Early Life Stress: Long lasting impact on Brain Circuitry and Behavior

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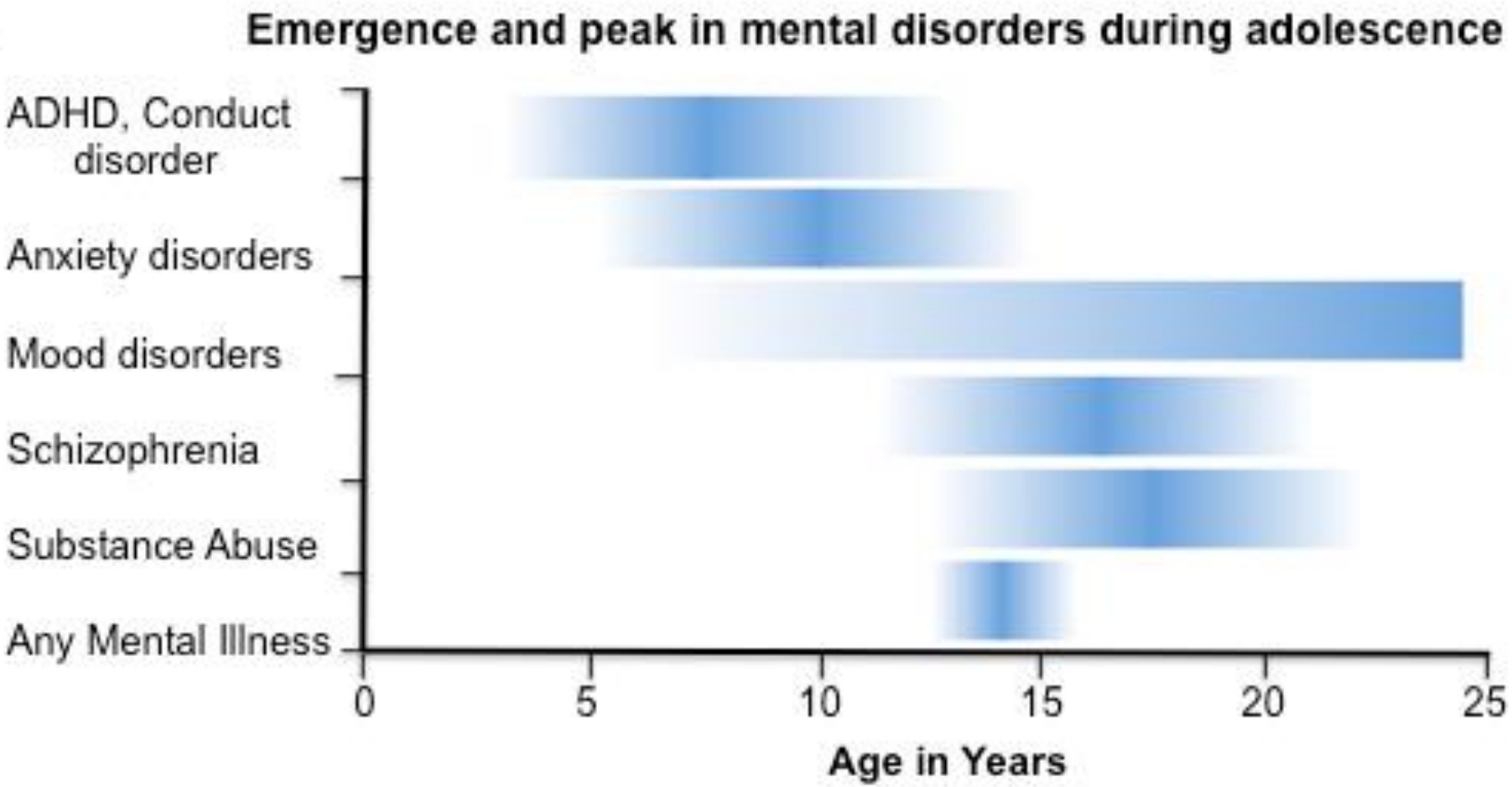
Significance

-Mental illness impacts 1 in 5 young people, and peaks during adolescence;

-Untreated, these disorders can lead to chronic mental and physical illness, even death (e.g., suicide).


Emergence and peak in mental disorders during adolescence
ADHD, Conduct disorder
Anxiety disorders
Mood disorders
Schizophrenia
Substance Abuse
Any Mental Illness
0
5
10
15
20
25
Age in Years

Significance

-Anxiety and stress related disorders are the most common illnesses affecting as many 1 in 10 young people today, emerging by early adolescence.

Cognitive behavioral therapy (CBT) is the only evidenced-based behavioral treatment

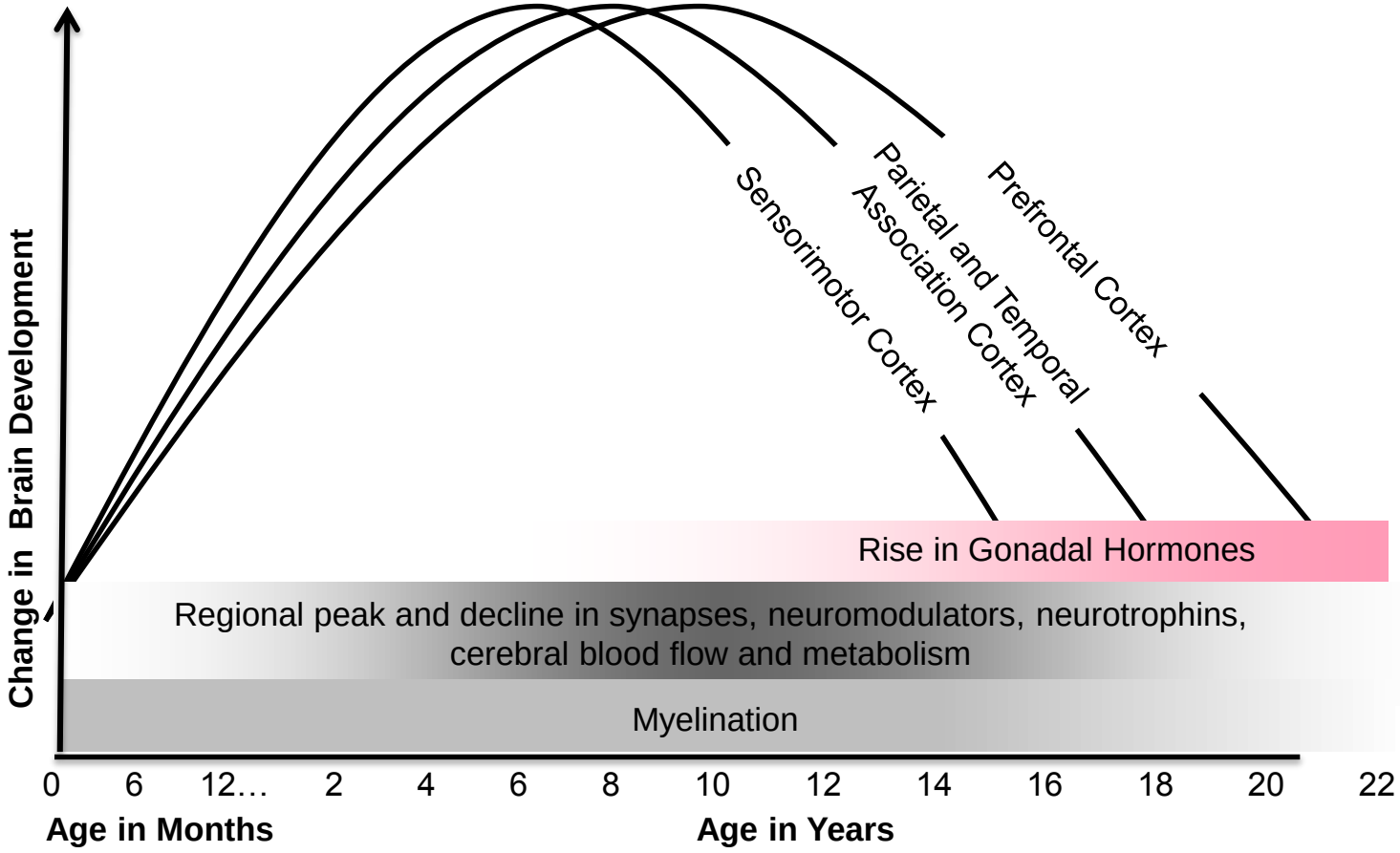
Yet 40% do not improve.

Objectives

-To understand changes in brain and behavior during the transition into early adolescence when there is a peak in psychopathology.

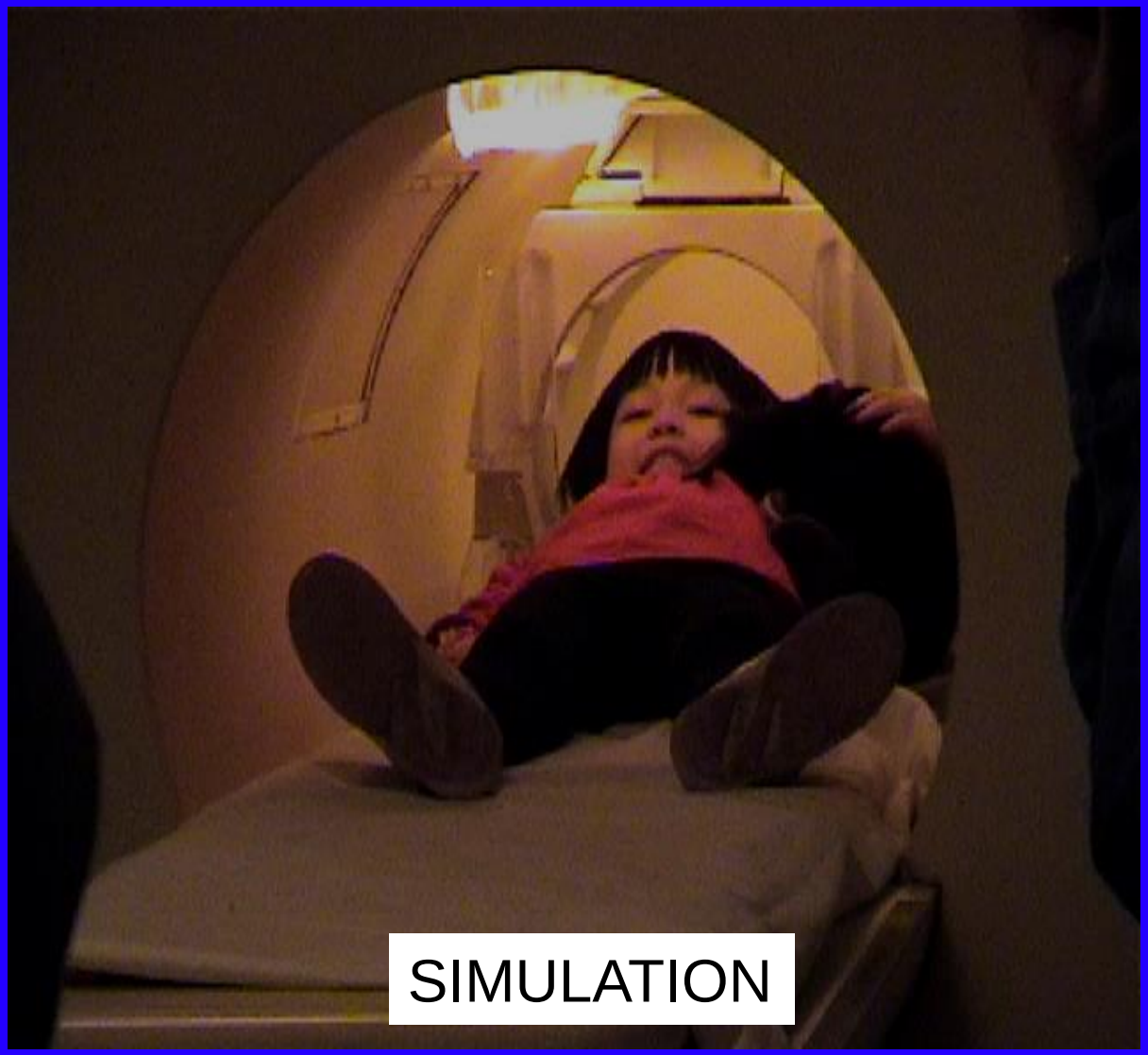
-To understand factors that may increase the risk for mental illness.

Developmental course of brain maturation

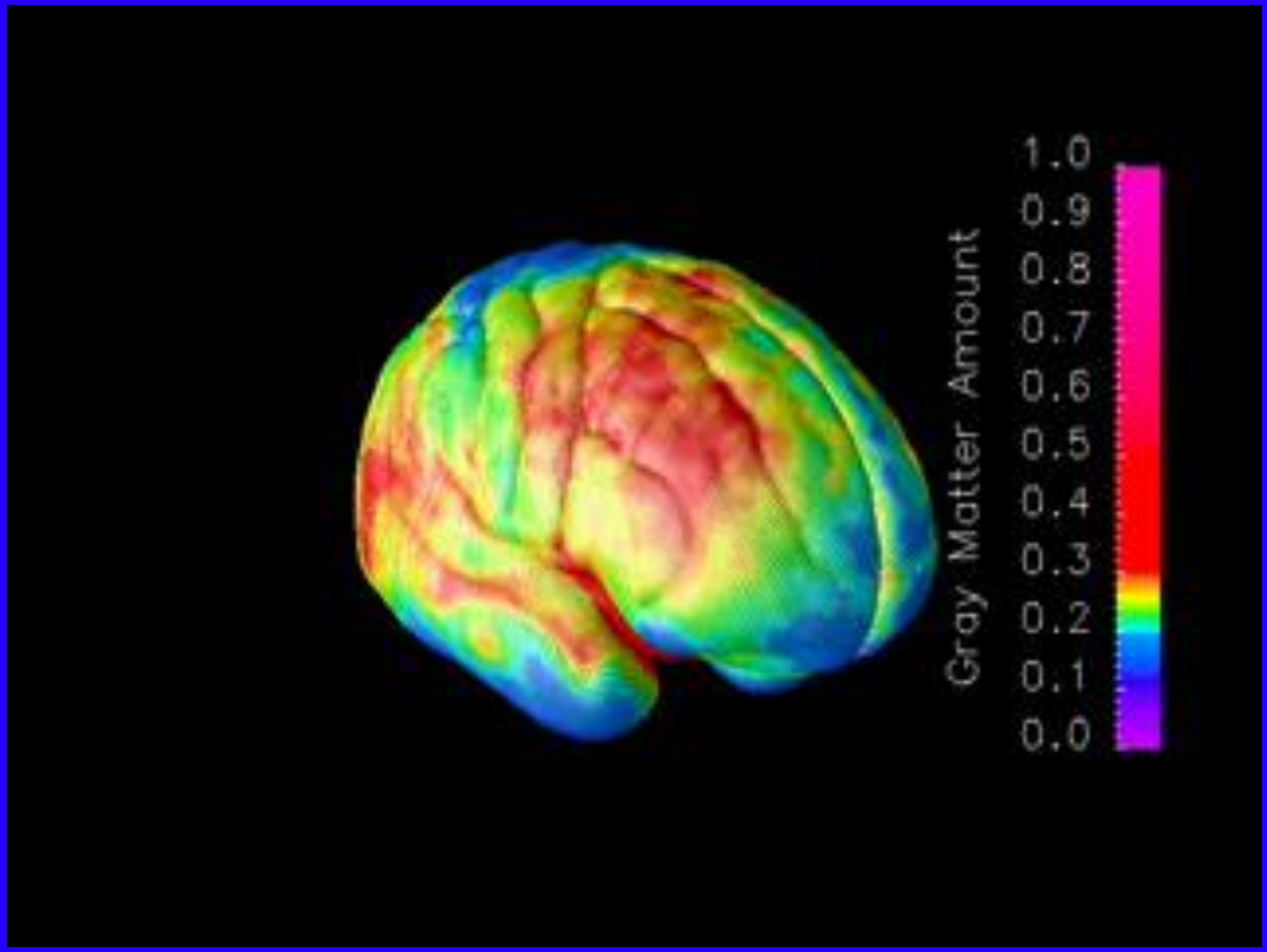


Imaging the Developing Brain


PRESIMULATION

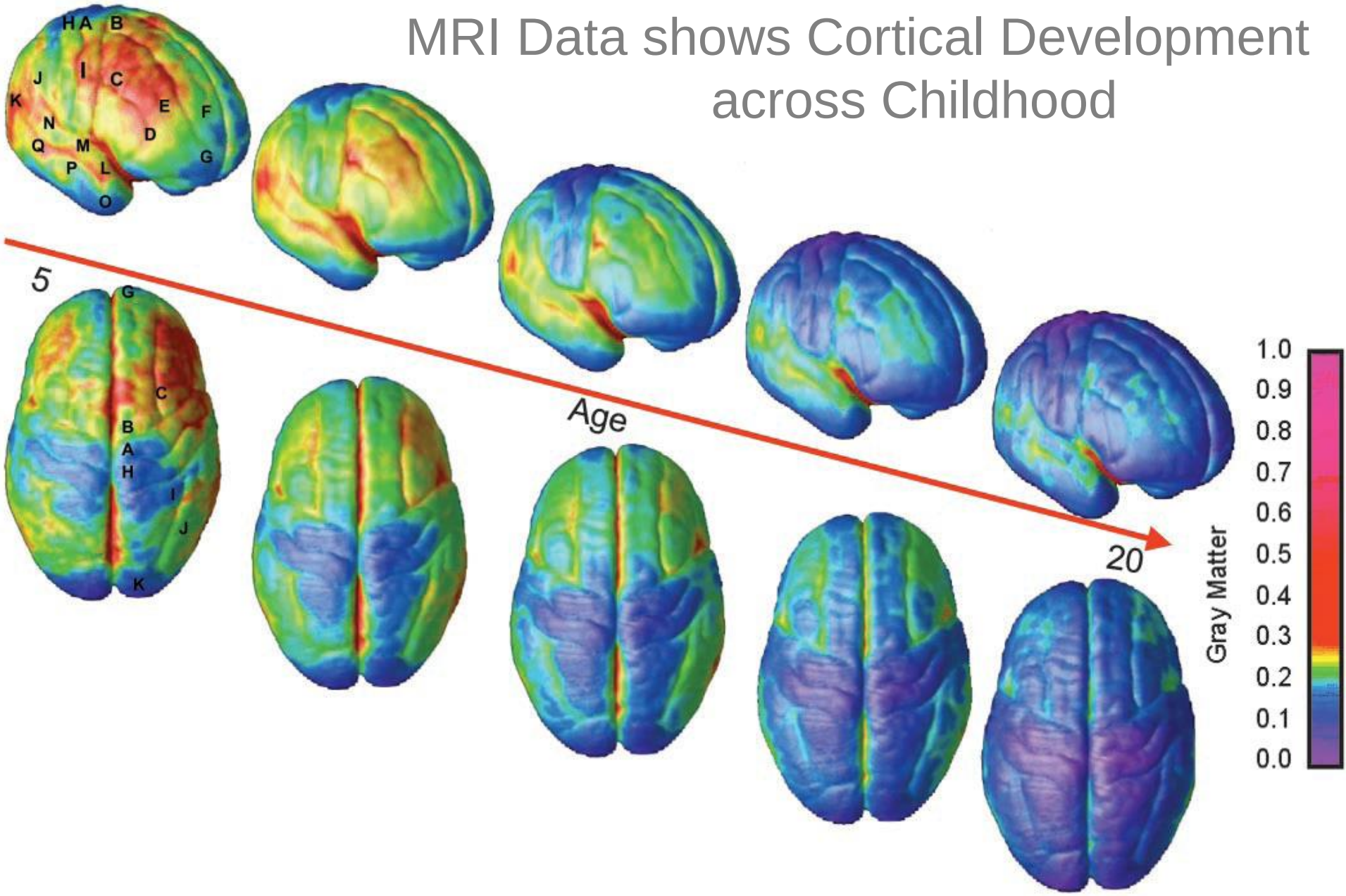

SIMULATION

Regional Brain development from childhood to adulthood



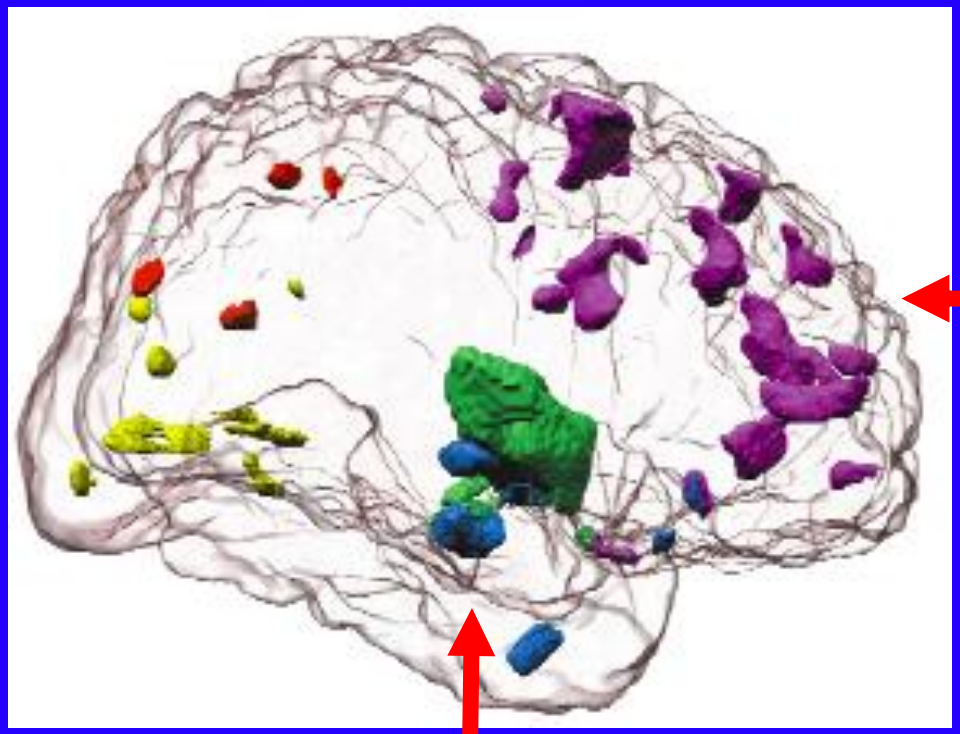
SOURCE: Gogtay et al 2004 *PNAS*, NIMH

MRI Data shows Cortical Development across Childhood



SOURCE: Gogtay et al 2004 *PNAS*

Dramatic changes in prefrontal cortex and deep subcortical regions from late childhood to adulthood



Focus has typically been on prefrontal cortex

Subcortical regions involved in desire, rage and fear show changes. (Sowell et al, 1999 *Nat Neuro*)

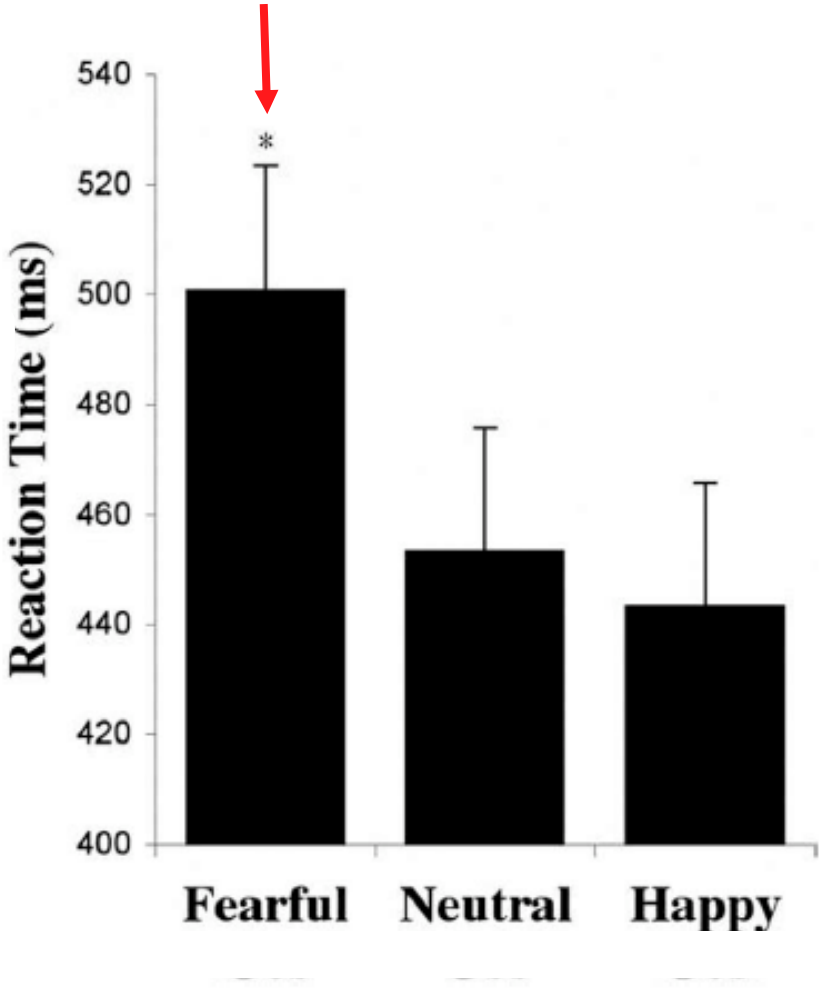
Adolescence is characterized by major changes in limbic areas involved in emotion reactivity relative to prefrontal regions involved in emotion regulation.

Source: PBS graphic based on Galvan et al 2006, Hare et al 2008, Sackler Institu

Measuring Emotional Reactivity and Regulation in the Lab

Cues of Threat

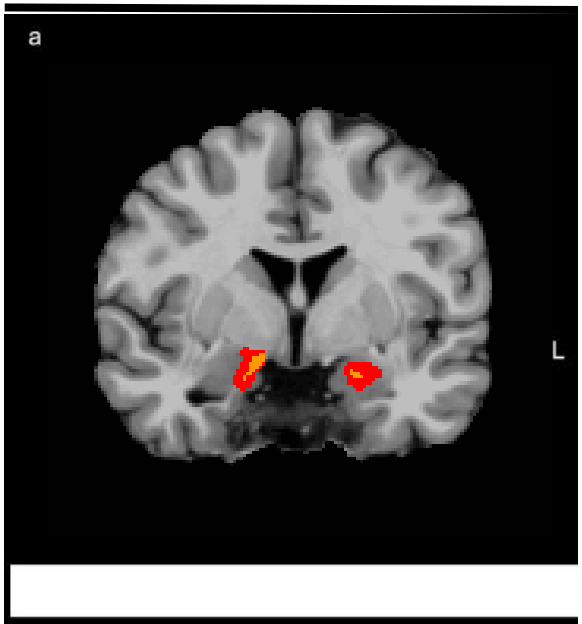
We are slower to approach Cues of Potential Threat



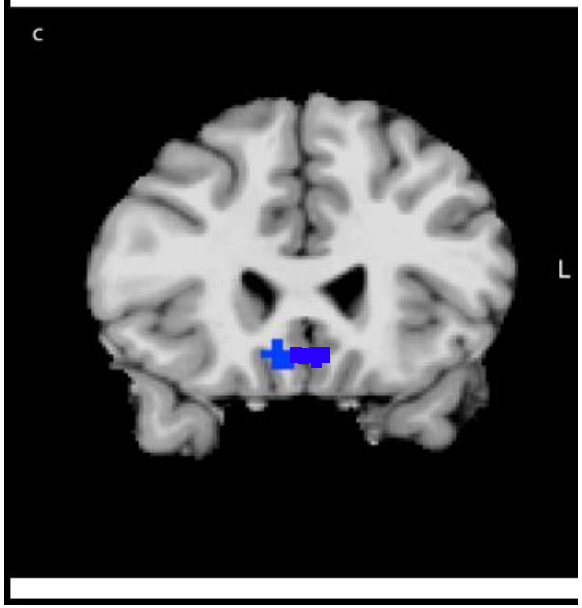
BIOL PSYCHIATRY 2005;57:624–632

T.A. Hare et al

Two brain regions are related to our reaction to threat

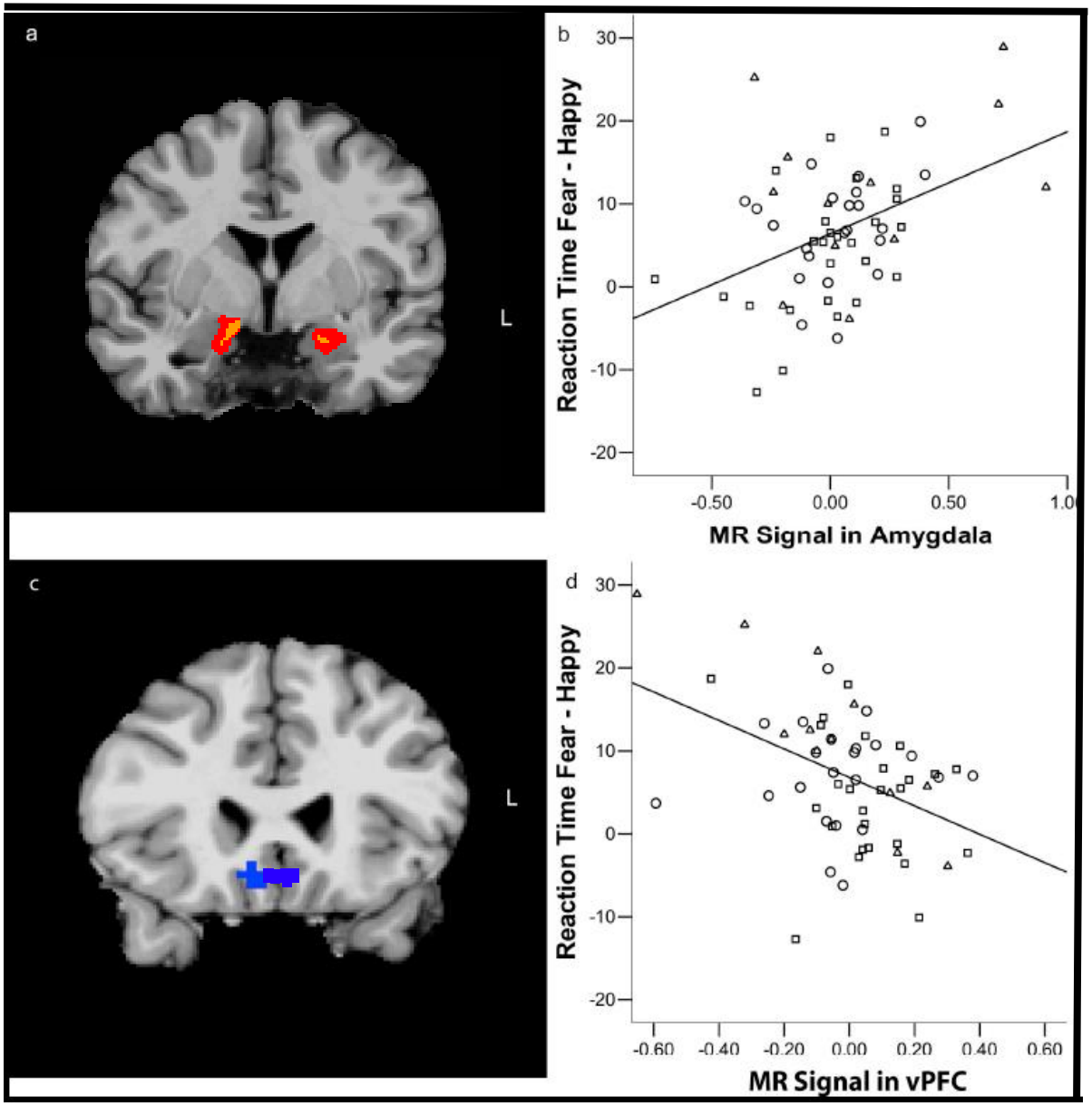


Amygdala

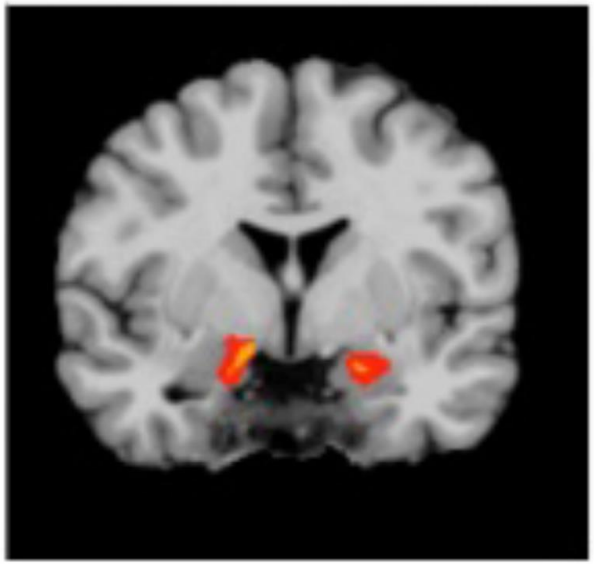


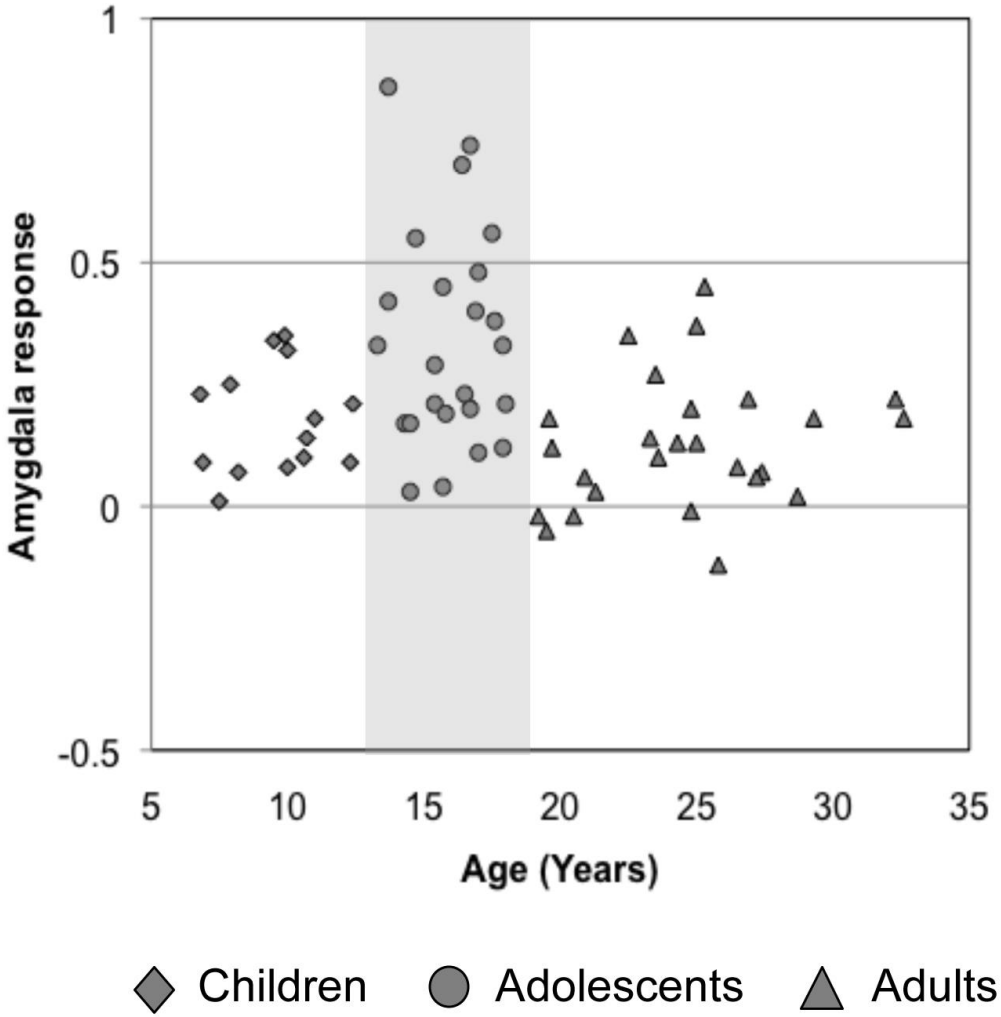
Prefrontal Cortex

These brain regions have opposing actions



Greater Amygdala Activity to Cues of Threat during Adolescence



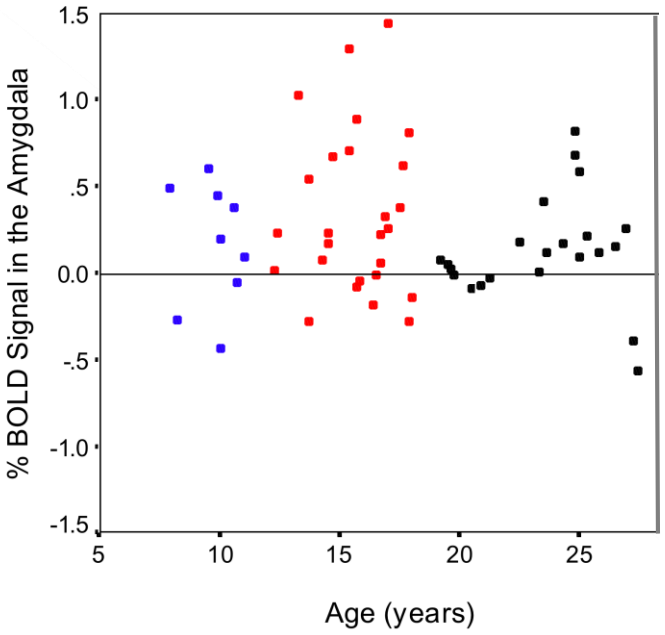


BIOL PSYCHIATRY 2008;63:927–934

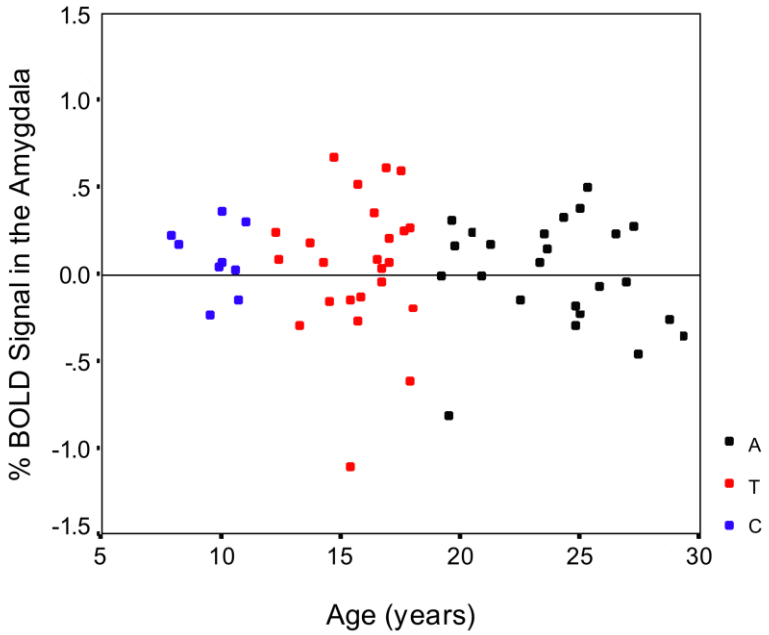
T.A. Hare *et al.*

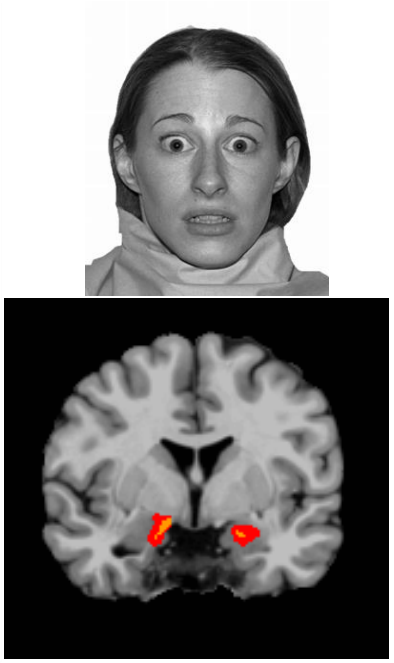
Amygdala Activity with repeated exposures to Threat

Early Trials



Late Trials

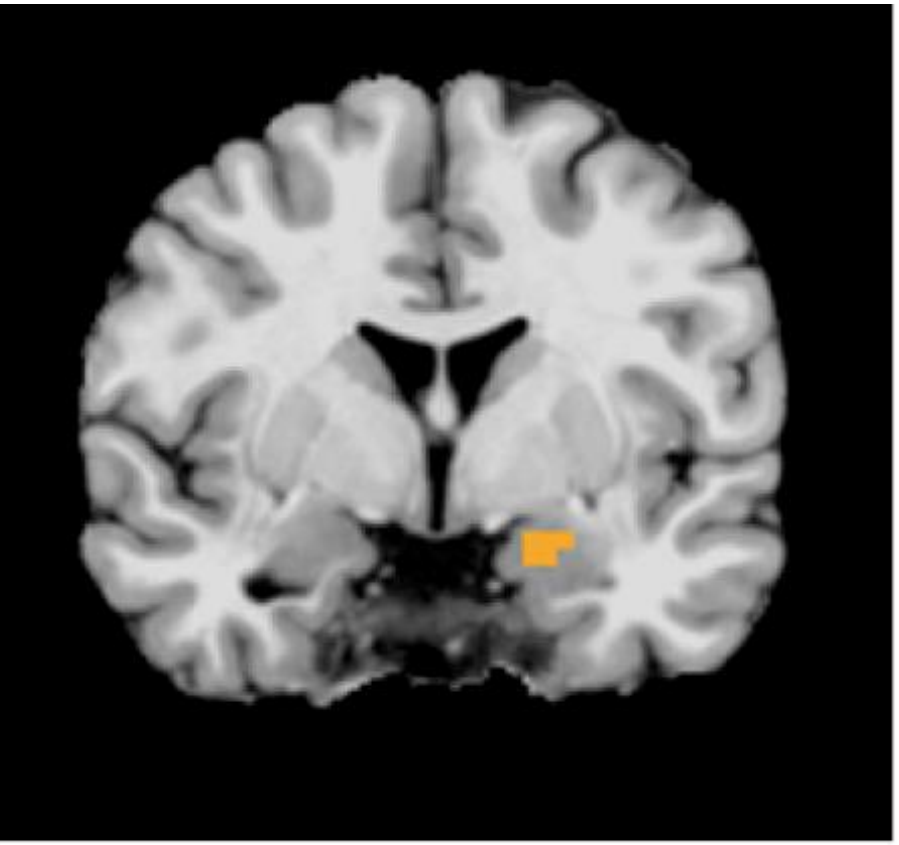




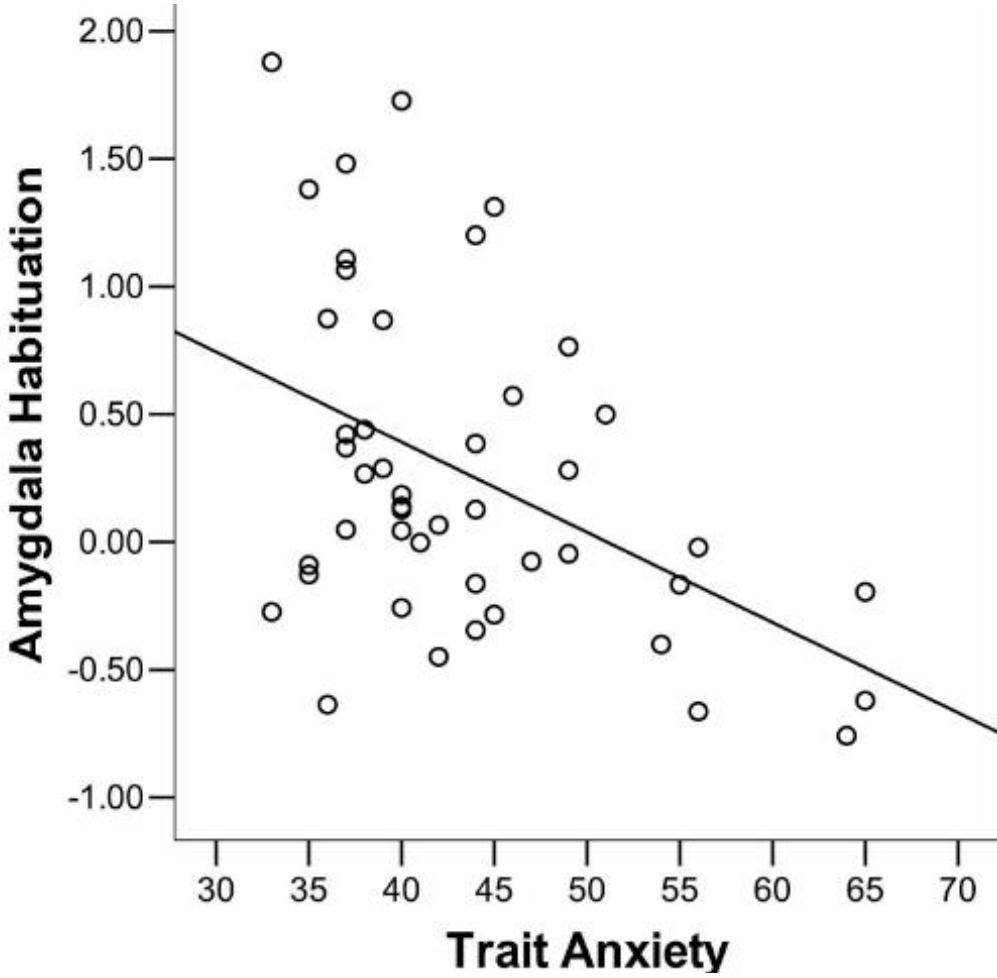
BIOL PSYCHIATRY 2008;63:927–934

T.A. Hare *et al.*

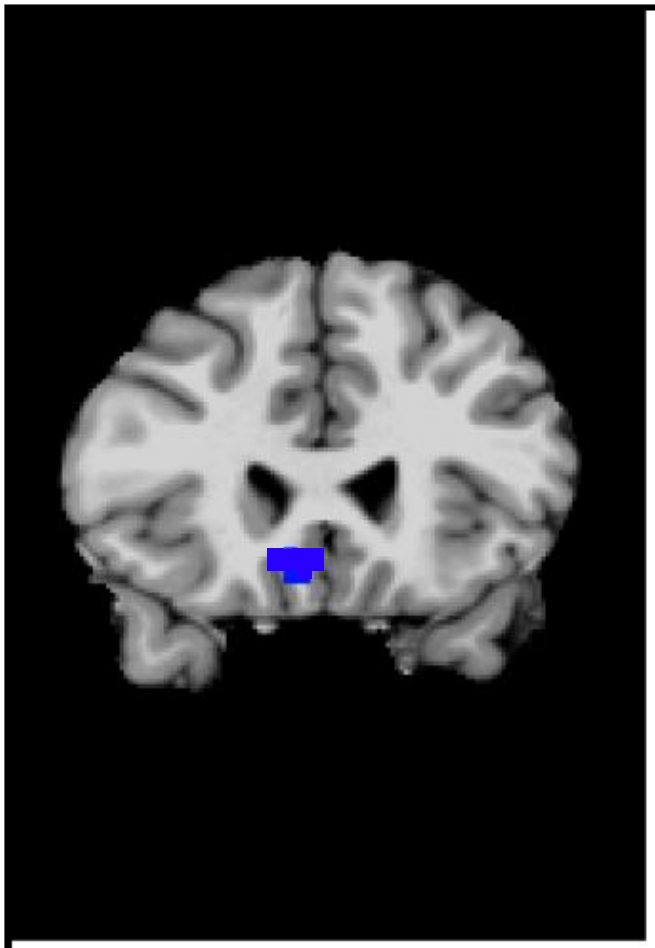
Prolonged amygdala activity with repeated exposure to empty threat is associated with Trait Anxiety

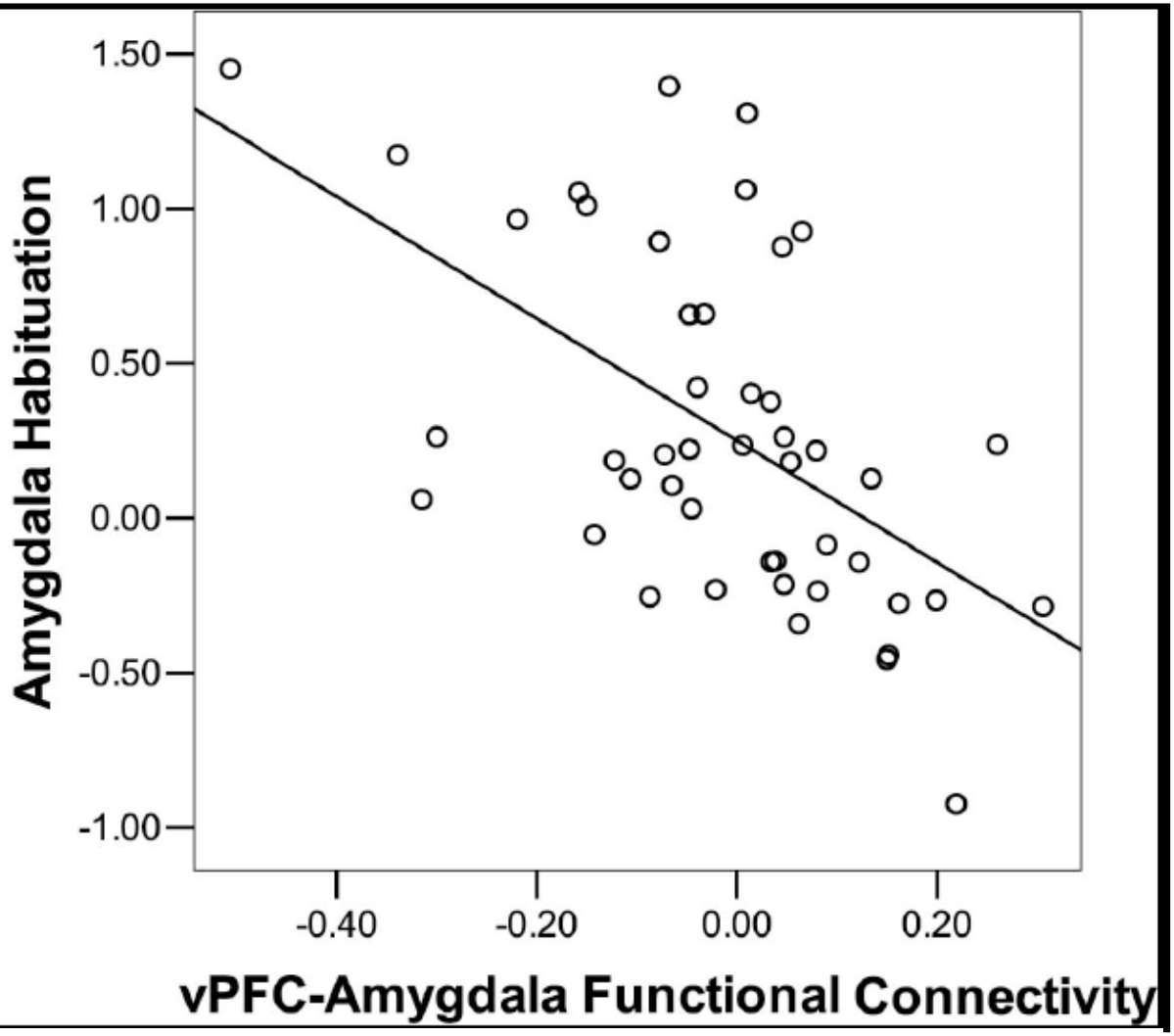


Amygdala



Development of Prefrontal Cortex and Amygdala connections underlies emotion regulation



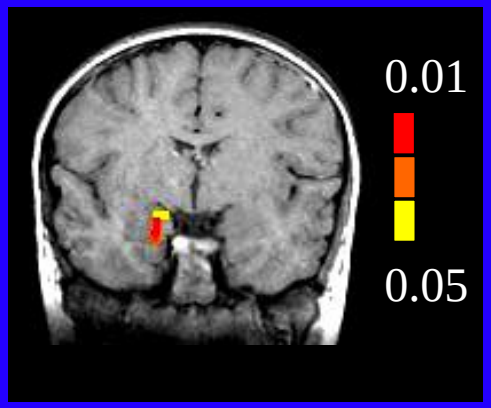


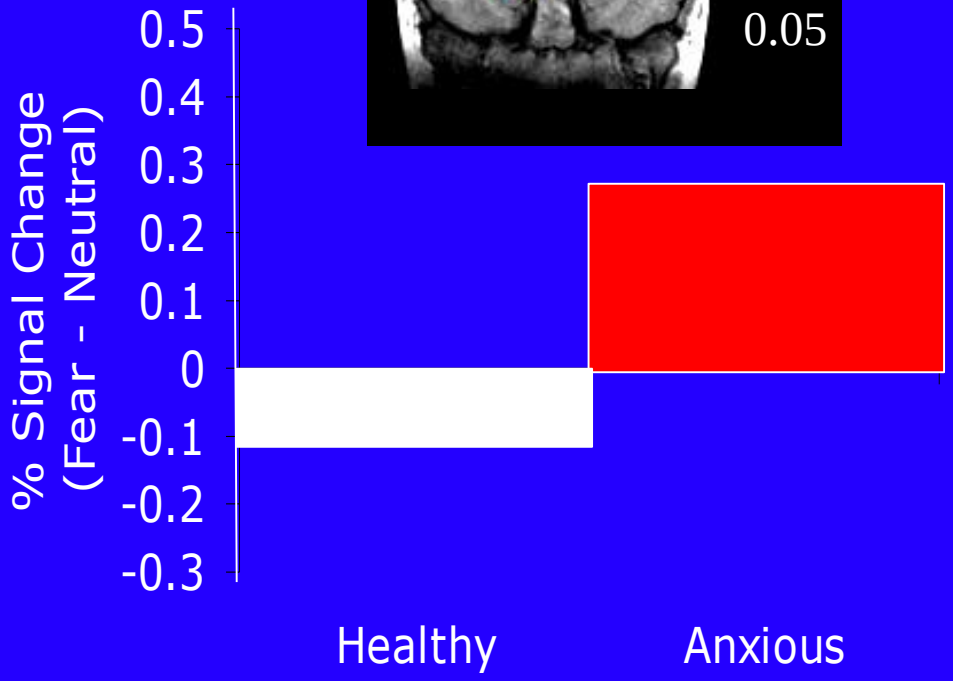
BIOL PSYCHIATRY 2008;63:927–934

Amygdala Activity to threat is associated with Anxiety Symptoms

Thomas, et al. (2001)

Archives of General Psychiatry





Amygdala Activity to Cues of Threat is Associated with Anxiety Symptoms

Thomas, et al. (2001)

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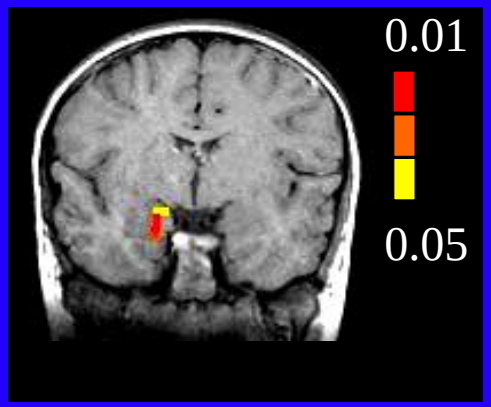
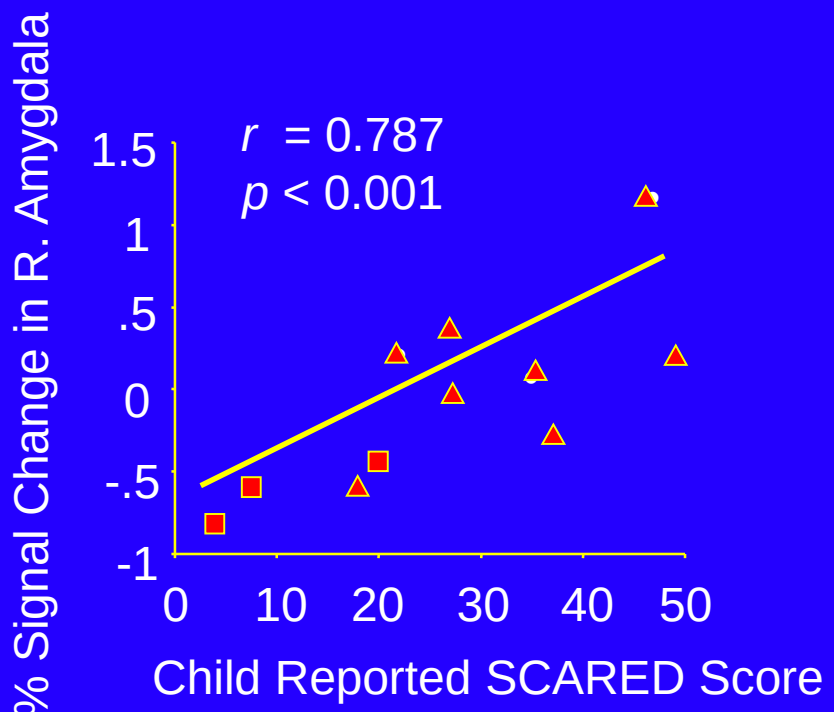
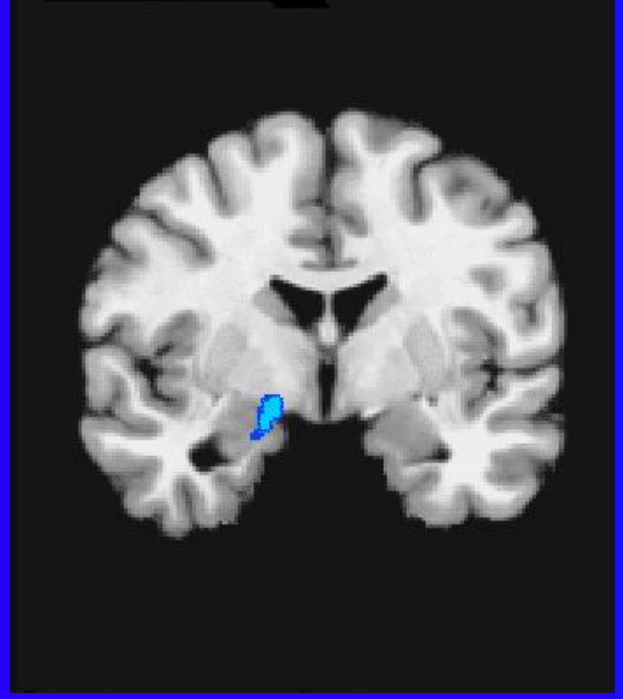




Low Anxiety



High Anxiety

Interim Summary

A hallmark of emotion regulation is the ability to learn when cues no longer signal a potential threat

Exposure based CBT builds on this principle- strengthening this ability with desensitization (repeated exposure to triggers of anxiety and stress)

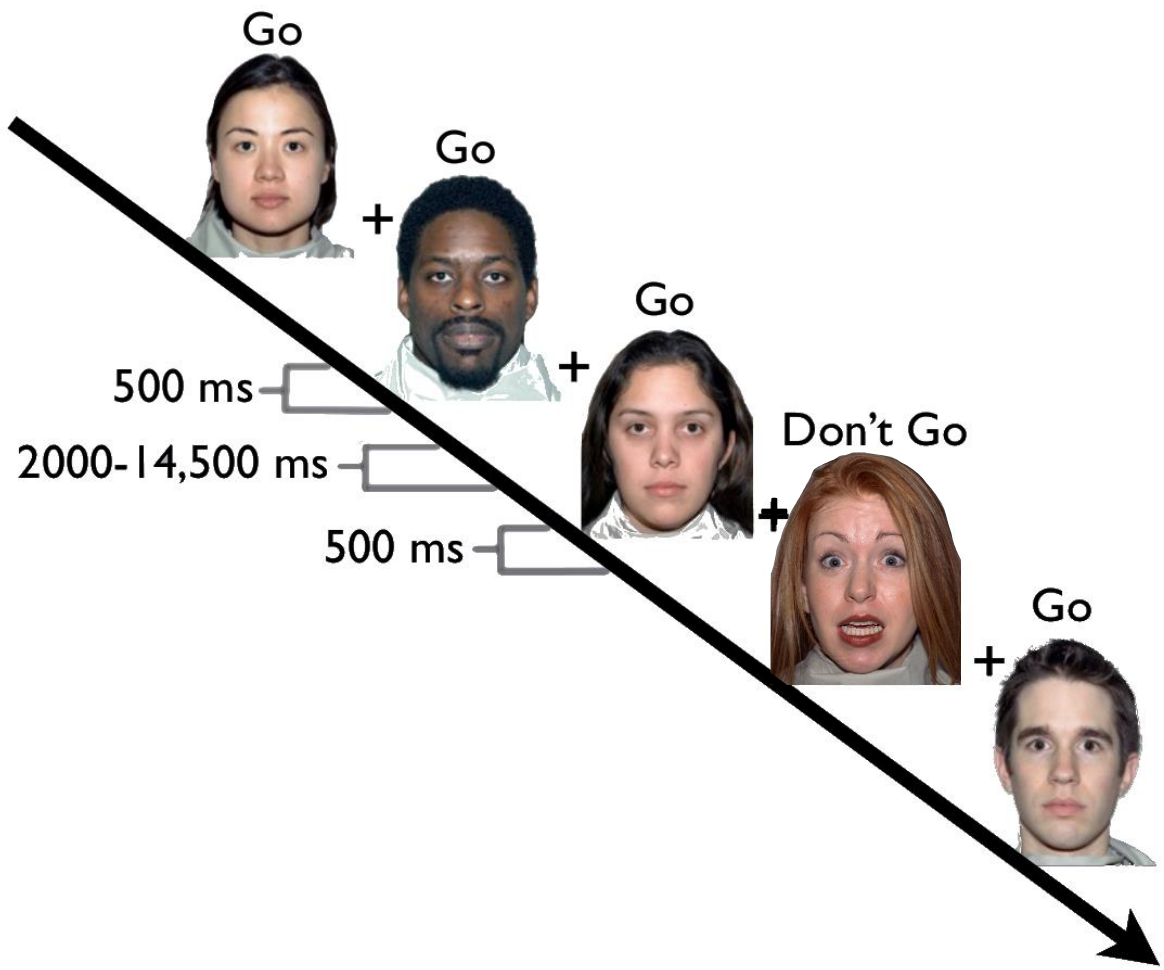
Environmental Factors:

Effects of Early Life Stress on Emotion Regulation

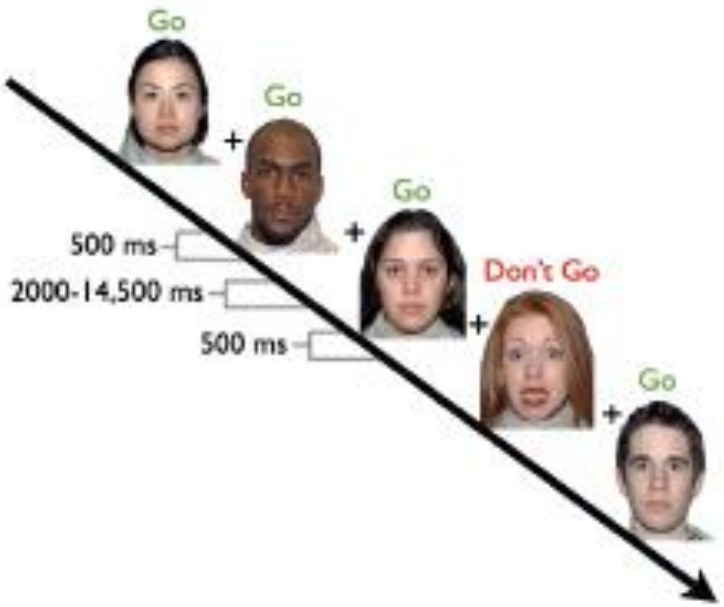
Early Experience of Institutionalization

Tested 2 or more years following adoption at 6-60 mo.

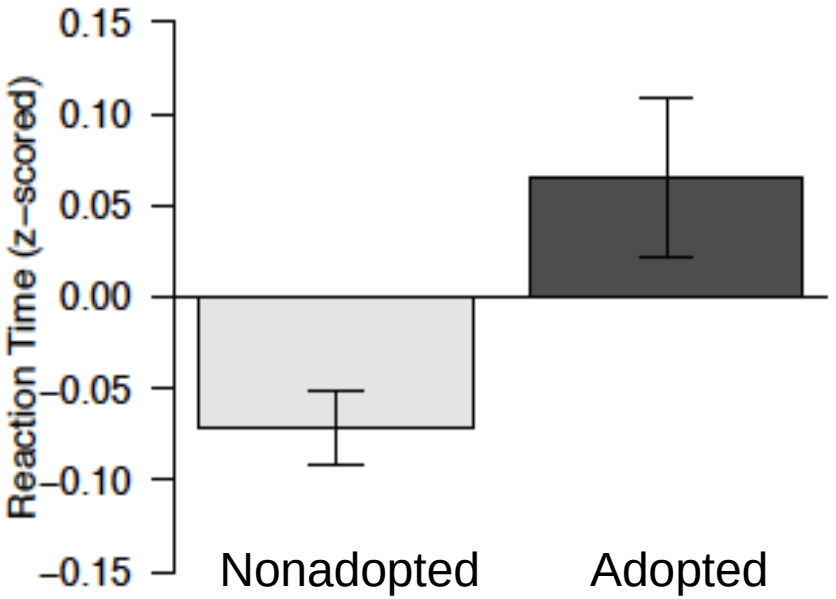
Emotion Regulation Paradigm



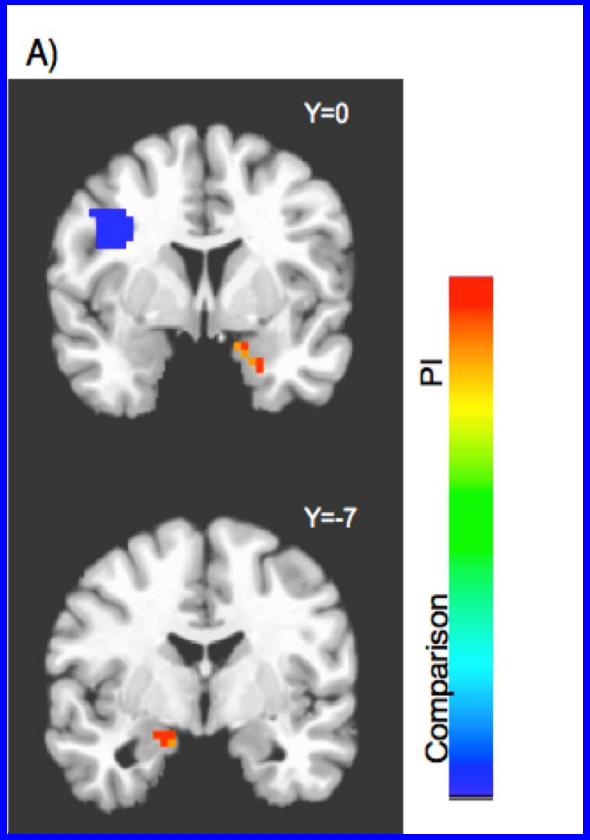
Emotion Regulation

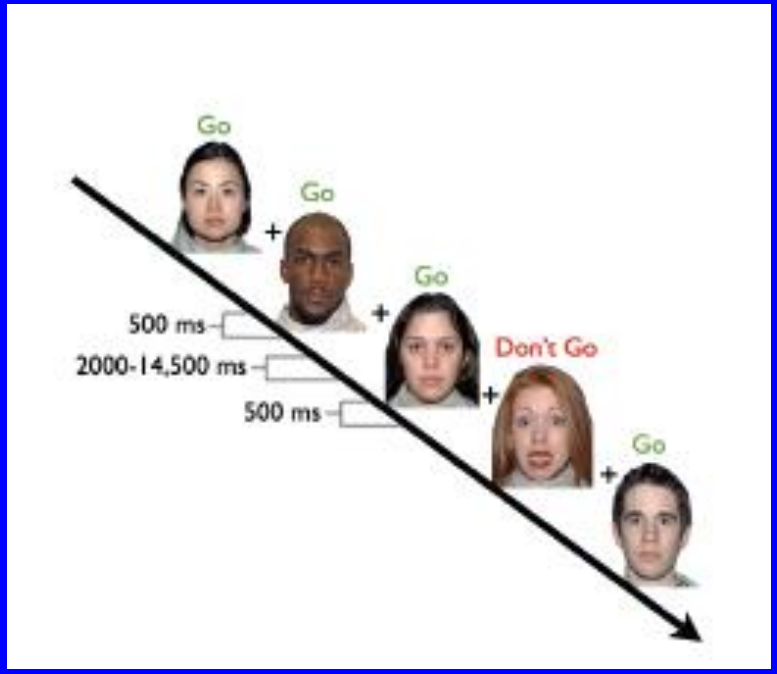


Response Latency in anticipation of Threat



Effects of Early Institutionalization: Amygdala response to irrelevant threat cues

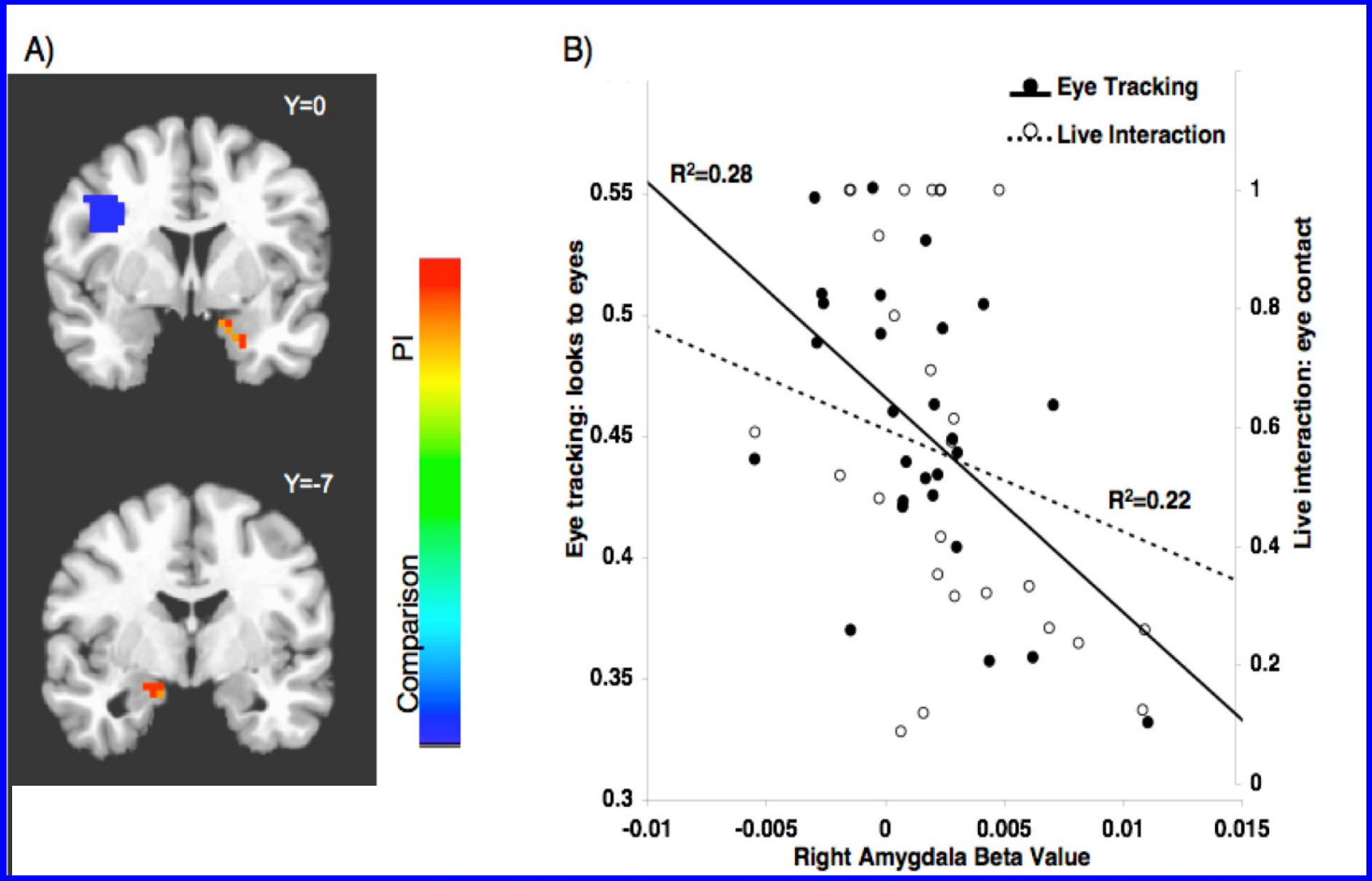




Tottenham et al 2011 *Dev Science*

Effects of Early Institutionalization:

Amygdala response to threat is associated with eye contact with mother and eye gaze



Tottenham et al 2011 *Dev Science*

Measuring Early Life Stress in Mice

Early Life Stress

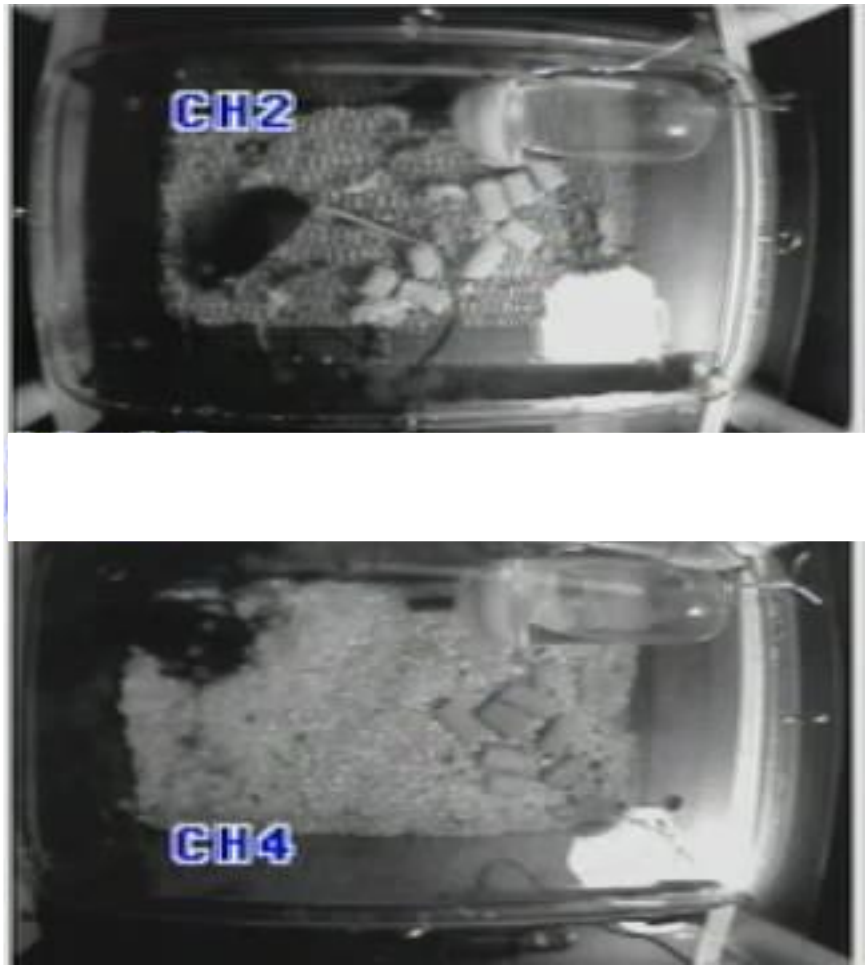
STRESS

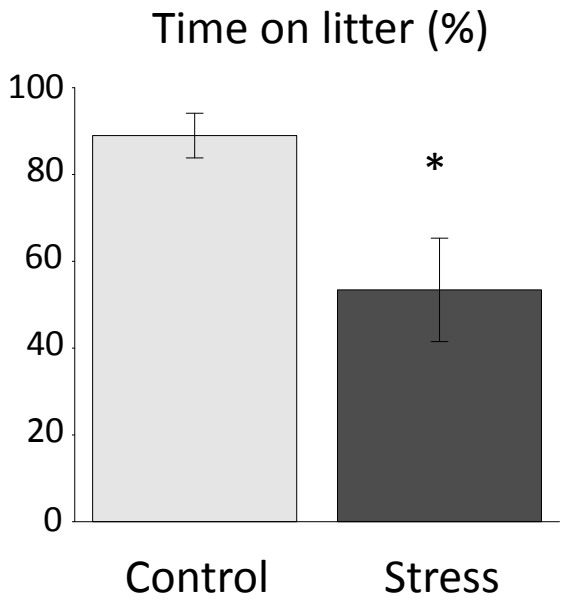
CONTROL

Early Life Stress

STRESS

CONTROL

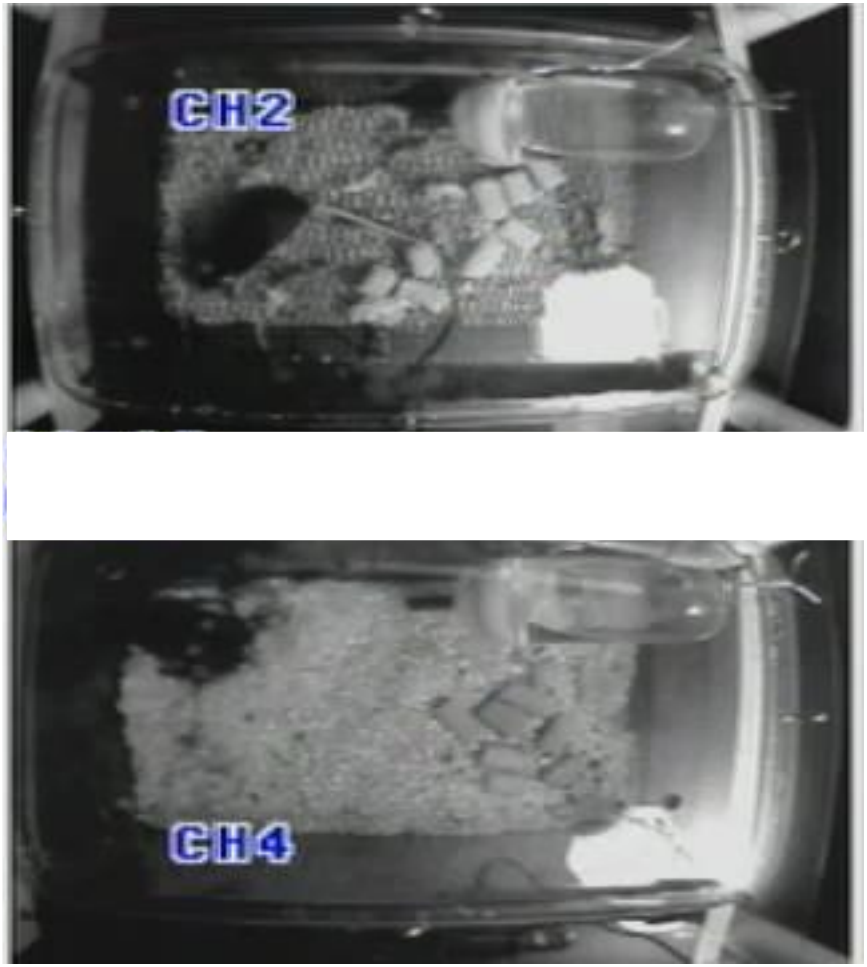


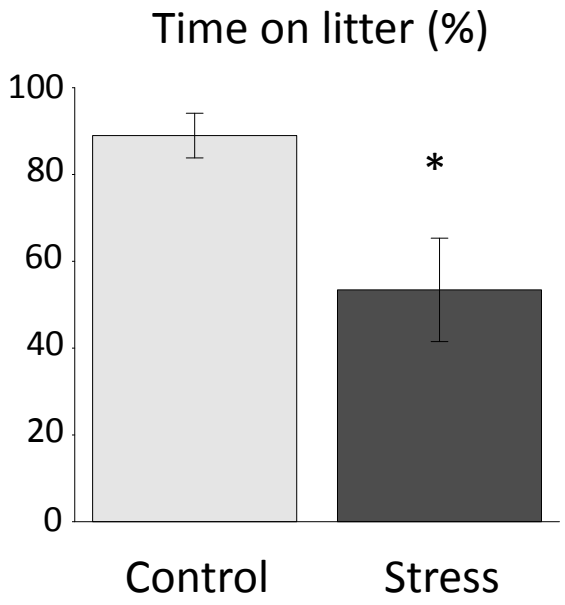


Early Life Stress

STRESS

CONTROL





Malter Cohen et al 2013 PNAS

But how do we get mice to ignore potential threat?

But how do we get mice to ignore potential threat?

Behavioral Task

Training
Days 1-3

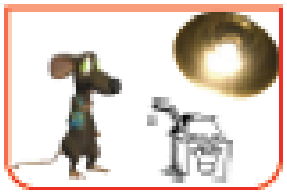
Go

Home Cage
Day 4

Go

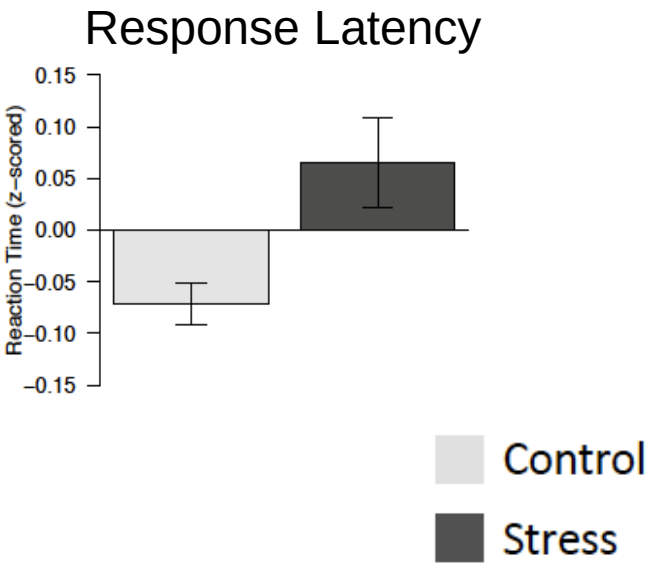
Novel Cage
Day 5

Don't Go



Effects of Early Life Stress on Brain and Behavior

HUMAN



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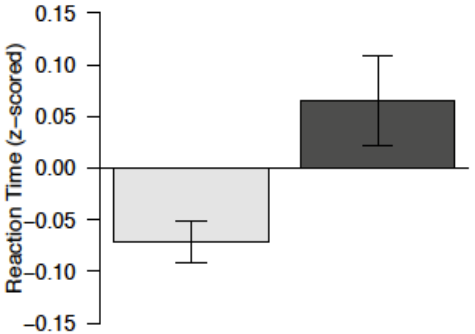
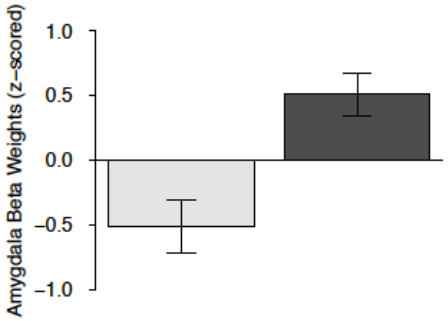
Effects of Early Life Stress on Brain and Behavior

HUMAN

Response Latency



Amygdala Activity



Control

Stress

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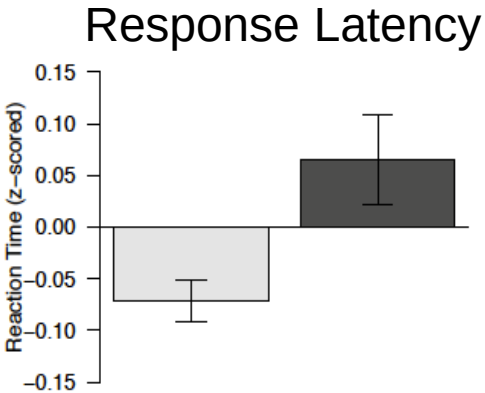
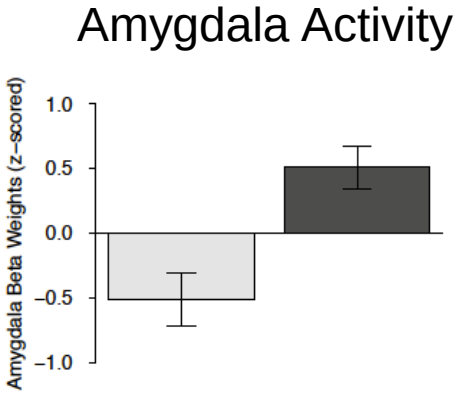
Effects of Early Life Stress on Brain and Behavior

HUMAN

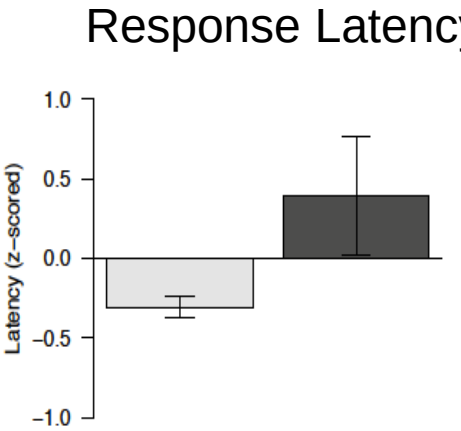




Control

Stress

MOUSE



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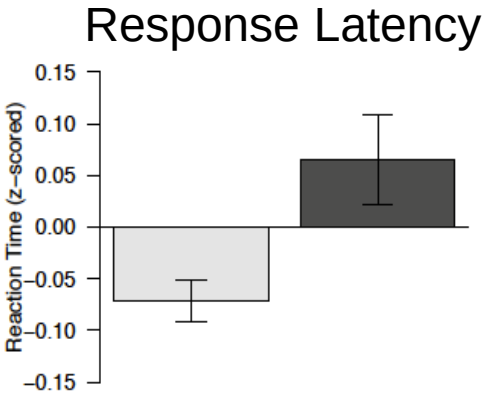
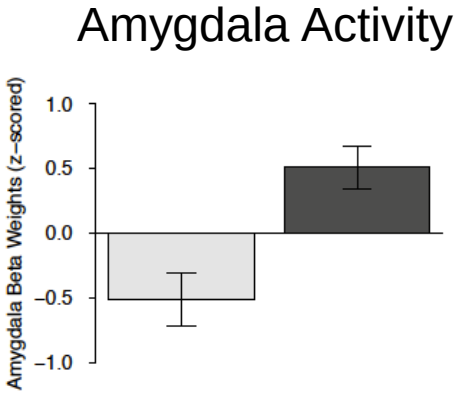
Effects of Early Life Stress on Brain and Behavior

HUMAN

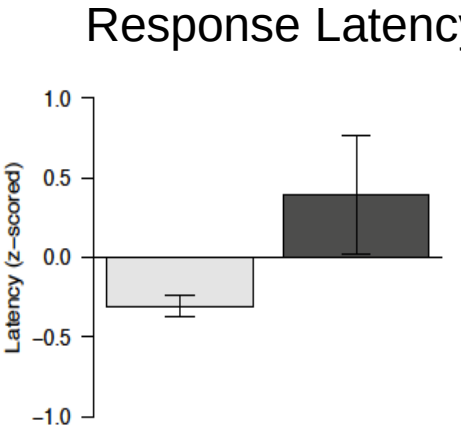


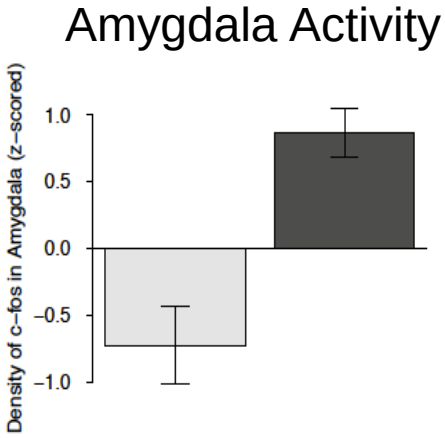


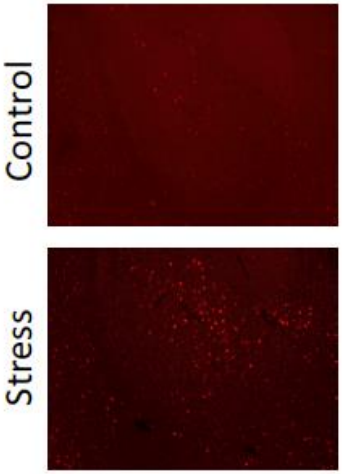
Control

Stress

MOUSE







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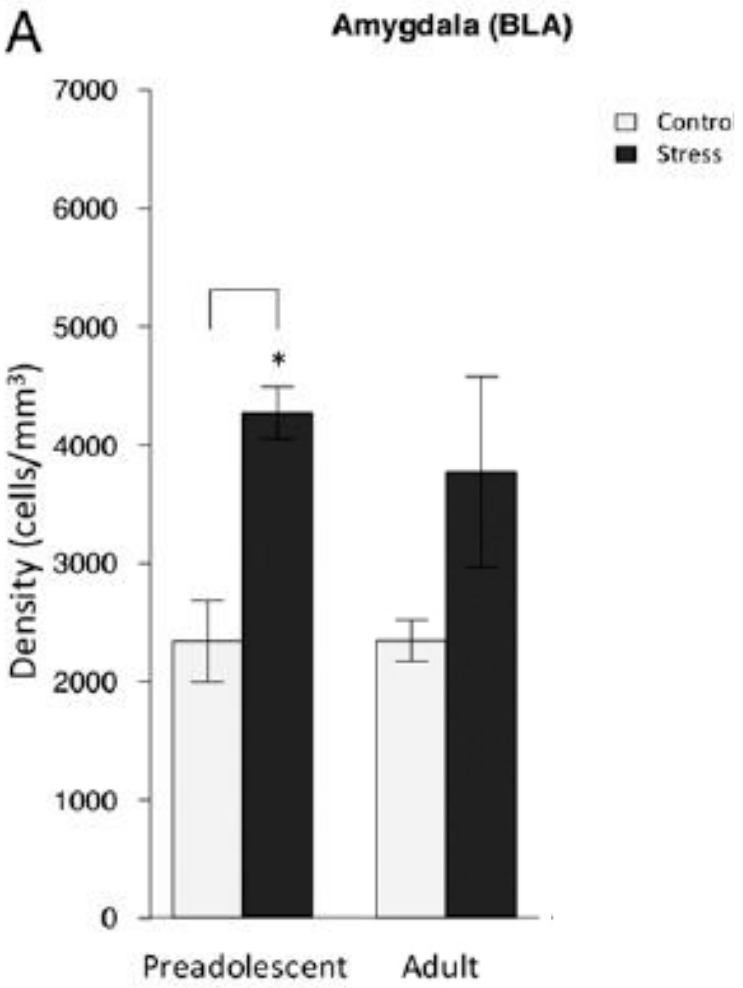
Persistence of Early Life Stress Effects



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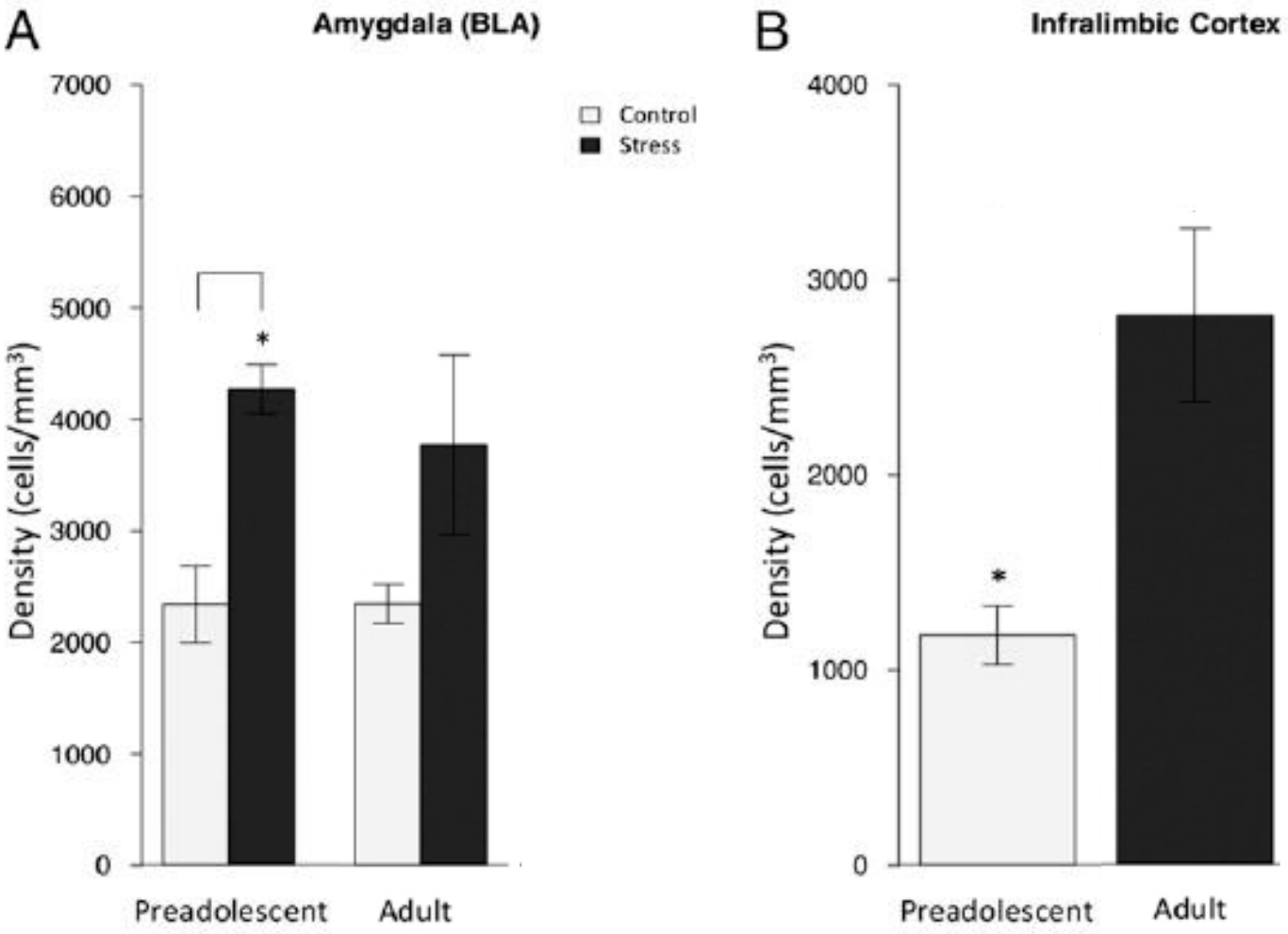
Persistence of Early Life Stress



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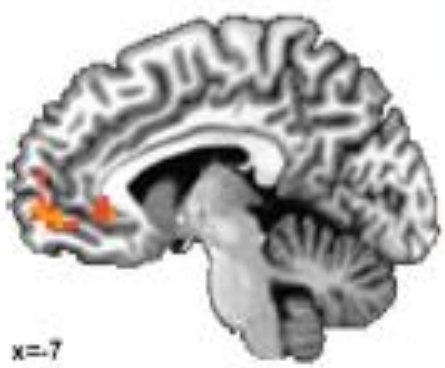
Early Life Stress leads to Closing of Sensitive Period of Neural Development



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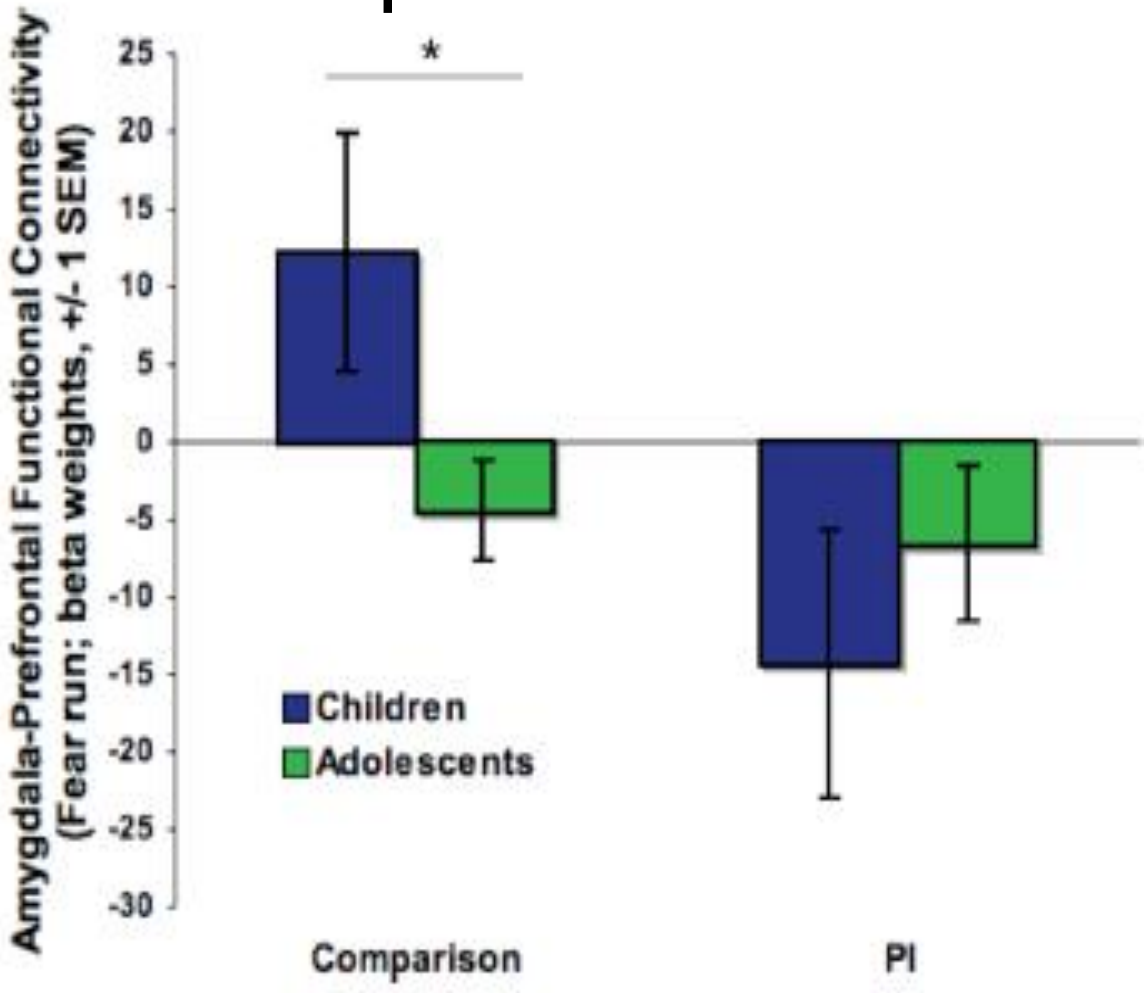

Gee et al 2013 PNAS

Effects of Early Life Stress

-Early and lasting alterations in amygdala circuitry and function with prolonged stress

-Effects are not reversed when the stressor is removed nor diminished with the development of prefrontal regulation regions.

Conclusions

These findings underscore the importance of:

- Intervening early to prevent atypical wiring of the brain during development;
- Developing novel treatments that bypass prefrontal circuitry, by altering fear memories (Monfils et al 2009; Schiller et al 2010) or teaching safety signals to reduce stress and anxiety (Christianson et al 2012 J Neuroscience).

FORMER AND CURRENT SACKLER FELLOWS

Dima Amso (Brown)
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Matt Malter Cohen
Matt Davidson (U Mass)
Hugo Decker
Andrew Drysdale
Stephanie Duhoux (Mt Sinai)
Sarah Durston (Utrecht)
Adriana Galvan (UCLA)
Dylan Gee
Todd Hare (Zurich)
Cate Hartley (Weill Cornell)
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Rebecca Jones (Weill Cornell)
Conor Liston (Weill Cornell)
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Leah Somerville (Harvard)
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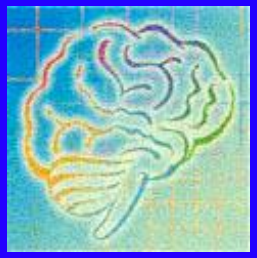
Nim Tottenham (Columbia)
Jason Zevin (USC)



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