Vulnerabilities and Opportunities in Adolescent Brain Development: Implications to Adolescent Health:

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Adolescence: Vulnerabilities

- There is a peak in sensation seeking
  - Sensation seeking can lead to risk-taking undermining survival
    - Despite peak physical health there is a twofold increase in mortality (Dahl 2004)
    - Substance abuse, unprotected sex, extreme sports, suicide
Adolescence: Vulnerabilities

- Major psychiatric disorders emerge in adolescence
  - Schizophrenia, Depression, Bipolar Disorder, Anorexia, Suicide, substance abuse, criminal behavior
Adolescence: Opportunities

Neurobiology and Environment Shape Development

Neurobiology

- Gray and White Matter
- Synaptic Pruning
- Myelination

Environment

- Neurotransmitters
- Hormones

Children
Adolescents
Adults
Adolescence

- Balance between motivation and executive planning/decision-making
Prefrontal Cortex

- The CEO/conductor of the brain
- Executive Function
  - Cognitive Control
- Deliberative thinking
- Logical reasoning
- Weighing costs and benefits
The Limbic System

- Experience of reward and punishment
- Processing emotions
- Associating emotions with memories
- Processing social information
Corticosubcortical Circuitry

• Connections Between PFC and Subcortical Areas
  – Cognitive control of emotions
    • Emotion regulation
    • Self-control
  – Motivation influences cognition
    • Reward driven behavior
Cortical Thinning

Gogtay et al., 2004
Brain Structure: PFC pruning

Huttenlocher et al., 1990

Petanjek et al., 2011
Dopamine (DA) is a neurotransmitter that supports motivation (reward and learning).

- The amount of DA available in the brain peaks in adolescence.
- The regions that contain DA are still maturing in adolescence.
Basal Ganglia Brain Structure Maturation

Striatal volume peaks after cortical volume has already begun to decline

Raznahan et al., 2014

Sowell et al., 1999
Dual Systems

(Somerville & Casey 2010)
Dual Systems

(Somerville & Casey 2010)

Driven Dual Systems

(Luna and Wright, in press)
Executive System Maturation
Cognitive Control

- **Voluntary Response Suppression:**
  - The ability to suppress responding to a compelling stimuli that leads to a suboptimal response, in favor of a response guided by a goal directed plan

![Image of a hand holding an apple and a cup](image-url)

![Graph showing the mean proportion of correct responses for children, adolescents, and adults](graph-url)

*Velanova 2008*
Oculomotor Studies of Cognition
Oculomotor Studies of Cognition

- Well-delineated Neural System in Monkeys
  - Anatomy, physiology, neurochemistry
Oculomotor Studies of Cognition

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• Simple Cognitive Tasks
  – No confound of instruction
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- Stimulus/response in same domain. No spinal cord.
Oculomotor Studies of Cognition

- Well-delineated Neural System in Monkeys
  - Anatomy, physiology, neurochemistry
- Simple Cognitive Tasks
  - No confound of instruction
- Stimulus/response in same domain. No spinal cord.
- Sensitive to adolescent development
Antisaccade Task

(Hallet, 1978)


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Luna B. Developmental changes in cognitive control through adolescence. Adv Child Dev Behav. 2009; 37:233-78. PMID: PMC2782527


Geier CF, Luna B. Developmental effects of incentives on response inhibition. Child Dev. 2012; 83(4):1262-74. PMID: PMC3399954


Longitudinal fMRI Study

- N=139 - 8-28yo (356, 1-6 yearly visits)

- Apriori ROIs (Neurosynth- Yarkoni et al., 2011)
  - Motor Control
    - FEF, SEF, PreSMA, IPS, Putamen
  - Executive System
    - dIPFC, vIPFC
  - Error Monitoring
    - -dACC

- Hierarchical Linear Modeling (HLM)
  - Test model shapes
  - Estimates Individual trajectories
  - Test for intercept and slope variability

\[
A_{\text{Serr}}_{it} = \pi_{0i} + \pi_{1i}(\text{InvAgeC})_{ti} + e_{it}
\]

Level 2:
\[
\pi_{0i} = \beta_{00} + r_{0i} \\
\pi_{1i} = \beta_{10} + r_{1i}
\]

(Neurosynth; Yarkoni..Wager..., 2011)

Sarah Ordaz, PhD

Accelerated Cohort
Longitudinal Design

Gamma function
of % signal change
Behavioral data

- AS performance improves into the late teen years
- Variability constant across development
• Function in motor control regions did not change with age.
• Variability was present in childhood but decreased with age.
  • *Motor control may serve as a core system supporting oculomotor control*
Executive control regions

- DLPFC function decreased from childhood to adolescence when it reached adult levels of minimal engagement.
- Variability was present throughout development with rank order stability.
- Performance was not associated with level of activity.
- DLPFC may provide scaffolding in childhood.
Activity in dACC during corrected inhibitory errors increased through adolescence into the twenties.
There was no significant variability in trajectories
  • ( Intercept p = 0.087 Slope p = 0.150)
Increased dACC activity predicted better performance
• dACC plays a primary role in support the development of cognitive control
Conclusions: Cognitive Control

- PFC recruitment decreases from childhood to adolescence where it reaches adult levels.

- Integration of dACC recruitment supporting error detection/performance monitoring is still immature in adolescence.
Motivation
• Teens show greater VS reactivity to rewards compared to adults or children
• VS reactivity is associated with increased risk taking

Galvan, 2006
Stages of Reward Processing

- **Reward Assessment**
  - Cue

- **Reward Anticipation**
  - Response Preparation

- **Reward Feedback**
  - Response

Chick Geier PhD
Results: Behavior

Correct Response Rate

**

Age Group

ADOLESCENTS

ADULTS

13-30yo.

Neutral

Rewards
Geier et al., 2009
When equating for reward value, there is increased activity of ventral striatum from 10-22 years of age.
Conclusions: Ventrall Striatum

• Adolescents have a delayed but hyperactive reward reactivity that becomes over active immediately previous to responding engaging response regions.

• Increased reward reactivity previous to response may contribute to impulsivity
Adolescents by themselves performed the same as adults. Adolescents with peers observing, had more crashes and activated the reward region to a greater degree.
Assessing Striatal Neurophysiology by Measuring Iron (Ferritin) in the Brain

• Iron is stored in oligodendrocytes and neurons as ferritin
• Basal ganglia and midbrain have the greatest concentration of iron
• Iron supports:
  – Myelin production, D2 receptor density, DA transporters, DA synthesis
• MRI time-averaged T2* (taT2*) weighted images are sensitive to tissue iron
• Vo et al., 2011 - Learning
Methods

• N=142:10-25 yo
• Reward antisaccade task, and 5min rest
• Multivariate linear support vector machine regression (SVR) (Vo et al., 2011; Dosenbach et al., 2010).
  – Regression based modeling of the multivariate relationship between voxel-wise taT2* values and age
• Developmental Pattern Characterization
  – Linear, quadratic, and inverse regression models

Larsen et al., 2014
Support vector regression (SVR) multivariate pattern analysis (MVPA) of striatal taT2* generated age predictions that accounted for over 60% of the sample variance in VS and its subregions.

Larsen & Luna under review
Iron increased in ventral (limbic) areas with age and showed a dip during adolescence in dorsal (executive) regions.
Conclusions: *Functional Specificity*

- Behavior in adolescence is undermined by limitations in error processing/performance monitoring and is affected by reward incentives.

- Adolescents have the ability to engage PFC systems for decision making but these may be driven by the pursuit of rewards.
Conclusions

• A hyperactive motivational system paired with access to adult level prefrontal systems, may underlie adolescents predisposition to plan actions for the service of immediate rewards – Sensation Seeking
Dual Systems

(Somerville & Casey 2010)

Driven Dual Systems

(Luna and Wright, in press)
Connectivity

• The interconnectivity of brain regions may also change with development through white matter changes and Hebbian processes playing a crucial role in age-related changes in behavior.
Functional Connectivity
Effective Functional Connectivity: Granger Causality

- **Granger Causality**
  - How region X could influence the activity in region Y based on the ability to predict Y from the past history of X.
  - Only Unidirectional measures


- Antisaccade and Prosaccade Blocks

- **Functional Connectivity** (confirmatory)

- 26 Children 8-12 years
- 25 Adolescents 13-17 years
- 26 Adults 18-27 years

(Hwang et al., 2010)
Top-down connectivity continues to improve through adolescence

- **Childhood**
  - *Parietal* connectivity predominates

- **Adolescence**
  - PFC guided connectivity emerges

- **Adulthood**
  - PFC guided connectivity strengthens

(Hwang et al., 2010)
Resting State Connectivity

rs-fcMRI signal

• Correlation of spontaneous fluctuations

Vogel et al., 2010
Resting State Connectivity: Functional Network Hubs

US Air travel

CORTICAL HUBS

LEFT

RIGHT

Buckner et al., 2009

N=99; 10-20yo

5min rest

Hubs are brain regions that interconnect distinct functionally specialized brain systems
Resting State Functional Connectivity: Hub Architecture

Children 8-12y

Adolescents 13-17y

Adults 18-27y

N=87; 5min eyes closed rest

Established by childhood (graph analyses):
• Hub number, location, degree density (number of connections), average strength, and betweenness centrality, the relative significance of a hub in supporting a high degree of connection paths
• Efficient and stable small-world network (path length and clustering coefficient)

Hwang et al., 2012

Threshold for Density
• Paths between hubs and other brain regions were in place by childhood.
• Strength of *frontal* hubs to other regions increased in childhood and decreased in adolescence.
• Cerebellar hubs to other regions increased into adulthood.

*Hwang et al., 2012*
Conclusions: Hub Architecture

• Cortical hub architecture is conserved over development, providing a stable communication backbone among brain regions to support specialization.

• With development fine-tuning of connections between cortical hubs and associated brain regions occurs, facilitating mature information processing.
Network Segregation and Integration
Methods

- 192 subjects (10-26 year olds)
  - 41 = 10-12 yo
  - 41 = 13-16 yo
  - 54 = 16-20 yo
  - 57 = 20-26 yo
- 5 min rest (200 TRs)
- Standard preprocessing
  - Including controlling for head movement
- 264 nodes (Power et al., 2011) ROIs = 10mm diameter spheres. Resulting in 5 networks
- Age as continuous and age groups
Network Development

- Network organization is stable by childhood
- Integration between networks supporting cognition but also visual processing continue through adolescence
Conclusions

• Network architecture is established first
• Network interaction provides specialization during adolescence

• The adolescent period is characterized by the specialization of internetwork communication of already established segregated networks.
Structural Connectivity
White Matter Growth Trajectories: *Longitudinal DTI (FA)*

- **128 8-29 yo (61 males) scanned 1-5 times for a total of 322 scans.**
- **Mixed-effects regression**
  - Visits – random effect

- (A) Overall white matter
- (B) Core Tracts (JHU-DTI81 atlas)
  - Callosal; cerebellar, projection, association, and limbic,
- Regional Termination Zones (RTZ’s) (Harvard-Oxford atlases)
  - (C) Cortical (frontal, sensorimotor, parietal, occipital, and temporal)
  - (D) Subcortical (cerebellum, BG, thalamus, and medial temporal lobe)
• Greatest overall growth occurs between 10-16y.

• Hierarchical maturation
  • Maturing into adolescence
    • RTZ: frontal, temp, parietal and BG
  • Last to Mature
    • Cingulum (Cing/limbic),
    • Uncinate Fasciculus (Hipp/Amyg/Temp/OFC)

• Males show greater and more protracted WM growth than females
Figure 2

Luna et al., in press ARN
Adolescence

- Adolescents have access to executive systems supporting decision making.
- Motivational systems are still immature influencing decision making.
Implications for Adolescent Health

• Vulnerabilities
  – Risk Taking
  – Mental Health

• Opportunities
  – Still maturing malleable system
  – Contextualize in terms of immediate rewards
  – Provide the “gist” of care
Adolescence is *Not* a Disease

- Adolescence is a crucial and necessary period of plasticity when brain circuitry and behavior is beginning to be established.

- Risk-taking behavior and novelty seeking may provide a mechanism for increasing exposure to the environment necessary for successful sculpting of the system and for acquiring independence skills to become adults.
What have I learned as a parent.

Mom its not our fault, you know we are not fully myelinated!
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