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?
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
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
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

Cell body (the cell’s life support center)

Dendrites

Axon

Myelin sheath

Terminal branches of axon

Neuronal Impulse

Donald Bliss, MAPB, Medical Illustration
White Matter

Nucleus
Axon
Oligodendro

White Matter

Age in years

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

- 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

Nature, 2000
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)

- 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
Doctor, what's the matter?

Grey, from the looks of it.

BRITISH NEUROSURGERY HUMOR
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

Age in years
Volume in ml
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, Scheibcl, 1998
Images by Diane Murphy, PhD, National Institutes of Health
Overproduction / Selective Elimination

- Postmortem
  - Animal
  - Human
- EEG
- MEG
- PET
Similar Pattern for Synaptic Density

Development Differences in Synaptic Density of Layer 3 Human Frontal Cortex (Huttenlocker 1979)
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?
Questions related to changing cortical thickness

- What are the social/judicial/parenting/personal implications of late DLPFC maturation?
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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
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 help understand intelligence in terms of the genetic childhood experiences that can promote it.

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 than those of average children.
IQ and cortical thickness

IQ > 125
110-125
95-110

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?
Oxy and Deoxy hemoglobin have different magnetic properties

fMRI
Probes cerebral blood flow-oxygen consumption during cortical activation

Rest
more oxyhemoglobin than deoxyhemoglobin

Event

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.
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

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Part 2 - Influences on Brain Development

- Nature / Nurture → Twin studies
- Male / Female
- Specific Genes
- Psychopathology
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• Nature / Nurture → Twin studies
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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?
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<th>MODEL</th>
<th>$A^2$</th>
<th>$C^2$</th>
<th>$E^2$</th>
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<td>0.89</td>
<td>0.00</td>
<td>0.11</td>
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<td></td>
<td>[.67 - .92]</td>
<td>[.00 - .22]</td>
<td>[.08 - .16]</td>
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<td>0.82</td>
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<td>0.18</td>
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<td>[.37 - .83]</td>
<td>[.00 - .38]</td>
<td>[.17 - .32]</td>
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<td>0.00</td>
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<td>[.44 - .86]</td>
<td>[.00 - .35]</td>
<td>[.14 - .29]</td>
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<td>0.00</td>
<td>0.20</td>
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<td>Corpus Callosum</td>
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<td>0.50</td>
<td>0.29</td>
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<td>[.00 - .63]</td>
<td>[.15 - .29]</td>
</tr>
</tbody>
</table>
The Unique Cerebellum!
(among our gross anatomic measures)

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

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 \( \rightarrow \) 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
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\textsuperscript{a,b,1}, Yohan Lee\textsuperscript{a}, Reva Stidd\textsuperscript{a}, Robert Long\textsuperscript{a}, Dede Greenstein\textsuperscript{a}, Liv Clasen\textsuperscript{a}, Anjene Addington\textsuperscript{a}, Nitin Gogtay\textsuperscript{a}, Judith L. Rapoport\textsuperscript{a}, and Jay N. Giedd\textsuperscript{a}

\textsuperscript{a}Child Psychiatry Branch, National Institute of Mental Health, Bethesda, MD 20892; and \textsuperscript{b}Department of Child and Adolescent Psychiatry, Institute of Psychiatry, King’s College London, London SE5 8BA, 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)
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Sex Differences in \textit{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?

Mid-Sagittal Corpus Callosum Area (cm$^2$)

$F = 4.50; \ p = .011$
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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
Summary of Sexual Dimorphism

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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

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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...
ApoE effects on brain morphometry during pediatric development

T statistical map of thinning in ε4 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
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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

**sMRI**
- WM ↑
- GM ∩

**fMRI**
- Diffuse → focal
- ↑“frontalization”
- ↑ integration

**EEG**
- Delta sleep ↓
- Cyclic power ↓

**PET**
- ↓ glucose utilization

**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)
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

Gray Matter Lobe by Diagnosis MANOVA F=3.68, p=.004
Regional percentage change differs by post-hoc test: *p<.05; **
Consideration, not explanation

- Increase in pre and perinatal 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

3. Genetic/Environmental

4. Health/Illness

Journey not just Destination
Summary

• The adolescent brain is developing not defective
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• Enormous plasticity confers both vulnerability and opportunity
They need their parents
They need their parents just as much as they do.