Youth Suicide Prevention Community of Practice – Seventh Meeting

The Connections between Adolescent Brain Development and Suicide Prevention

Wednesday, August 1, 2012
10:30 to 11:30 AM EDT

Featured Speakers:

Dr. Cecile Ladouceur and Dr. Lisa Pan

Moderator:

Erica Streit-Kaplan

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Meeting Orientation Slide

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Introductions

- Minnesota
- Missouri
- Nebraska
- North Carolina
- North Dakota
- Oklahoma
- Puerto Rico
- Tennessee
- Virginia
- West Virginia
- Other partners

Adolescent Brain Development: Implications for Mood Disorders

Cecile D. Ladouceur, Ph.D.

Department of Psychiatry and Psychology
University of Pittsburgh
Pittsburgh, PA

August 1, 2012

Objectives

- Overview of developmental changes in adolescence: maturational changes in brain structure and function.
- Discuss evidence suggesting that adolescence:
  - is a sensitive developmental period for the integration of regulatory systems (i.e., goals and emotions).
  - creates unique vulnerabilities but also opportunities for intervention.
- Discuss the importance of integrating research in developmental neuroscience and early intervention.

What is Adolescence?

- *That awkward period between sexual maturation and the attainment of adult roles and responsibilities.*
- Transition from "child" status (requires adult monitoring) to "adult" status (*self-responsibility for behavior).*

Interposed with physical and brain changes of puberty

Health Paradox of Adolescence

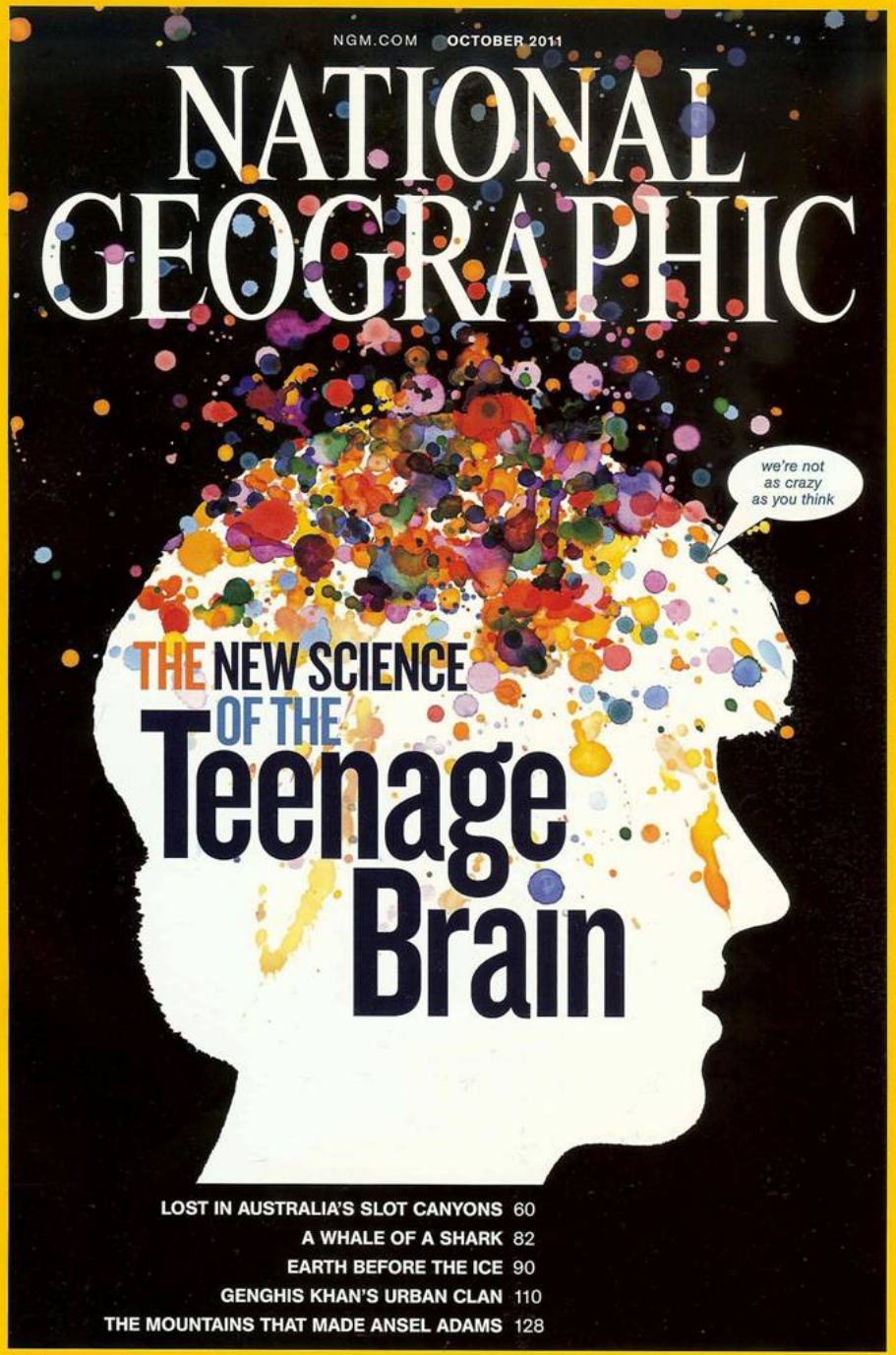
- Measures of most abilities suggest that adolescence is the healthiest and most resilient period of the lifespan.
- From childhood to adolescence:
  - Improvements in strength, speed, reaction time, reasoning abilities, immune function …
  - Increased resistance to cold, heat, hunger, dehydration, and most types of injury …
- Yet: overall morbidity and mortality rates increase 200-300% from childhood to late adolescence.

Sources of Morbidity & Mortality in Adolescence

- Primary causes of death/disability are related to problems with *control of behavior and emotion*.
- High rates of risk-taking, sensation-seeking, and erratic (emotionally-influenced) decisions….behaviors with long-term health consequences.
- Increasing rates of accidents, suicide, homicide, depression, alcohol & substance use, violence, reckless behaviors, eating disorders, health problems related to risky sexual behaviors…

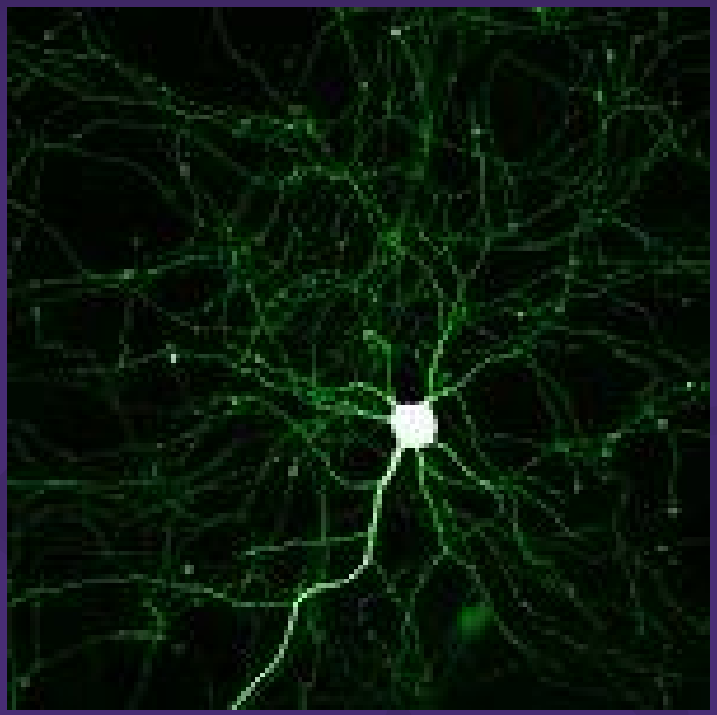
Adolescence: Component Processes

- Rapid Physical Growth
- Sexual Maturation
- Secondary Sexual Characteristics
- Motivational and Emotional Changes
- Cognitive Development
- Maturation of Judgment, Self-Regulation Skills
- Brain Changes Linked to *each Component*

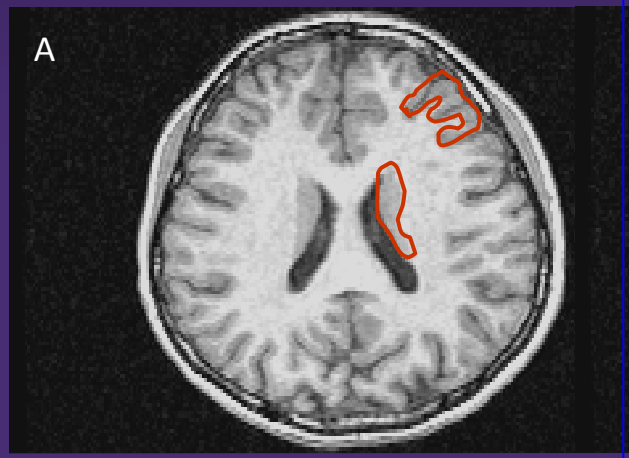

NGM.COM OCTOBER 2011
NATIONAL GEOGRAPHIC
we're not as crazy as you think
THE NEW SCIENCE OF THE Teenage Brain
LOST IN AUSTRALIA'S SLOT CANYONS 60
A WHALE OF A SHARK 82
EARTH BEFORE THE ICE 90
GENGHIS KHAN'S URBAN CLAN 110
THE MOUNTAINS THAT MADE ANSEL ADAMS 128

The Brain

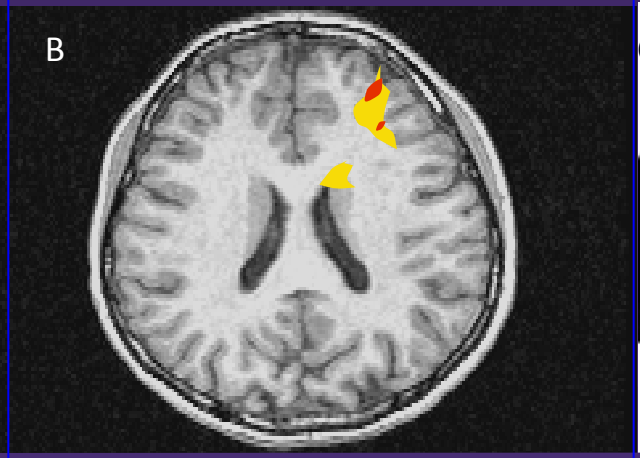
- Main components
  - Gray matter
    - Neuronal cell bodies
    - Neurophil
      - Dendrites
      - Unmyelinated axons
    - Glial cells
    - Capillaries
  - White matter
    - Myelinated axon tracks
  - Cerebrospinal fluid



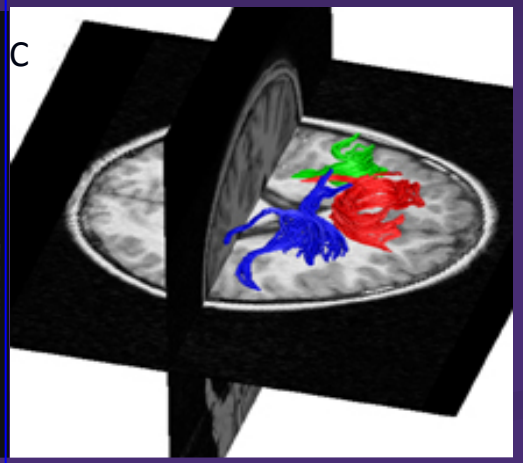
Measuring Change in the Developing Human Brain



Structural MRI to track changes in size and shape of neuroanatomical structures with development



Functional MRI (fMRI) to track changes in brain and behavior with development

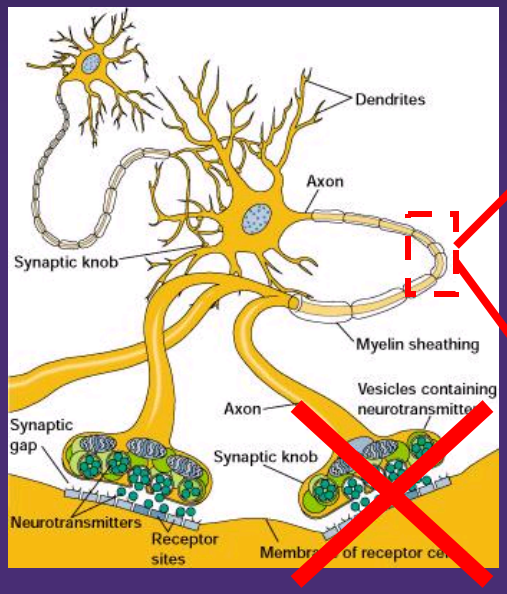


Diffusion Tensor Imaging (DTI) to track strengthening of brain connections with development

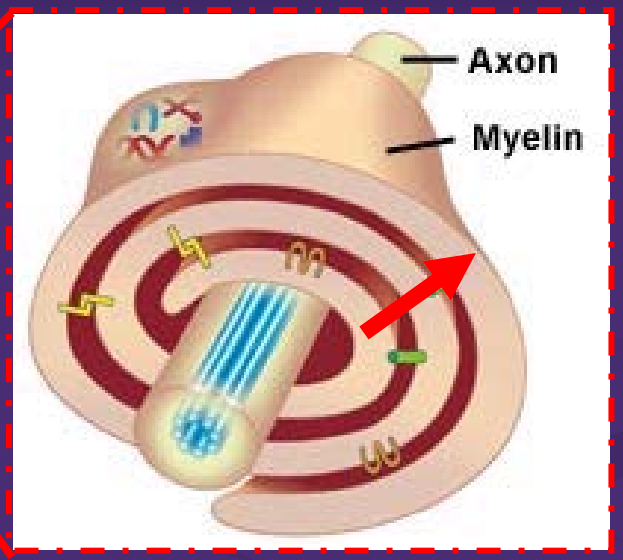
Casey et al 2005 Current Opinions in Neurobiology

Brain Maturation in Adolescence

Synaptic Pruning



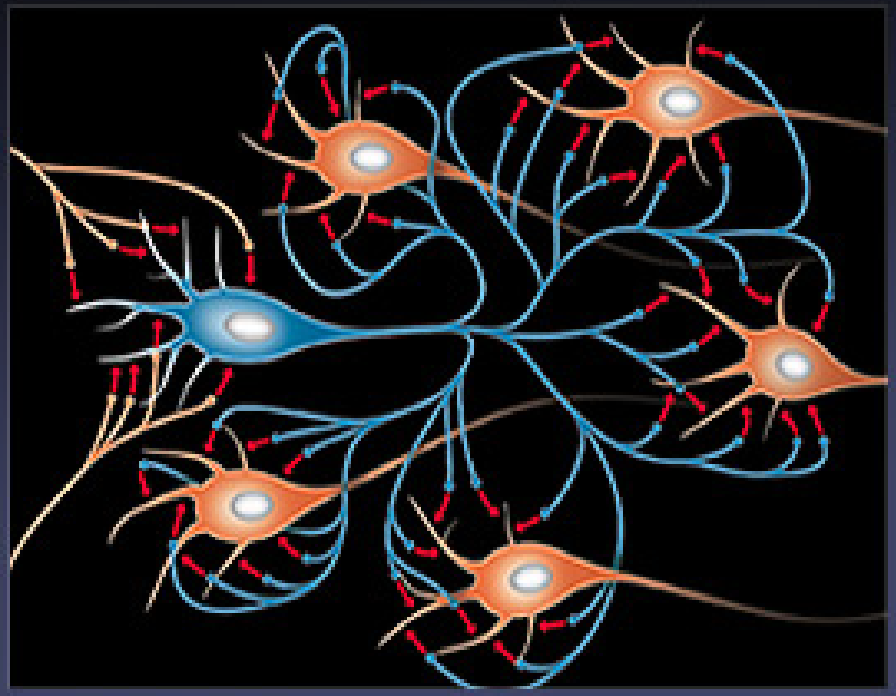
Myelination



- **Improved Brain Function**
  - Increased efficiency of local computations
  - Increased speed of neuronal transmission

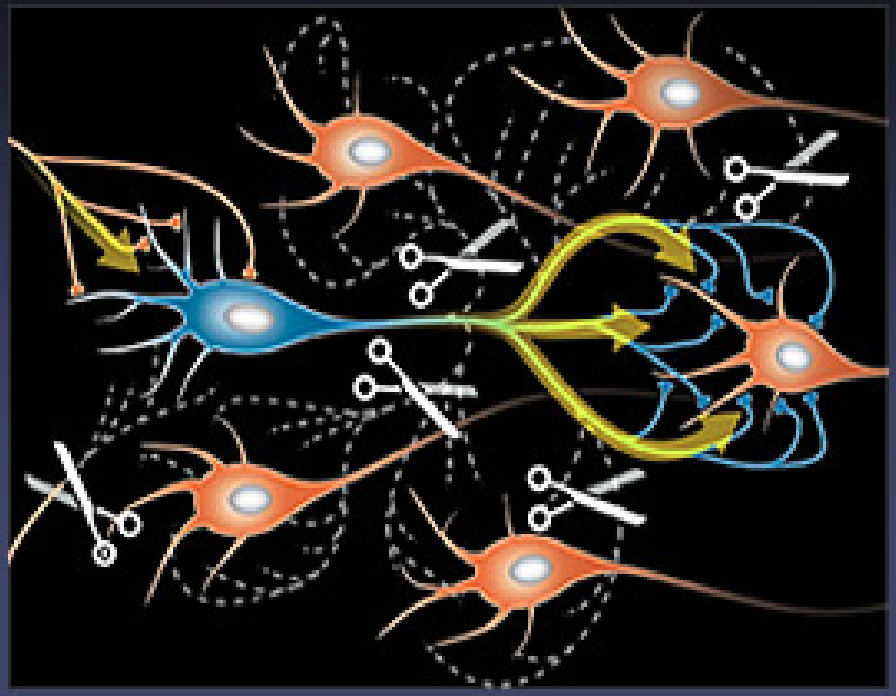
Nerve Proliferation...

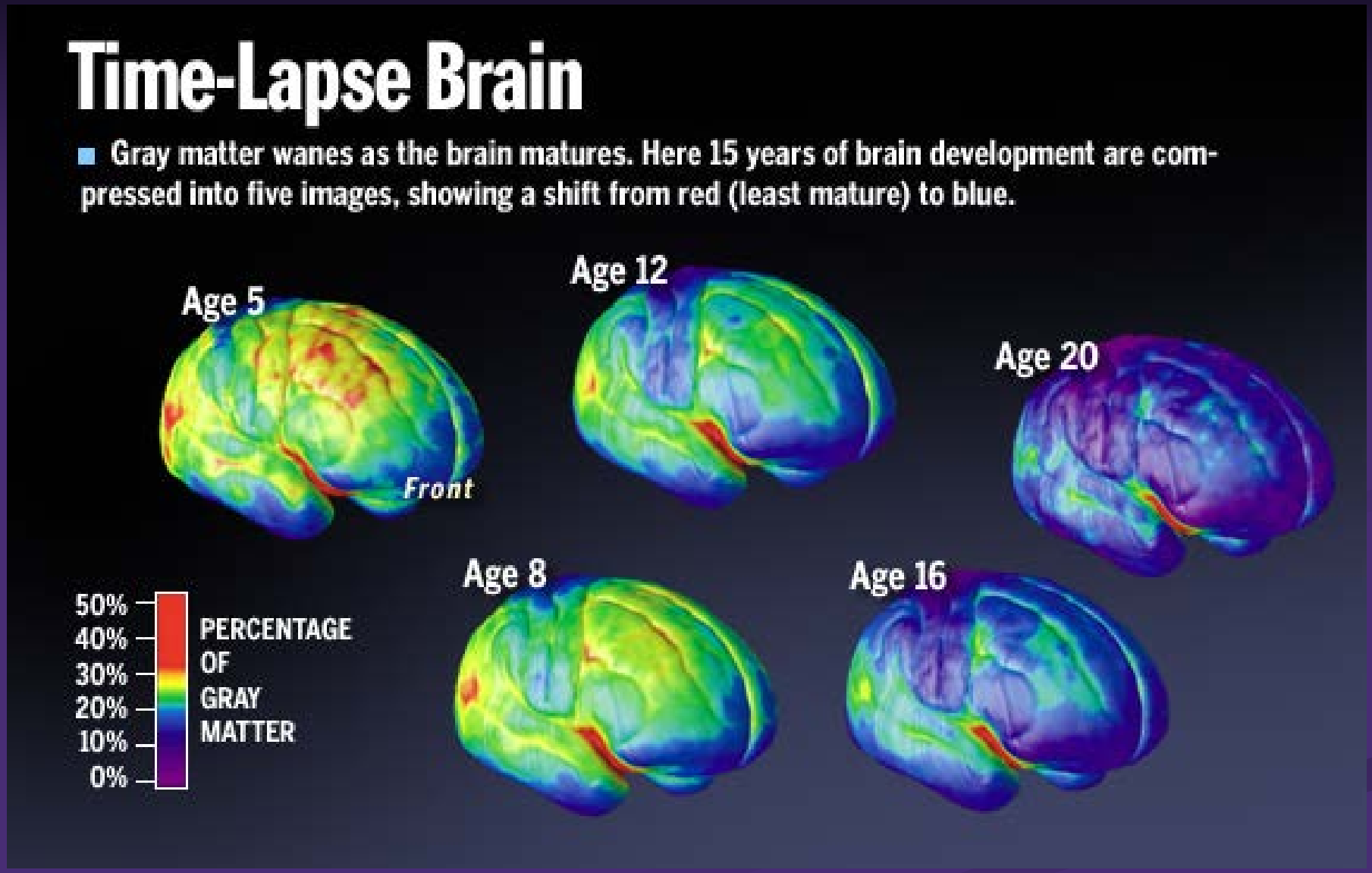
- By age 11 for girls and 12 for boys, the neurons in the front of the brain have formed thousands of new connections. Over the next few years most of these links will be pruned.



...and Pruning

- Those that are used and reinforced — the pathways involved in language, for example — will be strengthened, while the ones that aren't used will die out





Lenroot & Giedd, 2006

Changes in White Matter Volume in Adolescence

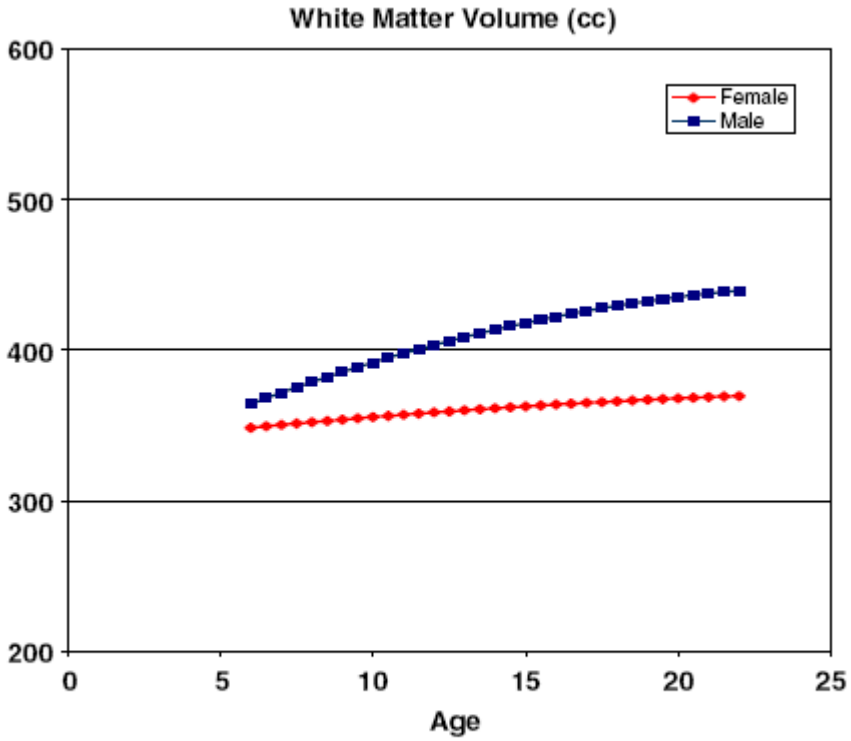


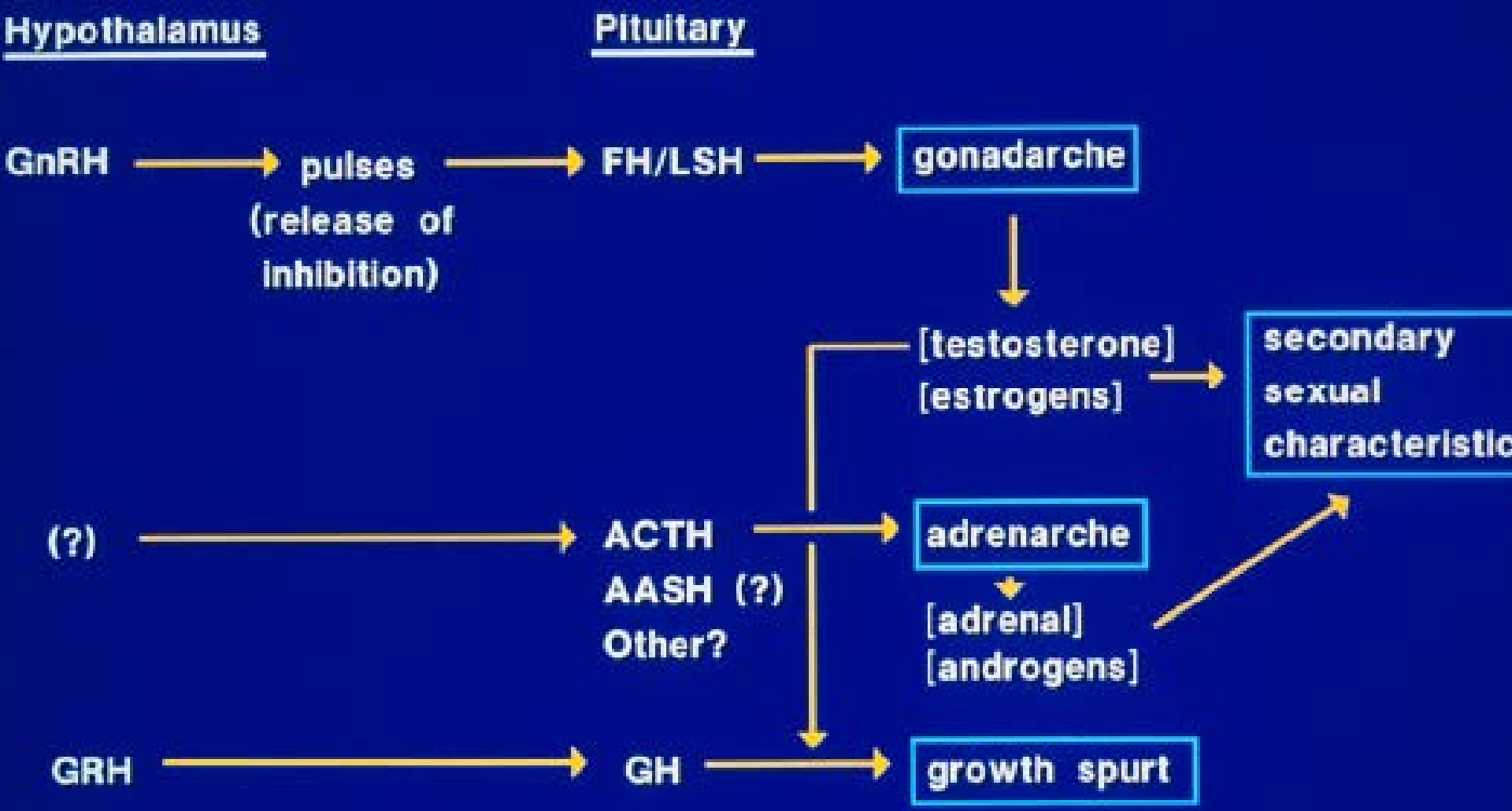
Fig. 8. White matter volume by age for 224 females (375 scans) in red and 287 males (532 scans) in blue.

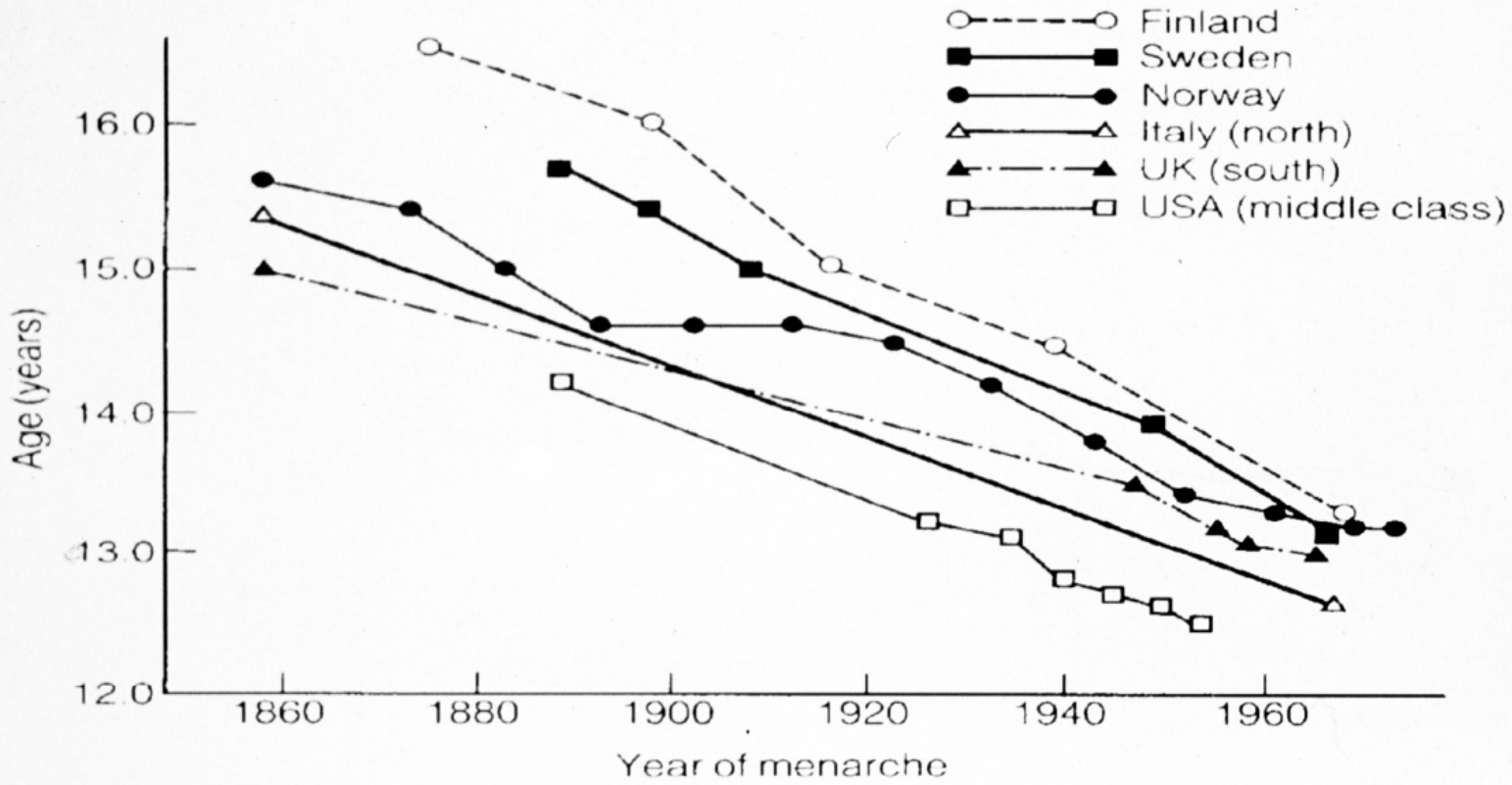
- White matter develops continuously from birth onward, with a slight increase in early adolescence.
- Increases: age 11 in girls, around age 13 in boys.

Lenroot & Giedd, 2006

Does Puberty Influence Brain Maturation?

Puberty


Hypothalamus
Pituitary
GnRH
pulses
(release of
inhibition)
FH/LSH
gonadarche
[testosterone]
[estrogens]
secondary
sexual
characteristic
(?)
ACTH
AASH (?)
Other?
adrenarche
[adrenal]
[androgens]
GRH
GH
growth spurt



7.2 Age at menarche, 1860–1970.
Sources of data and method of plotting detailed in J.M. Tanner, *Foetus into Man*, 2nd edn, Castlemead Publications, 1989.

Puberty: Changes in Motivation/Emotion

- Strongest *direct* links to puberty:
  - changes in romantic motivation, sexual interest, emotional intensity, sleep/arousal regulation, appetite, and risk for affective disorders
  - A general increase in risk taking, novelty seeking, sensation seeking (status seeking).
  - Greater emotional reactivity to social threat (e.g., peer rejection).

Puberty & Brain Development

- Some of the brain developmental changes precede pubertal increase in hormones and body changes.
- Some brain changes appear to be the consequence of pubertal processes (e.g. hormone effects feeding back upon the brain*).*
- Some adolescent brain maturation appears to be independent of pubertal processes*.*

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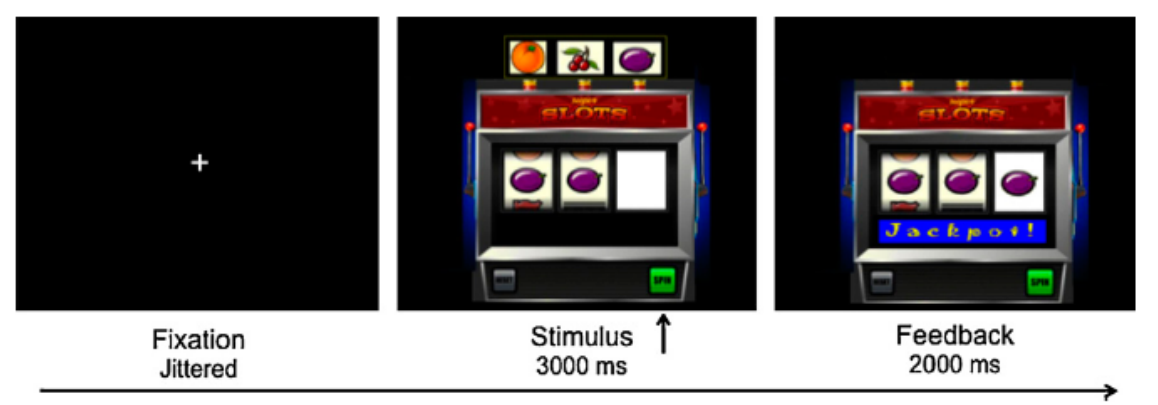
Review

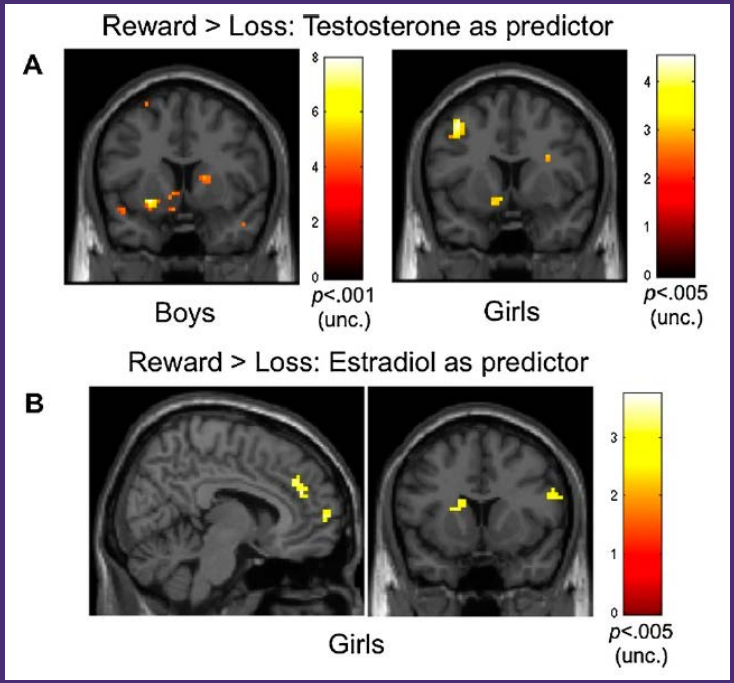
White matter development in adolescence: The influence of puberty and implications for affective disorders

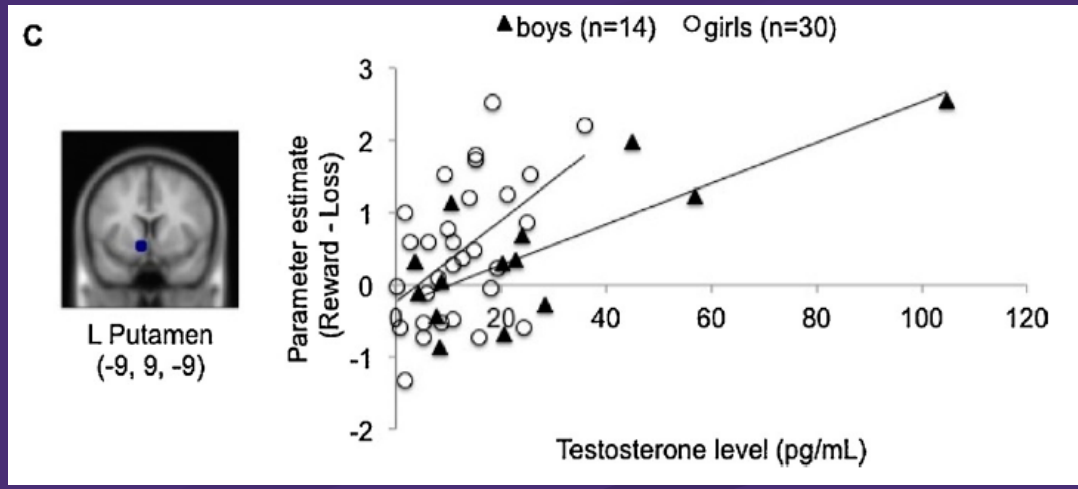
Cecile D. Ladouceur[a,*], Jiska S. Peper[b], Eveline A. Crone[b], Ronald E. Dahl[c]

[a] Department of Psychiatry, University of Pittsburgh School of Medicine, 3811 O'Hara St., Pittsburgh, PA 15213, United States
[b] Institute of Psychology, Leiden University, Leiden, The Netherlands
[c] School of Public Health, UC Berkeley, Berkeley, CA, United States

Testosterone levels associated with increased striatal activation to monetary reward



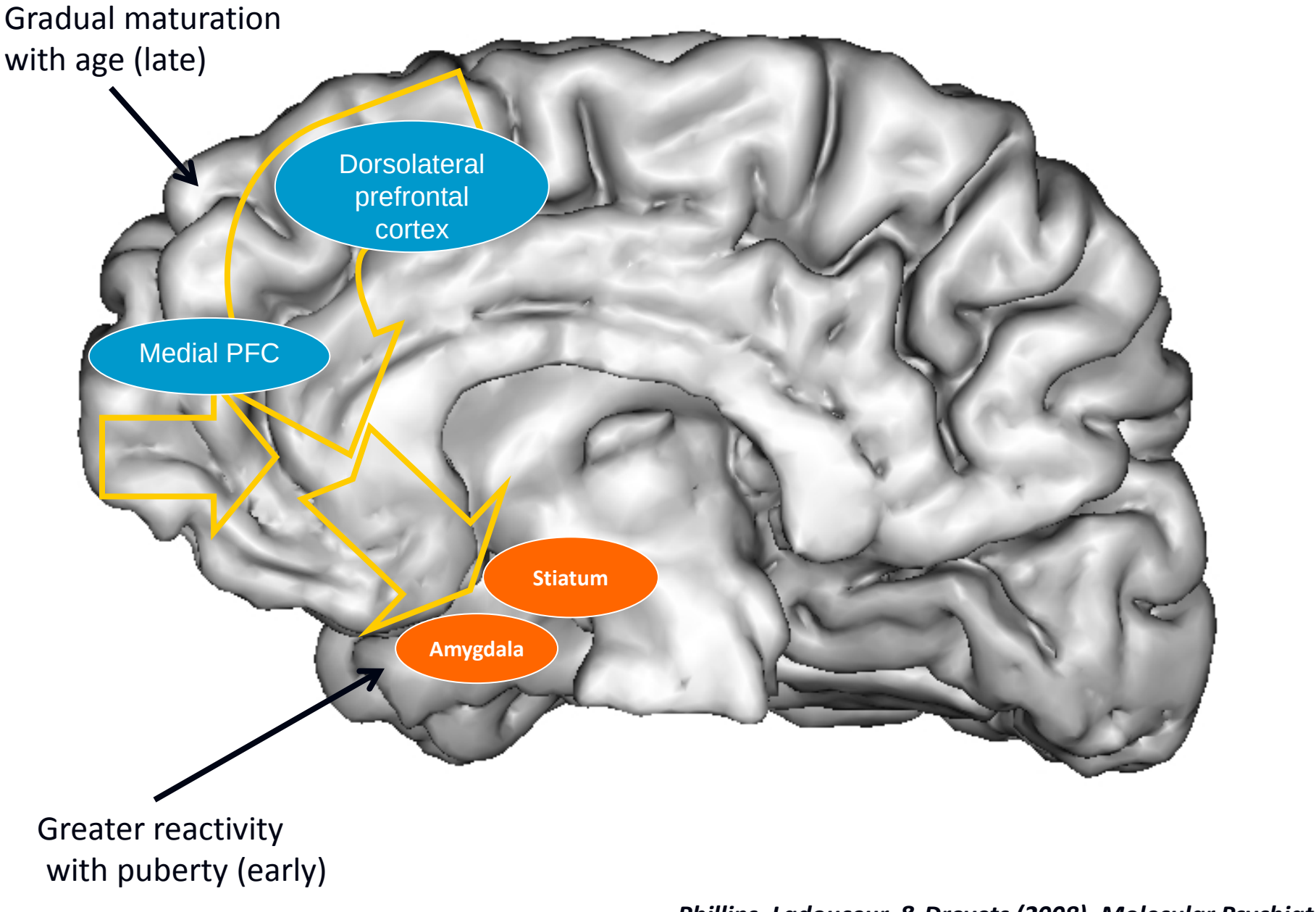




Op de Macks et al., 2011

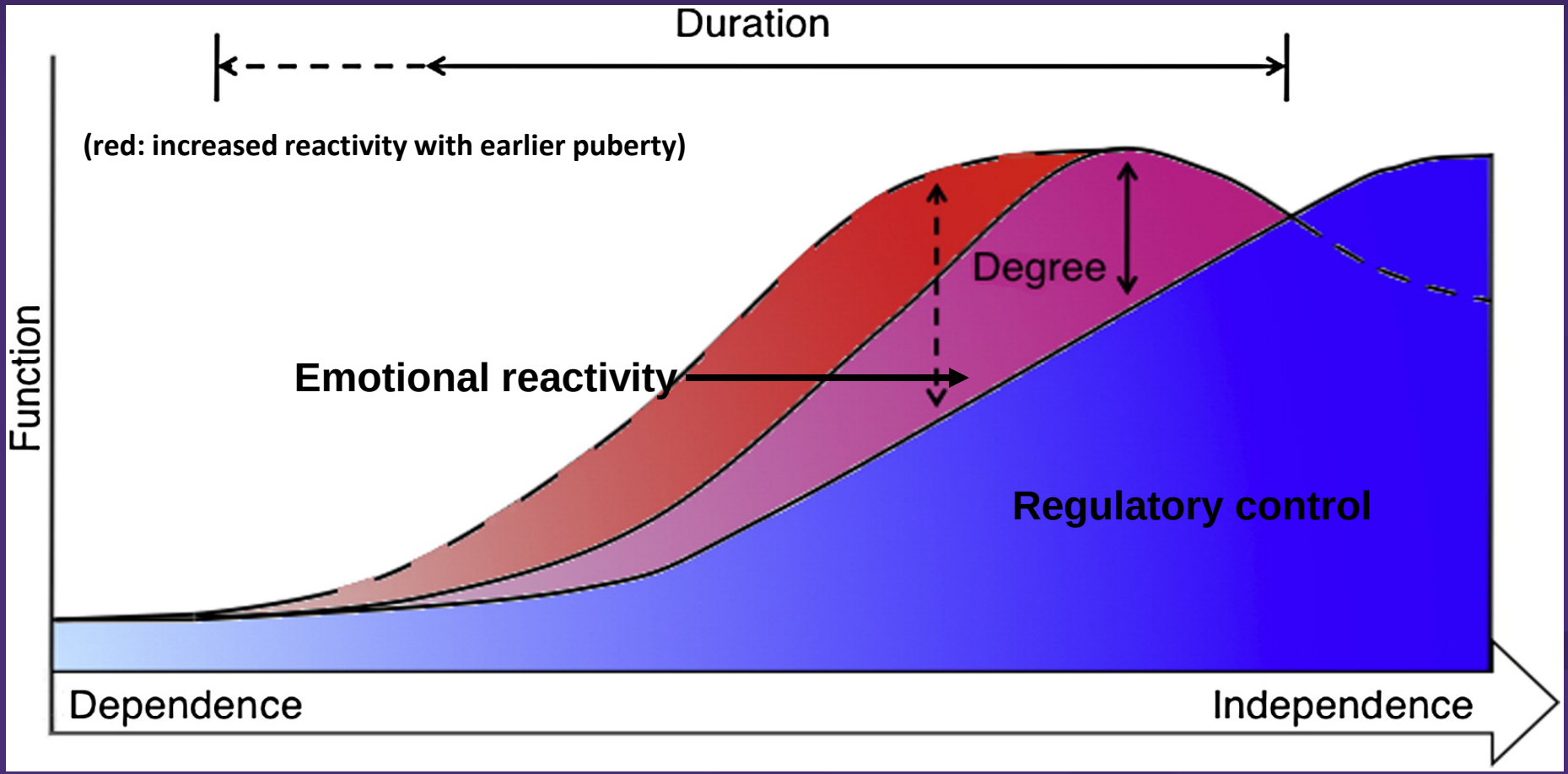
What Are the Implications for the Development of Mood Disorders?

Voluntary Self-Regulation of Emotion



Phillips, Ladouceur, & Drevets (2008). Molecular Psychiatry

From Dependence to Independence



Casey et al., 2010

Adolescence: Increased Vulnerabilities

- Earlier timing of puberty:
  - several years with a sexually-mature body and sexually-activated brain circuits
  - surge in emotional reactivity & behavior

- Yet with *relatively immature brain systems necessary for self-regulation of emotion.*

- Predict: increased risk for disorders of self-control and difficulties in navigating complex socio-emotional situations.

Adolescence: Window of Opportunity

- Potential sensitive developmental window for early intervention:
  - greater brain plasticity
  - development of new natural motivations
  - important ongoing changes in self-regulation

- Important changes in the influence of peers:
  - motivated by peer acceptance
  - impact of groups for early intervention

Take-Home Message…

- During adolescence, there are important maturational changes in brain systems that support emotional regulation.
- Puberty is associated with increased activity in subcortical limbic systems associated with emotional reactivity.
- Prefrontal brain systems that support self-regulation develop later in adolescence (long after puberty is over).

- Adolescence therefore represents a window of vulnerability for emotion dysregulation (e.g., mood disorders) and risky behavior in at-risk youth.
- It is also a window of opportunity for early intervention strategies (e.g., new motivations, develop adaptive self-regulation).

Acknowledgments

- Ronald Dahl
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- Crystal Klein
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- Kelly Monk

Funding: NIMH K01 MH083001; NARSAD Young Investigator Award .

Understanding Suicidal Behaviors in Adolescents: Markers of Early-Onset Suicide Attempt

Lisa Pan M.D.
Assistant Professor of Psychiatry
University of Pittsburgh

Topics to be covered

- Neural circuitry of depression.
- Indicators of brain differences in suicidal behavior.
- New findings in 3 tasks exploring brain changes in depression and suicidal behavior.
- New diagnostic and treatment approaches to depression and suicidal behavior.
- Possible new ways of looking at suicide attempt as illness, not an act of volition.

The Brain and Depression

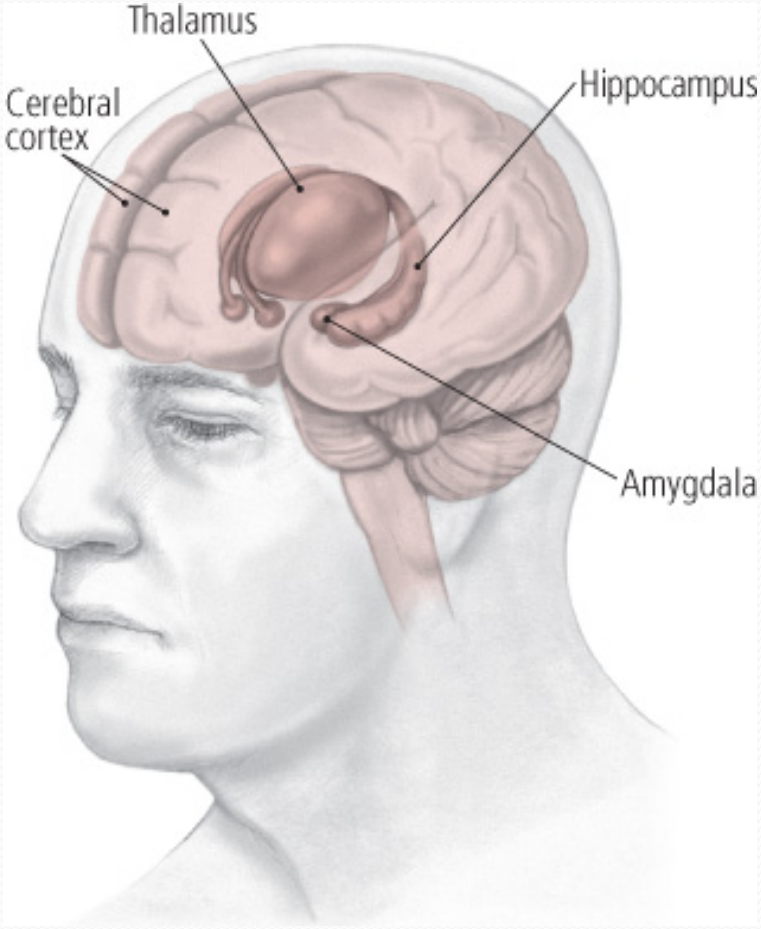


Image from harvard.health.edu

Prefrontal Cortex

- Planning
- Understanding outcomes
- Social control – salience , appropriate response
- Executive function: what is best, what are the consequences, working toward goals, prediction of outcomes

Hippocampus

- Processes long term memory
- Comparison of current situation to past danger
- Smaller in depression, may be damaged by stress.

Insula

- Pain perception in self and other
- Self awareness
- Consciousness

What is known about brain function and suicide?

- Many people with past suicide attempt are less able to "shift set", more "cognitive rigidity"
- More difficulty with tasks measuring executive function (Planning, and understanding consequences)
- Suicide attempt is more common with Axis I diagnosis, especially depression or bipolar disorder, but may happen with no diagnosis.
- Impulsivity, especially in the setting of emotional stress.

Background

- As the prefrontal cortex matures, there is more ability to perform more difficult cognitive tasks.
- Suicidal behavior in adolescence may reflect abnormal prefrontal cortical function, but we have not studied this.

FMRI

- 45 adolescents evaluated for current symptoms
- Trained to complete tasks described on a computer
- Allowed to try a mock scanner
- Responded to tasks shown on a screen in the scanner with button glove.

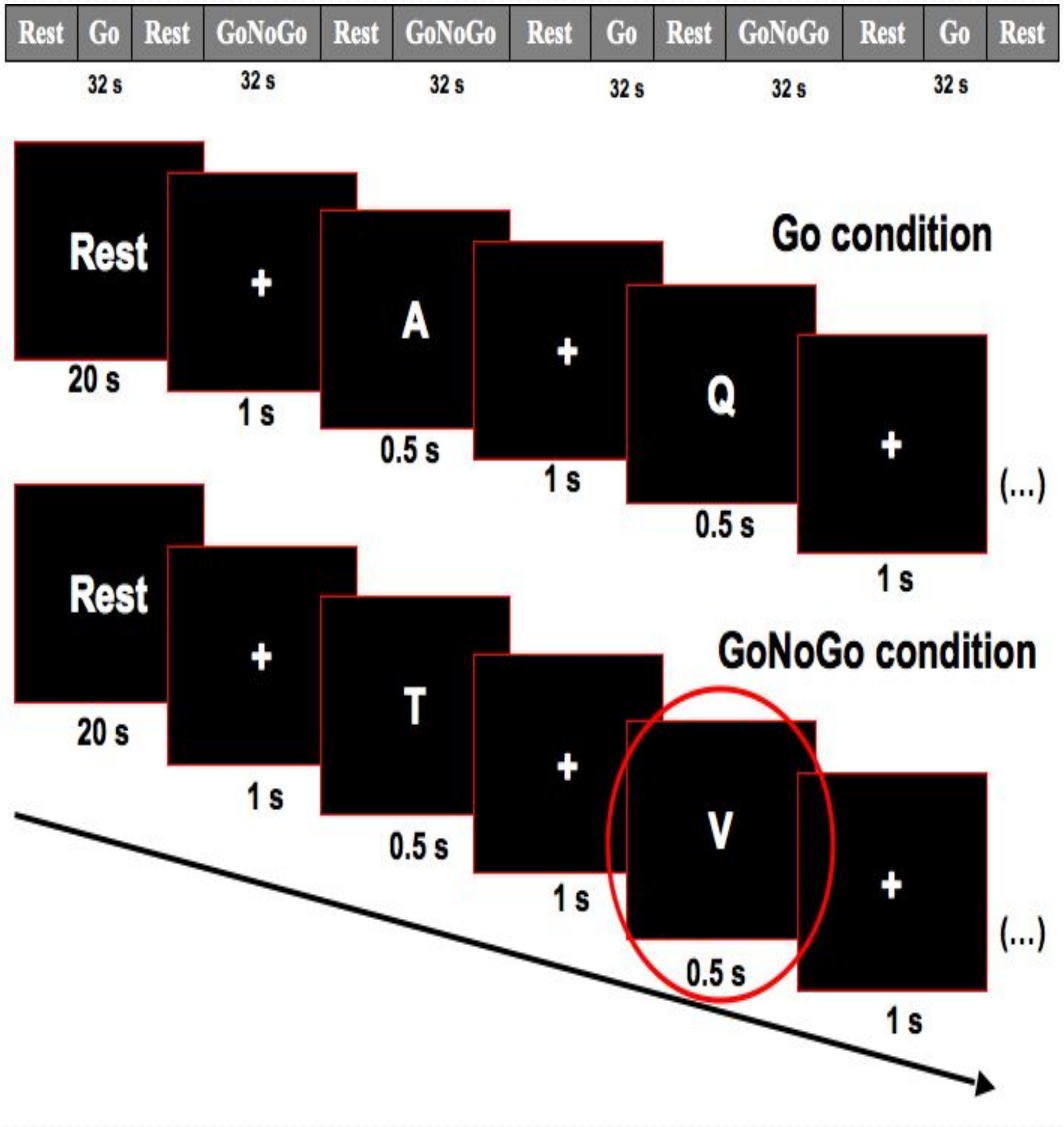
FMRI Go-No-Go Task

- “Cognitive control.”
- Simple motor control.
- Inhibiting a motor response.

GONOGO Task

- 15 adolescent suicide attempters with history of major depressive disorder (MDD; ATT), 15 adolescents with history of MDD but not suicide attempt (NAT), and 14 healthy controls (HC).

- Participants were shown a series of 120 letters, and pressed a button in response to visually presented letter stimuli ("Go" trials), but avoided responding to a rare non-target ("NoGo" trials, the letter "V").



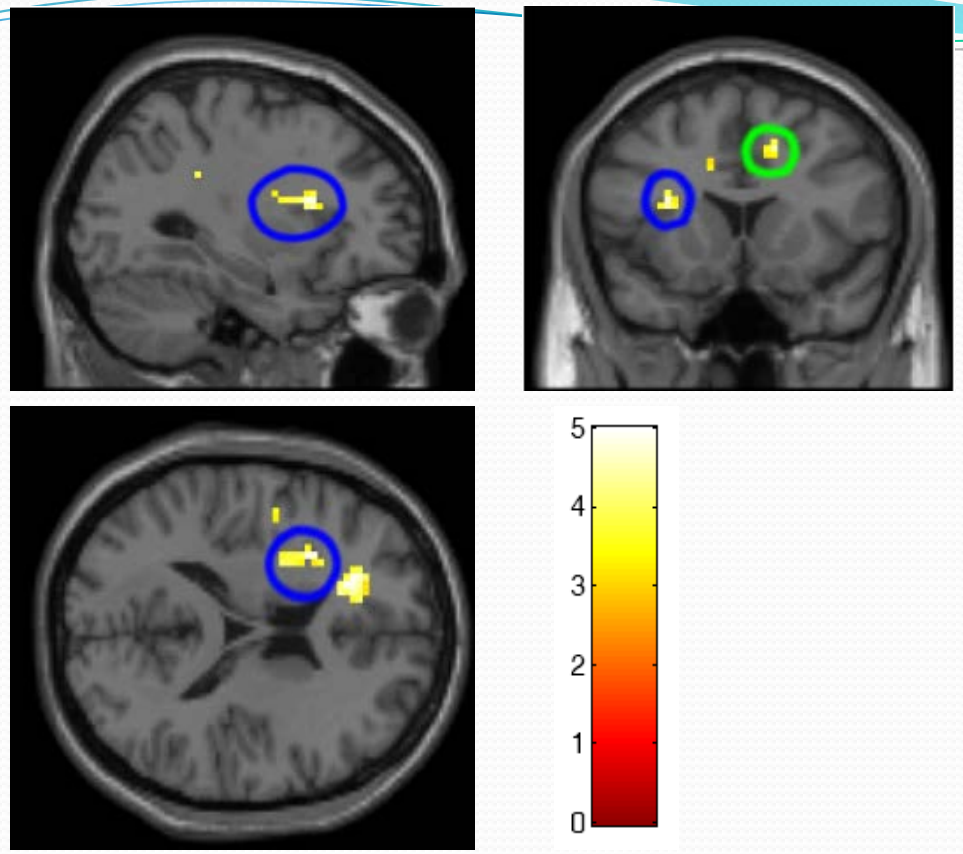
Hypothesis

- The present study tested the hypothesis that during the GoNoGo task, adolescent suicide attempters would show decreased activity compared with healthy adolescents in areas of the brain associated with response inhibition, especially within the prefrontal cortex and anterior cingulate gyrus.

Results-ATT more like HC

- NATs showed significantly greater activity during go-no-go response inhibition blocks than HCs in the left insula and significantly greater activity during these blocks than ATTs in the right anterior cingulate gyrus .

- In contrast, ATTs did not show this pattern of differential activity compared with HCs during go-no-go blocks.



During go-no-go blocks, nonattempters showed significantly greater activity than attempters in the **right anterior cingulate gyrus (circled in green)** and significantly greater activity than healthy controls in the **left insula (circled in blue)**.

GONOGO Conclusions

- ATTs were not different from HCs during the go-no-go response inhibition blocks, but ATTS had less activity than NAT of the right anterior cingulate gyrus during response inhibition.

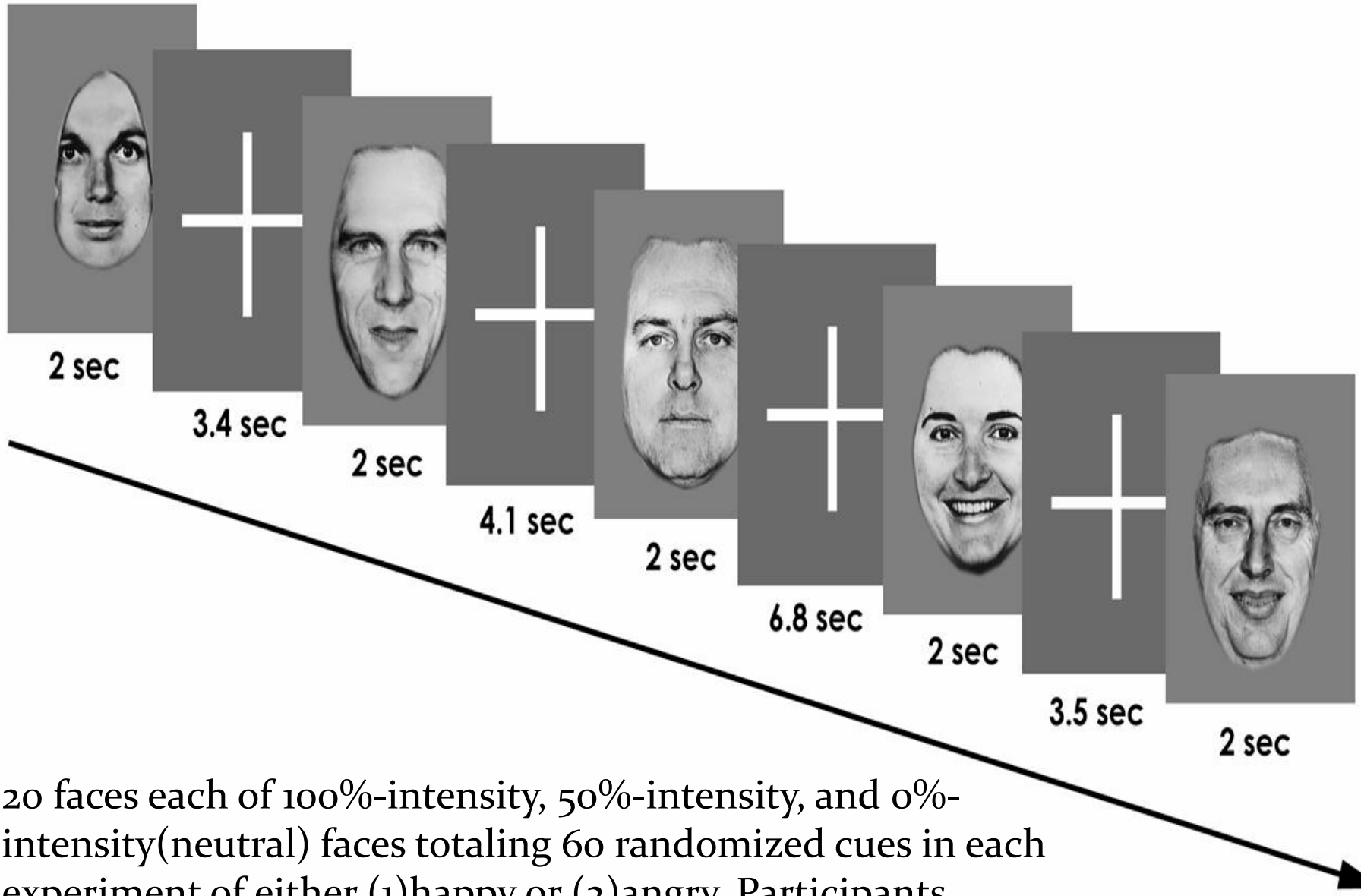
- ATTs are more like healthy controls than NAT during simple response inhibition.

FMRI Faces Task

- Emotion Processing.
- Attention to emotional faces.
- Measures response to happy and angry faces.

Faces Task

- We used fMRI with neutral, 50%- or 100%-intensity angry and happy faces in the same participants.
- Participants were asked to identify gender, but we were really measuring their response to emotion.
- This task previously showed more activity in the prefrontal cortex in adults who attempted suicide (Jollant, et al)



20 faces each of 100%-intensity, 50%-intensity, and 0%-intensity(neutral) faces totaling 60 randomized cues in each experiment of either (1)happy or (2)angry. Participants viewed each image for 2 seconds and determined the gender of the face with a button press.

Hypothesis

- We hypothesized that ATT relative to the other two groups would show elevated prefrontal cortical activity to both angry and happy faces, as in adults.

- Functional connectivity measures how associated brain activity in one area is with brain activity in another area.

- We also examined functional connectivity in this emotion task and expected reduced functional connectivity among anterior cingulate gyri, prefrontal, temporal cortices and insulae to all face emotion conditions relative to HC as seen in adults.

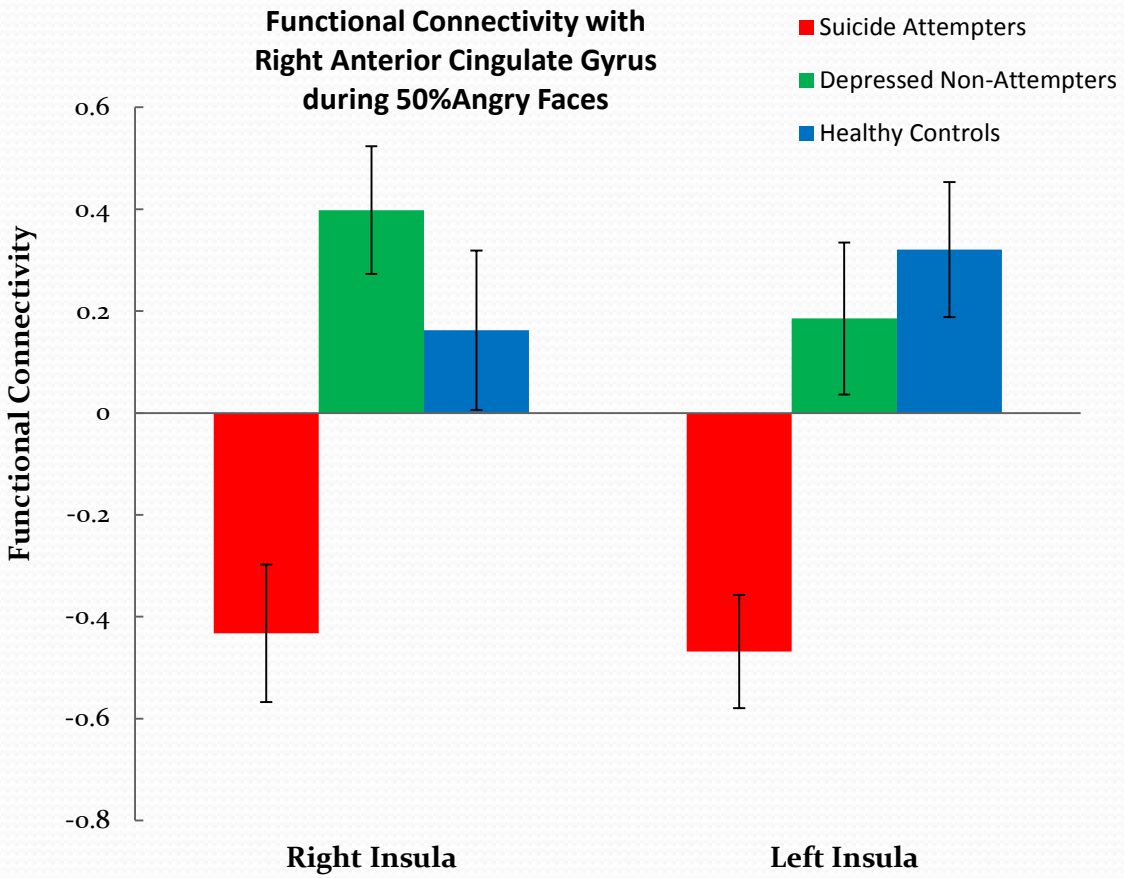
Results

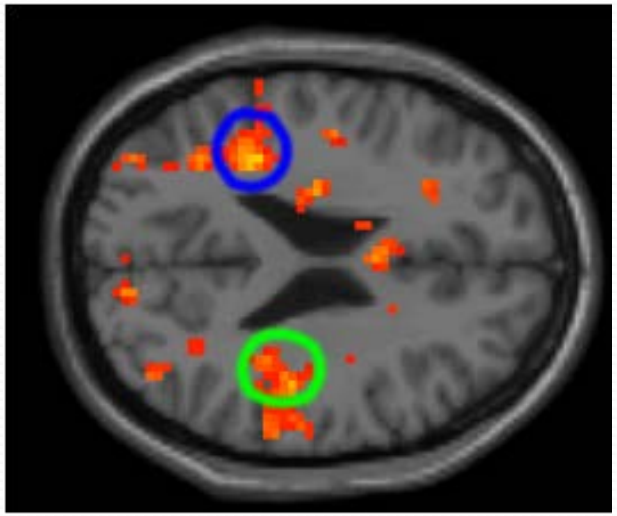
- To 50%-intensity **angry faces, ATT showed greater activity than NAT** in anterior cingulate gyral-dorsolateral **prefrontal cortical attentional control circuitry**, primary sensory and temporal cortices; and greater activity than HC in primary sensory cortex, while NAT had significantly lower activity than HC in anterior cingulate gyrus and ventromedial prefrontal cortex.

- ATT also showed significantly lower activity than HC to 100%-intensity happy faces in primary sensory cortex, and to neutral faces in the happy run in anterior cingulate and left medial frontal gyri.

- Psychophysiological interaction analyses revealed **significantly reduced anterior cingulate gyral-insula functional connectivity to 50%-intensity angry faces in ATT versus NAT or HC.**

Attempters show significantly lower functional connectivity between the right anterior cingulate gyrus and bilateral insulae when viewing 50%-intensity angry faces than Non-Attempters and Healthy Controls . Blue: Left Insula Green: Right Insula





Faces Conclusions

- When viewing **50%-intensity angry faces, ATT had significantly greater activity** than NAT and HC to 50%-intensity angry faces.

- **ATT showed decreased functional connectivity** from an anterior cingulate gyral seed region to bilateral insulae than other groups to 50%-intensity angry faces.

- **ATT may show inefficient recruitment of attentional control neural circuitry when regulating attention to mild intensity angry faces, that may represent a potential biological marker for suicide risk.**

FMRI Iowa Gambling Task

- Combines cognitive and emotional components for learning in the context of risk.
- Make high or low risk decisions from four decks of cards.
- Not what we expected.

Iowa Gambling Task

- Functional magnetic resonance imaging(fMRI) was used to assess decision-making and learning-related neural activity during Iowa Gambling Task(IGT) performance.

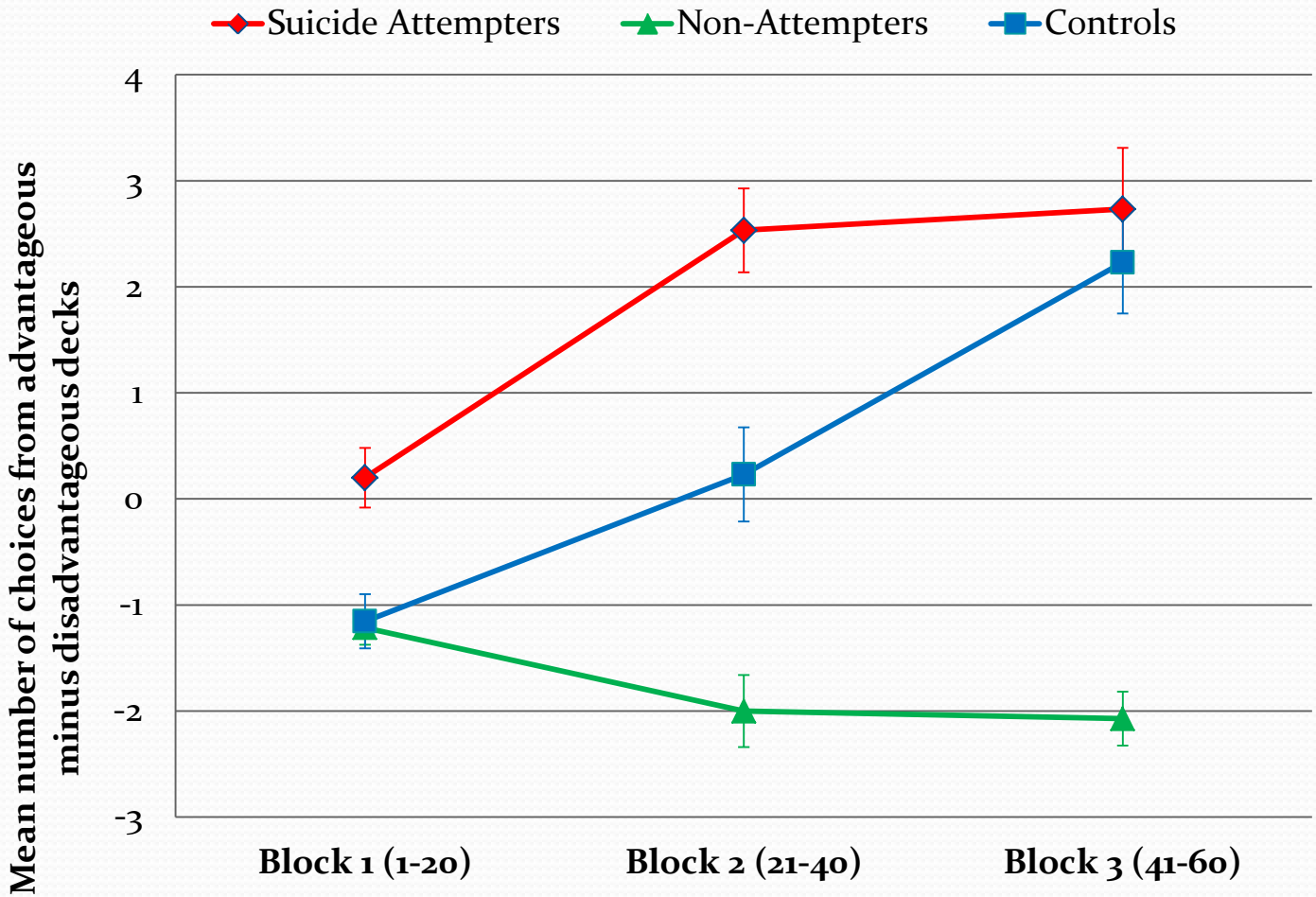
- Participants are asked to pick from four decks of cards, two of which are high risk, poor gain and two of which are low risk with better gain.

Hypothesis

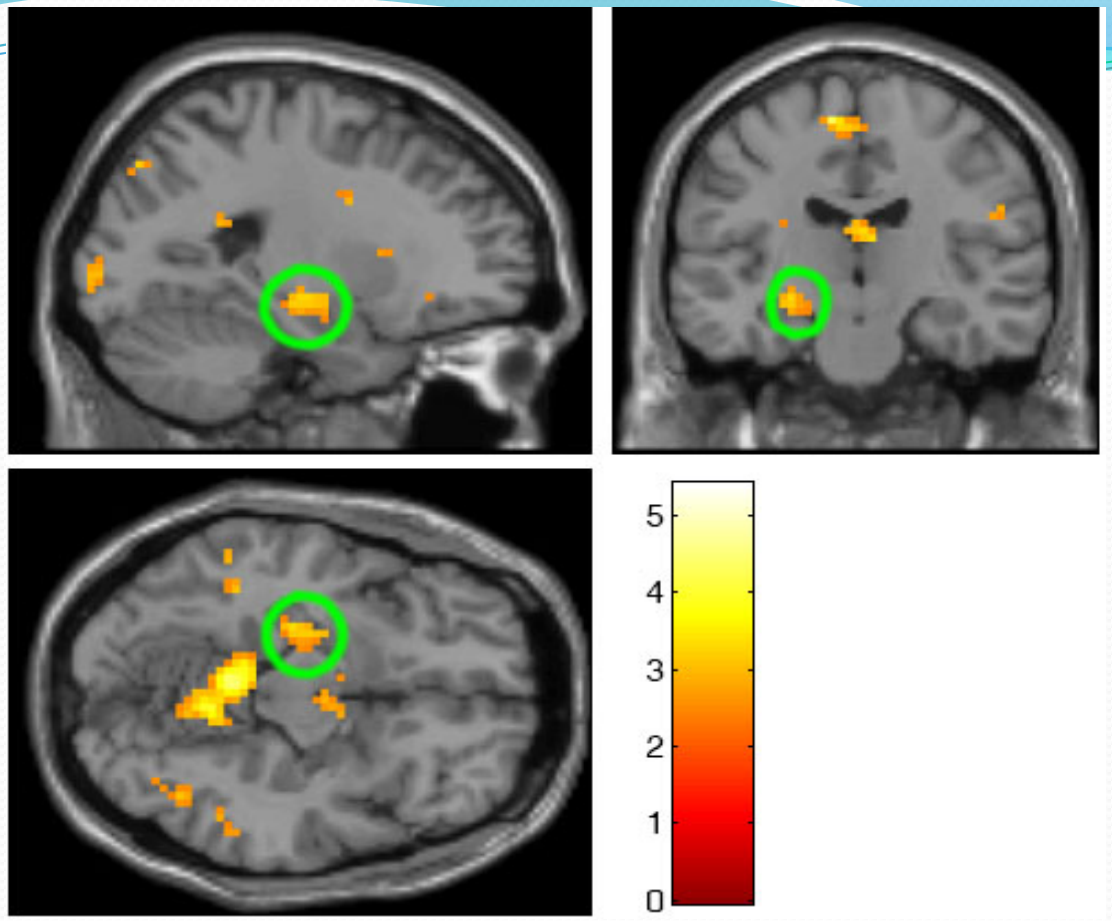
- We hypothesized that ATT would perform more poorly (make higher risk choices) on the IGT than depressed and healthy controls, and that ATT would show decreased activity in areas implicated in IGT performance.

Results

- **ATT had the best performance** on the IGT.
- Overall, in blocks associated with learning **NAT, but not ATT, showed greater activation versus HC.**
- **NAT, but not ATT are differentiated from HC during performance of the IGT.**



Performance on the modified Iowa Gambling Task. Median net scores by block of 20 choices.



In **the left hippocampus, NAT, but not ATT, showed significantly greater activity than HC**. Hippocampus circled in green.

IGT Conclusions

- The present findings indicate **NAT, but not ATT are differentiated from HC during learning in the context of risk.**

- Our findings thereby suggest that functional abnormalities in **neural circuitry implicated in learning in the context of risk may underlie risk for MDD, but not risk for suicide attempt, in adolescence.**

Overall

- Cognitively, ATT are more able than NAT despite worse depression scores, cognitively more like healthy participants
- In emotion processing, ATT are impaired

- First look at connectivity between regions show ATT with less functional connectivity than other groups.

- Poor decision-making or impulsivity may be a greater risk with regard to emotion for teens already biologically at risk for suicidal behavior.

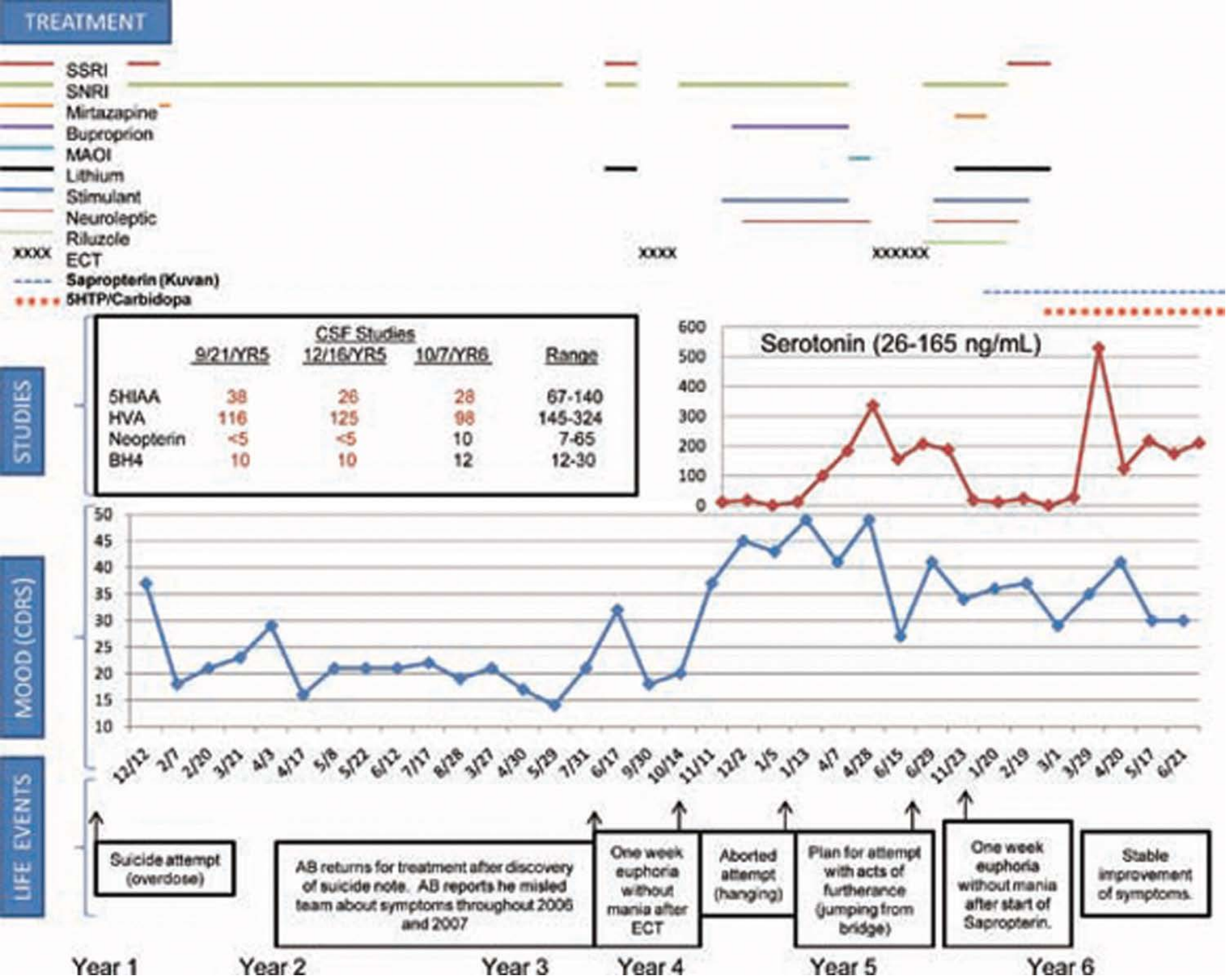
Atypical presentation

What if a patient presents with

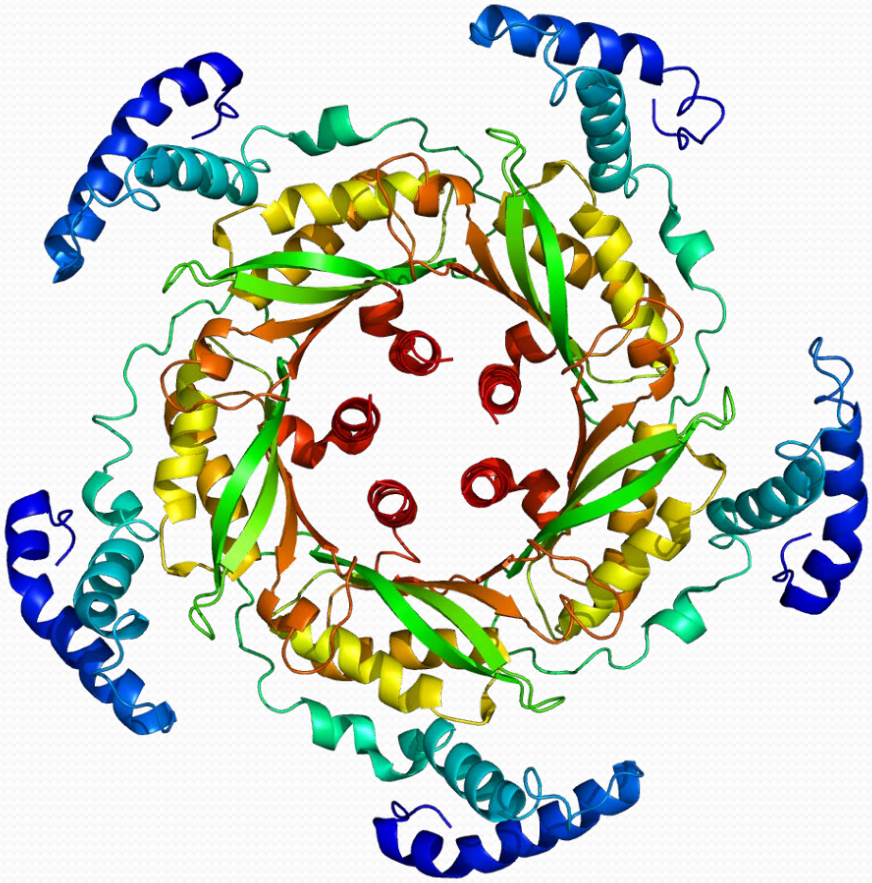
- None of the known risk factors?
- Atypical symptoms of depression?
- Mood disorder unresponsive to known treatments?
- Suicidal behavior in the absence of identifiable diagnosis?

AB, Patient with treatment refractory depression and suicidal behavior

- Depression and self injury, age 11
- Suicide attempt age 14
- Age 15 suicide attempt 80 pills, discovered by chance, ICU stay.
- No response to available medications.
- Age 18, ECT with one week of response.
- Refused ECT due to non-response, 49 day hospital stay and evaluation for state hospitalization. No response of suicidal ideation despite polypharmacy.


TREATMENT
SSRI
SNRI
Mirtazapine
Bupropion
MAOI
Lithium
Stimulant
Neuroleptic
Riluzole
ECT
Sapropterin (Kuvan)
5HTP/Carbidopa
STUDIES
CSF Studies
9/21/YR5 12/16/YR5 10/7/YR6 Range
5HIAA 38 26 28 67-140
HVA 116 125 98 145-324
Neopterin <5 <5 10 7-65
BH4 10 10 12 12-30
Serotonin (26-165 ng/mL)
MOOD (CDRS)
LIFE EVENTS
Suicide attempt (overdose)
AB returns for treatment after discovery of suicide note. AB reports he misled team about symptoms throughout 2006 and 2007
One week euphoria without mania after ECT
Aborted attempt (hanging)
Plan for attempt with acts of furtherance (jumping from bridge)
One week euphoria without mania after start of Sapropterin.
Stable improvement of symptoms.
Year 1
Year 2
Year 3
Year 4
Year 5
Year 6

GTP-Cyclohydrolase



Tetrahydrobiopterin

- **Function of tetrahydrobiopterin**
- Cofactor to make needed amines, serotonin, norepinephrine, dopamine.
- Replacement therapy with analogue sapropterin (Kuvan)
- Led to improvement of **suicidal ideation but not depression**, patient was " able to make decisions better."

Supply pathway

- Added 5-HTP
- Added carbidopa to protect periphery (heart)
- Also to move 5HT to brain
- Unexpected effects

Gradual improvement

- AB initially reported “clearer decision making”
- Short period of euphoria after start of Kuvan, then plateau with partially remitted depression
- Added 5-HTP with some remarkable initial changes.
- Able to discontinue other pharmacology.
- Sleep returned last.
- Some difficulty with tolerability (N/V, delivery)
- Eventually attending college in outpatient treatment.

BMJ Case Reports

New disease

GTP-cyclohydrolase deficiency responsive to sapropterin and 5-HTP supplementation: relief of treatment-refractory depression and suicidal behaviour

Lisa Pan,[1] Brian William McKain,[1] Suneeta Madan-Khetarpal,[2] Marianne Mcguire,[2] Rasim S Diler,[1] James M Perel,[1] Jerry Vockley,[2] David A Brent[1]

[1]Department of Psychiatry, University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania, USA;
[2]Department of Medical Genetics, University of Pittsburgh, Children's Hospital, Pittsburgh, Pennsylvania, USA

Correspondence to Dr Lisa Pan, thomasla@upmc.edu

Summary

The authors describe a new variant of guanosine triphosphate (GTP)- cyclohydrolase deficiency in a young man with severe and disabling major depressive disorder with multiple near-lethal suicide attempts. His cerebrospinal fluid levels showed that the concentration of tetrahydrobiopterin (BH4), neopterin, 5-hydroxyindoleacetic acid and homovanillic acid were below the reference range, suggesting a defect in the pterin biosynthetic pathway and in synthesis of dopamine and serotonin indicative of GTP-cyclohydrolase deficiency. Patient was started on sapropterin, a BH4 replacement protein, for the defect in the above pathway. In addition, the authors started 5-hydroxytryptophan titrated to 400 mg orally twice daily with concomittant carbidopa 37.5 mg orally four times a day, and he responded with remission of suicidal ideation and significant improvement in depression and function.

BACKGROUND

Our hope is that other patients presenting with treatment-refractory, life-threatening depression will be evaluated for defects in this pathway. A brief summary of the scientific bases for selecting the replacement therapies is included. For future research, we propose that potential pharmacogenetic characterisation might also be evaluated so that these 'rare' syndromes are treated, if possible, at an earlier age

mood stabilisers and electroconvulsive therapy (ECT) (figure 1), the patient did not improve. Serotonin reuptake inhibitors (SSRIs) resulted in worsening. At age 17, after 32 treatments of ECT, he remitted for only 1 week followed by immediate onset of suicidal intent and an aborted suicide attempt. The patient refused further ECT due to non-response. He demonstrated significant suicidality during a 49-day hospitalisation. With maximal dose polyphar-

Overview

- Areas of brain that may function differently in suicidal behavior compared to depression alone, especially in adolescence.
- Inborn errors of metabolism may contribute to suicidal behavior, with onset variable.
- Support suicide as a disorder on its own.
- There are individuals with inherent risk during development.

Implications

- For identification of those at risk
- For alternative treatment strategies
- For community response
- Stigma—How much more successful if we were screening for medical illness?
- If IEM, is this psychiatric illness?

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Discussion

For more information contact:

Erica Streit-Kaplan

617-618-2178

estreit-kaplan@edc.org

www.ChildrensSafetyNetwork.org

Upcoming Meeting

- September: small group action plan meetings
- October: Webinar on connection between bullying and suicide
- November: small group action plan meetings
- December: Wrap-up webinar for the whole CoP group

Teams should continue to meet monthly to implement their action plans.