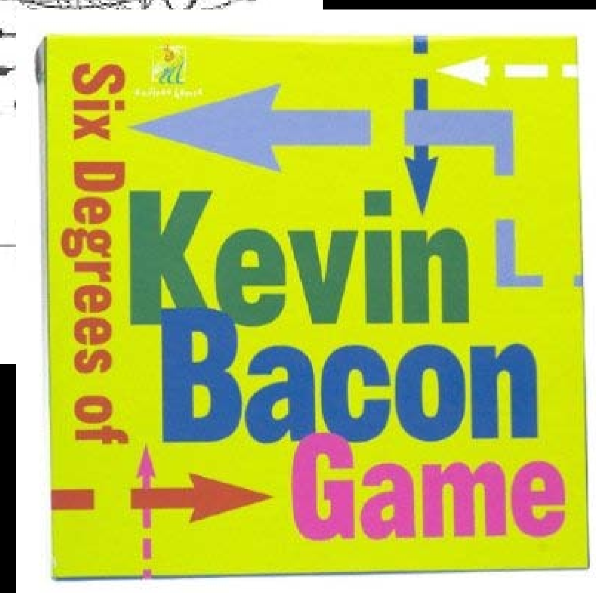
- LTP
- White Matter
- EEG coherence
- fMRI coactivation
- Temporally coupled developmental trajectories
  - Fire together, wire together, … grow together?
- Similarly affected by same genetic/environmental factors

\- - - - Graph Theory (Nodes and Edges) - - - -

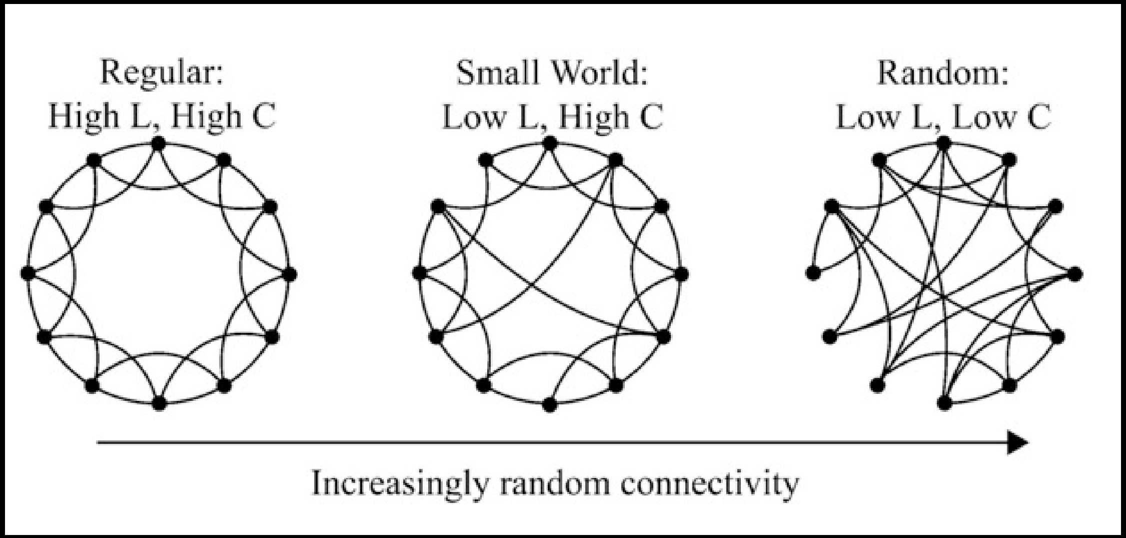
Graph Theory: Is it a small world after all? (strangers linked by mutual acquaintance)





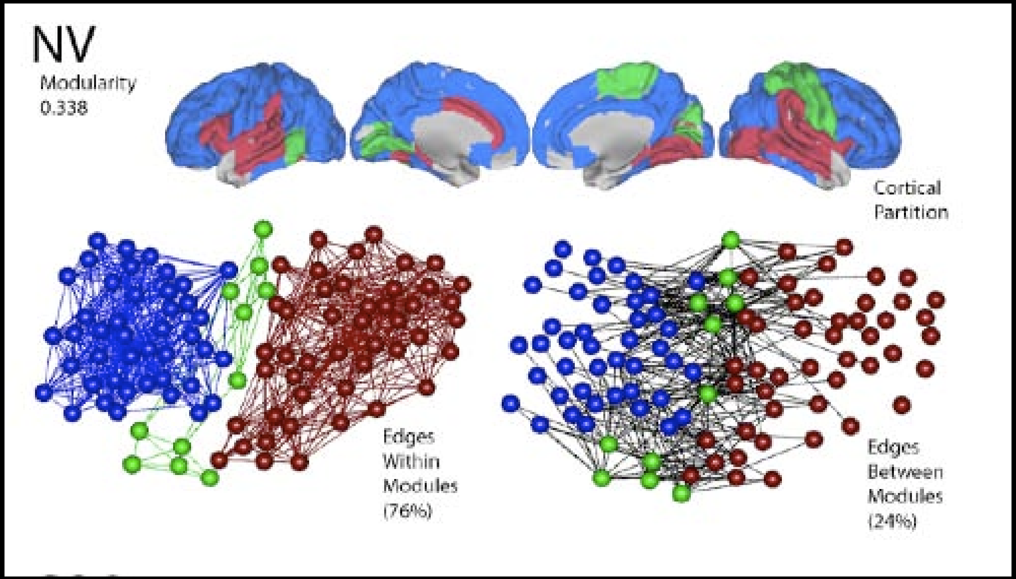


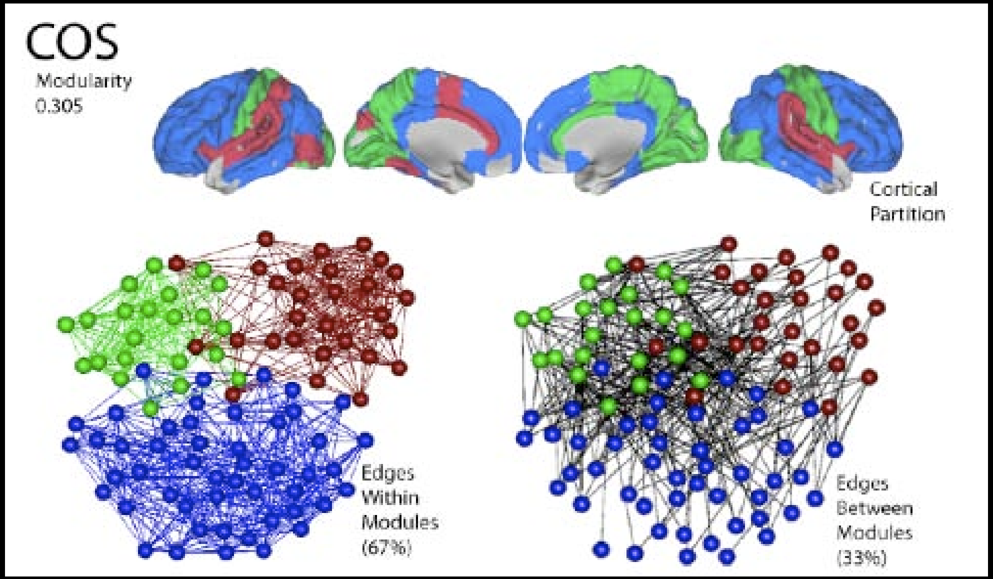
Collective dynamics of 'small-world' networks (Nature, *June 1998)*



- 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

Part 1 – Mapping Trajectories of Anatomic Brain Development

- White Matter
- Gray Matter

Bizarro | *Dan Piraro*

White Matter vs Gray Matter

White Matter

– Linear increase

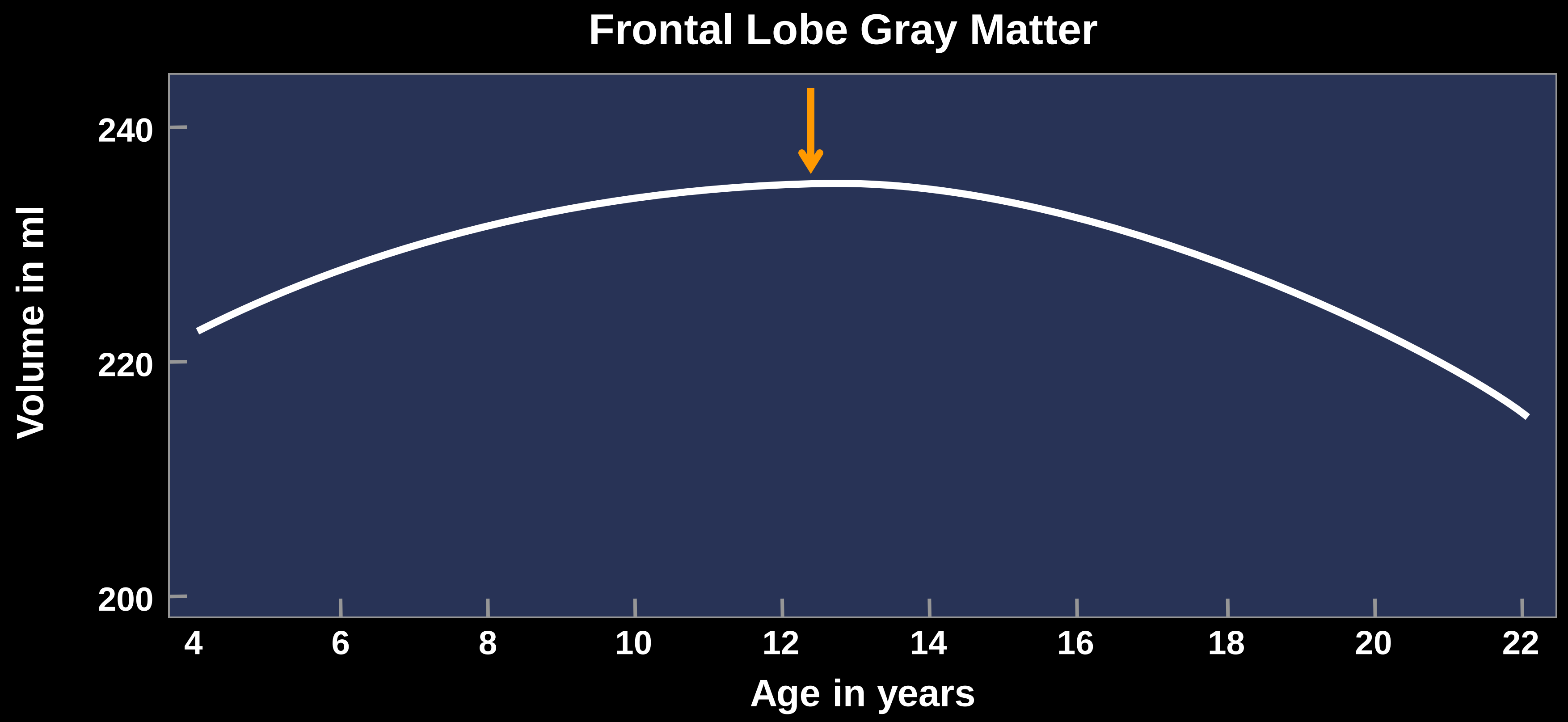
– Not different by region

Gray Matter

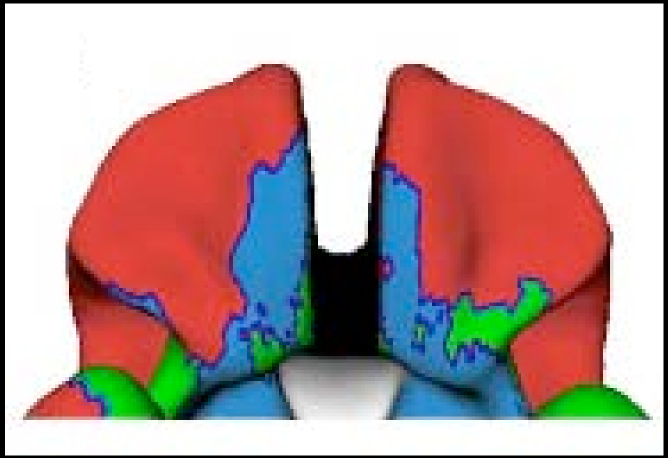
– Inverted "U"

– Regionally specific

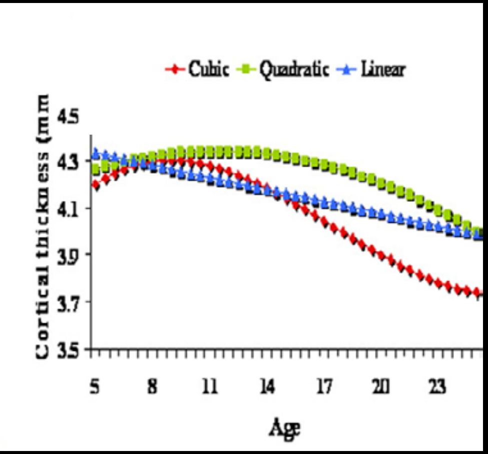
Gray Matter Development
in Healthy Children & Adolescents
(1412 Scans from 540 Subjects)



Architectonic complexity aligns with the complexity of cortical growth trajectories



Complexity of developmental trajectories throughout the orbitofrontal cortex, projected onto a standard brain template.

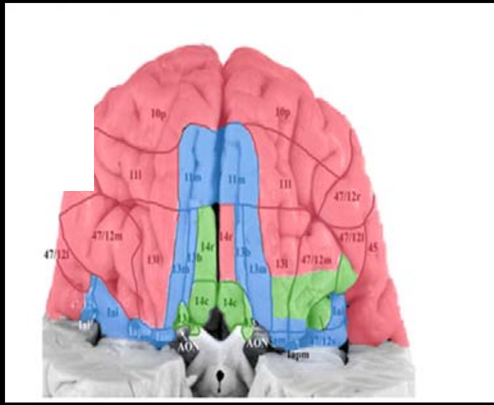


The trajectory of each of the divisions.

Red - cubic fit

Green - quadratic

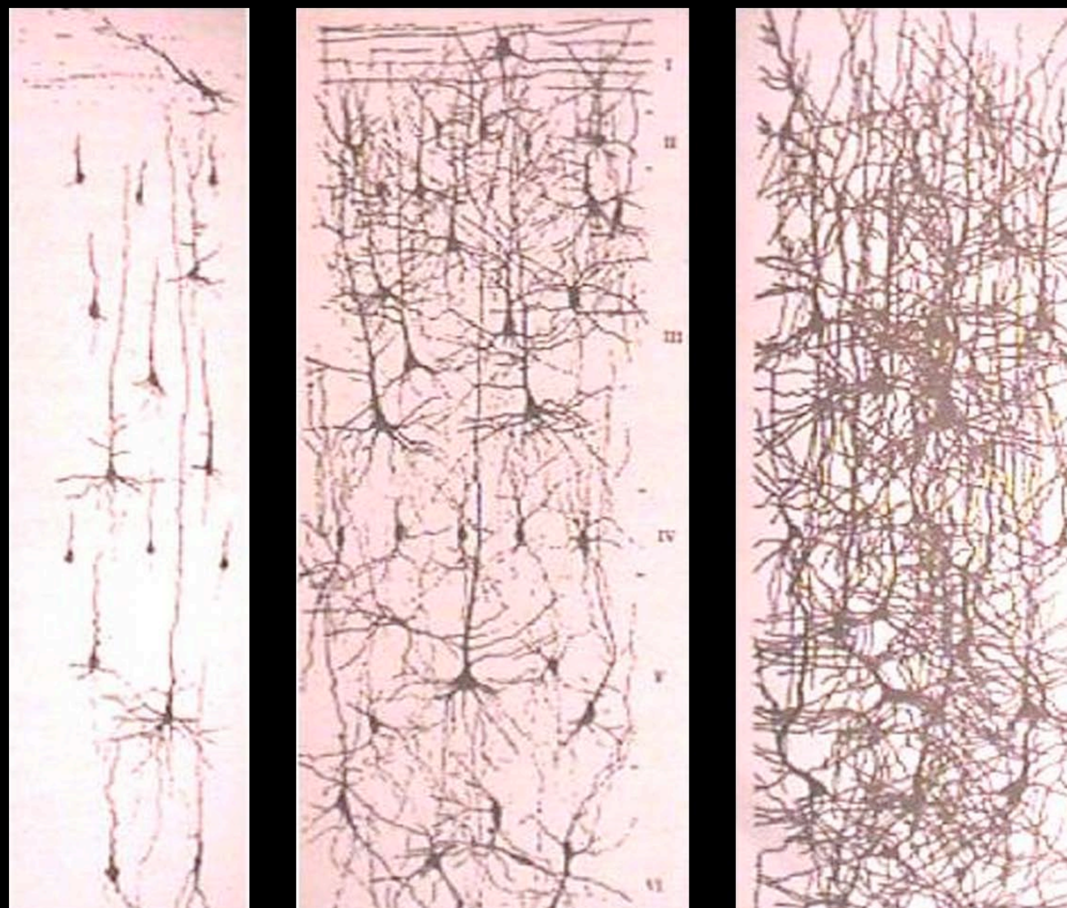
Blue - linear



The trajectories are superimposed on a cytoarchitectonic map of the region (Ongur et al., 2003) to illustrate the overlap between the cytoarchitectonic fields and regional trajectory differences.

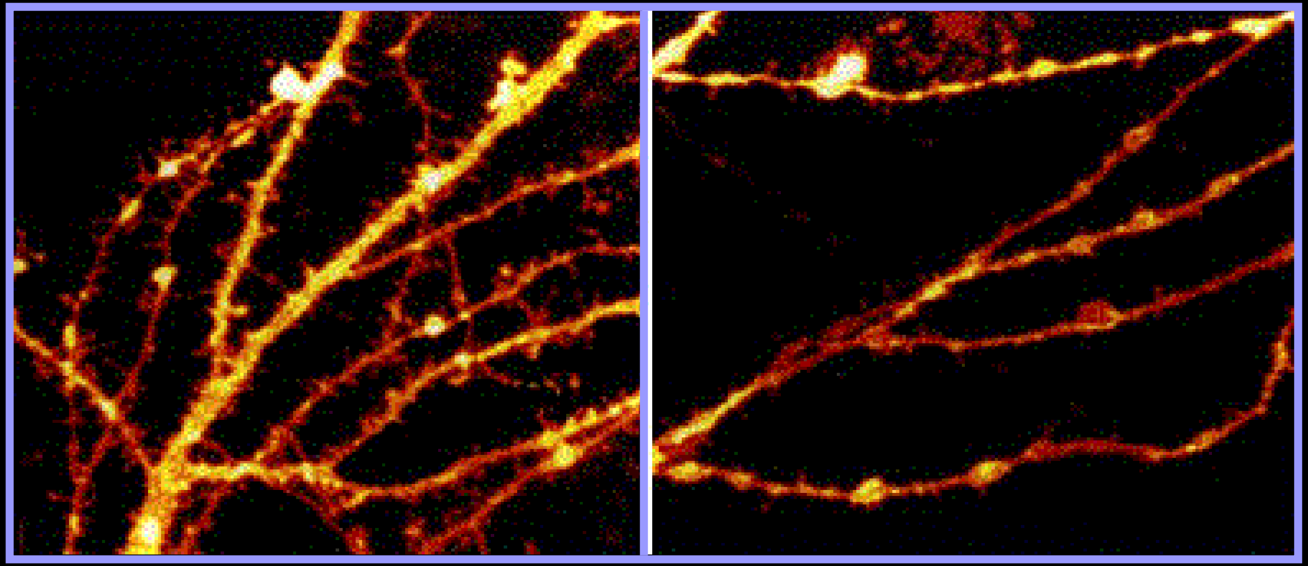
Neuronal Branching

Dendrites
& Synapses



BIRTH **3 MONTHS OLD** **2 YEARS**

Diamond, Hopson, Scheibel, 1998

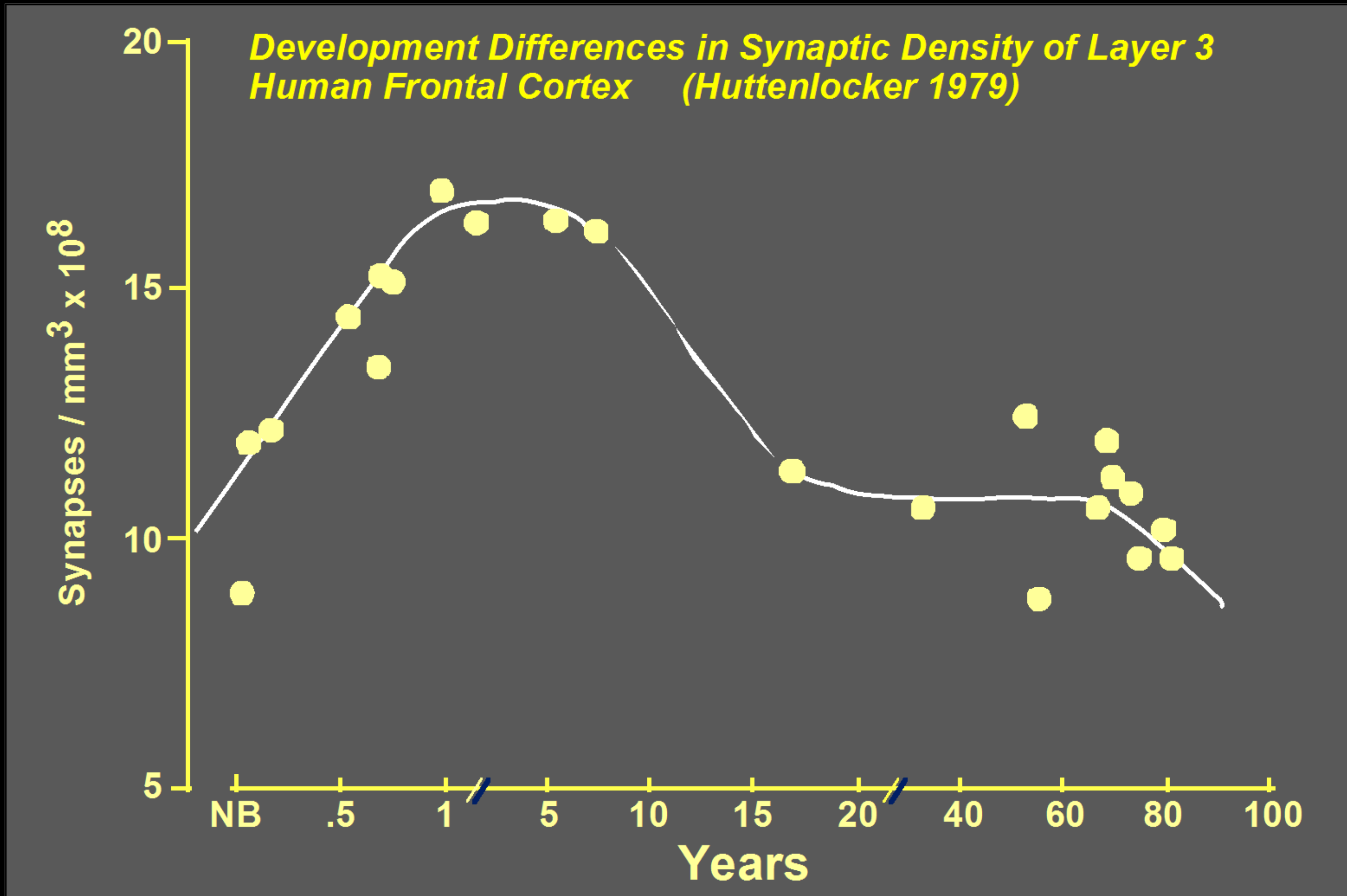


Images by Diane Murphy, PhD, National Institutes of Health

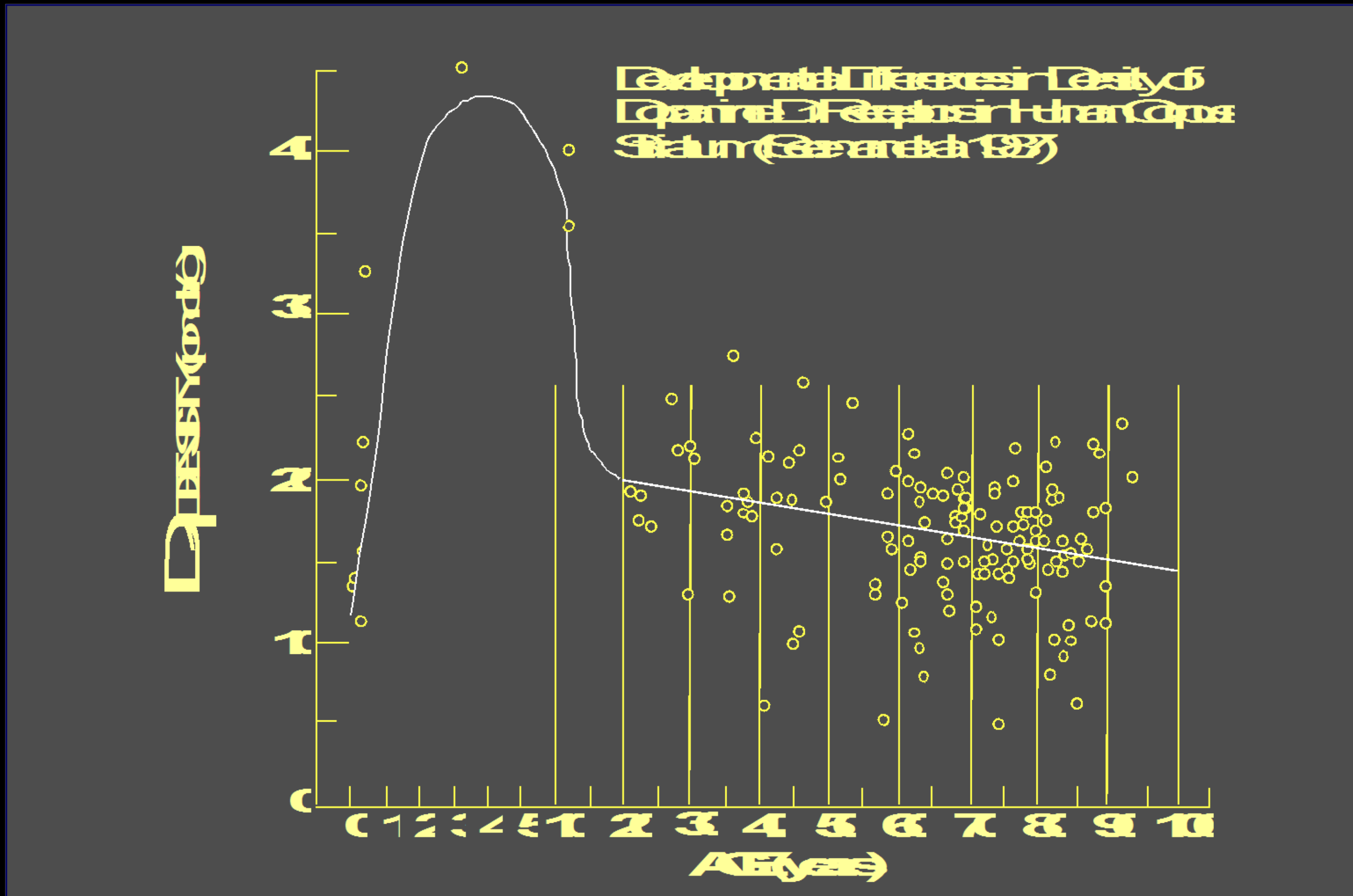
Overproduction / Selective Elimination

- Postmortem
  - Animal
  - Human
- EEG
- MEG
- PET

Similar Pattern for Synaptic Density

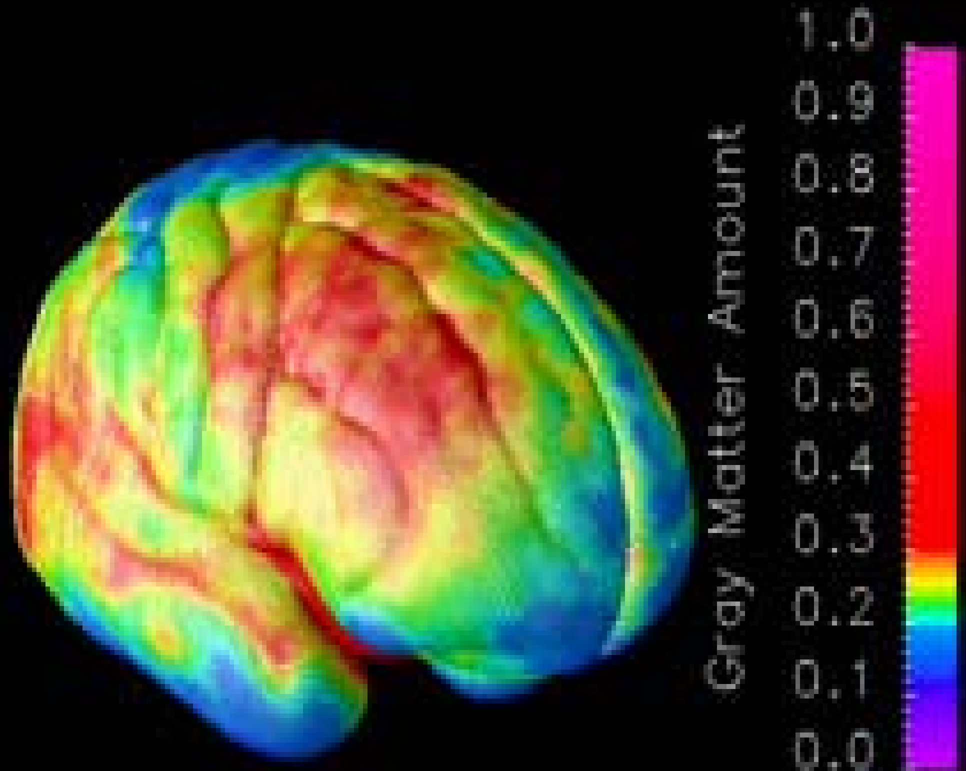


And for D1 Receptor Density in Striatum

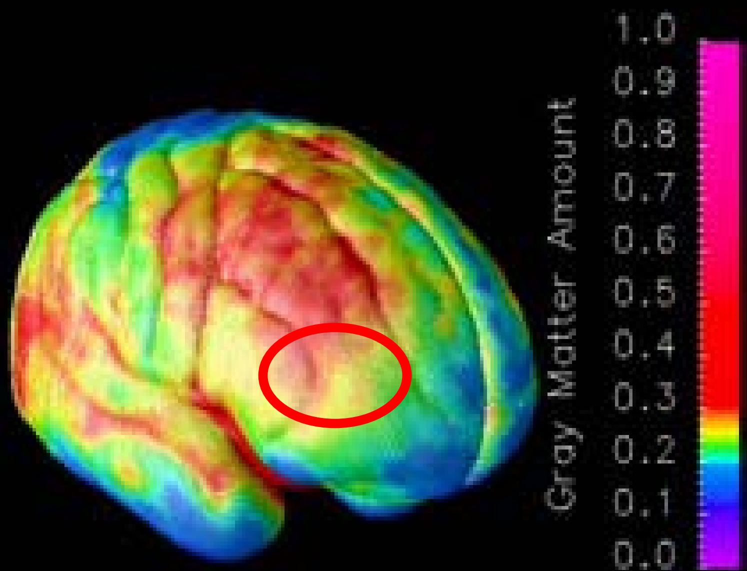


Movie for adolescent students

Gray Matter Thickness:
Ages 4 to 25 years

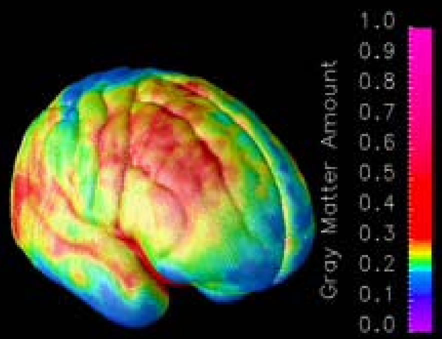


Prefrontal Cortex



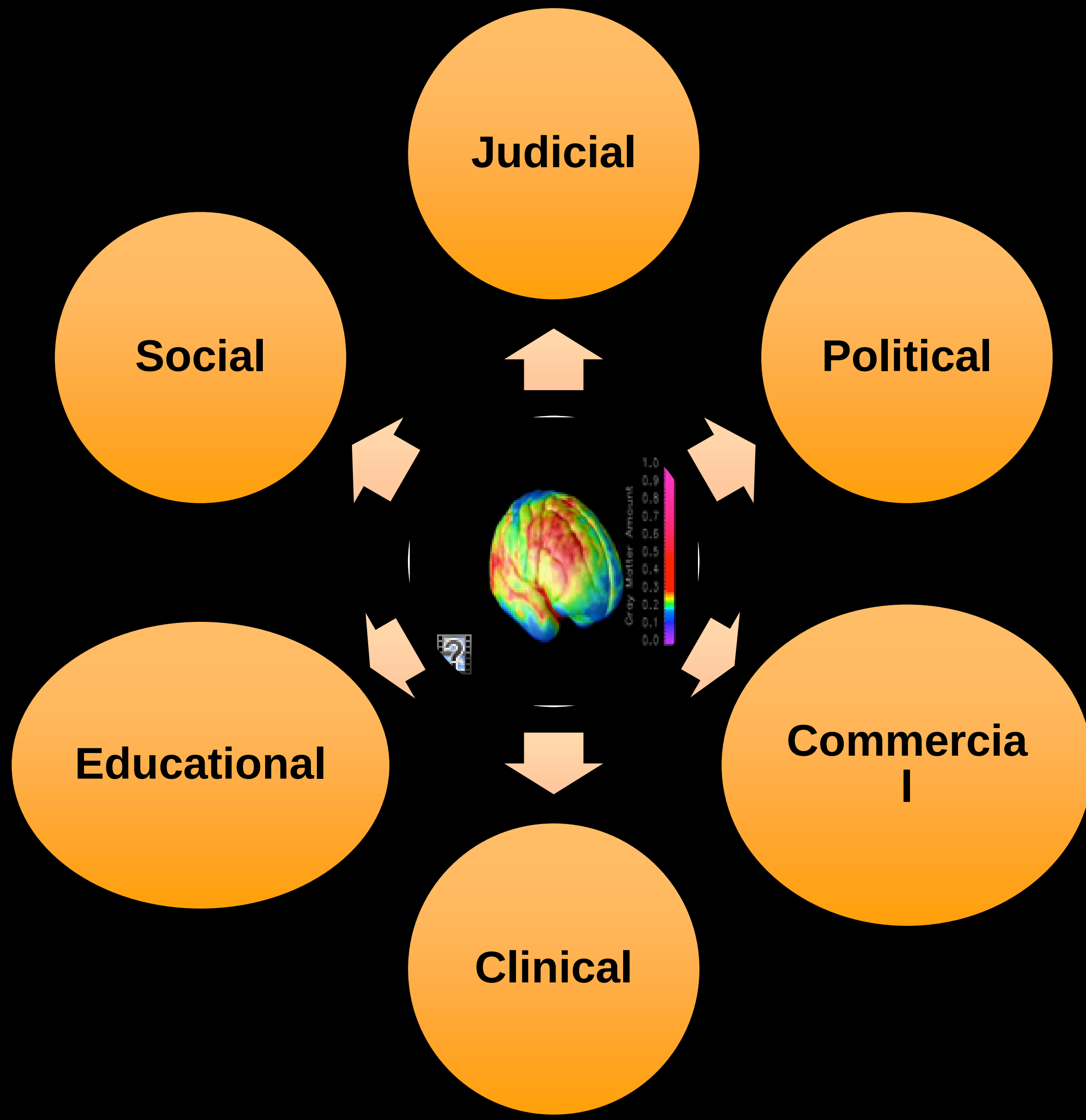
- “Executive” functions
  - Long term strategy
  - Planning
  - Organization
  - Impulse control
- Integrates input from rest of the brain
- “Time Travel”
- Multi tasking bottle neck?

Questions related to changing cortical thickness

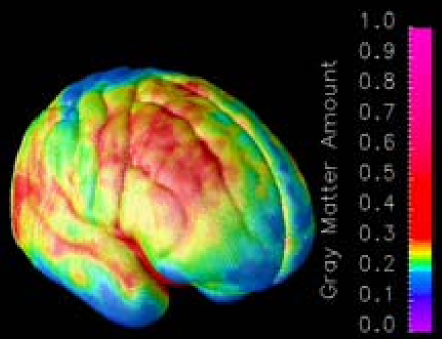


- What are the social/judicial/parenting/personal implications of late DLPFC maturation?
- What influences the build up stage?
  - Parenting / Medications / Diet / Video games / Other
- Does the “use it or lose it” principle guide the adolescent pruning?

Overproduction/Selective Elimination as a construct to understand developmental pathology?


Judicial
Political
Commercia
l
Clinical
Educational
Social

Questions related to changing cortical thickness



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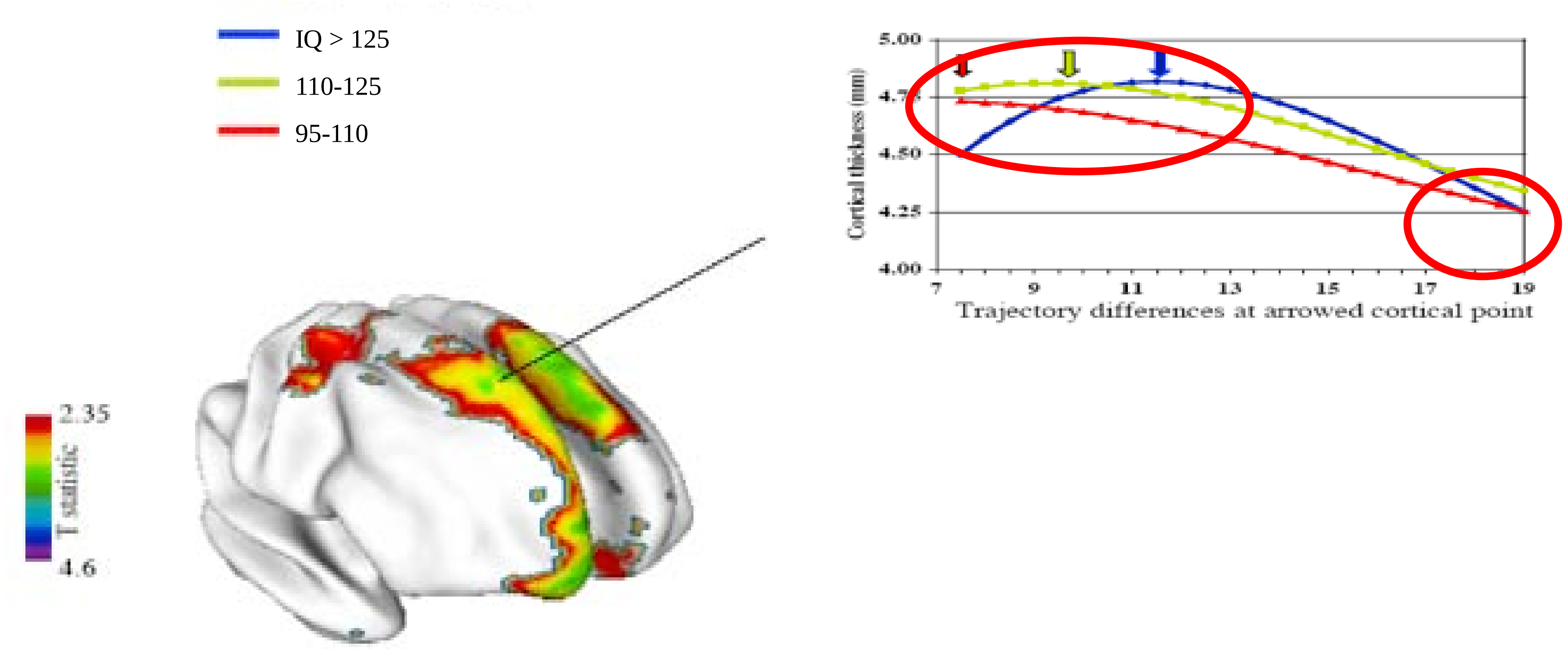
Overproduction/Selective Elimination as a construct to understand developmental pathology?

“Life is a journey not a destination”

-fortune cookie from the Peking Duck, Bethesda, MD 2002

IQ and cortical thickness



Philip Shaw, 2006

nature Vol 440|30 March 2006|doi:10.1038/nature04513

LETTERS

Intellectual ability and cortical development in children and adolescents

P. Shaw[1], D. Greenstein[1], J. Lerch[2], L. Clasen[1], R. Lenroot[1], N. Gogtay[1], A. Evans[2], J. Rapoport[1] & J. Giedd[1]

Scans Show Different Growth for Intelligent Brains

By NICHOLAS WADE
Published: March 30, 2006

The brains of highly intelligent children develop in a different pattern from those with more average abilities, researchers have found after analyzing a series of imaging scans collected over 17 years.

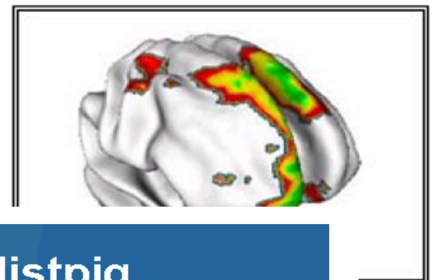
The discovery, some experts expect, will h[...] understand intelligence in terms of the gene[...] childhood experiences that can promote it.

RESEARCH NEWS

Study Makes Case for Late Bloomers

npr

Listen by Jon Hamilton



All Things Considered, March 29, 2006 · It usually makes parents proud when their children reach a developmental milestone ahead of other kids. But when it comes to intelligence, researchers say, the smartest children appear to have brains that develop later.

capitalistimperialistpig

897

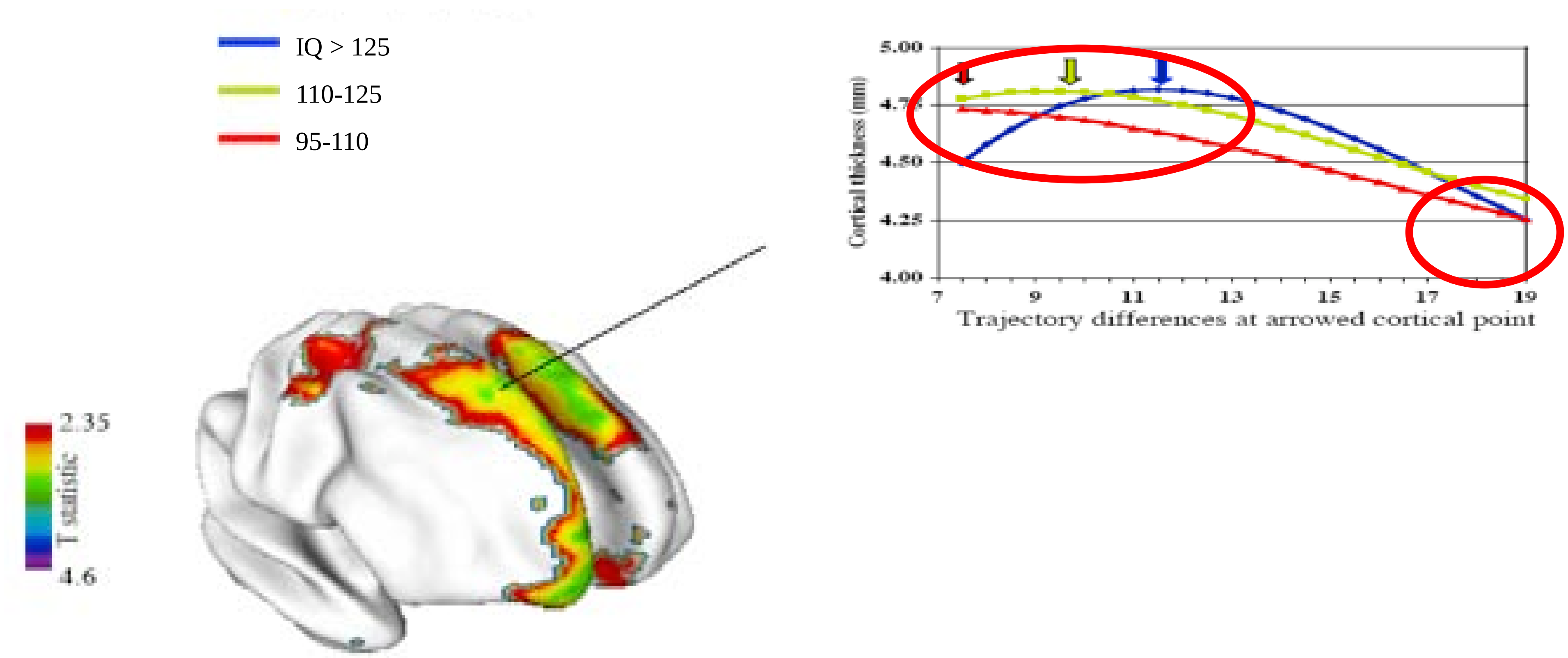
THOSE WHO WOULD GIVE UP ESSENTIAL LIBERTY TO PURCHASE A LITTLE TEMPORARY SAFETY DESERVE NEITHER LIBERTY NOR SAFETY - BENJAMIN FRANKLIN

friday, march 31, 2006

IQ and Brain Growth

One of the most hyped stories of the past few days has been that of how high IQ children's brains grow differently that those of average children.

IQ and cortical thickness



Philip Shaw, 2006

Anatomic MRI of the brain during typical pediatric development

- White Matter Increase (Myelination)
- Inverted U Gray Matter (Synaptic Pruning?)
- Relatively late maturation of:
  - Prefrontal Cortex
  - Superior Temporal Sulcus
  - Inferior Parietal Cortex
- Journey / Destination
- Critical / Sensitive periods?

fMRI

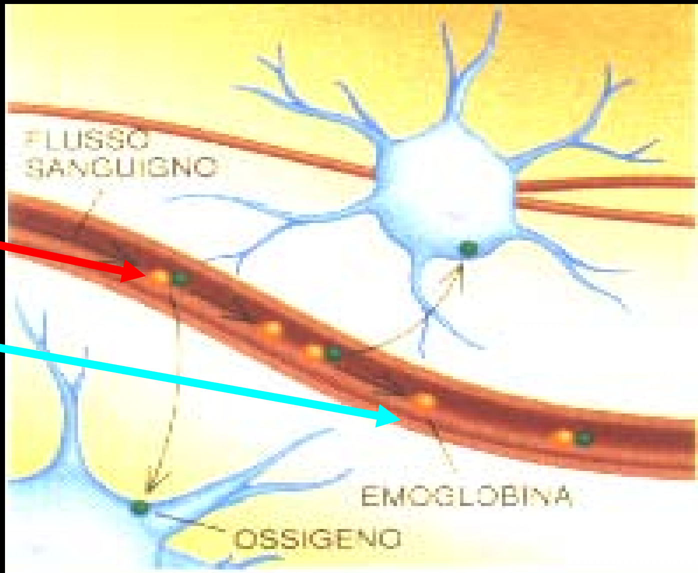
Probes cerebral blood flow-oxygen consumption during cortical activation

- *Oxy* and *Deoxy* hemoglobin have different magnetic properties

rest

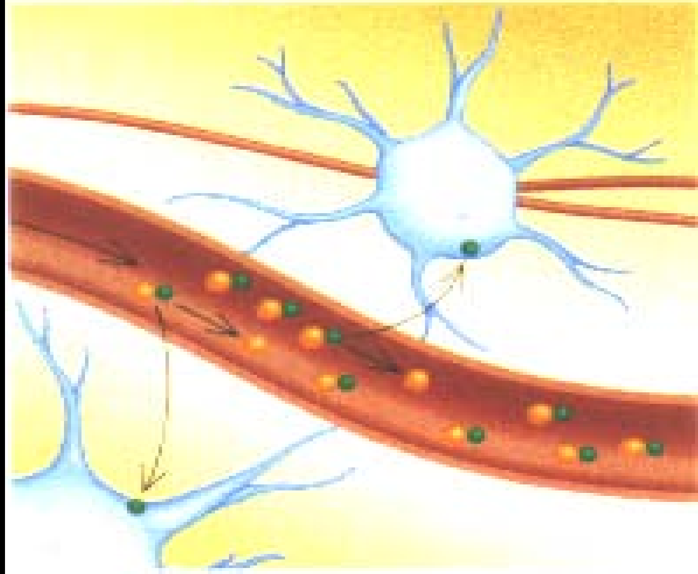
oxyhemoglobin

deoxyhemoglobin



event

more oxyhemoglobin than deoxyhemoglobin



- Resolution?

Space - few millimeters

Time – few seconds

Functional MRI of the brain during typical pediatric development

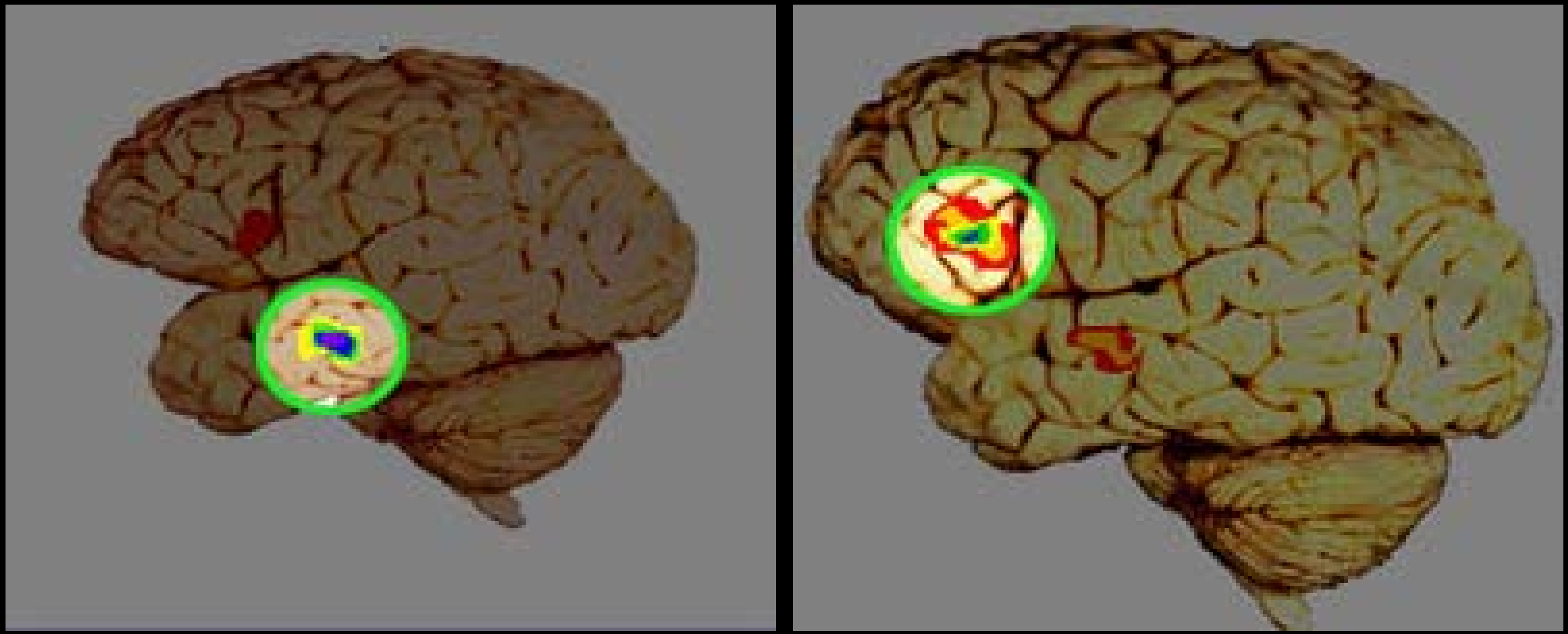
- Changing Frontal / Limbic balance
- Diffuse to Focal activation patterns
- Increased integration of widely distributed brain circuitry
  - Fast connections for top down modulation
  - More efficient neuronal processing?

Do Teens and Adults process emotions differently?

- Adults and teen subjects have been shown to process emotions differently, they use different areas of their brain to recognize feelings

- Many teen subjects failed to interpret the emotion in faces like this one as fear.

Recognizing emotions from pictures of faces: Adults vs Teens



When reading emotion, teens **(left)** rely more on the amygdala, while adults **(right)** rely more on the frontal cortex.

Deborah Yurgelon-Todd, 2000

Functional MRI of the brain during typical pediatric development

- Changing Frontal / Limbic balance
- Diffuse to Focal activation patterns
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Part 2 - Influences on Brain Development

- Nature / Nurture → Twin studies
- Male / Female
- Specific Genes
- Psychopathology

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Twins

- 130 Monozygotic (“identical”) pairs
- 105 Dizygotic (“fraternal”) pairs

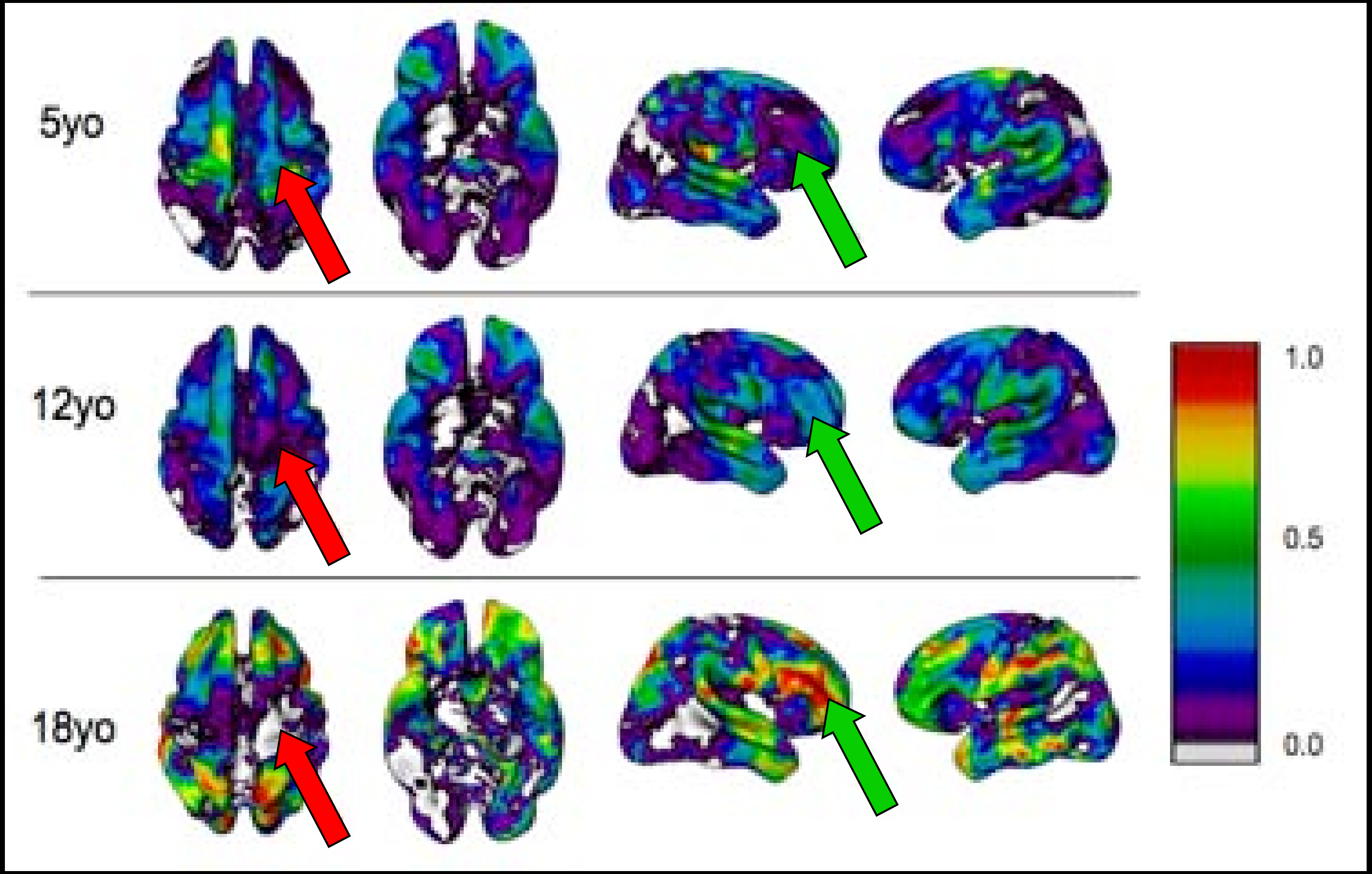
- Structural Equation Modeling

A Additive Genetic Factors

C Common Environment

E Error/ Unique Environment

Heritability varies by age and region



Heritability (a2) at ages 5,12, and 18 years. Colorbar shows heritability values from 0.0 to 1.0

Red arrows- heritability higher at younger ages

Green arrows- heritability higher at older ages

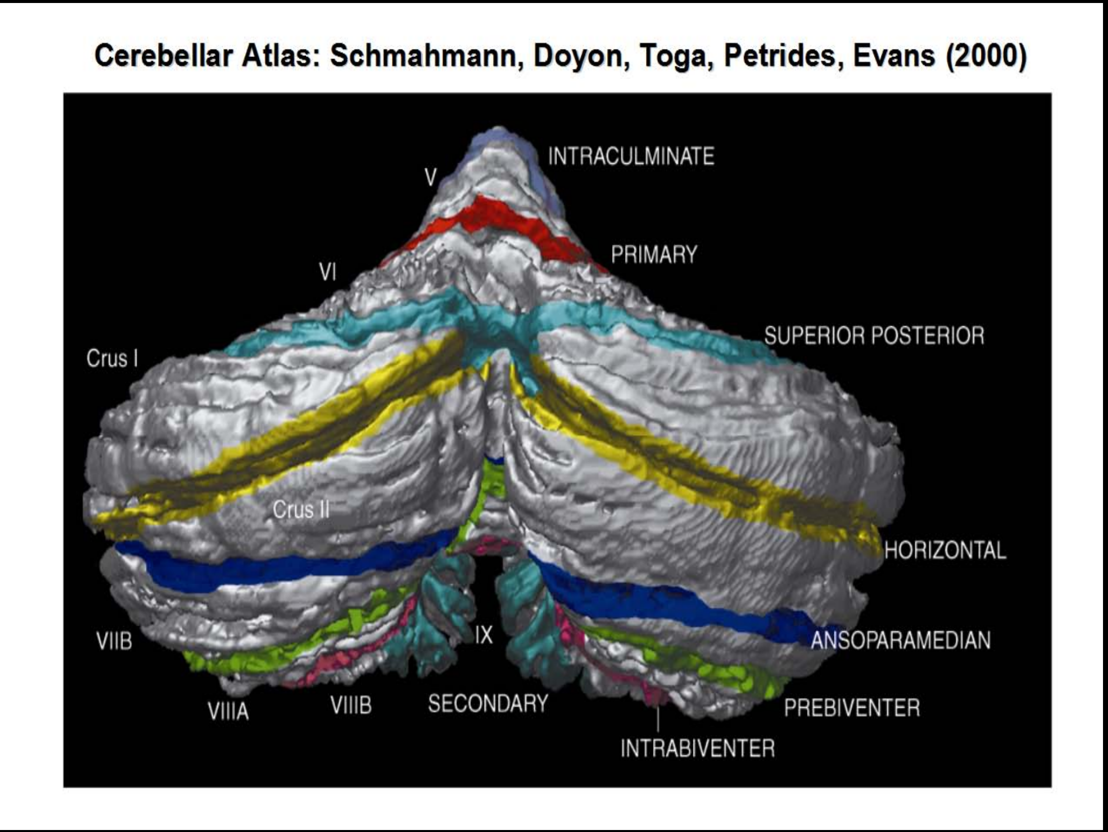
Lenroot et al, 2008

What are the implications of substantial age x heritability interactions for the design and interpretation of imaging/genetic studies?

MODEL	**A^2**		**C^2**		**E^2**	
Total Cerebrum	0.89	[.67 - .92]	0.00	[.00 - .22]	0.11	[.08 - .16]
Gray Matter	0.82	[.50 - .87]	0.00	[.00 - .30]	0.18	[.13 - .26]
White Matter	0.85	[.56 - .90]	0.01	[.00 - .29]	0.15	[.10 - .21]
Frontal GM	0.77	[.37 - .83]	0.00	[.00 - .38]	0.23	[.17 - .32]
Parietal GM	0.80	[.44 - .86]	0.00	[.00 - .35]	0.20	[.14 - .29]
Temporal GM	0.80	[.46 - .86]	0.00	[.00 - .33]	0.20	[.14 - .28]
Caudate	0.80	[.57 - .86]	0.00	[.00 - .22]	0.20	[.14 - .29]
Corpus Callosum	0.84	[.41 - .89]	0.01	[.00 - .43]	0.15	[.11 - .22]
Cerebellum	0.50	[.14 - .84]	0.29	[.00 - .63]	0.21	[.15 - .29]

The Unique Cerebellum!
(among our gross anatomic measures)

- Least heritable
- Latest to reach adult volume
- Most sexually dimorphic (male >female, surviving TCV covariate)



Cerebellar Atlas: Schmalmann, Doyon, Toga, Petricles, Evans (2000)

Multivariate Analysis (degree to which same factors contribute to multiple structures)

- Single factor accounts for 60% of genetic variability in cortical thickness.
  - When covaried for mean global cortical thickness 6 PCA factors explained 58%
  - 5 groups of structures strongly influenced by the same underlying genetic factors

Schmitt et al, 2008

Part 2 - Influences on Brain Development

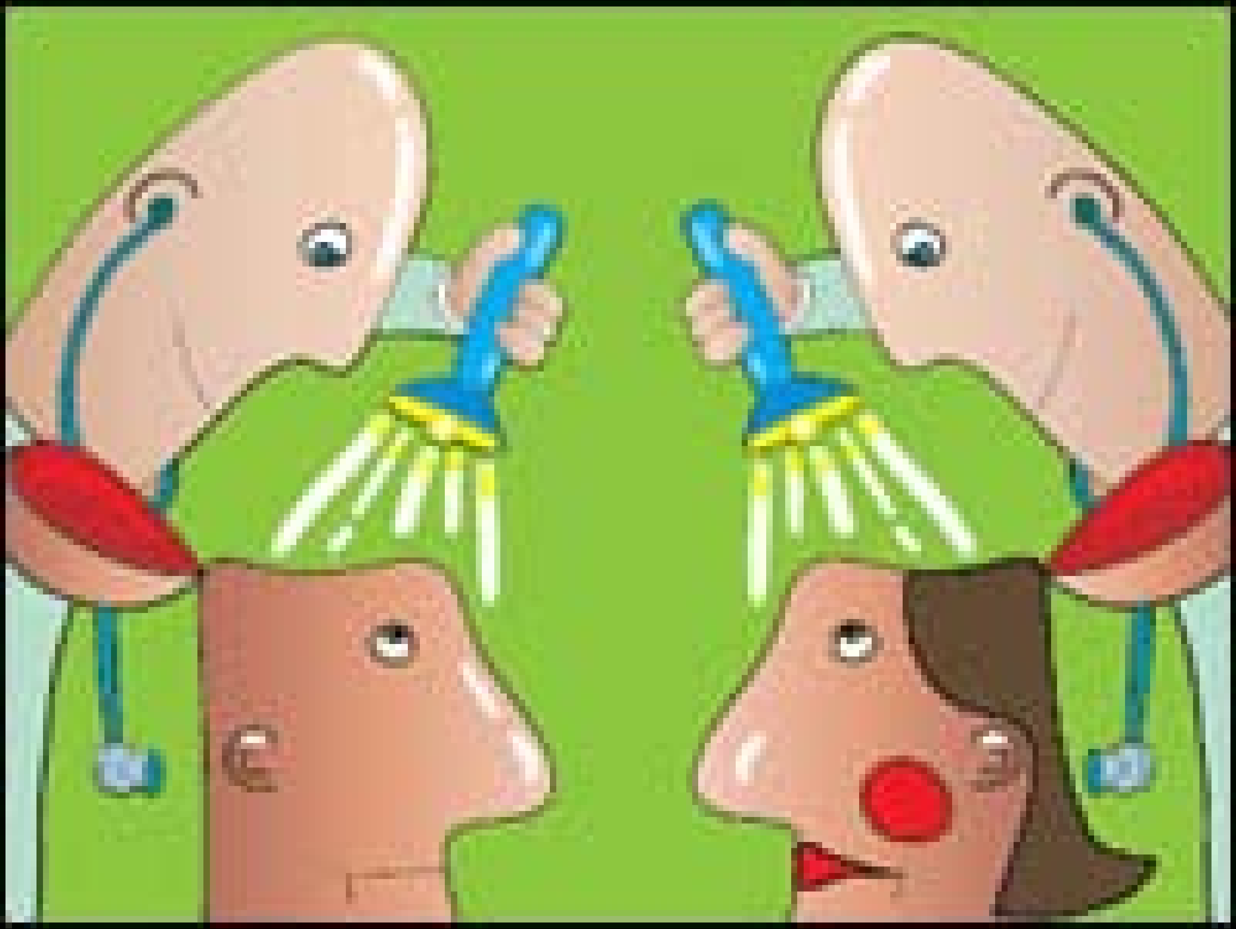
- Nature / Nurture → Twin studies
- Male / Female
- Specific Genes
- Psychopathology

Brain Maturation and Sex Differences – Implications for Development, Health, and School Achievement

School, Educational Achievement and Mental Health among Children and Adolescents

Stockholm
April 26, 2010

Jay N. Giedd, MD
Child Psychiatry Branch, NIMH, USA



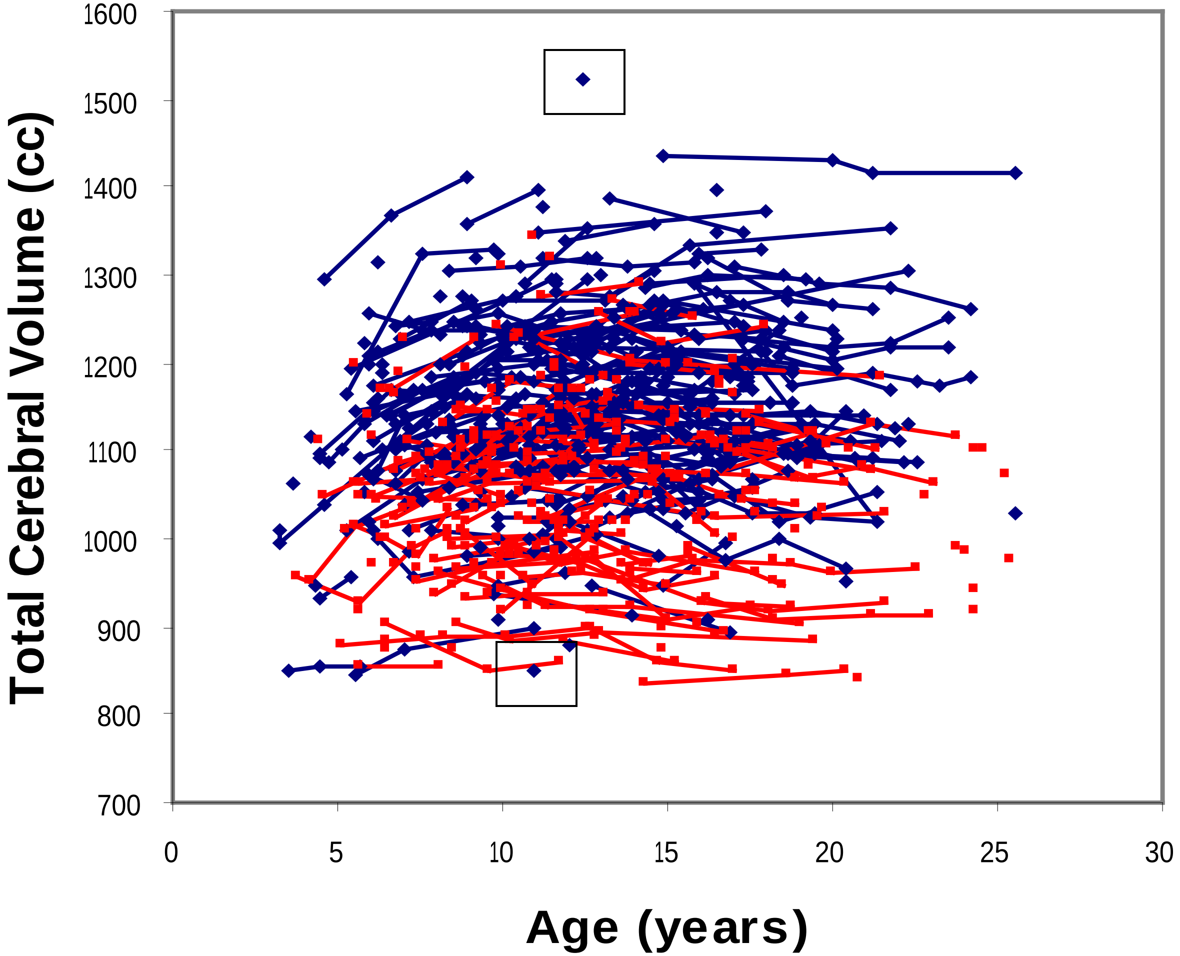
Sex Differences in Child & Adolescent Psychiatry

- Nearly all neuropsychiatric disorder of childhood onset have different prevalences, ages of onset, and symptomatology between boys and girls.
- Might sexually distinct patterns of normal brain development may interact with other environmental or genetic factors to account for some of these clinical differences?

Summary of Sexual Dimorphism

- Overwhelming more alike than different
- Developmental *trajectories* more different than final destination
- Male brain morphometry more variable
- Differences are between groups – does NOT imply constraints for individual boys or girls
- Effects of environment, sex chromosomes, hormones being elucidated

Total Cerebral Volume by Age for
224 Females (375 scans) and 287 Males (532 scans)

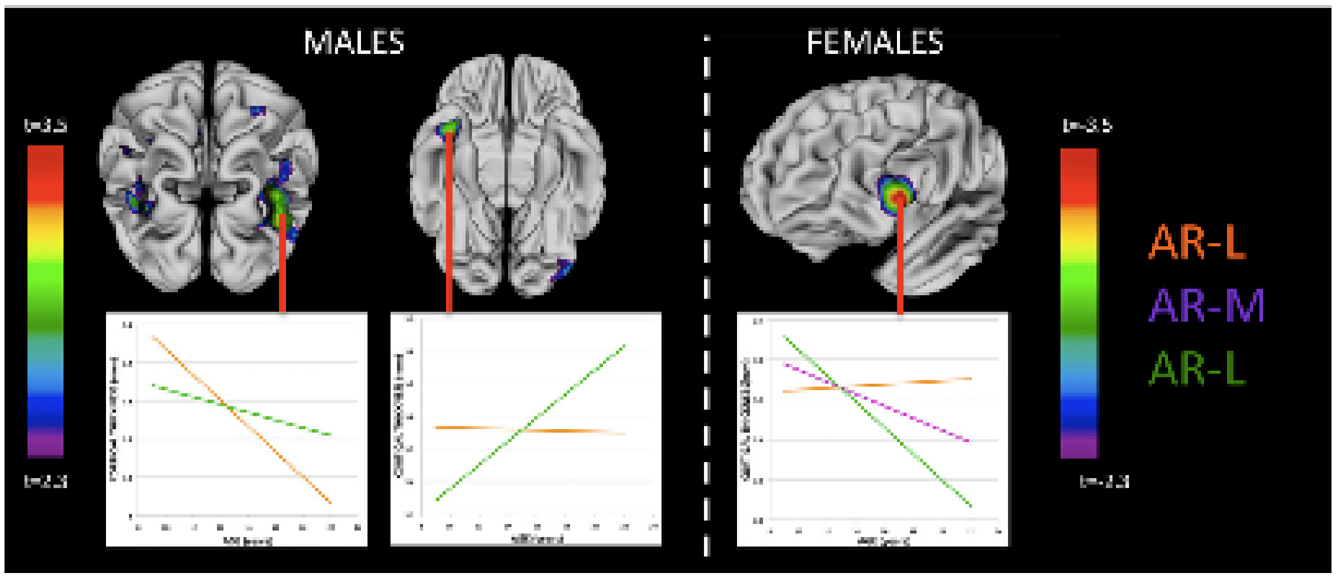


Longitudinally mapping the influence of sex and androgen signaling on the dynamics of human cortical maturation in adolescence

Armin Raznahan[a,b,1], Yohan Lee[a], Reva Stidd[a], Robert Long[a], Dede Greenstein[a], Liv Clasen[a], Anjene Addington[a], Nitin Gogtay[a], Judith L. Rapoport[a], and Jay N. Giedd[a]

[a]Child Psychiatry Branch, National Institute of Mental Health, Bethesda, MD 20892; and [b]Department of Child and Adolescent Psychiatry, Institute of Psychiatry, King's College London, London SE5 8AF, United Kingdom

Edited by Leslie G. Ungerleider, National Institute of Mental Health, Bethesda, MD, and approved August 17, 2010 (received for review April 30, 2010)



Summary of Sexual Dimorphism

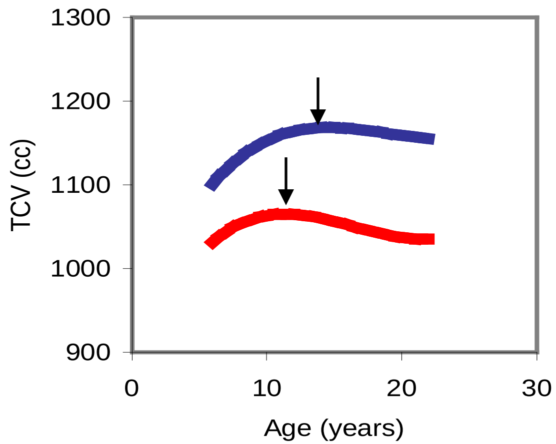
- Overwhelming more alike than different
- Developmental *trajectories* more different than final destination
- Male brain morphometry more variable
- Differences are between groups – does NOT imply constraints for individual boys or girls
- Effects of environment, sex chromosomes, hormones being elucidated

Sex Differences in *Trajectories*

224 Females (375 scans) 287 Males (559 scans)

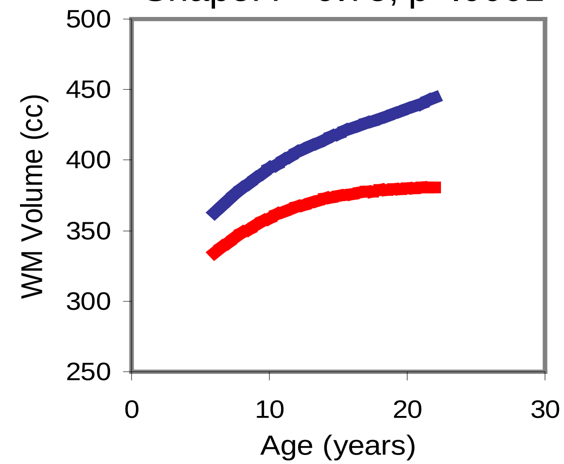
Total Cerebral Volume

Shape: F=9.26; p<.0001



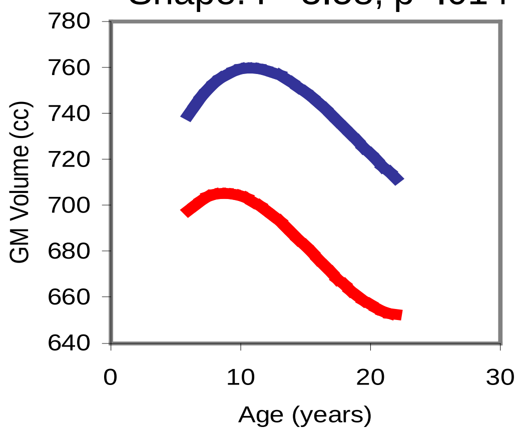
Total White Matter

Shape: F=9.75; p<.0001



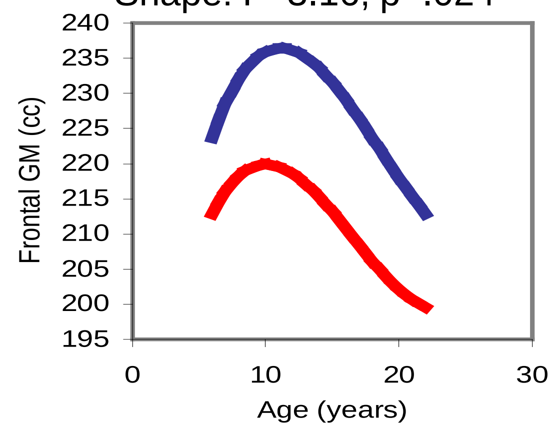
Total Gray Matter

Shape: F=3.58; p=.014

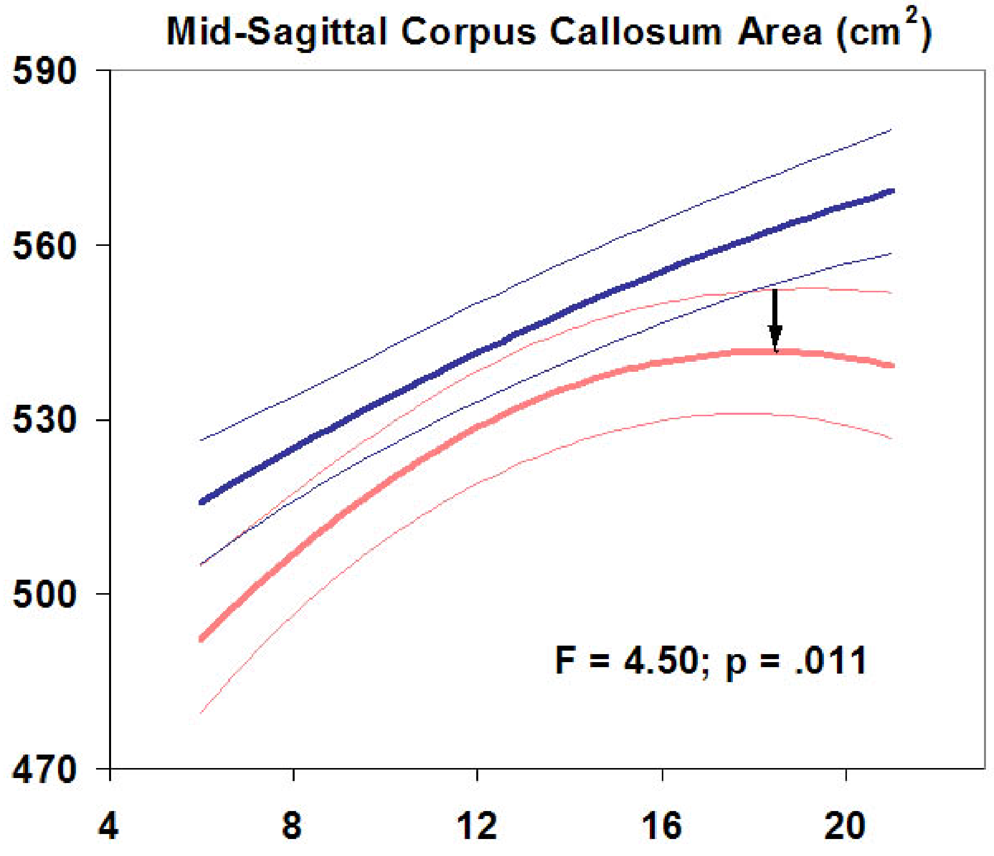


Frontal Gray Matter

Shape: F=3.16; p=.024



Is the Corpus Callosum Sexually Dimorphic?



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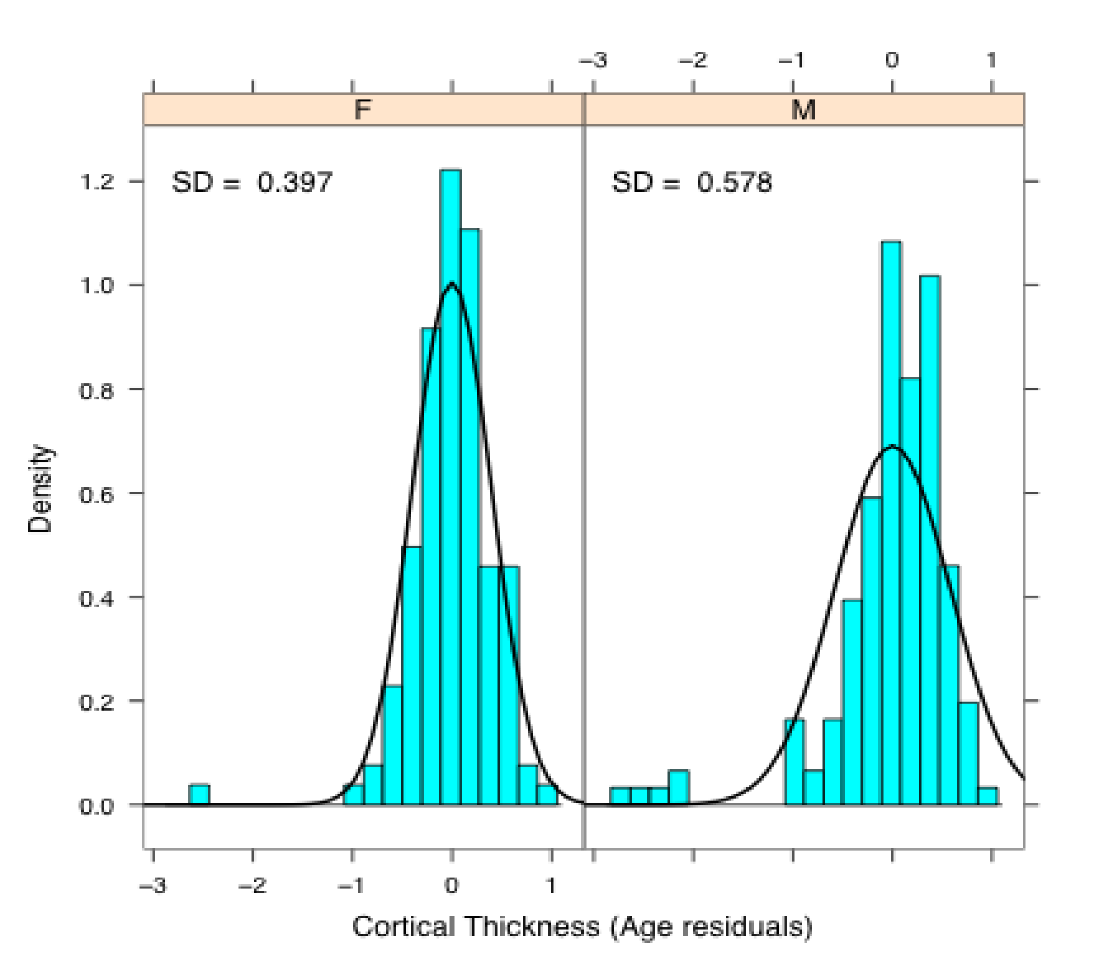
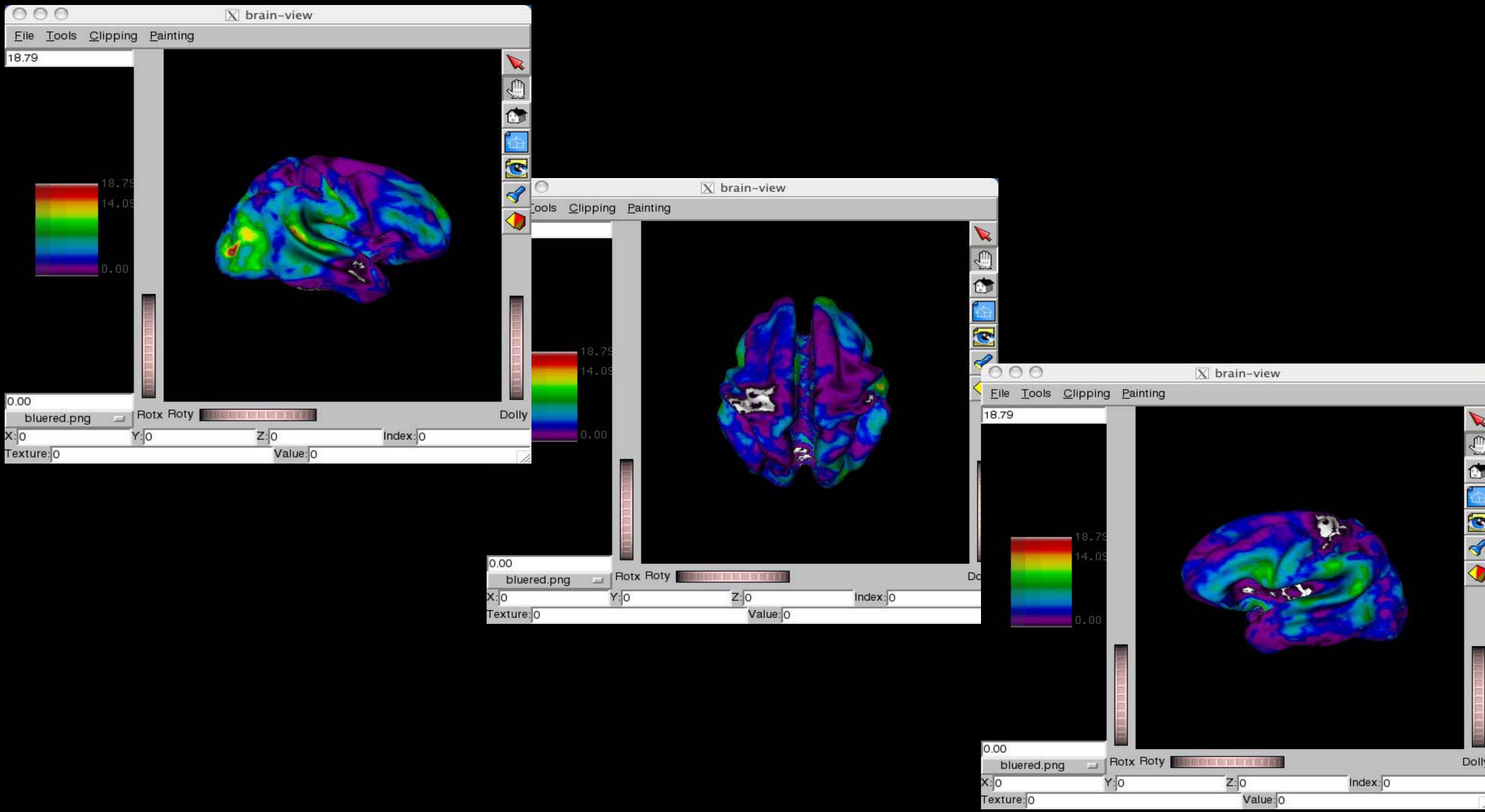
Variance greater in males



Levene's test for difference of variance between males and females at each point on vertex. (white is zero)



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Male/Female Differences Greatest at Extremes

- Example – height
  - @1.78 m (5'10") – 30:1 male
  - @1.83 m (6'0") – 2000:1 male

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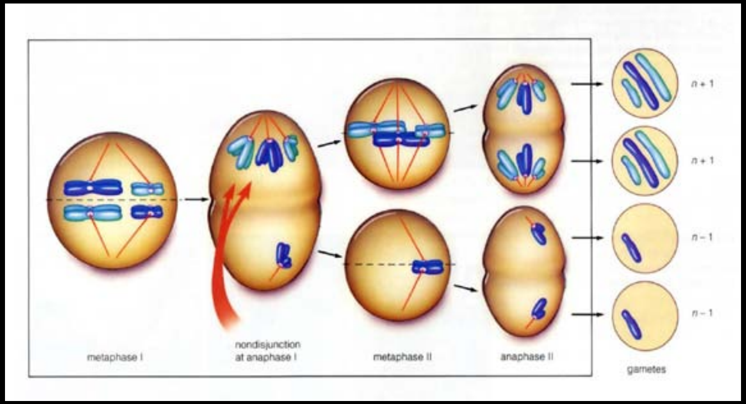
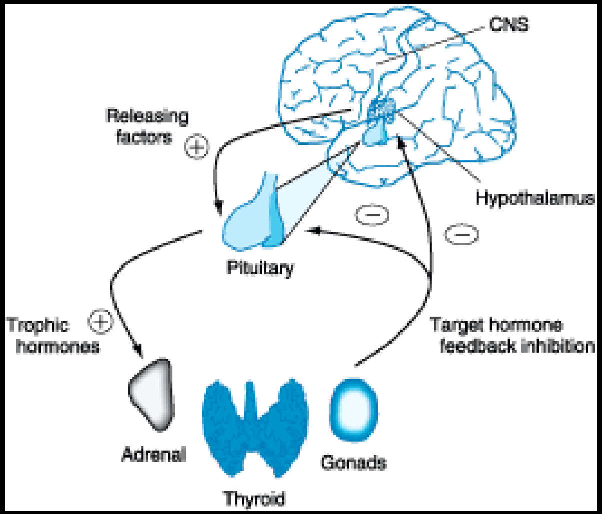
Social Influences

Sex Difference Investigations Involving Clinical Populations

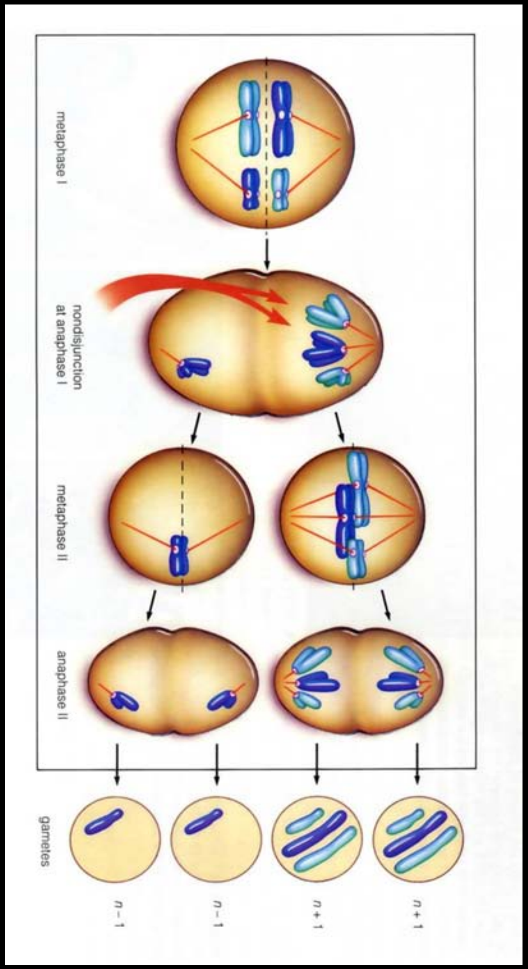
- Anomalous numbers of X and Y chromosome
  - XXY (Klinefelter's Syndrome)



- Anomalous hormone profiles
  - Congenital Adrenal Hyperplasia
  - Androgen Insensitivity Syndrome
  - Familial Precocious Puberty
  - Kallmann Syndrome



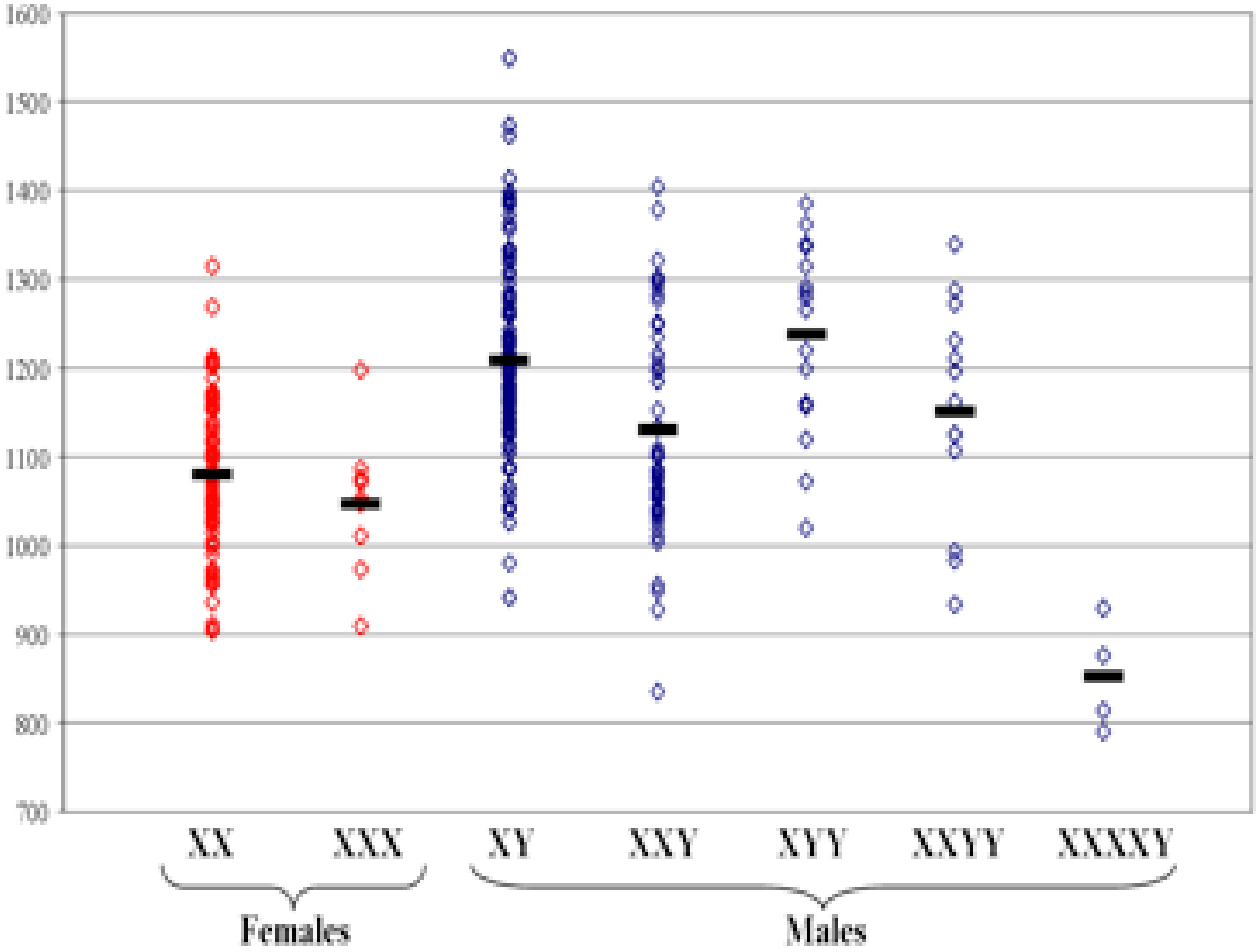
Sex Chromosome Dosage Effects



- XO, XYY, XXY, XXYY, XXX, XXXY, XXXXY
- Clinical severity worsens with increasing number
- X gene dosage effects should be related to the 15% of the X chromosome genes that are not inactivated.

Impact of sex chromosome dosage

Total Gray and White Matter (cc)



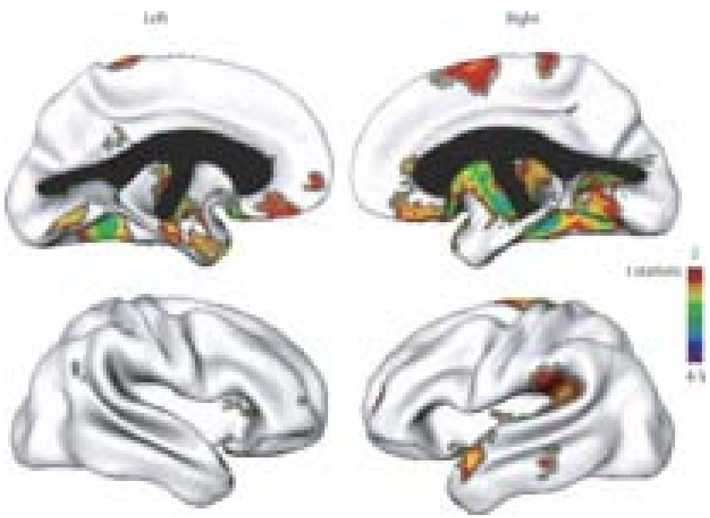
Part 2 - Influences on Brain Development

- Nature / Nurture → Twin studies
- Male / Female
- Specific Genes
- Psychopathology

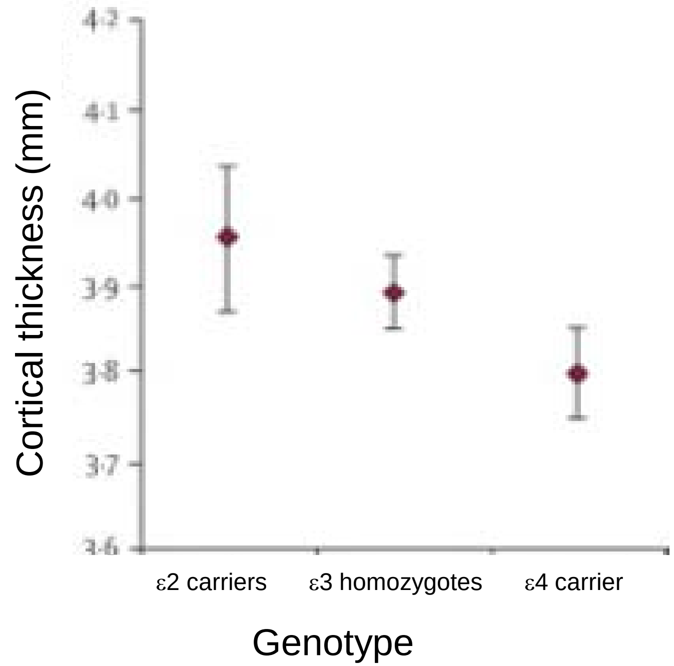
MIKE RITTER


We paid $500,000 for the egg of a supermodel and the sperm of a Nobel laureate...
...She didn't quite turn out like we planned...
2+2= 5

ApoE effects on brain morphometry during pediatric development



T statistical map of thinning in e4 carriers compared to non-carriers



Thickness of the entorhinal cortex by ApoE genotype during childhood

Part 2 - Influences on Brain Development

- Nature / Nurture → Twin studies
- Male / Female
- Specific Genes
- Psychopathology

Why Adolescence?

- Time of dramatic change in brain, body, and behavior
- Time of peak emergence of:
  - Schizophrenia
  - Depression
  - Anxiety
  - Substance Abuse
  - Eating Disorders

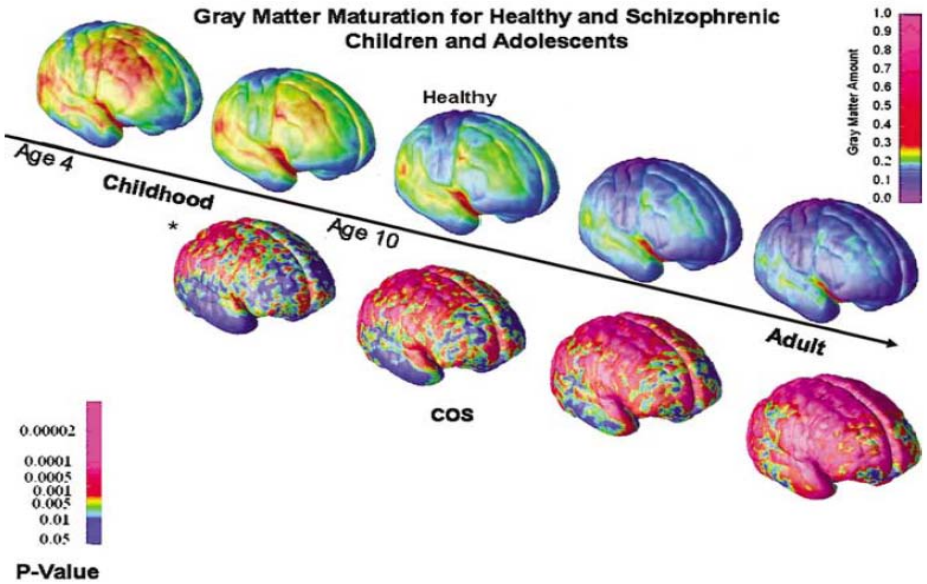
      - Not Autism, ADHD, Alzheimer’s

- Moving parts get broken?

Adolescent Brain Changes

<u>sMRI</u>
WM ↑
GM ∩

<u>EEG</u>
Delta sleep ↓
Cyclic power ↓



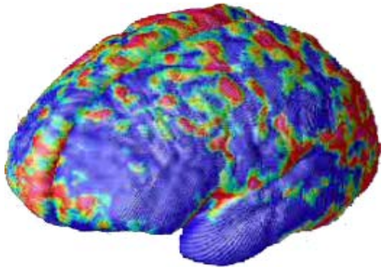
<u>PET</u>
↓ glucose utilization

<u>fMRI</u>
Diffuse → focal
↑"frontalization"
↑ integration

<u>Postmortem</u>
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

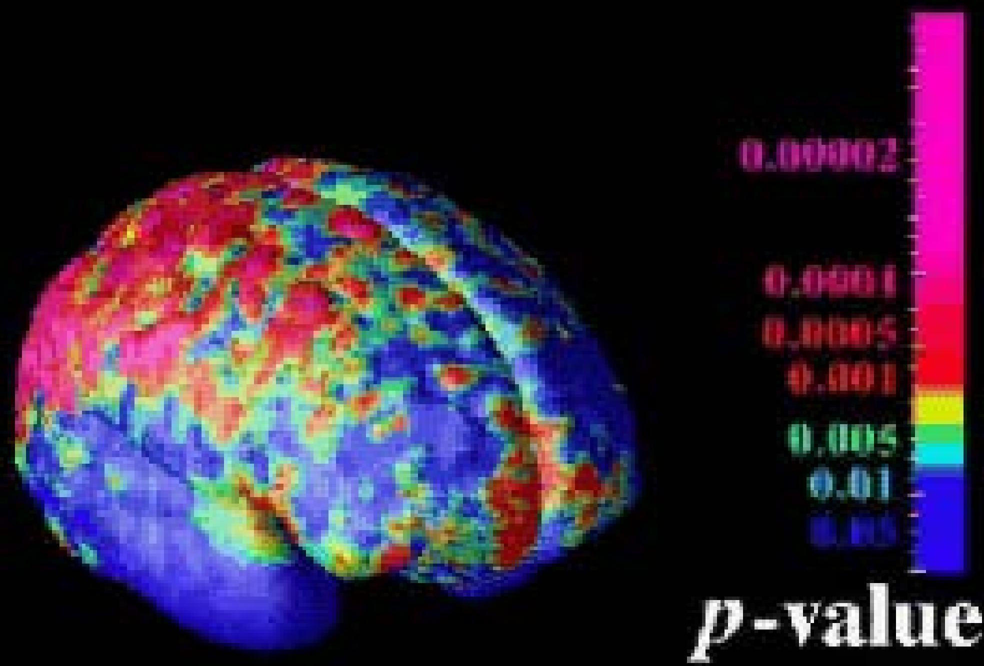
Depression
Hormonally mediated limbic effects preceeding maturation of cognitive-regulatory system

Why Adolescence: Schizophrenia

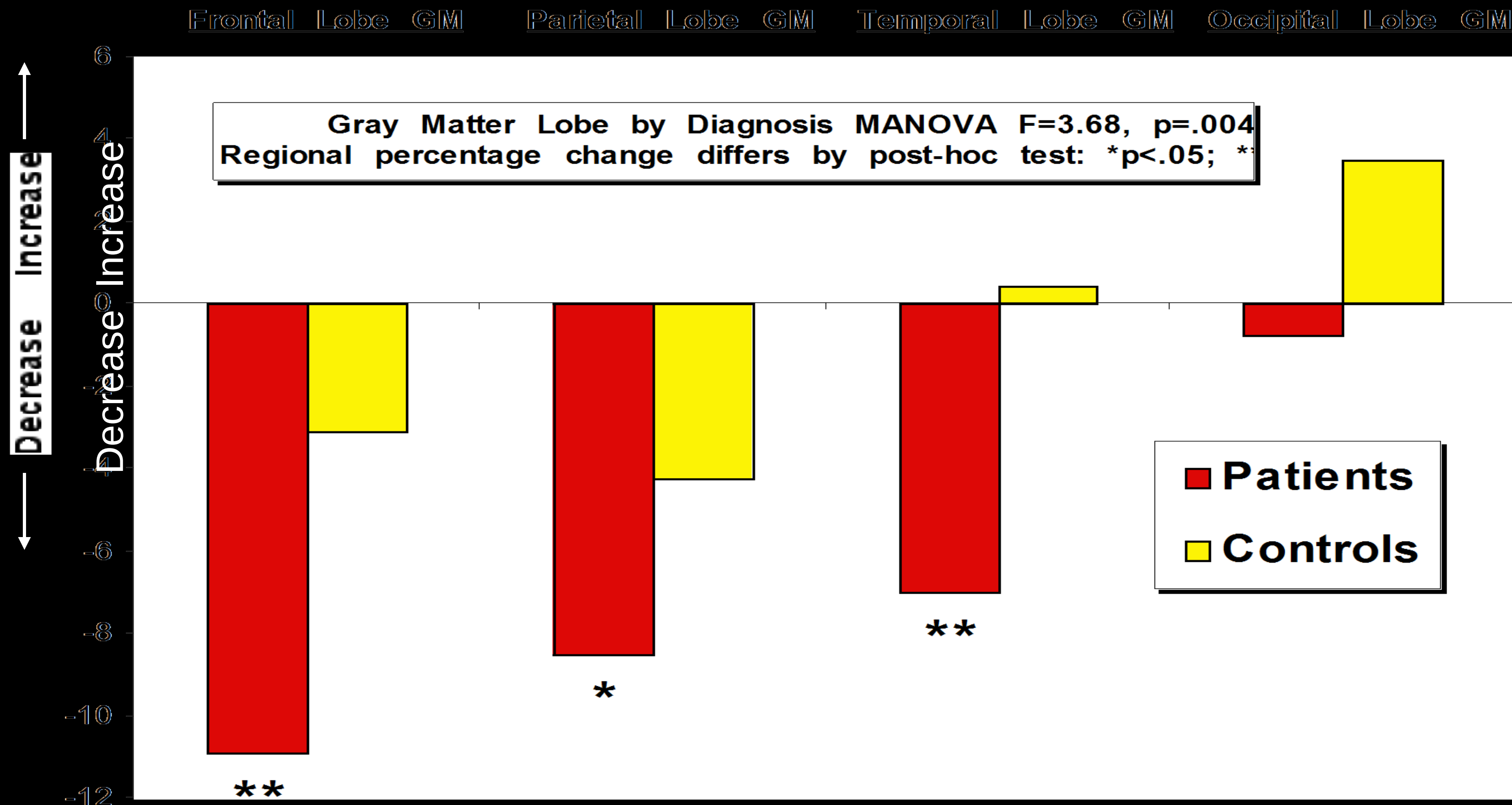
- Is schizophrenia related to an exaggeration of typical regressive changes of adolescence?

- 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)

Gray Matter thickness changes in Childhood Onset Schizophrenia



Percentage Change in Regional Cortical Gray Matter Volumes Between Healthy Volunteers (N=34) and Childhood-Onset Schizophrenics (N=15) Ages 13-18

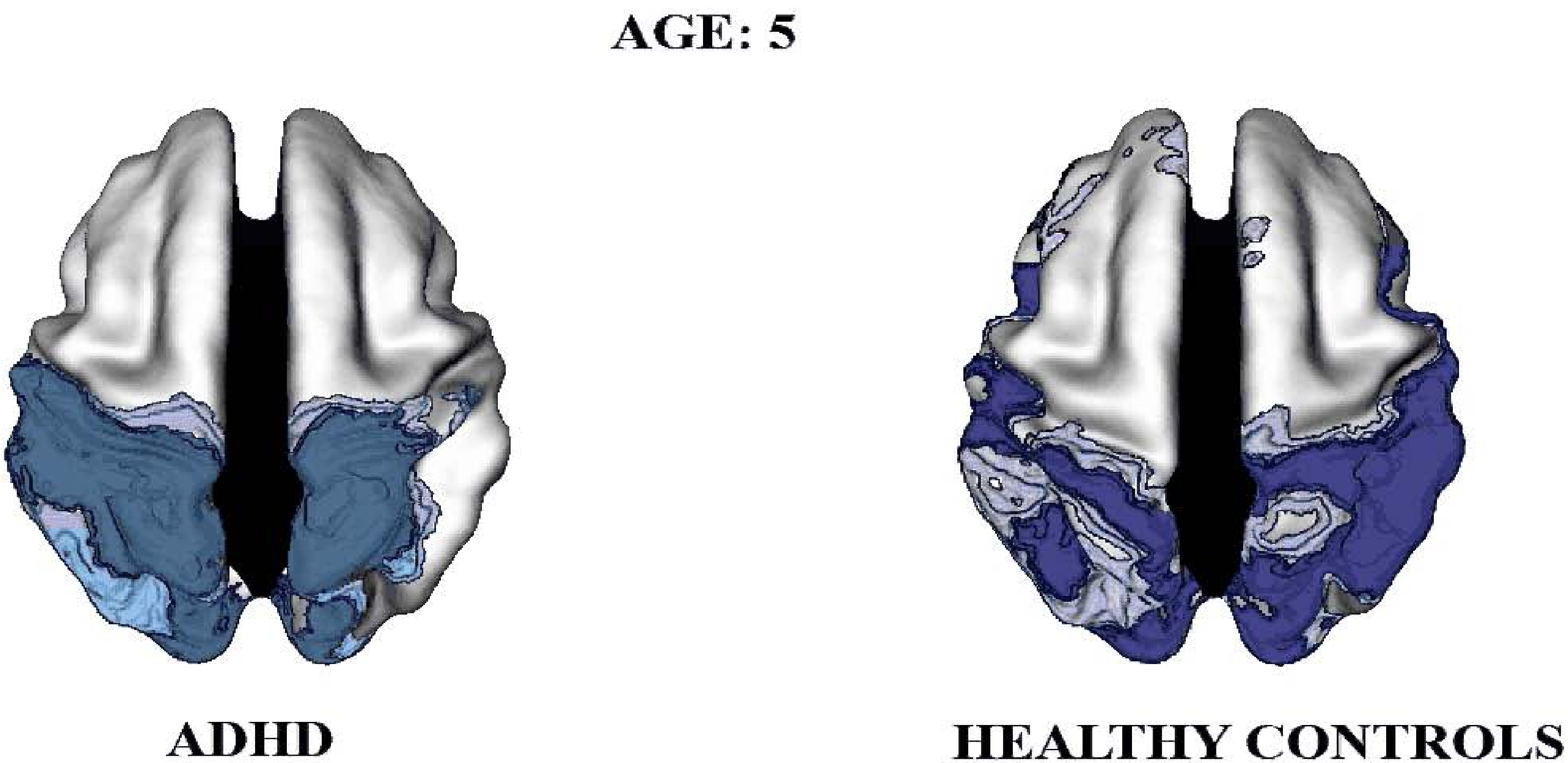


Consideration, not explanation

- Increase in pre and peri natal adverse events
- Subtle cognitive, motor, and behavioral anomalies during childhood years before illness onset

Support for earlier developmental disturbances underlying the abnormal maturational events during adolescence.

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

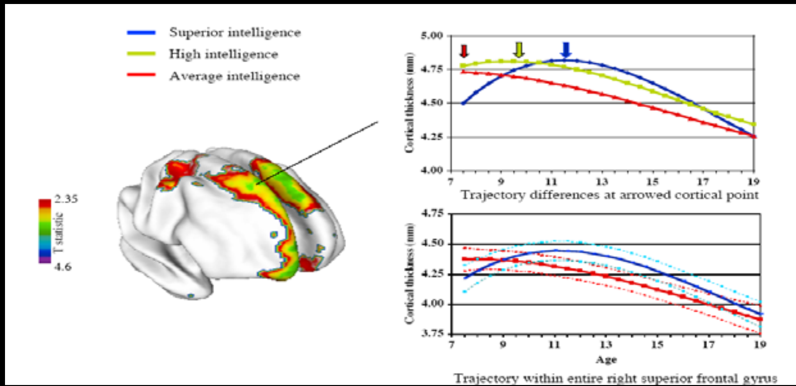


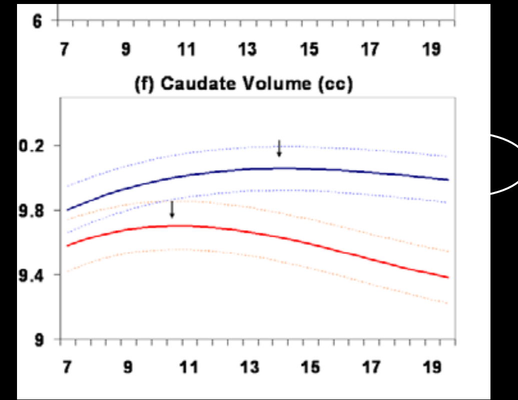
The darker colors indicate regions where a quadratic model was not appropriate and thus a peak age could not be calculated, or that the peak age was estimated to lie outside the age range covered

Shaw et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *PNAS*, *104(49): 19649-19654*

Summary

- The adolescent brain is developing not defective
- 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
- Enormous plasticity confers both vulnerability and opportunity

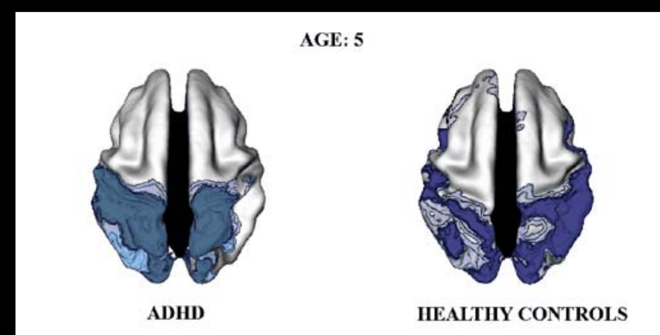




1. Cognitive/Behavioral

2. Male/Female Differences

Journey not just Destination



3. Genetic/Environmental

4. Health/Illness

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They need their parents

They need their parents

just as much as they do.