The Teen Brain: Insights from Neuroimaging

Jay N. Giedd, MD
Child Psychiatry, NIMH
Johns Hopkins School of Public Health (Dept of Family and Reproductive Medicine)
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?
Brain volume increase driven by change in environment
Rapid dental development in a Middle Paleolithic Belgian Neanderthal

Tanya M. Smith*, Michel Toussaint*, Donald J. Reid†, Anthony J. Olejniczak*, and Jean-Jacques Hublin*

*Department of Human Evolution, Max Planck Institute for Evolutionary Anthropology, Deutscher Platz 6, D-04103 Leipzig, Germany; †Direction de l’Archéologie, Ministère de la Région Wallonne, 1 rue des Brigades d’Irlande, 5100 Namur, Belgium and ‡Department of Oral Biology, School of Dental Sciences, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4BW, United Kingdom

The evolution of life history (pace of growth and reproduction) was crucial to ancient hominin adaptations. The study of dental development and the timing of molar eruption is the best indicator to predict development and life history parameters across primates.

letters to nature

Surprisingly rapid growth in Neandertals

Fernando V. Ramirez Rozzi¹ & José Maria Bermudez de Castro²

¹UPR 2147, Dynamique de l’Evolution Humaine, CNRS, 44, Rue de l’Amiral Mouchet, 75014 Paris, France
²Museo Nacional de Ciencias Naturales (CSIC), C/ José Gutierrez Abascal 2, 28006 Madrid, Spain

Life-history traits correlate closely with dental growth¹, so differences in dental growth within Homo can enable us to determine how somatic development has evolved and to identify developmental shifts that warrant species-level distinctions²-⁴.
Digital Revolution

- Remarkable advances in technologies that enable the distribution and utilization of information encoded as sequences of 1s and 0s have dramatically changed our way of life.
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.
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
GOAL:
To explore the **path**, **mechanisms**, and **influences** on brain development in health and illness through longitudinal studies combining brain imaging, genetics, and **psychological/behavioral** assessments.
NIMH Child Psychiatry Data Base

• Longitudinal Assessment (~ 2 year intervals)
  – Imaging (sMRI, fMRI, DTI, MTI)
  – Genetics (blood, saliva)
  – Neuropsychological / Clinical

• 9000+ Scans from 3500+ Subjects
  – ~ ¼ Typically-Developing Singletons
  – ~ ¼ Typically-Developing Twins
  – 25 Clinical Populations
    • ADHD, Autism, Childhood Onset Schizophrenia, Sex Chromosome Variations (XXY, XXX, XXY, XXYY, XXXXY), …
3 Key Points of Brain Maturation

• The brain matures by becoming more specialized (gray matter) and more “connected” (white matter)

• A changing prefrontal/limbic balance affects reward circuitry, hot vs cold cognition, temporal discounting, and decision making

• Enormous plasticity confers both vulnerability and opportunity
How the Brain Looks to MRI
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*
How the Brain Looks to MRI

3 km of axons

90,000 neurons
400 m of dendrites
4,500,000 synapses
Mapping Trajectories of Anatomic Brain Development

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

Frontal Lobe Gray Matter

Volume in ml

Age in years
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
- “social” brain circuitry
- “Time Travel”
- Multi tasking bottle neck?
Prefrontal Cortex

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HG Wells (1866-1946) Time Machine (1895)

• Frontal lobe allows integration of past, present, future
  – “counterfactuals”
  – ability to play scenarios out in our minds instead of the physical world
Prefrontal Cortex

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  – Long term strategy
  – Planning
  – Organization
  – Impulse control

• Integrates input from rest of the brain

• “social” brain circuitry

• “Time Travel”

• Multi tasking bottle neck?
Limbic circuitry – ignites at puberty

Scientific American, September 1998
Braking and Accelerating of the Adolescent Brain

B. J. Casey, Rebecca M. Jones, and Leah H. Somerville
How does the brain keep score? Dopamine
addiction

movement

motivation

Dopamine

Reward & well-being
Part 2 - Influences on Brain Development

- Nature / Nurture → Twin studies
- Male / Female
- Specific Genes
- Psychopathology
- Environment / Stress / Activities
Rewiring the Brain After Trauma

- Changes in the brain caused by trauma are not necessarily permanent.
- The brain is constantly forming new neural pathways, removing old ones and altering the strength of existing connections.

NEUROPLASTICITY: The ability of the brain to alter its structure in response to experience.
They need their parents
They need their parents just as much as they do.
The Infant From Hell
3 Key Points of Brain Maturation

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END HERE
Addiction = hijacking of this reward system
Nothing that is highly addicting has ever been found that does not jack up dopamine in the nucleus accumbens. Nothing.
Mapping Trajectories of Anatomic Brain Development

- Gray Matter
- White Matter
Doctor, what's the matter?

Grey, from the looks of it.

BRITISH NEUROSURGERY HUMOR
Gray Matter vs White Matter

**Gray Matter**
- Inverted “U”
- Regionally specific

**White Matter**
- Linear increase
- Not different by region
White Matter

Nucleus
Axon
Oligodendroglia

95% Confidence Intervals

Male (152 scans from 90 subjects)
Female (91 scans from 55 subjects)

Volume in cubic cm

Age in years
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

• 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 (2010)
Maturational Coupling Echoes White Matter and FMRI Connectivity

Gray Matter Change

White Matter

rsFMRI

Raznahan, 2011, Neuron

Honey, 2009, PNAS
anatomical coupling correlates with vocabulary scores in linguistically relevant regions

Lee et al. 2013
Time?

• Twins – skip to 77 (3 minutes)

• Male/Female – skip to 85 (5 minutes)

• Specific Genes – skip to 111 (2 minutes)

• Psychopathology – skip to 114 (3 minutes)
Summary

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- Graph theoretical approaches provide a new target for diagnostic and behavioral correlates
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1. Cognitive/Behavioral

2. Male/Female Differences

Journey not just Destination

3. Genetic/Environmental

4. Health/Illness
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MENTAL ILLNESS

A Public Health Crisis...

With Early Roots ...
Age at first diagnosis for Adults with Mental Health Problems

Burden of diseases worldwide: Disability adjusted life years (DALYs), 2001

- Nutritional deficiencies 2%
- Perinatal conditions 7%
- Maternal conditions 2%
- Respiratory infections 6%
- Malaria 3%
- Childhood diseases 3%
- Diarrheal diseases 4%
- HIV/AIDS 6%
- Tuberculosis 2%
- Other CD causes 6%
- Injuries 12%
- Congenital abnormalities 2%
- Musculoskeletal diseases 2%
- Other NCDs 1%
- Malignant neoplasms 5%
- Diabetes 1%
- Sense organ disorders 3%
- Cardiovascular diseases 10%
- Respiratory diseases 4%
- Digestive diseases 3%
- Diseases of the genitourinary system 1%

Source: WHR, 2002

Causes of death and disability, by 'Disability Adjusted Life Years' (DALY)

Kim-Cohen, 2003
Why do many psychiatric disorders emerge during adolescence?

Tomáš Paus, Matcheri Keshavan and Jay N. Giedd

Abstract | The peak age of onset for many psychiatric disorders is adolescence, a time of remarkable physical and behavioural changes. The processes in the brain

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?
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Part 2 - Influences on Brain Development

- Nature / Nurture → Twin studies
- Male / Female
- Specific Genes
- Psychopathology
- Environment / Stress / Activities
Twins

- 130 Monozygotic ("identical") pairs
- 105 Dizygotic ("fraternal") pairs

- Structural Equation Modeling
  - A Additive Genetic Factors
  - C Common Environment
  - E Error/ Unique Environment
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
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?
THE LASTING ECHO OF EARLY ENVIRONMENTS

SUBTLE DIFFERENCES IN BIRTH WEIGHT AMONGST HEALTHY CHILDREN

LASTING DIFFERENCES IN BRAIN DEVELOPMENT INTO THE THIRD DECADE IF LIFE
Part 2 - Influences on Brain Development

- Nature / Nurture → Twin studies
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- Psychopathology
- Environment / Stress / Activities
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, 2009

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
Postmortem Differences
MEN ARE FROM MARS, WOMEN ARE FROM VENUS

JOHN GRAY

THE DEFINITIVE GUIDE TO RELATIONSHIPS
Men are from North Dakota, women are from South Dakota
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Total Cerebral Volume by Age for 224 Females (375 scans) and 287 Males (532 scans)
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
Amygdala and Hippocampus Volume vs Age for Healthy Children and Adolescents (N=118)

Males (N=71)

Females (N=47)

Amygdala

Hippocampus

(Fiedel et al., 1998)
Is the Corpus Callosum Sexually Dimorphic?
Puberty vs Age Effects

The diagrams illustrate the changes in volume (mm³) of various brain regions (Amygdala, Hippocampus, N. accumbens, Caudate, Putamen, Globus pallidus) between males and females from age 7 to 19 years. The graphs represent the % difference from volume at Tanner stage 5 for both males and females.

- **Females**: The graphs show a general trend of decreasing volume with age for all regions, with some peaks at certain stages.
- **Males**: The trend is similar, but there are noticeable differences in the rates of change and the specific stages at which peak volumes occur.

The graphs are color-coded by Tanner stage, with different colors indicating distinct stages of pubertal development.
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Variance of cortical thickness is greater in males
Male/Female Differences
Greatest at Extremes

• Example – height
  – @1.78 m (5’10”) – 30:1 male
  – @1.83 m (6’0”) – 2000:1 male
Levene’s test for difference of variance between males and females at each point on vertex (white is zero)

Philip Shaw (2008)
Global Sex Differences in Test Score Variability
Stephen Machin and Tuomas Pekkarinen (Science, 2008)

<table>
<thead>
<tr>
<th>Gender Gaps Vary But Differences in Variability Are a Robust Phenomenon</th>
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</thead>
<tbody>
<tr>
<td>Reading</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Mean M-F gap</td>
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<tr>
<td>M-F gap at 5th quantile</td>
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<tr>
<td>M-F gap at 95th quantile</td>
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<tr>
<td>M-F Variance Ratio</td>
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<td>M-F Ratio in bottom 5%</td>
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<td>M-F Ratio in top 5%</td>
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<tr>
<th>Mathematics</th>
<th>Global</th>
<th>OECD</th>
<th>Non-OECD</th>
<th>United States</th>
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<tr>
<td>Mean M-F gap</td>
<td>0.10''</td>
<td>0.10''</td>
<td>0.11''</td>
<td>0.07'</td>
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<tr>
<td>M-F gap at 5th quantile</td>
<td>0.03''</td>
<td>0.02</td>
<td>0.06''</td>
<td>-0.11''</td>
</tr>
<tr>
<td>M-F gap at 95th quantile</td>
<td>0.20''</td>
<td>0.22''</td>
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</tr>
<tr>
<td>M-F Variance Ratio</td>
<td>1.13''</td>
<td>1.13''</td>
<td>1.16''</td>
<td>1.19''</td>
</tr>
<tr>
<td>M-F Ratio in bottom 5%</td>
<td>0.94''</td>
<td>0.98</td>
<td>0.86''</td>
<td>1.21''</td>
</tr>
<tr>
<td>M-F Ratio in top 5%</td>
<td>1.70''</td>
<td>1.69''</td>
<td>1.70''</td>
<td>1.72''</td>
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WZ = Female; Variability pattern reversed
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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
Y Effects: Social language

-110 youth with X/Y aneuploidies
-52 typical youth

Parent completed:
-Children’s Communication Checklist – II
-Evaluates social & non-social language deficits

Lee (2012). JCPP
Y Effects: Social language
X Effects: Nonsocial language

↑ X dosage,
↑ Nonsocial language imp.

Non-social language imp.
Social language deficits
Non-social language imp.
GRAY MATTER DEFICITS WITH GREATER X-CHROMOSOME DOSE

Convergence on Language Cortices

XXX < XX

XXY < XY

Raznahan, in preparation
Part 2 - Influences on Brain Development

- Nature / Nurture → Twin studies
- Male / Female
- Specific Genes
- Psychopathology
- Environment / Stress / Activities
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 e4 carriers compared to non-carriers

Thickness of the entorhinal cortex by ApoE genotype during childhood

Philip Shaw, 2008
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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: $^*p<.05; ^**p<.01$.
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”

Shaw et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *PNAS, 104*(49): 19649-19654
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END HERE
How many neurons in the cerebrum?

Herculano-Houzel & Lent, 2005
Isotropic fractionator

It is possible to count absolute cell numbers in the brain, by use of the isotropic fractionator (Herculano-Houzel & Lent, 2005).
(A) A sector of the human brain, with its high anisotropy. Cell counts within the three red circles give largely different values.
(B) If this same sector is rendered isotropic, cell counts within the same circles give very similar values.
(C) The brain can be rendered isotropic by fractionation in potters, to arrive at a nuclear suspension, aliquots of which can be counted under the microscope in hemocytometers.
(D and E) The same field, where some of the 4¢,6-diamidino-2-phenylindole (DAPI)-labeled nuclei do not appear to be labeled by NeuN (yellow arrows) – these are non-neuronal nuclei.
How many neurons in the brain?

- 86B in whole
- 16B in cerebrum
- 69B in cerebellum
- Only .69B subcortical
Pediatric Neuroimaging
Historical Progression

1. Gross Pathology
2. Group Average Size Difference
3. Developmental Trajectories
4. Neural Network Characterization
Pediatric Neuroimaging
Historical Progression

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1. More “connected” (white matter)

2. More “specialized” (gray matter)

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White Matter vs Gray Matter

White Matter
- Linear increase
- Not different by region

Gray Matter
- Inverted “U”
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Gray Matter Development in Healthy Children & Adolescents
(1412 Scans from 540 Subjects)

Frontal Lobe Gray Matter

Age in years

Volume in ml
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
Natures One-Two Punch for Emergence of Complexity

1. Overproduction

1. Selective Elimination