fMRI of Development

Clinical Applications?

Daniel S. Pine, MD

Emotion & Development Branch

NIMH
National Institute of Mental Health

Outline

- **Introduction**
- **Diagnostic Specificity**
- **Risk versus Disorder**
- **Novel Therapeutics**

Outline

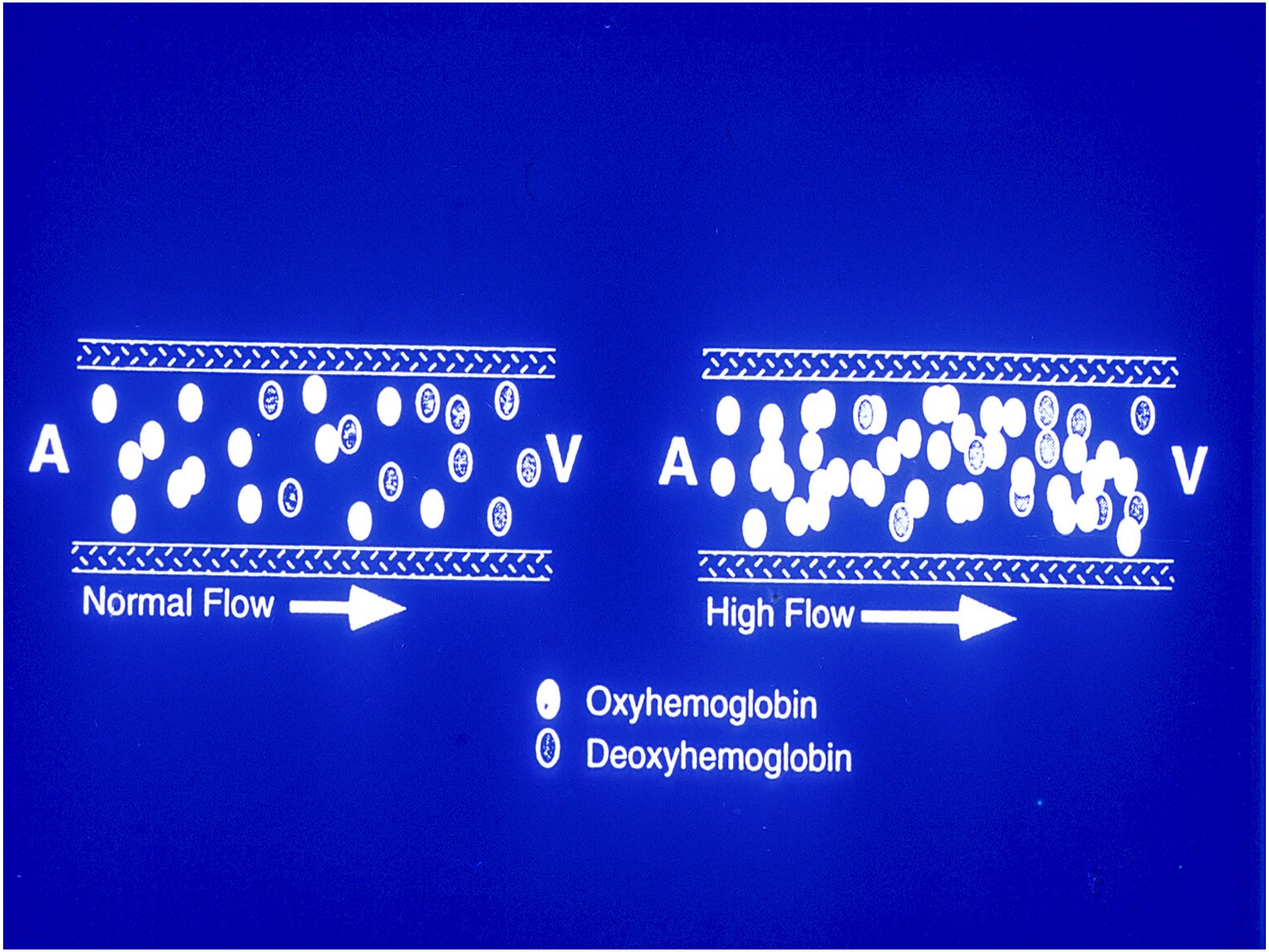
- **Introduction**
- **Diagnostic Specificity**
- **Risk versus Disorder**
- **Novel Therapeutics**

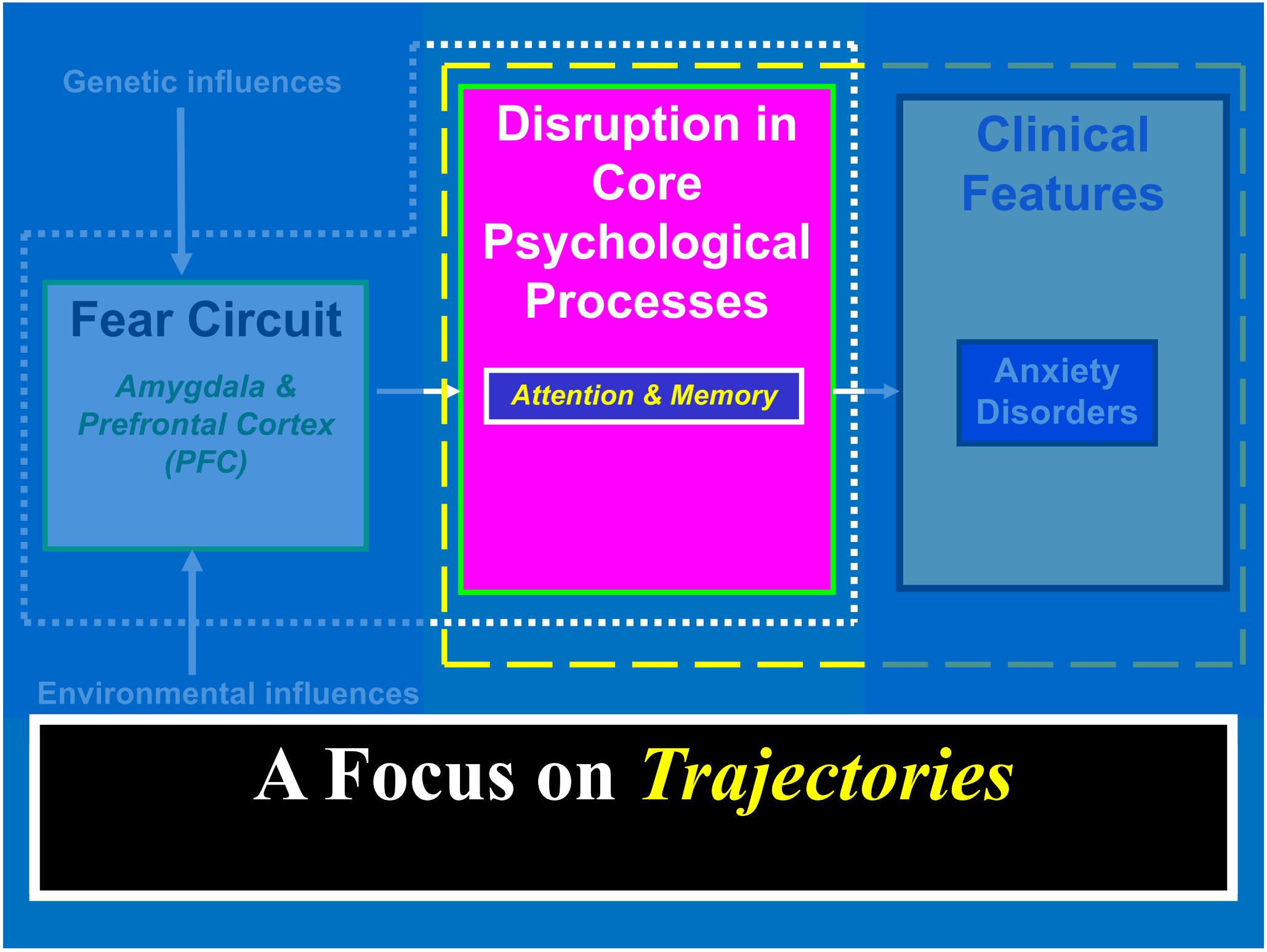
Pediatric Mental Illnesses

- **Extremely Common**
- **Usually Transient**
  - ***But…predicts long-term problems***
- **Prediction, Therapeutics**

Pediatric Mental Illnesses

- Ground research in Neuroscience
- Unique role of fMRI
- Integration of clinical & basic


A
V
Normal Flow
A
V
High Flow
Oxyhemoglobin
Deoxyhemoglobin


Genetic influences
Fear Circuit
Amygdala & Prefrontal Cortex (PFC)
Environmental influences
Disruption in Core Psychological Processes
Attention & Memory
Clinical Features
Anxiety Disorders
A Focus on Trajectories

Outline

- **Introduction**
- **Diagnostic Specificity**
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Outline

- Introduction
- **Diagnostic Specificity**
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Outline

- Introduction
- **Diagnostic Specificity** ***Nosology***
- Risk versus Disorder
- Novel Therapeutics

MAY 16, 2013

THE RATS OF N.I.M.H.

POSTED BY GARY GREENBERG

THE NEW YORKER

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Psychiatry's Guide Is Out of Touch With Science, Experts Say

By PAM BELLUCK and BENEDICT CAREY
Published: May 6, 2013

Health The New York Times

NIH National Institute of Mental Health

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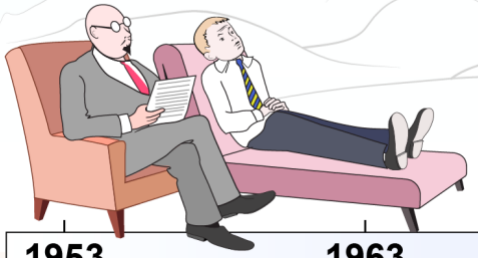
Sixty Years of Child Psychiatry Nosology



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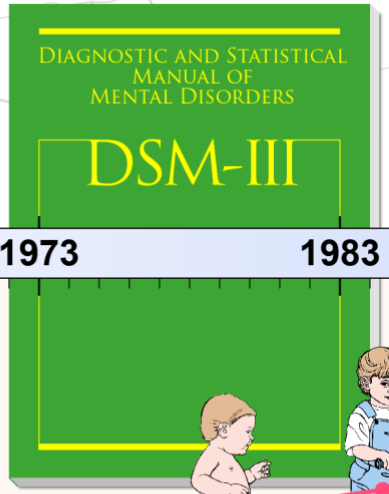
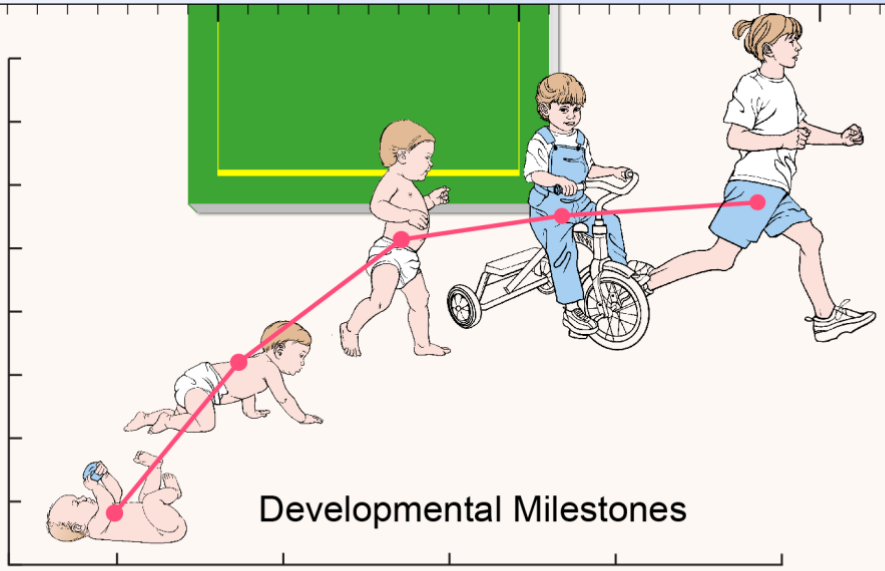
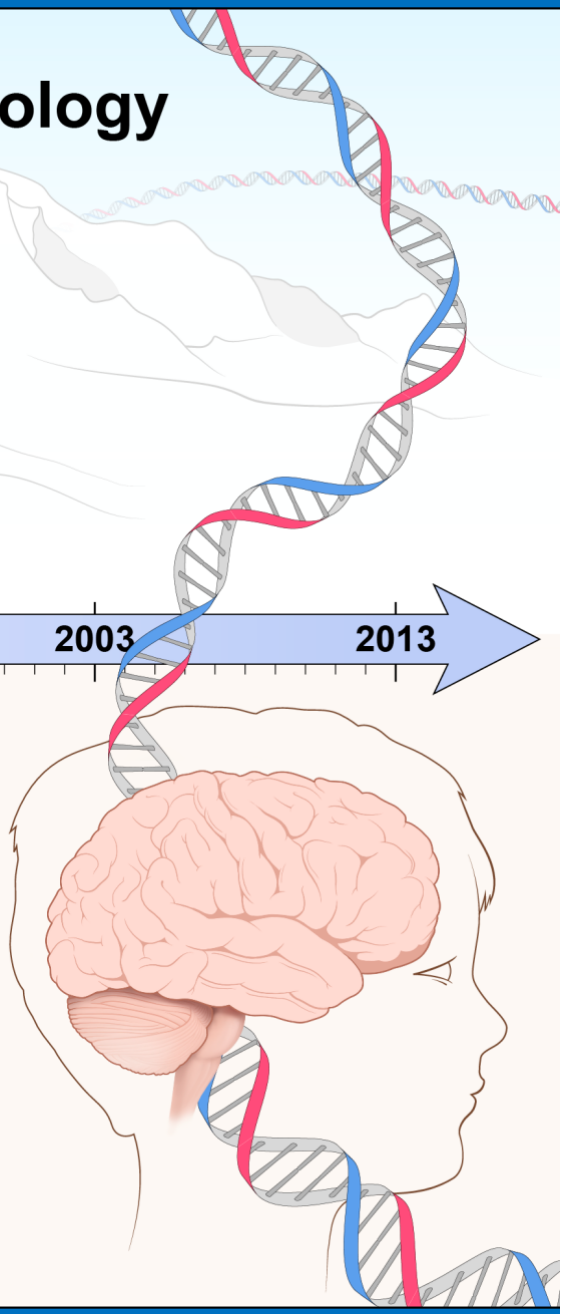






Diagnostic Specificity

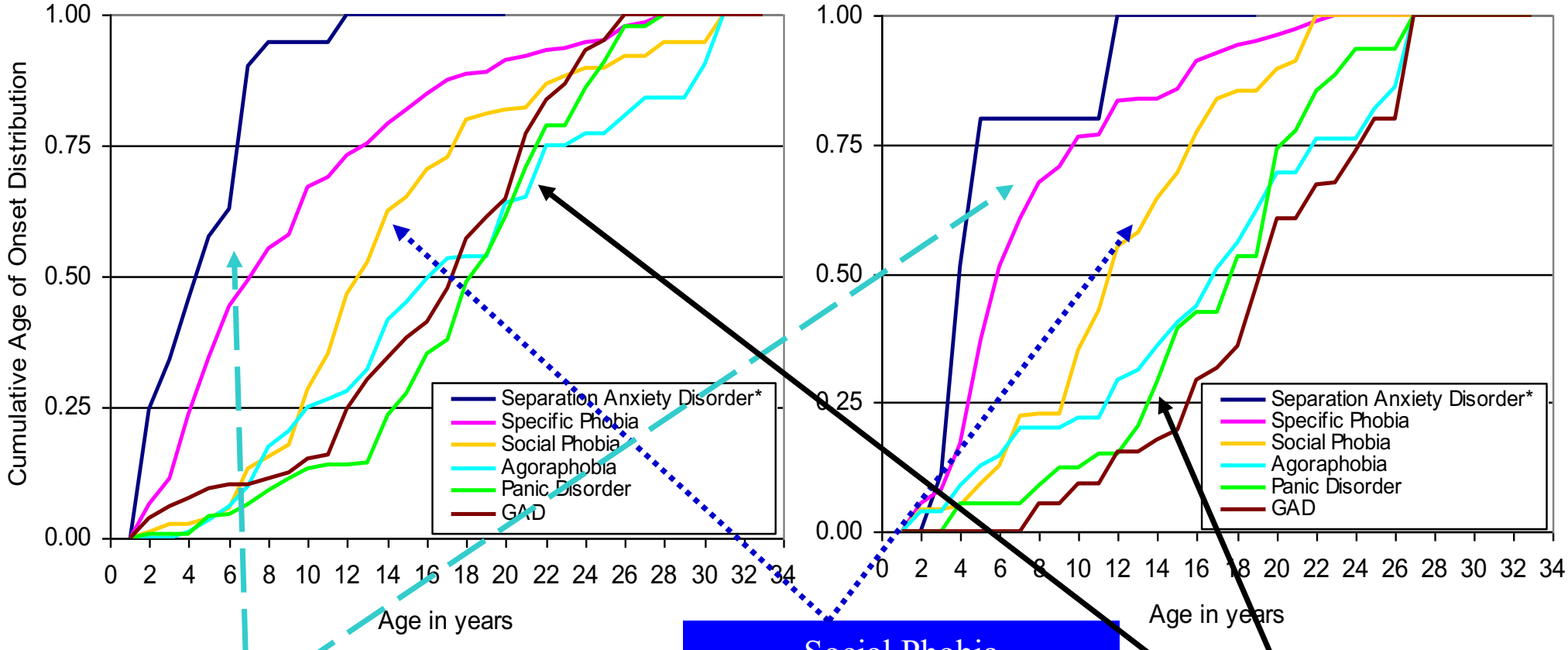
- Unique, stable patterns manifest
- Comorbidity is rampant
- Vexing questions on anxiety

Age of Onset of Specific Anxiety Disorders

Females

Specificity?

Males



Social Phobia

Separation Anxiety Disorder & Specific Phobia

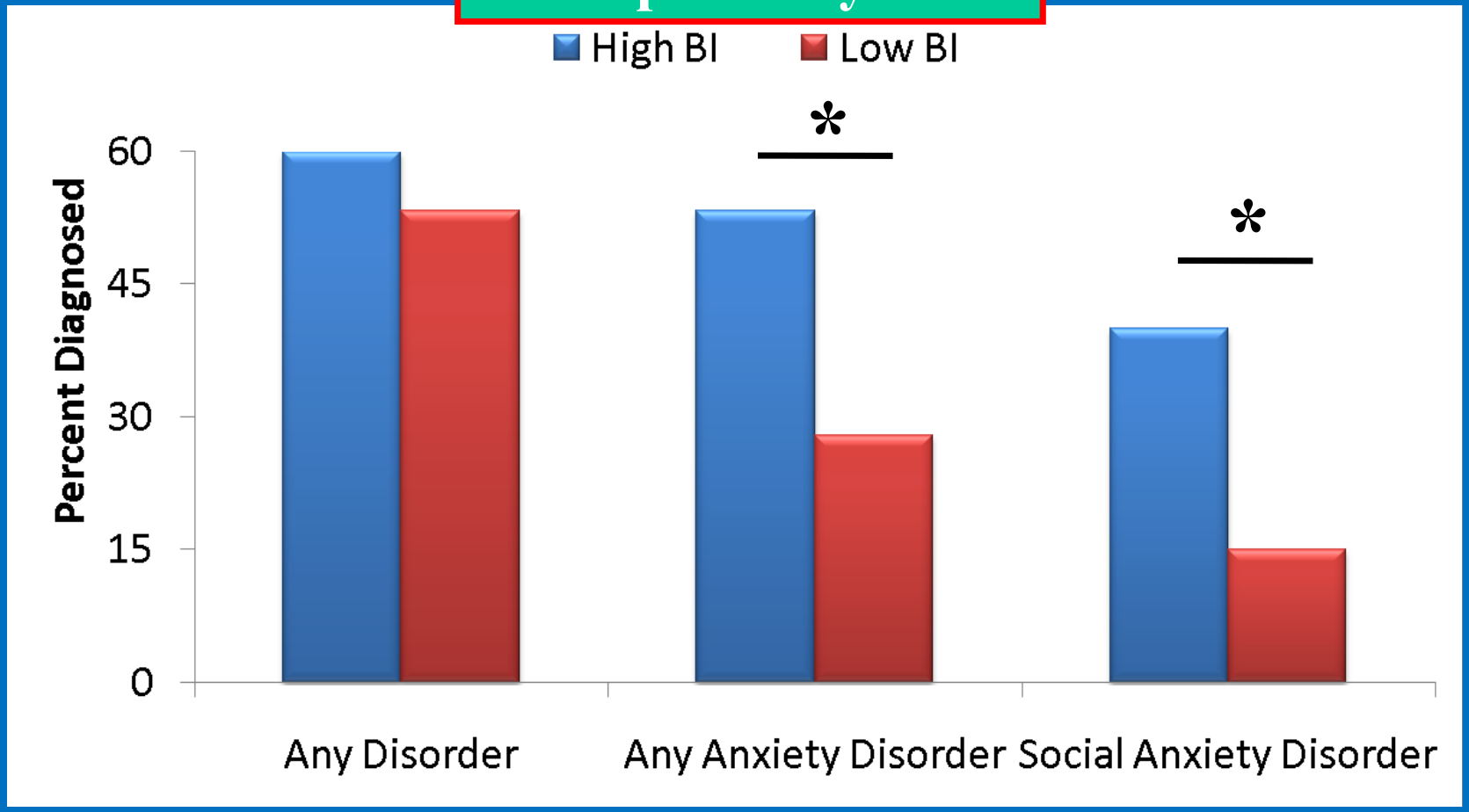
Panic Disorder/Agoraphobia & Generalized Anxiety Disorder

Behavioral Inhibition and Anxiety

Specificity?

Behavioral Inhibition and Anxiety

Specificity?



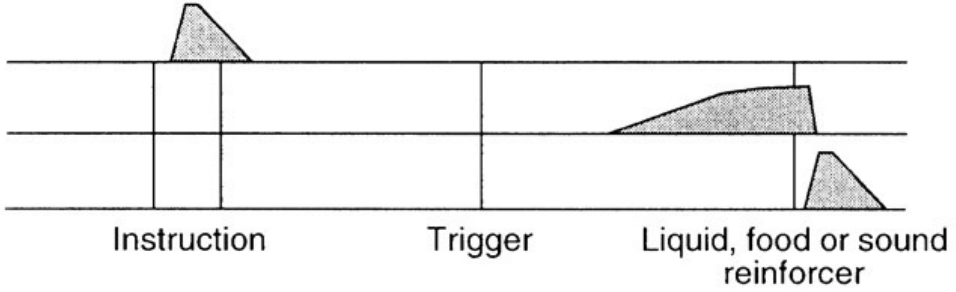
Chronis-Tuscano et al, 2009

ORBITOFRONTAL CORTEX

Response to reward-predicting instruction

Activation during expectation of reward

Response to primary reward



STRIATUM

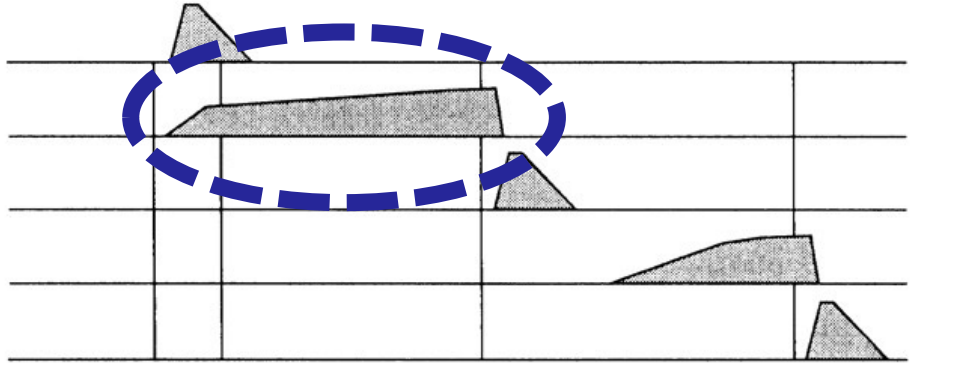
Reward-dependent response to movement preparatory instruction

Reward-dependent activation during movement preparation

Reward-dependent response to movement trigger

Activation during expectation of reward

Response to primary reward

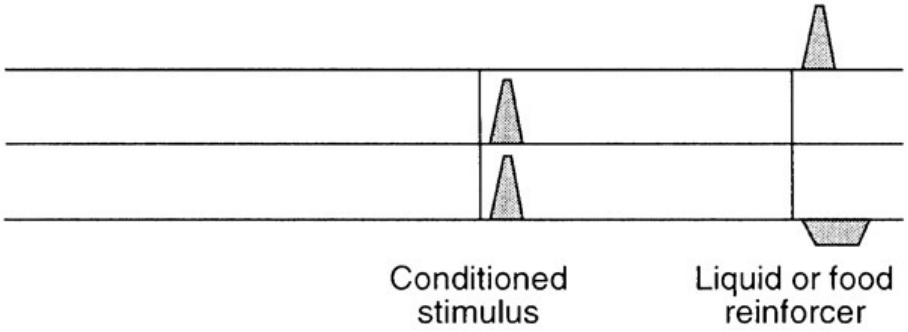


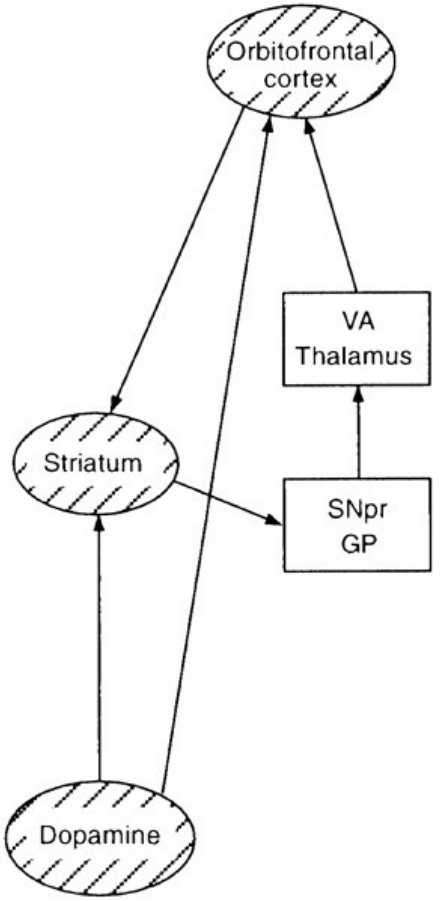
DOPAMINE NEURON

Response to unpredicted primary reward

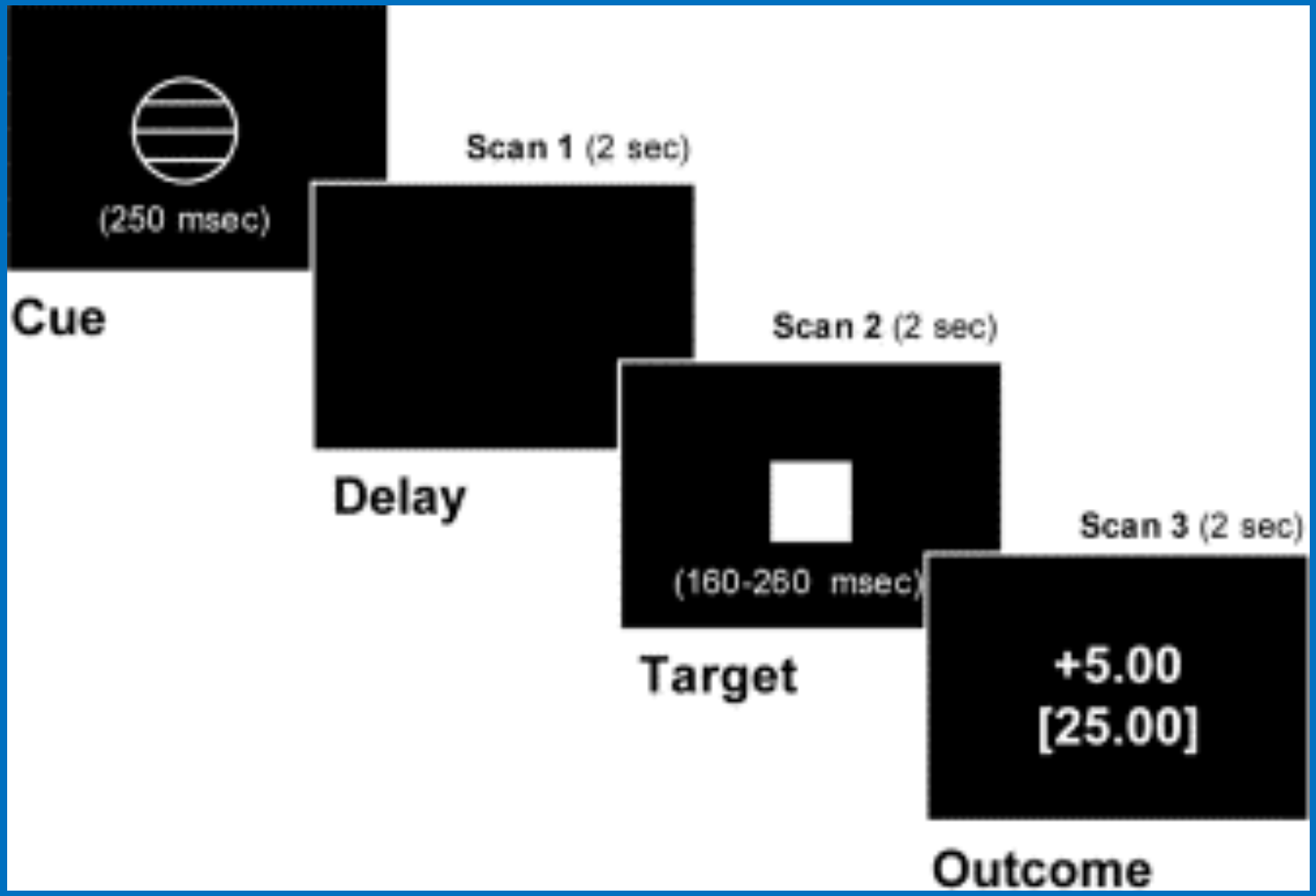
Response to reward-predicting stimulus

Response to reward-predicting stimulus and omitted reward





Assessing Reward Systems Function



BEHAVIORAL INHIBITION

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14 Months:	Behavioral Inhibition
24 Months:	Behavioral Inhibition
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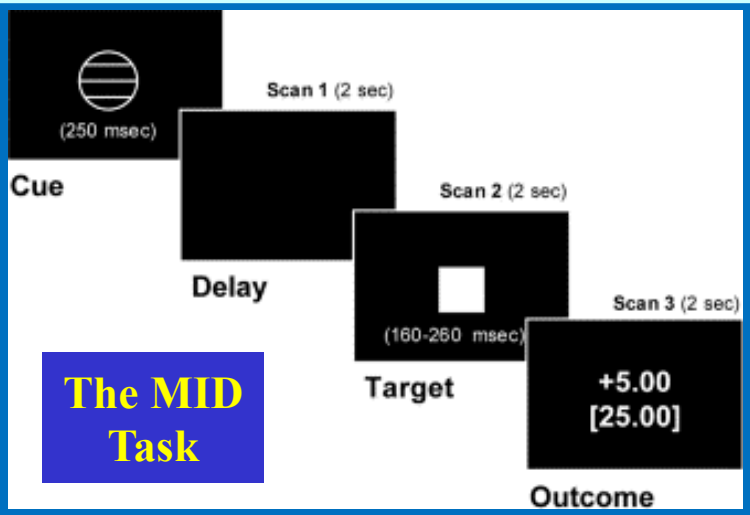
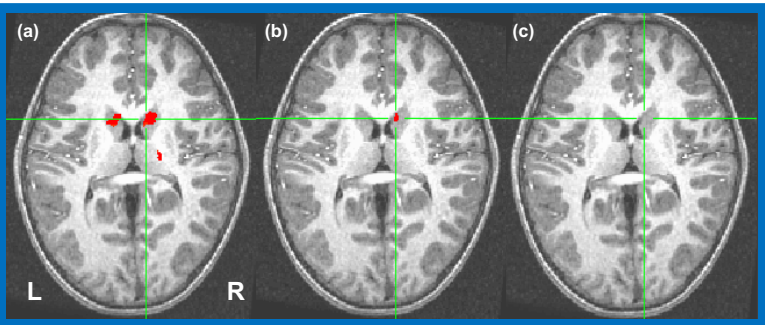
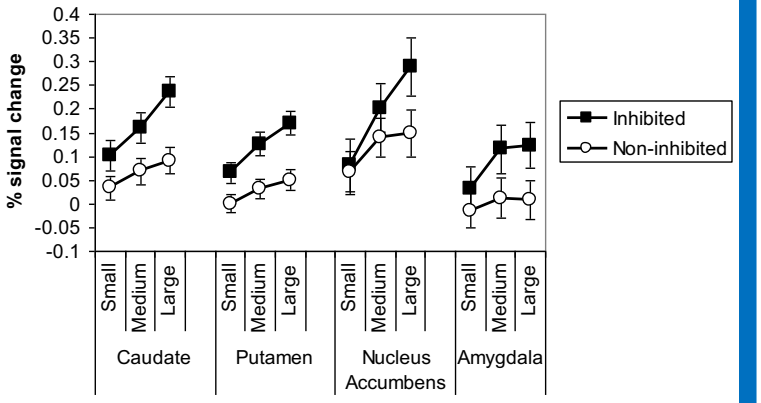
7 Years:	Quartet Peer Interaction
14 Years:	Clinical Assessment, fMRI
17 Years:	Clinical Assessment, fMRI

Fox et al. 2006

Behavioral Inhibition, Anxiety, & Reward Processing

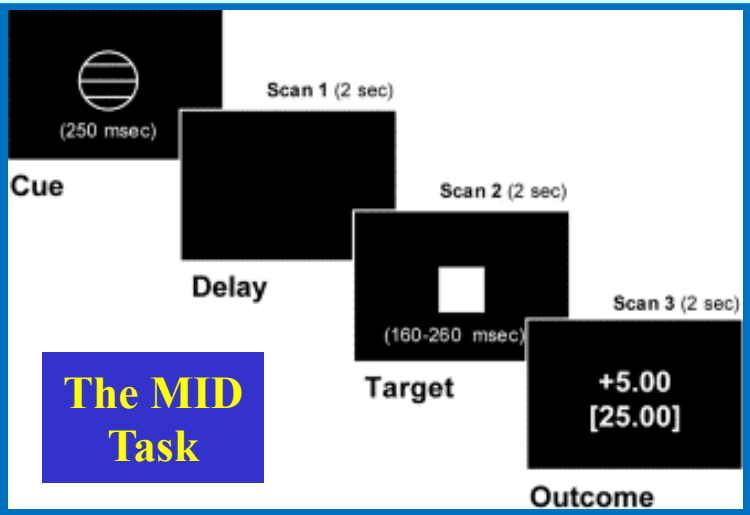


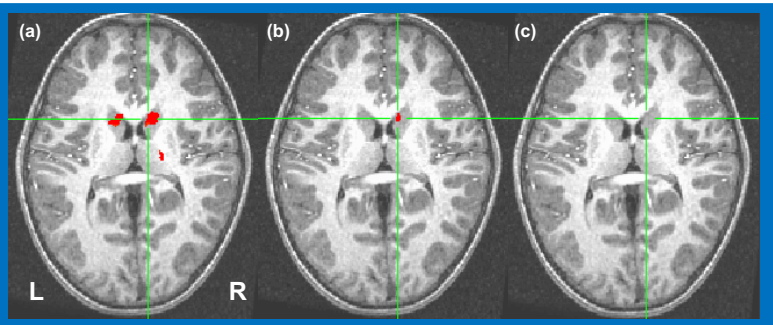


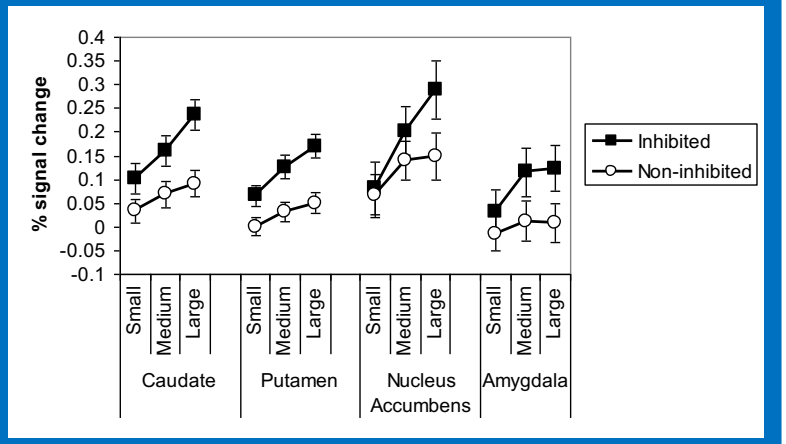


Behavioral Inhibition *Guyer et al. 2006*

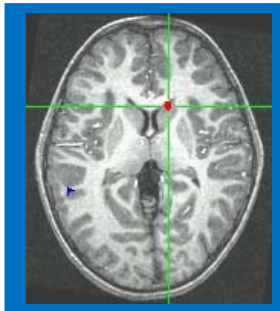
Behavioral Inhibition, Anxiety, & Reward Processing



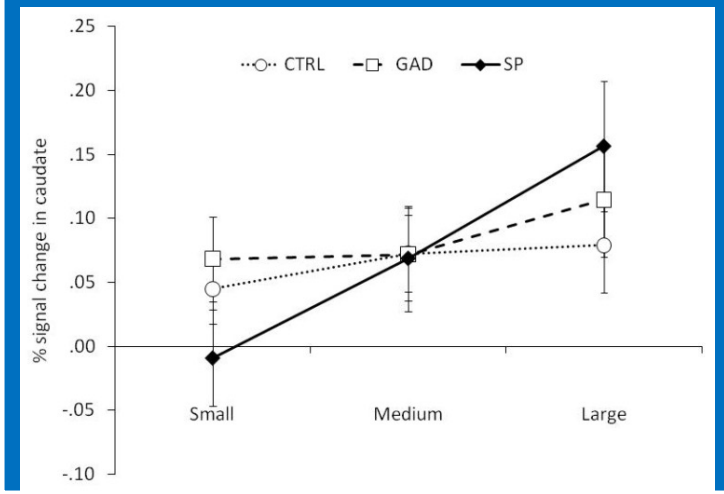




Behavioral Inhibition *Guyer et al. 2006*



Anxiety *Guyer et al. 2012*



Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

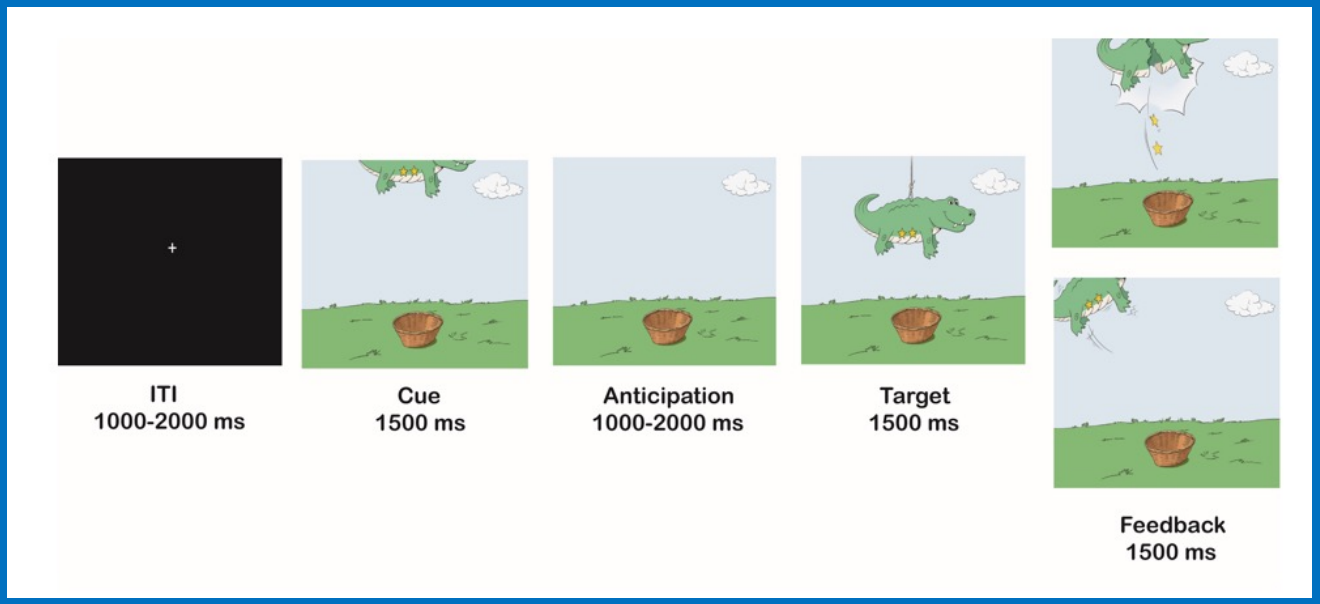
Contradicted and Initially Stronger Effects in Highly Cited Clinical Research

John P. A. Ioannidis, MD

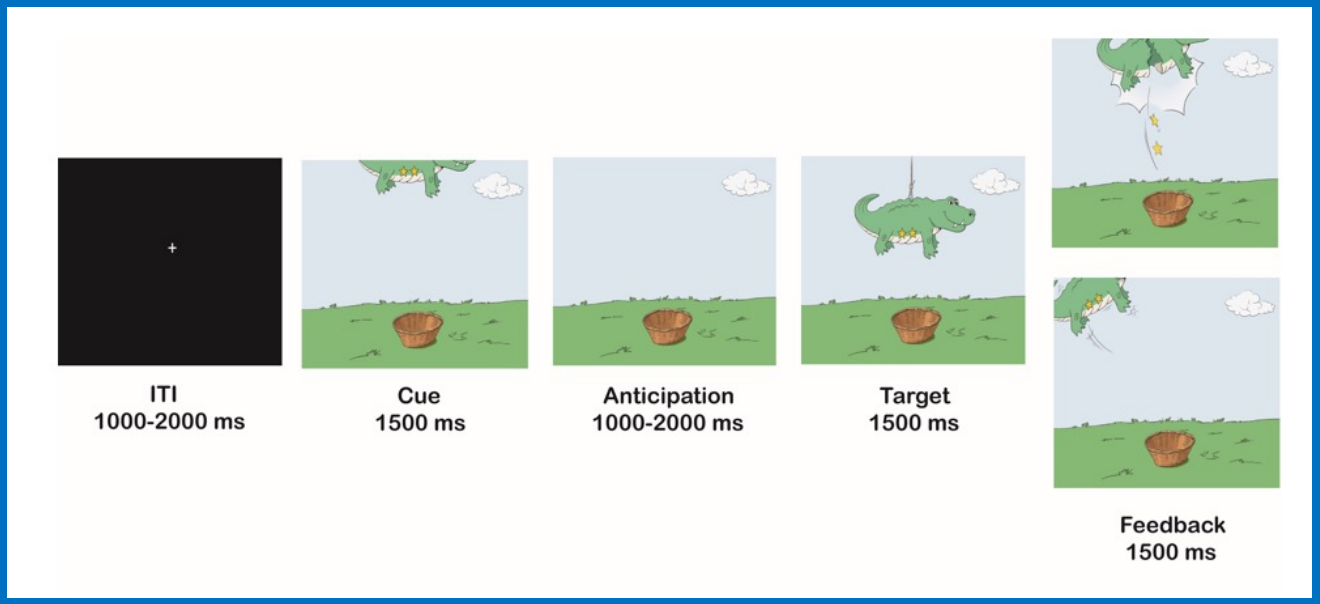
Excess Significance Bias in the Literature on Brain Volume Abnormalities

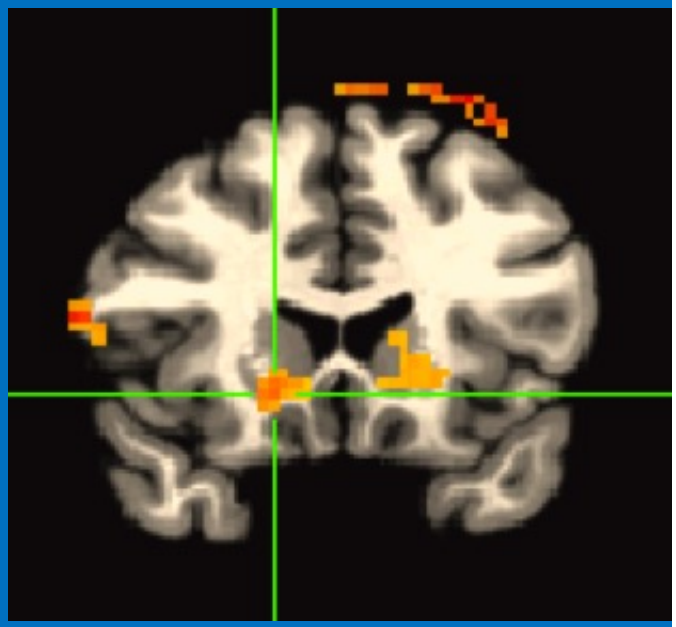
John P. A. Ioannidis, MD, DSc

Behavioral Inhibition, Anxiety, & Reward Processing



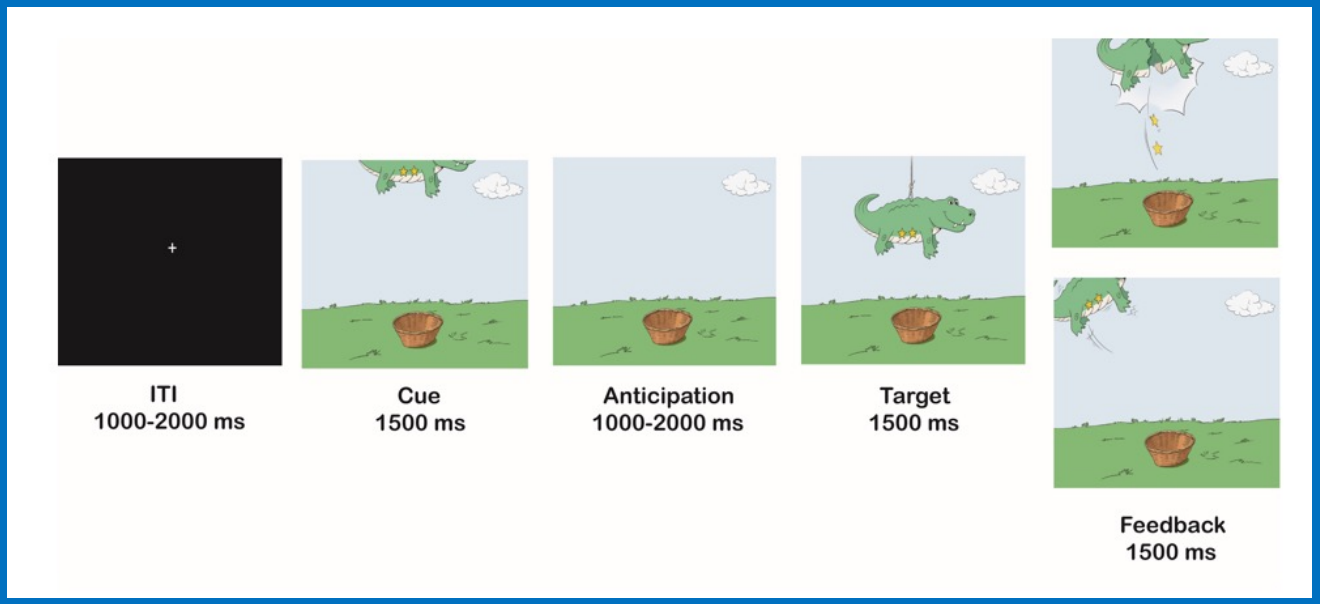
Behavioral Inhibition, Anxiety, & Reward Processing

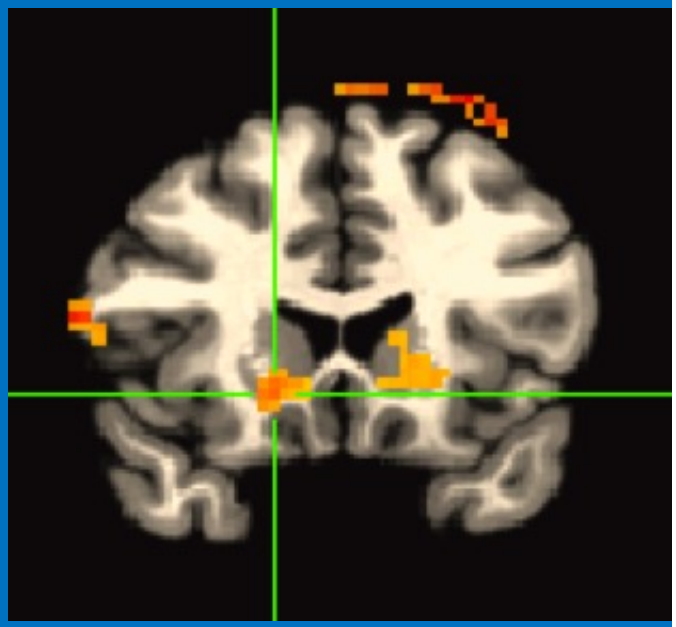


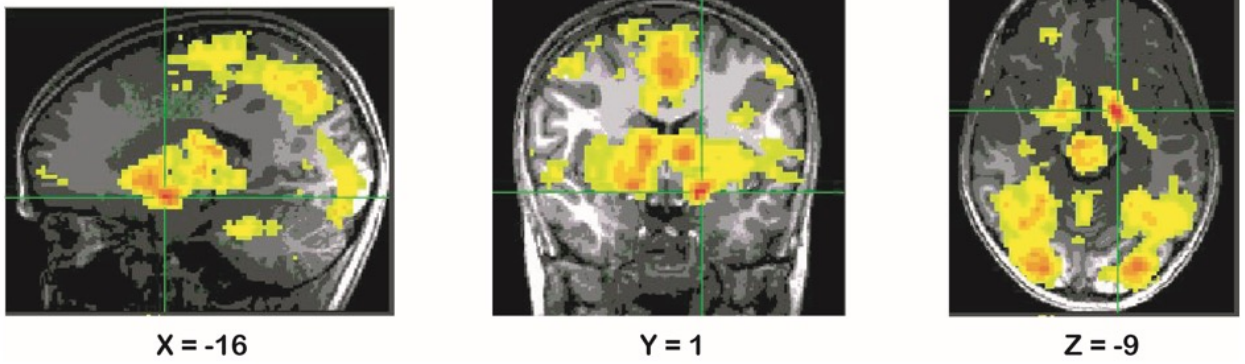


ICC=0.81
(0.60 threshold)

Behavioral Inhibition, Anxiety, & Reward Processing







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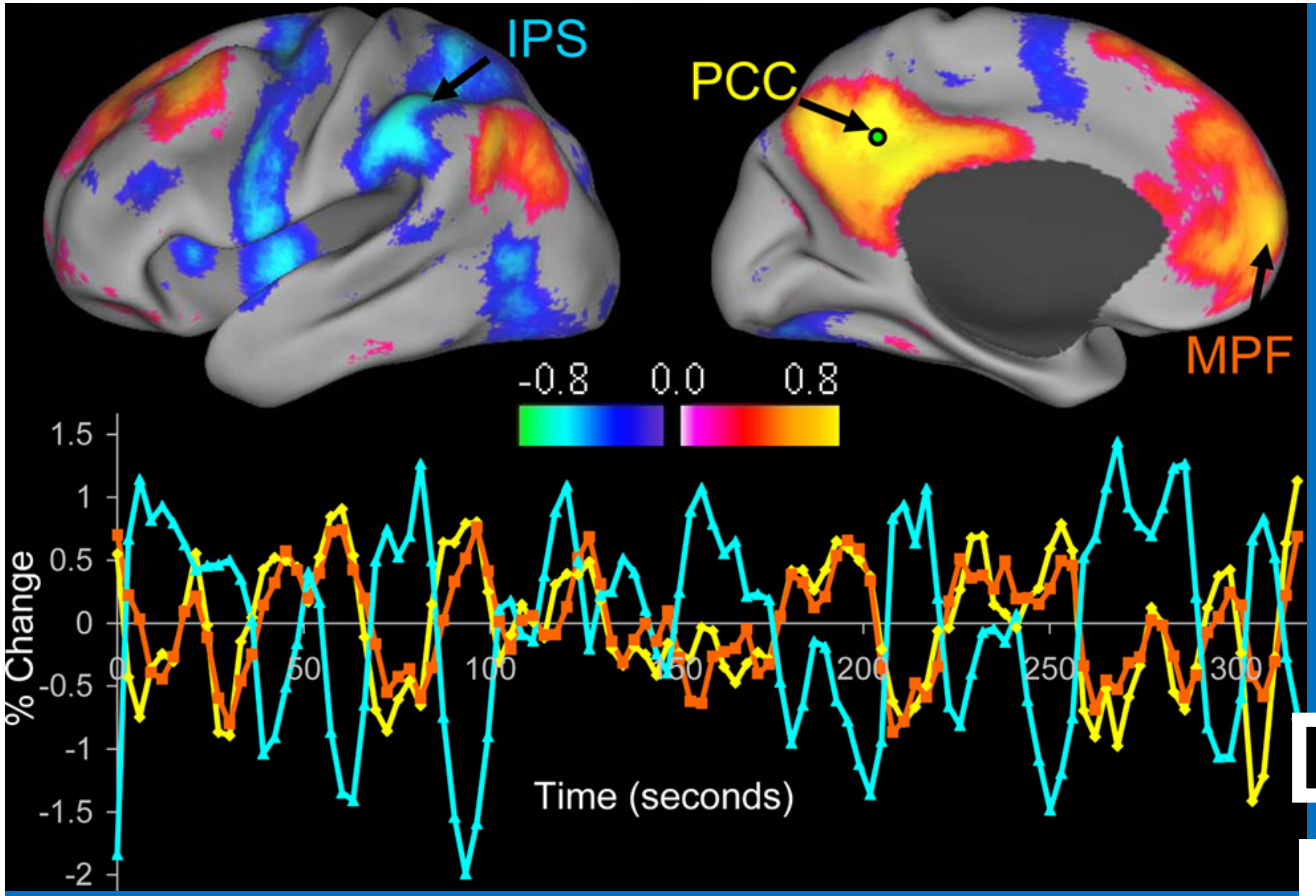
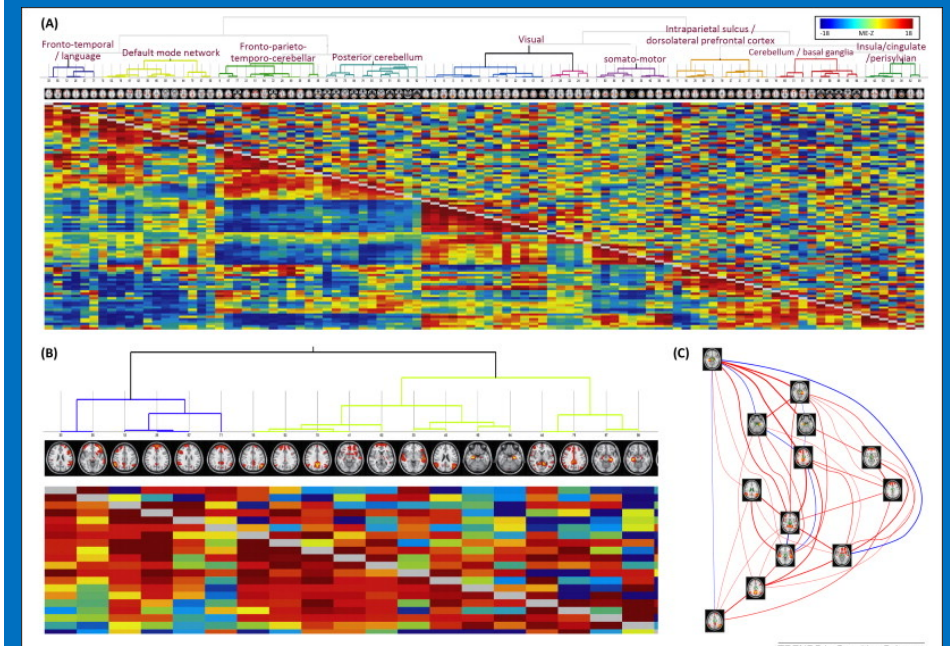
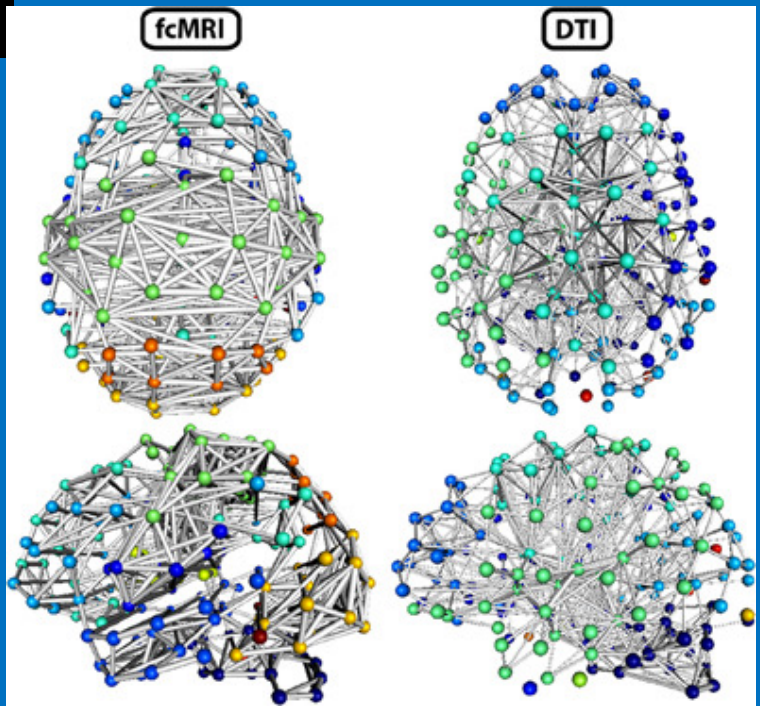
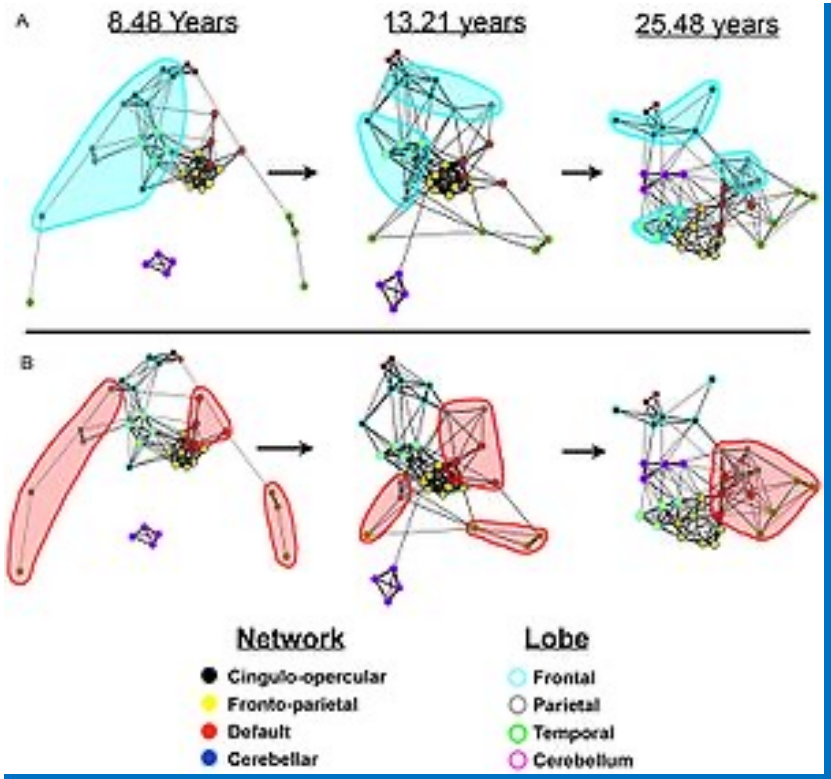


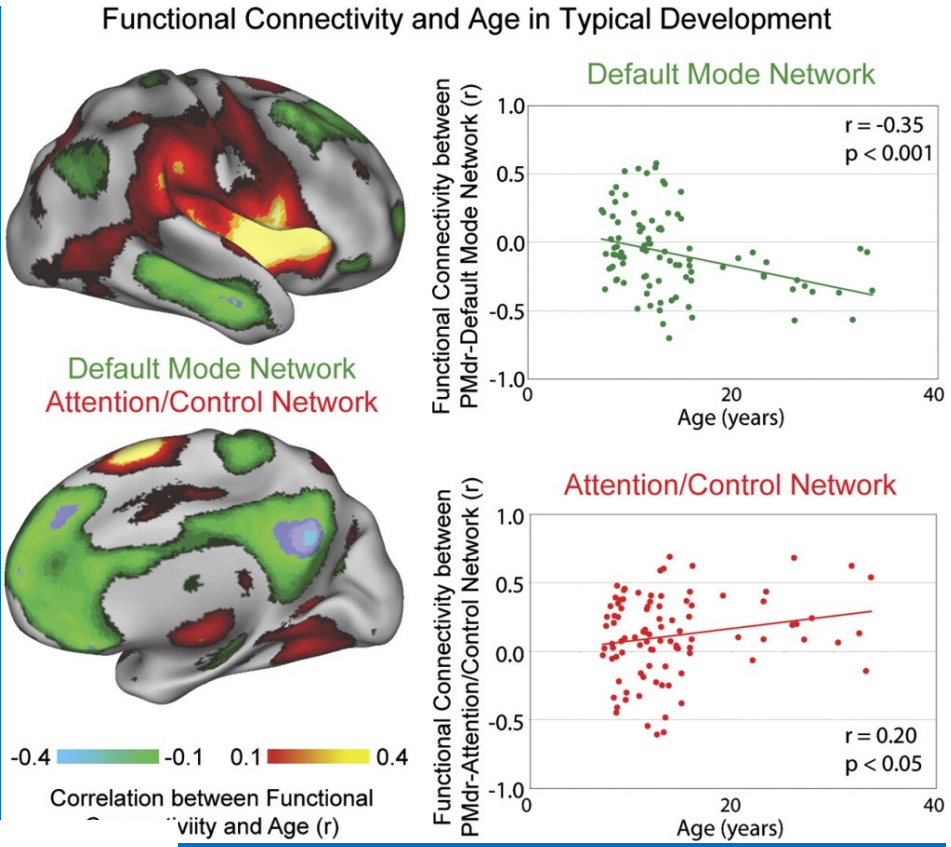
Biswal et al. 1995

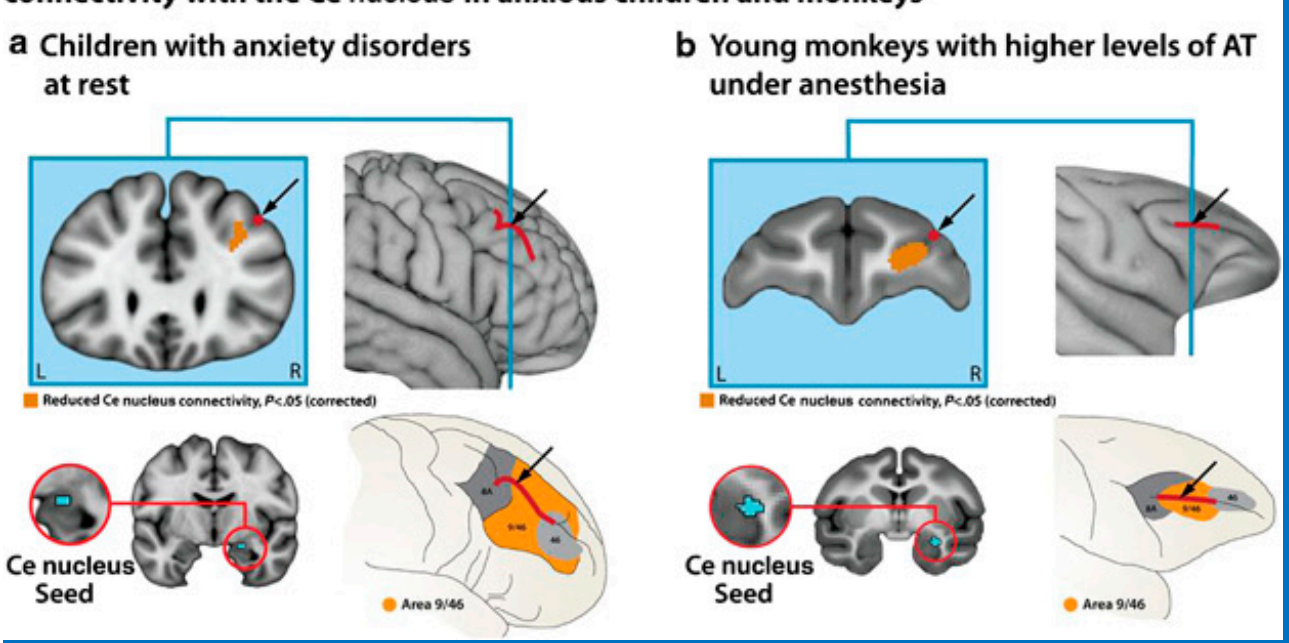
Fair, Schlagger, Peterson & others











Fair, Schlagger, Peterson & others

Birn et al. 2014

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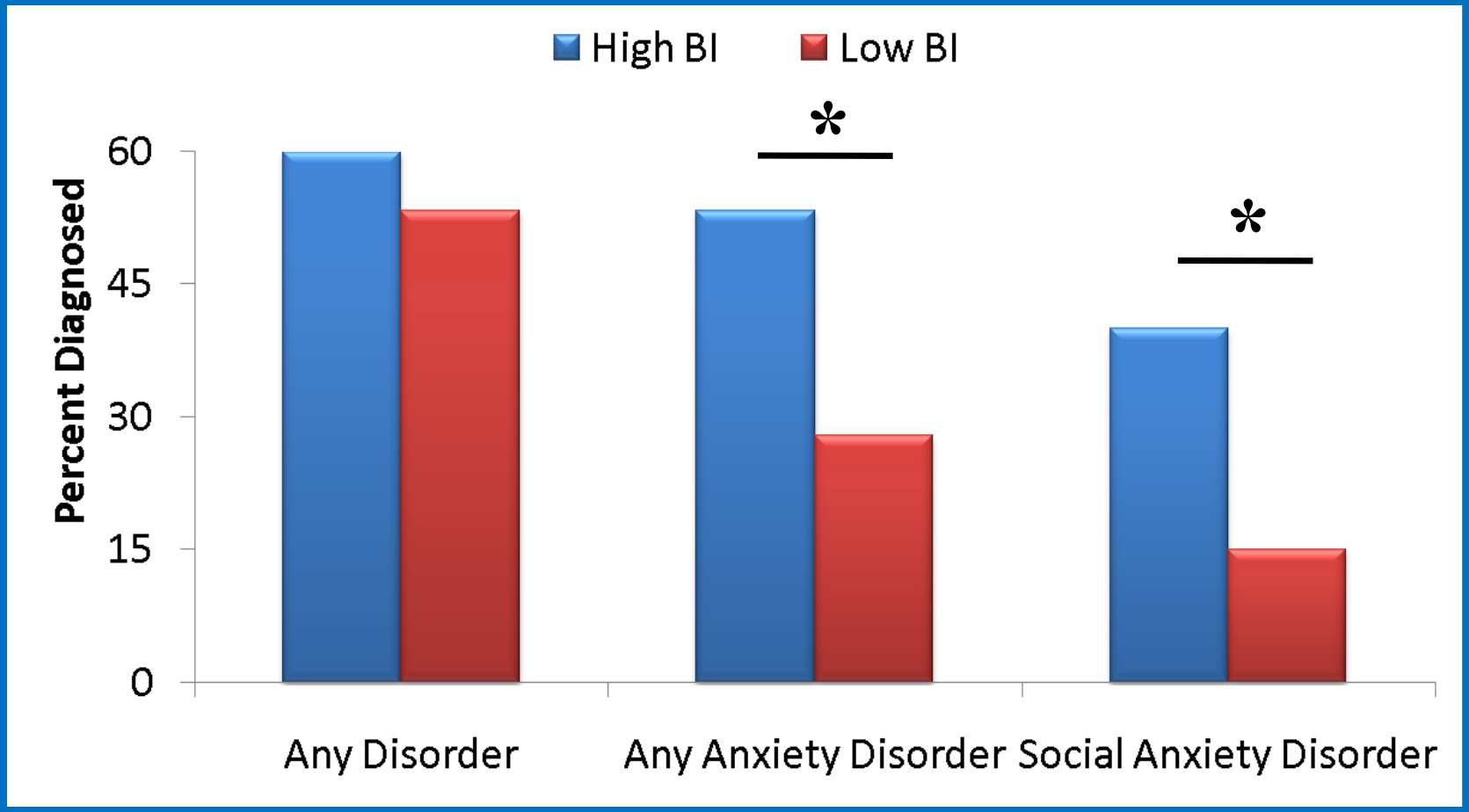
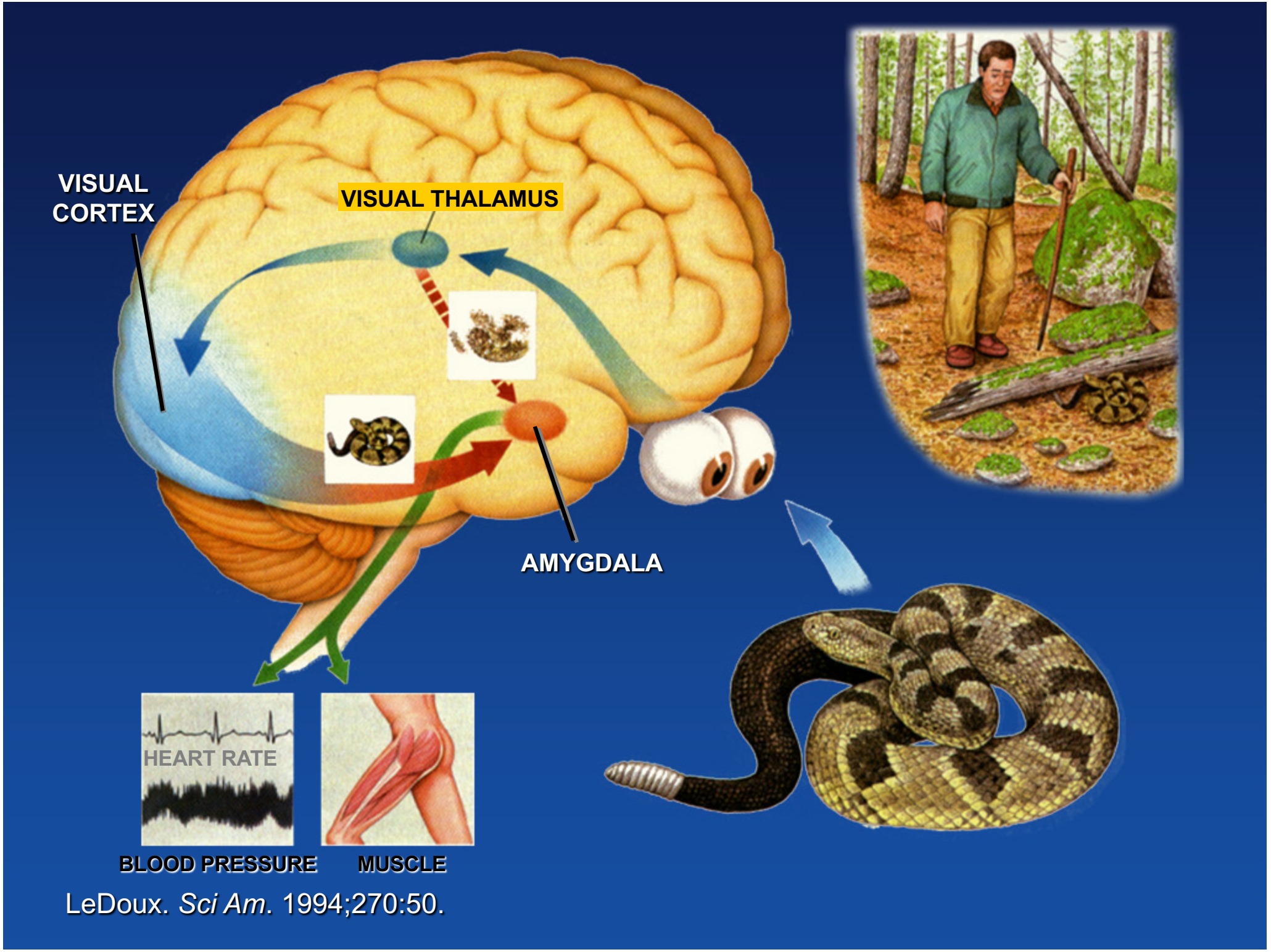
Behavioral Inhibition and Anxiety



Chronis-Tuscano et al, 2009



LeDoux. *Sci Am*. 1994;270:50.

The Dot-Probe Task

time

*

+

Mogg & Bradley

Bar-Haim et al. (2007)

d=0.45

The Dot-Probe Task

time

+

The Dot-Probe Task

time

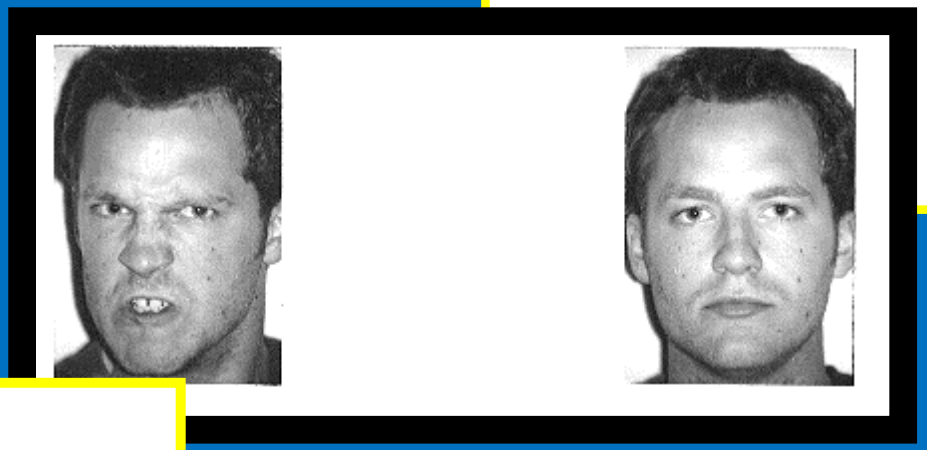
*

+

The Dot-Probe Task

time

*



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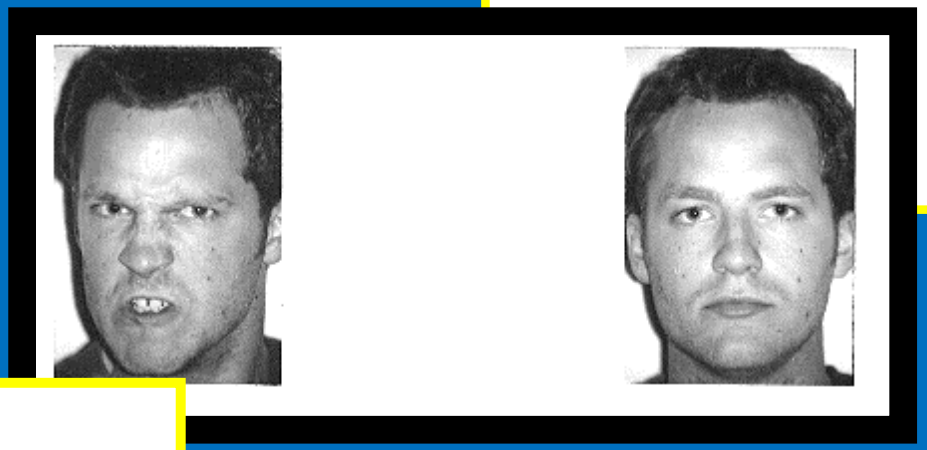
The Dot-Probe Task

time

*



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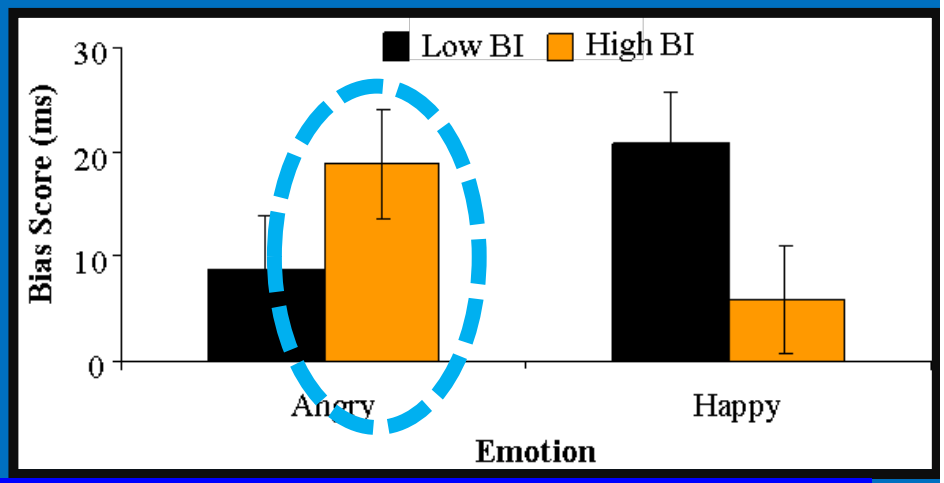

Vigilance for threat = Faster RTs to probes replacing threat vs. neutral faces

Study Design

4 Months:	Recruitment and Selection
9 Months:	EEG
14 Months:	Behavioral Inhibition
24 Months:	Behavioral Inhibition
4 Years:	Quartet Peer Interaction
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Fox et al. 2006

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***-assessment of attention

Fox et al. 2006

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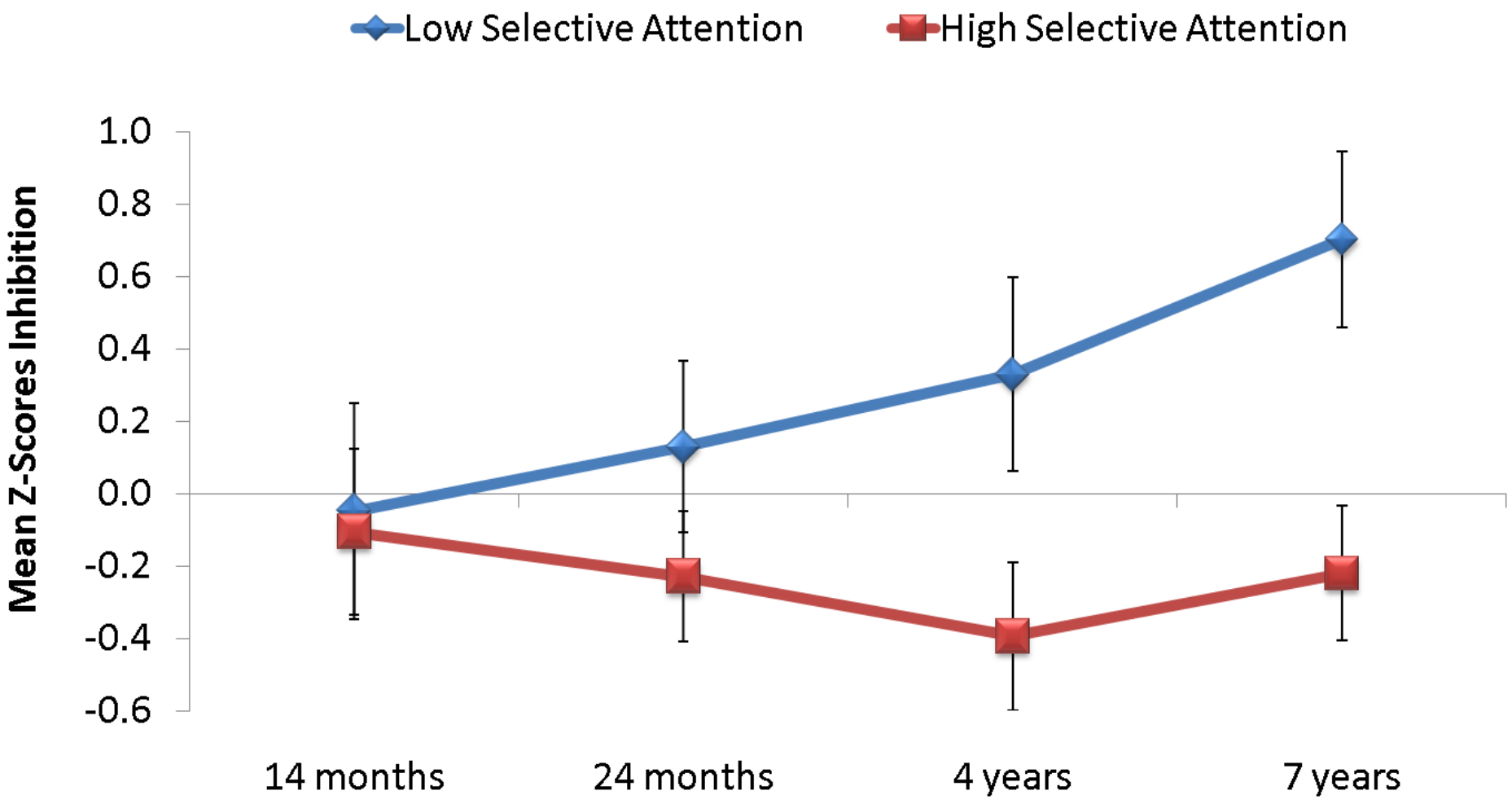
***-assessment of attention

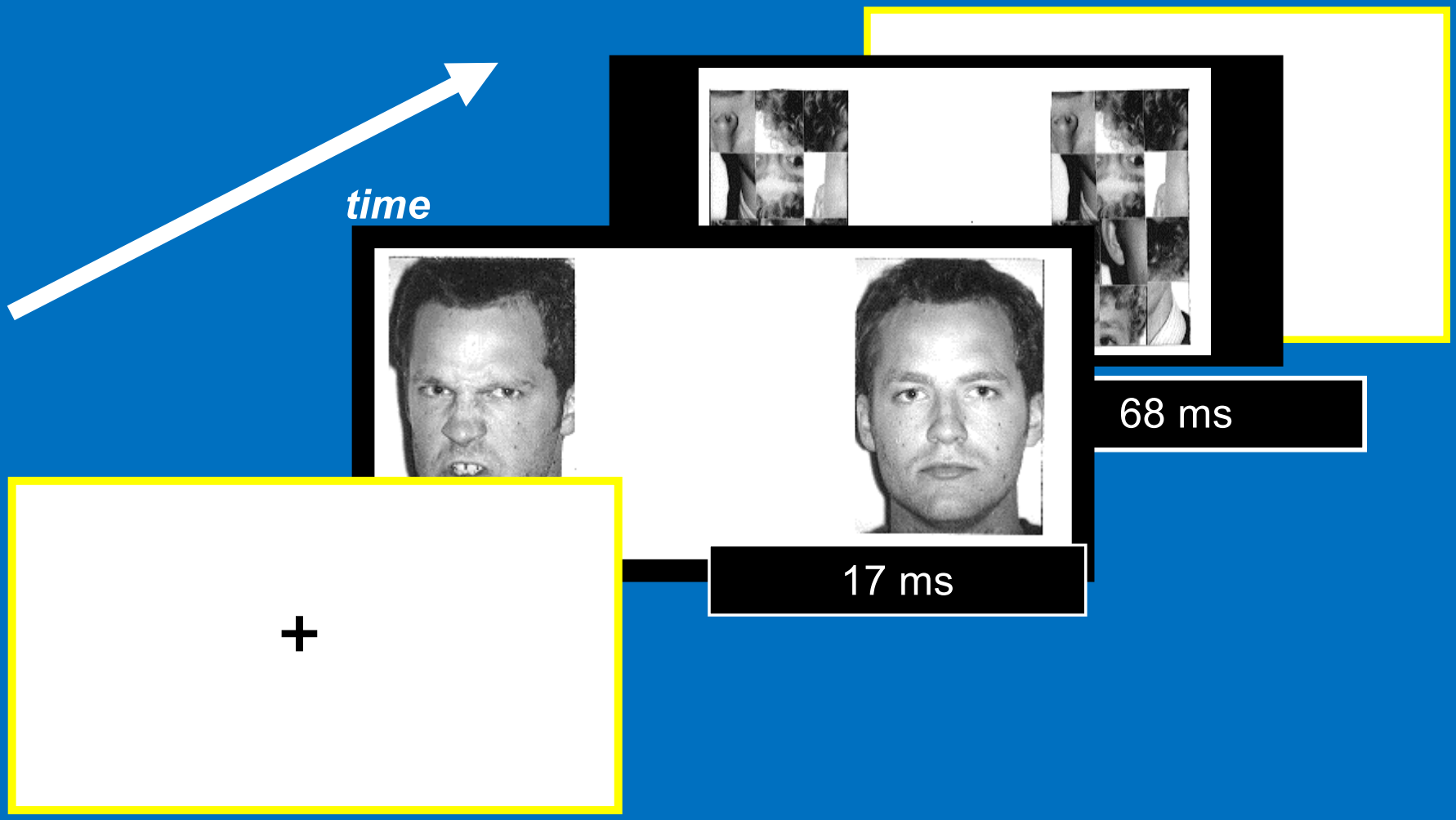
Fox et al. 2006

Persistent Anxiety Emerges Over Time

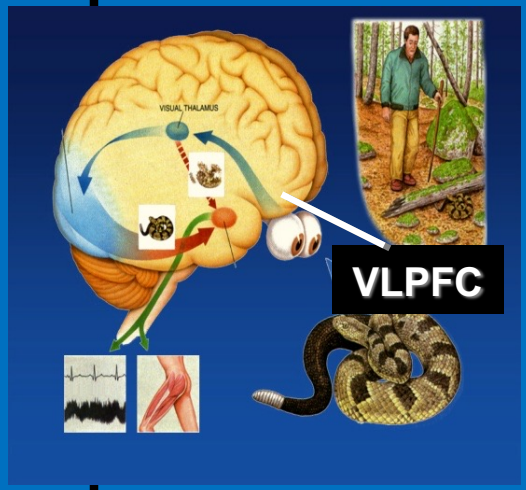


Perez-Edgar et al. 2010

The Dot-Probe Task



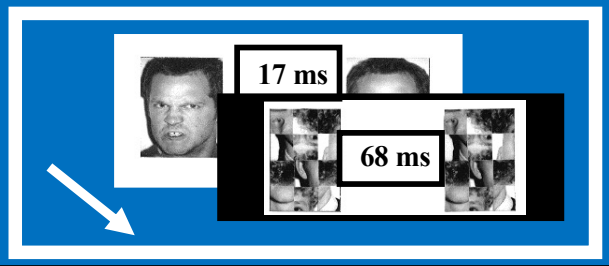
Attention, PFC-Amygdala-Circuitry, and Pediatric Anxiety

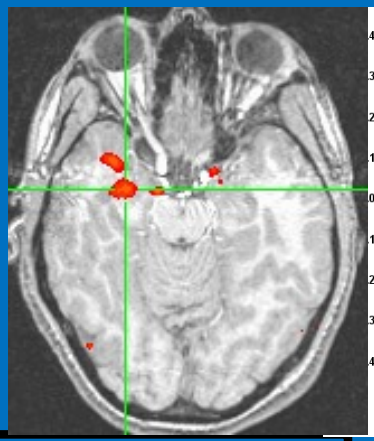


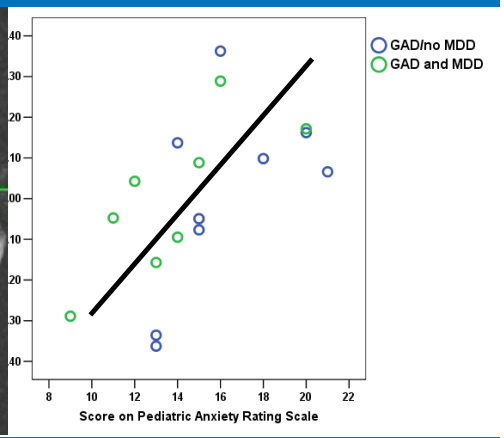
Monk et al. 2006, 2008

Attention, PFC-Amygdala-Circuitry, and Pediatric Anxiety

Brief Subliminal Threat: ***Amygdala instantiates anxiety***







Monk et al. 2006, 2008

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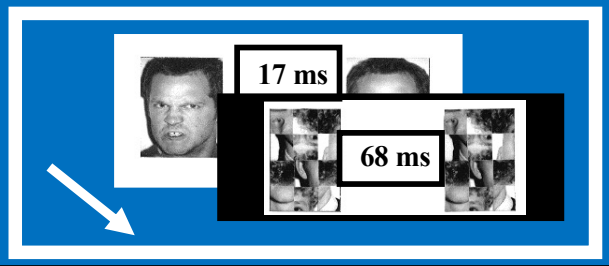
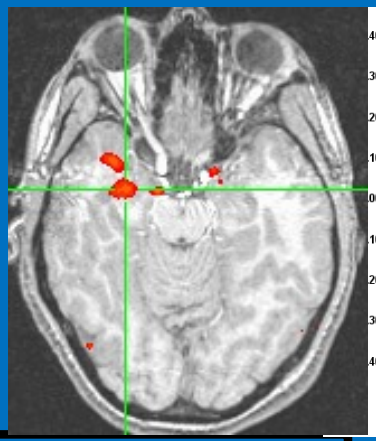
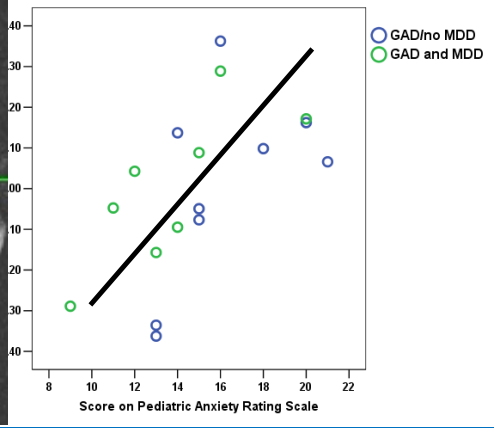
Brief Subliminal Threat: *Amygdala instantiates anxiety*

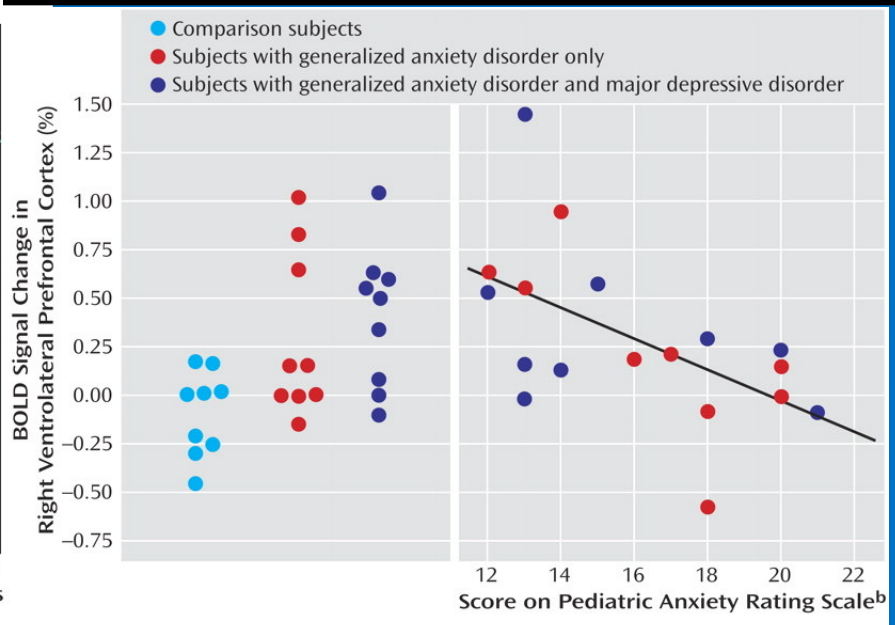






Prolonged Threat: *PFC regulates attention in anxiety*

Site in Right Ventrolateral Prefrontal Cortex Where Activation Was Greater in Adolescents With Generalized Anxiety Disorder Than in Comparison Subjects[a]



Monk et al. 2006, 2008

THE AMERICAN JOURNAL OF PSYCHIATRY

psychiatryonline

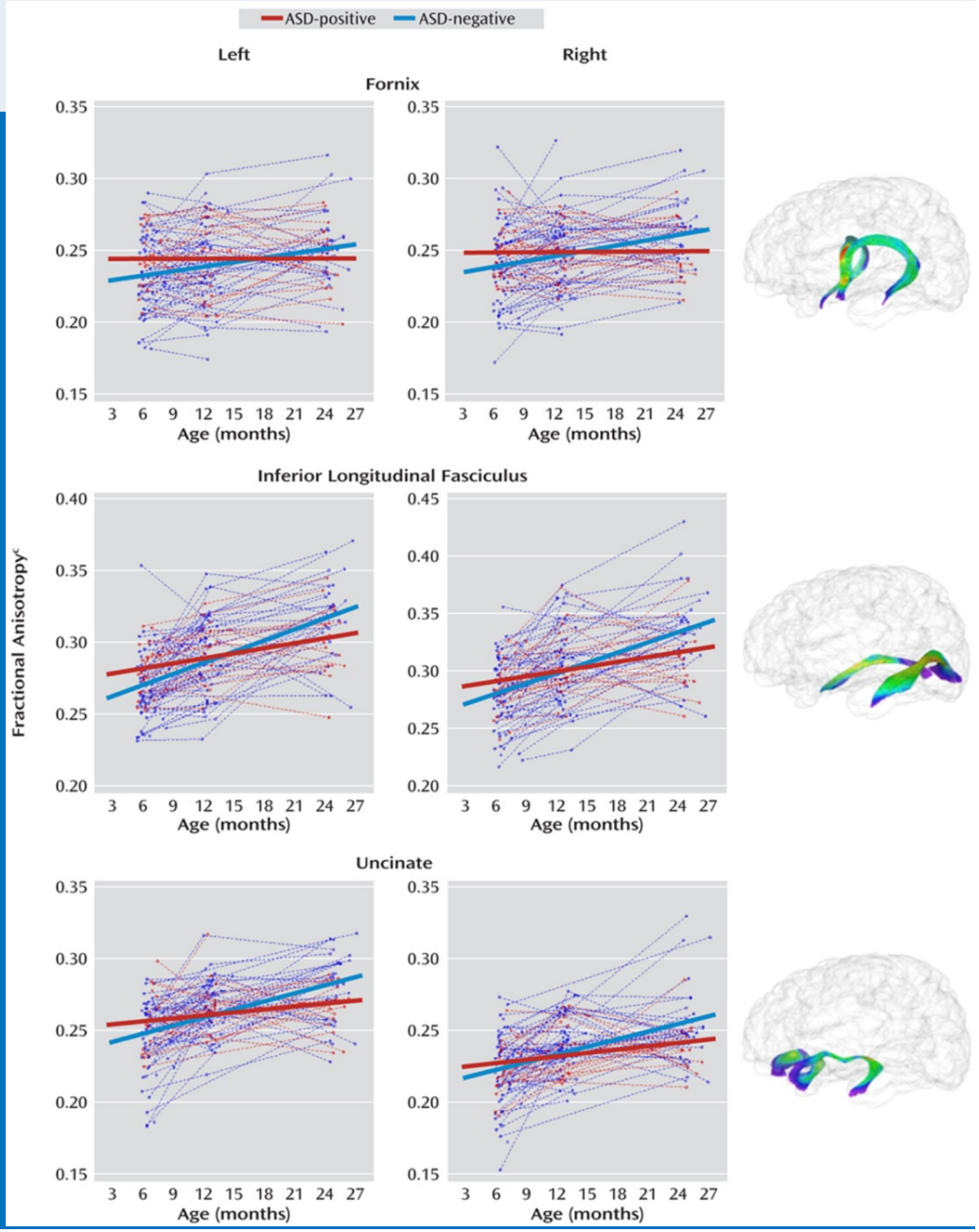
From: Differences in White Matter Fiber Tract Development Present From 6 to 24 Months in Infants With Autism

Am J Psychiatry. 2012;169(6):589-600. doi:10.1176/appi.ajp.2011.11091447

Autism Spectrum Disorder

- *Onset in first year of life*
- *Siblings at high risk*
- *Less than half will be affected*

Wolff et al. 2012



Outline

- Introduction
- Diagnostic Specificity
- **Risk versus Disorder**
- Novel Therapeutics

Outline

- Introduction
- Diagnostic Specificity
- Risk versus Disorder
- **Novel Therapeutics**

Any Adolescent Anxiety Disorder & Any Adult Mood/Anxiety Disorder

	Disorder as Adults?		
Disorder as Adolescents?	No	Yes	
No	390	36	426
Yes	191	62	253
	581	98	679

Pine et al. 1998, 2001, 2002

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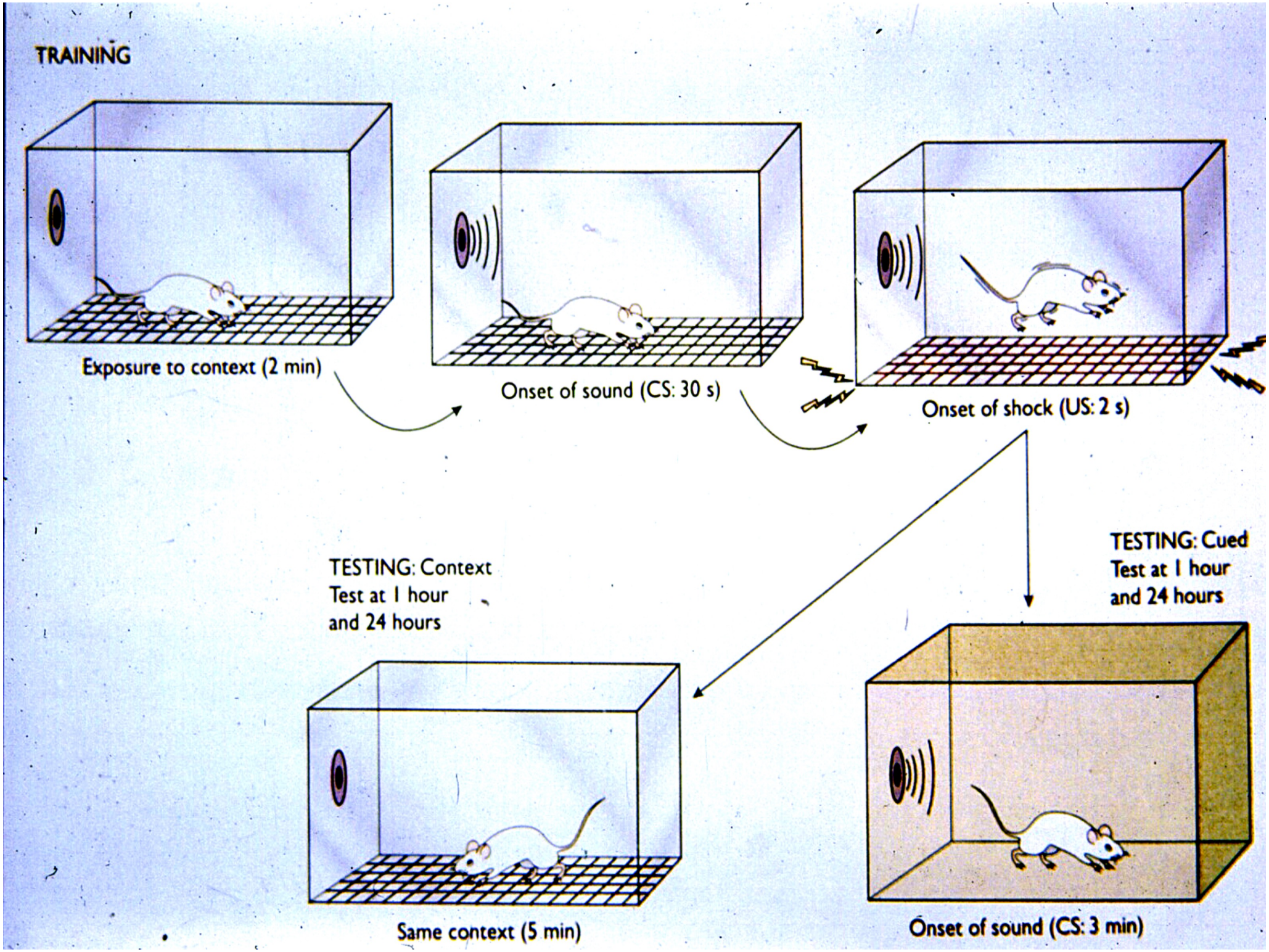
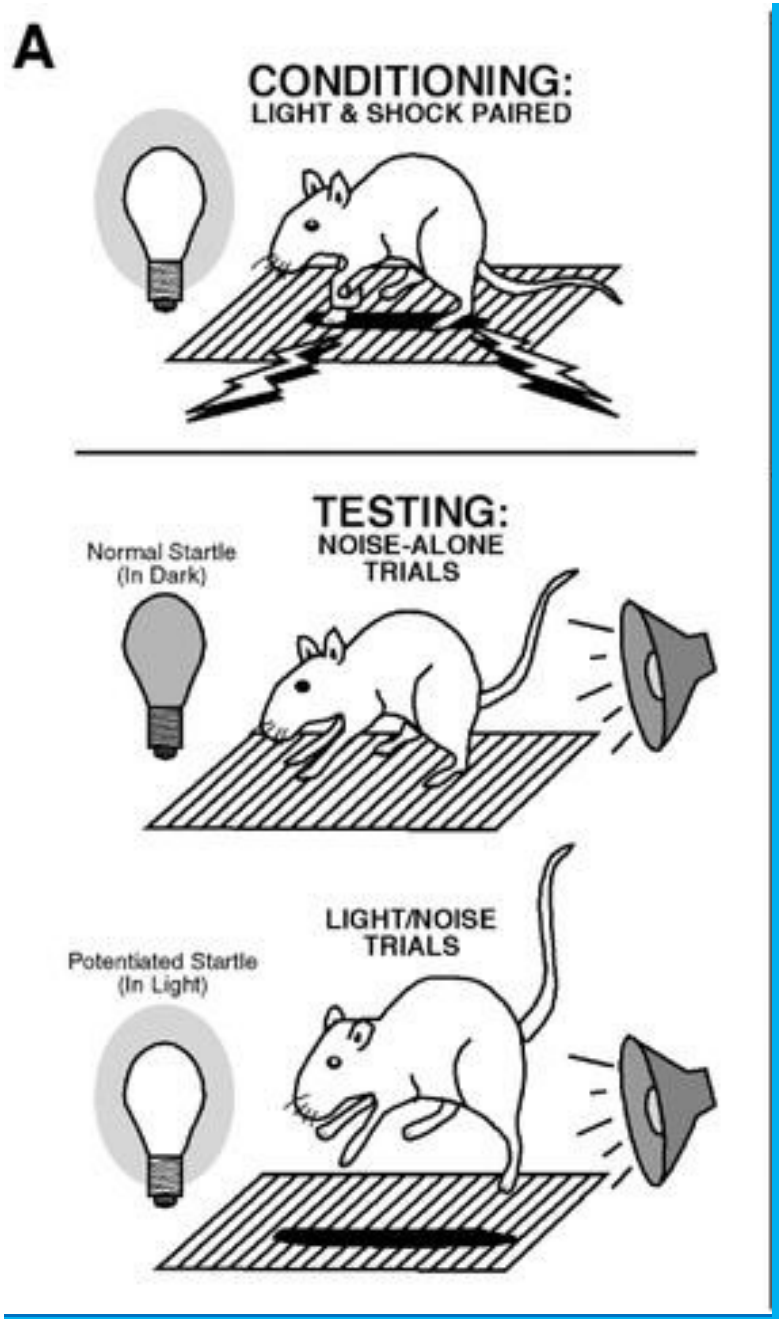
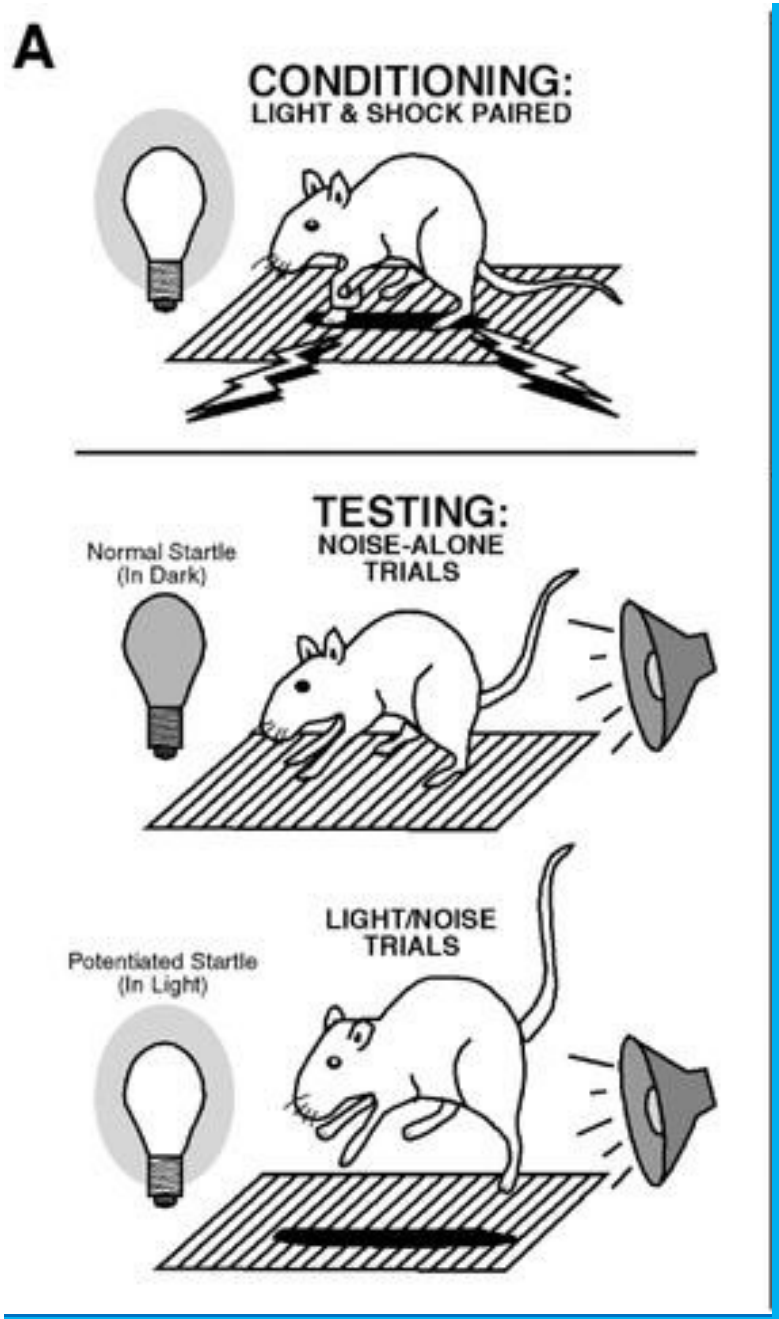

TRAINING
Exposure to context (2 min)
Onset of sound (CS: 30 s)
Onset of shock (US: 2 s)
TESTING: Context
Test at 1 hour
and 24 hours
TESTING: Cued
Test at 1 hour
and 24 hours
Same context (5 min)
Onset of sound (CS: 3 min)



Ressler & Davis 2003

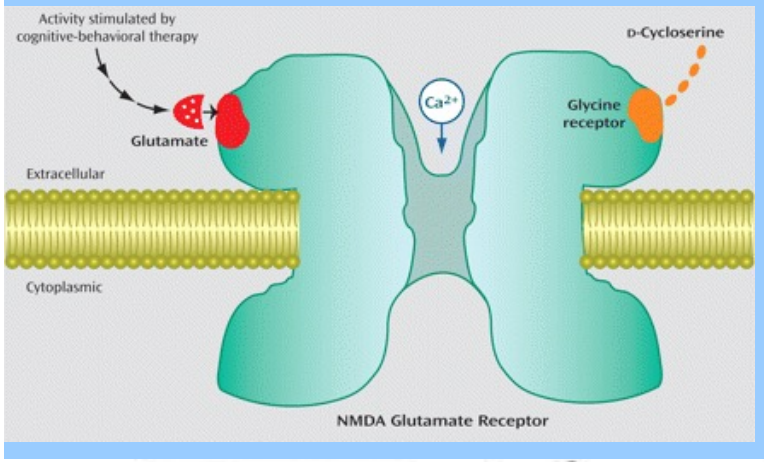


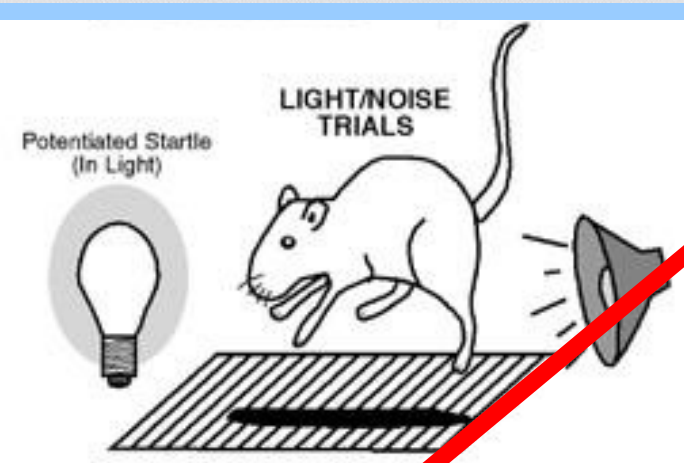
Extinction Recall:
Remembering the Boundary Between Danger and Safety

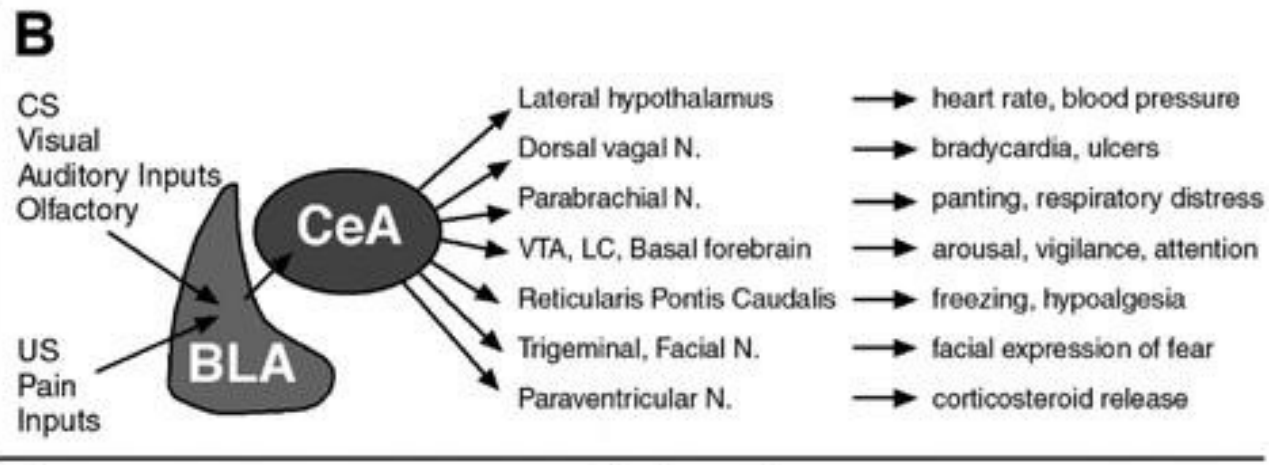
Ressler & Davis 2003

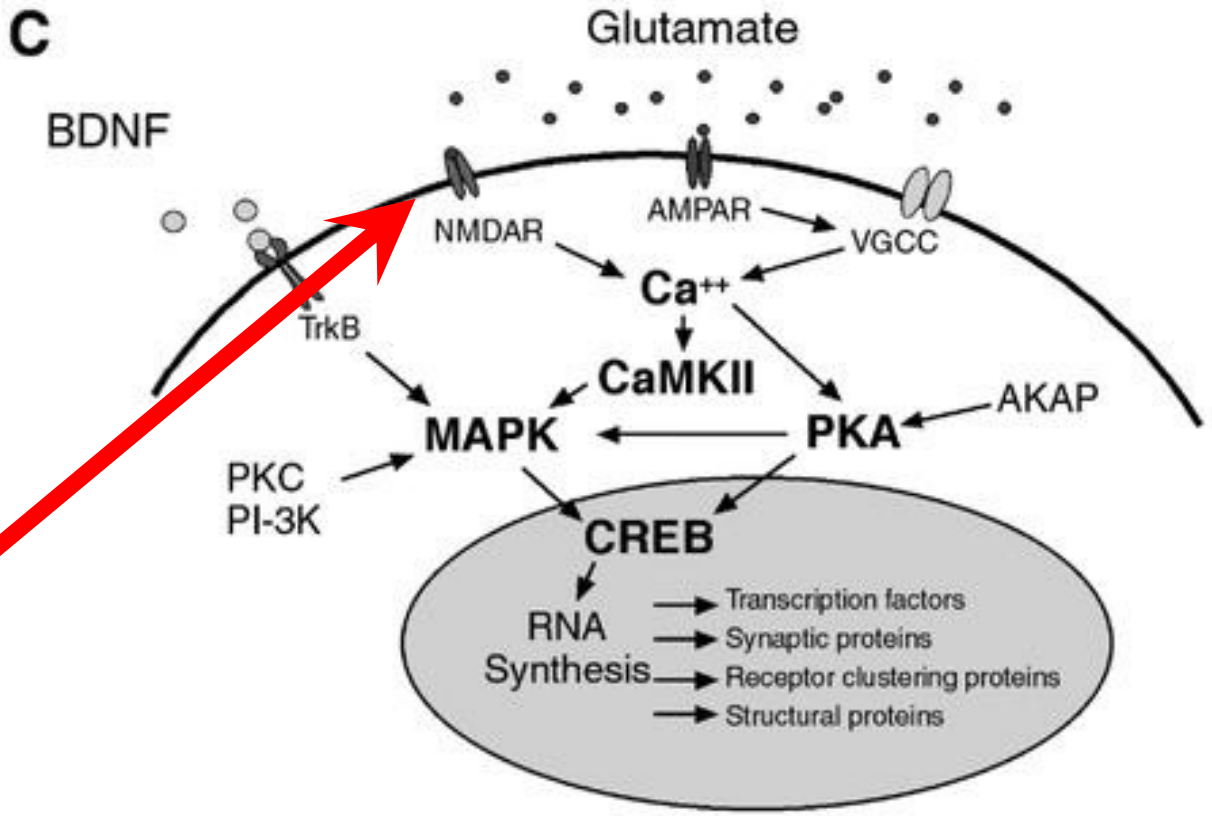
EXTINCTION

Insights on Therapeutics









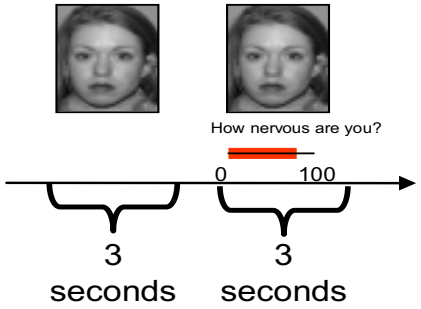
NMDA manipulations?

Ressler & Davis 2003

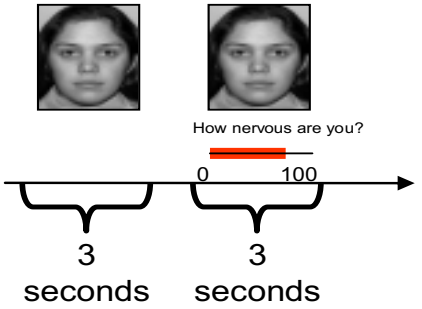
How do we study fear learning in youth?

FACE-SCREAM CONDITIONING

CS MINUS



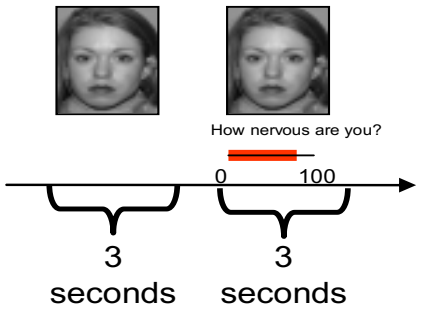
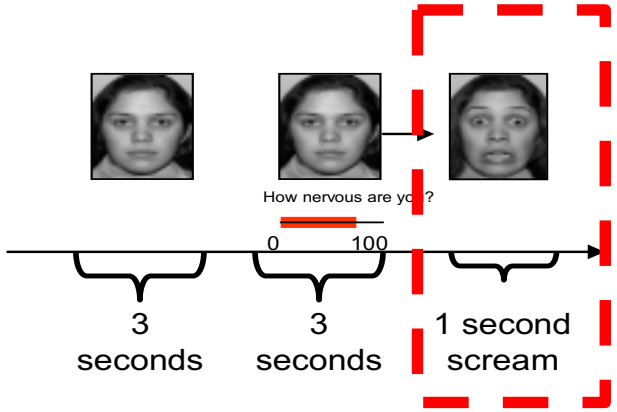
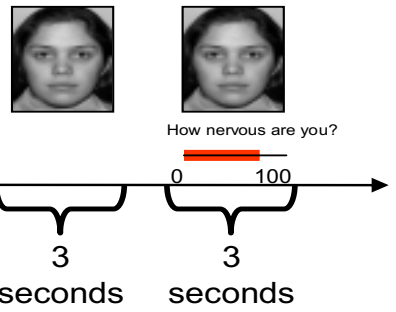
CS PLUS



Conditioning of Fear Reactions:

Neutral Face CS; Screaming Lady UCS

FACE-SCREAM CONDITIONING

CS MINUS	CS PLUS *(paired)*	CS PLUS
		

Conditioning of Fear Reactions:

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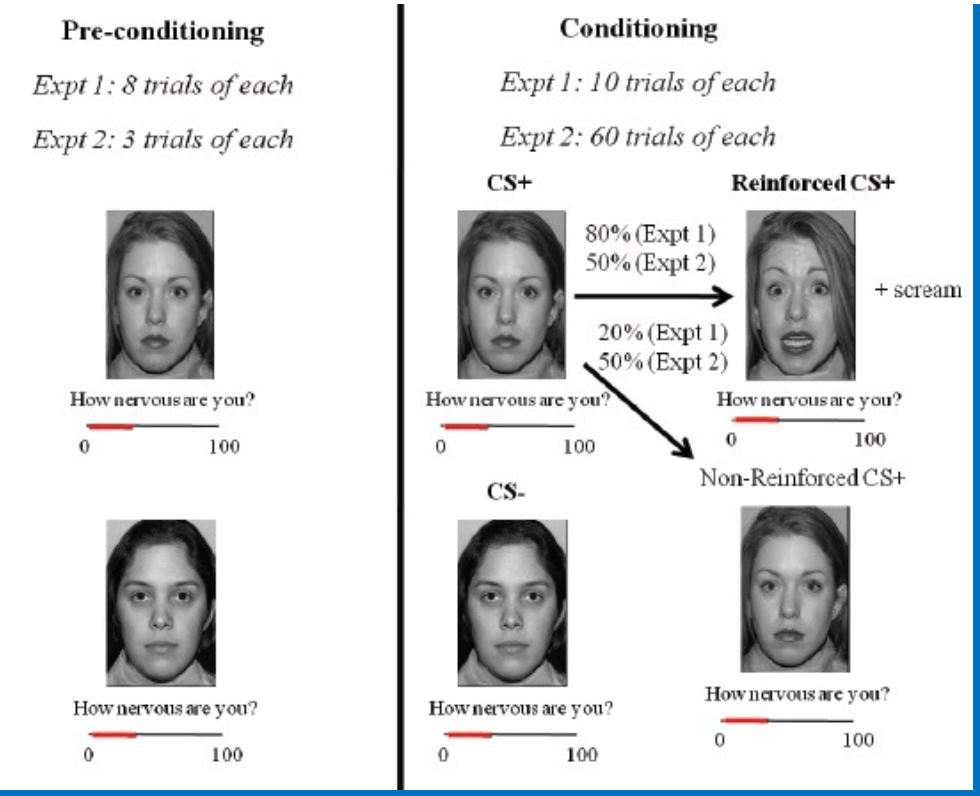
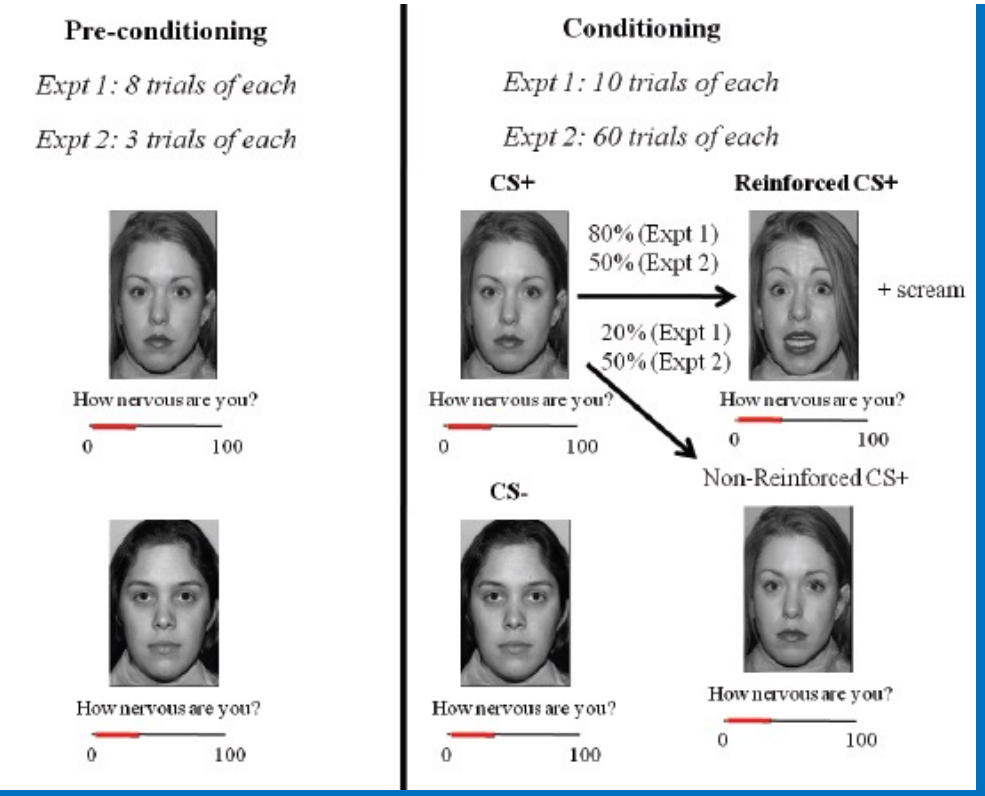


Attention-State & Anxiety:

The importance of threat appraisal

Lau et al. (2011)



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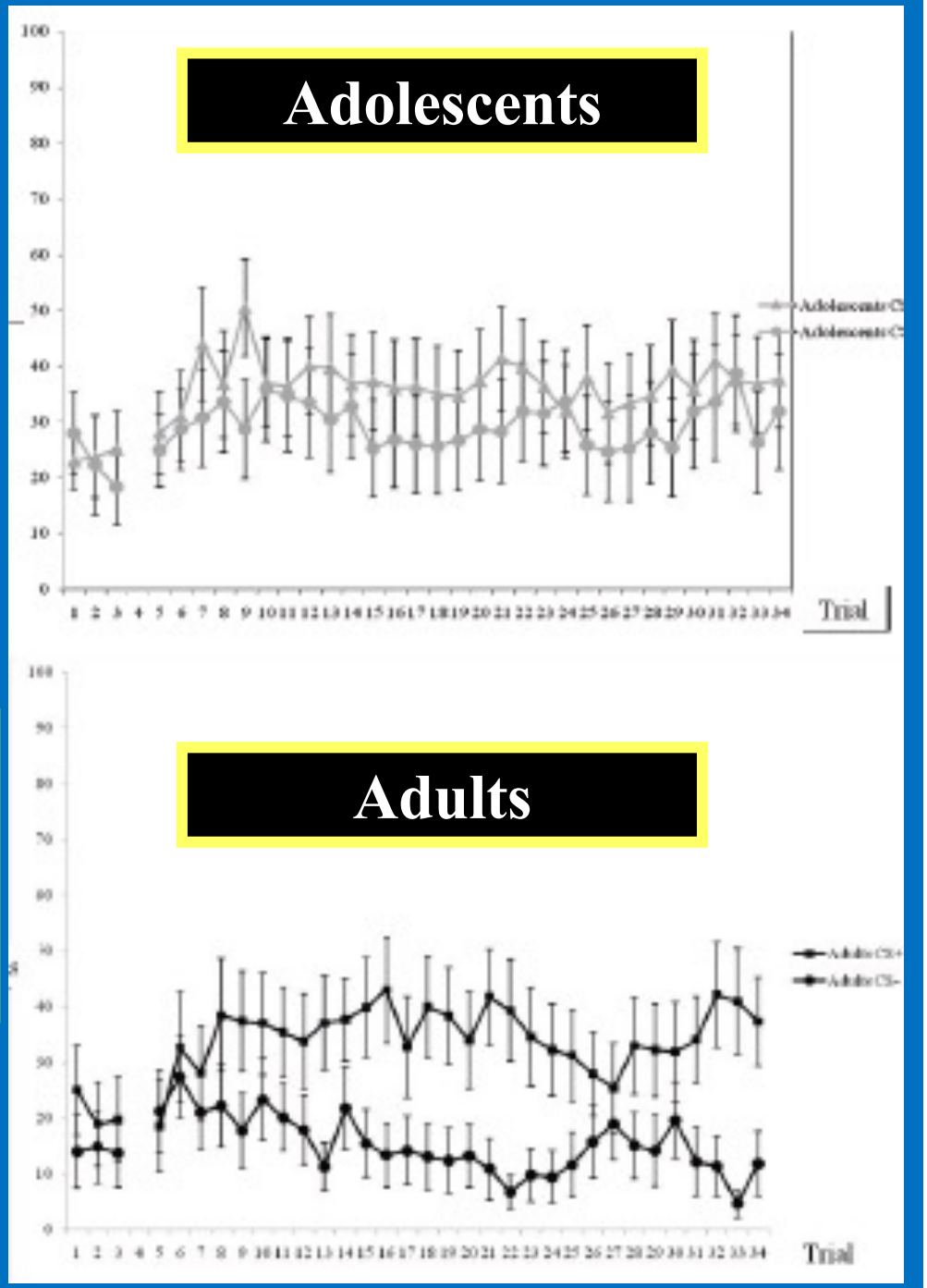

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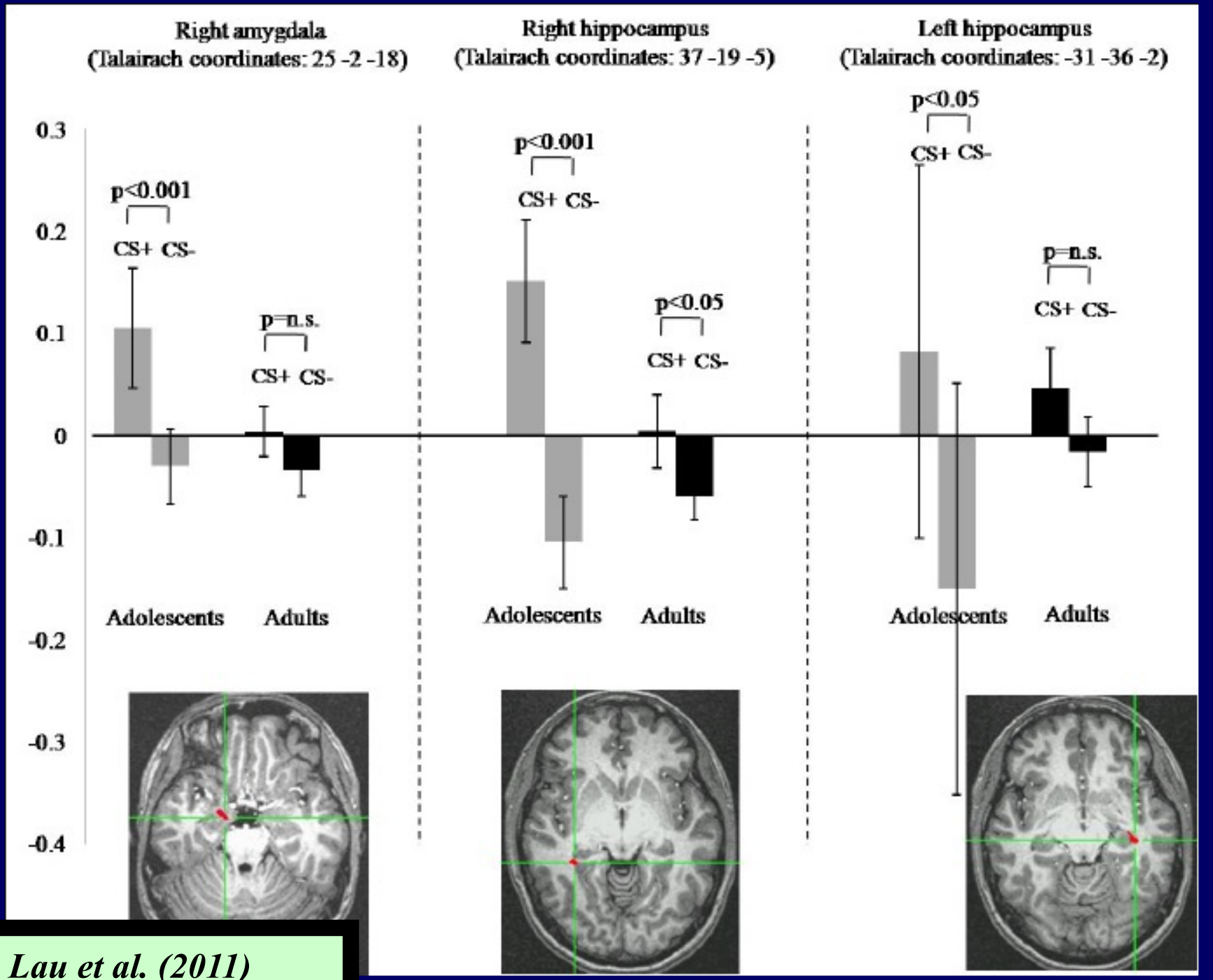
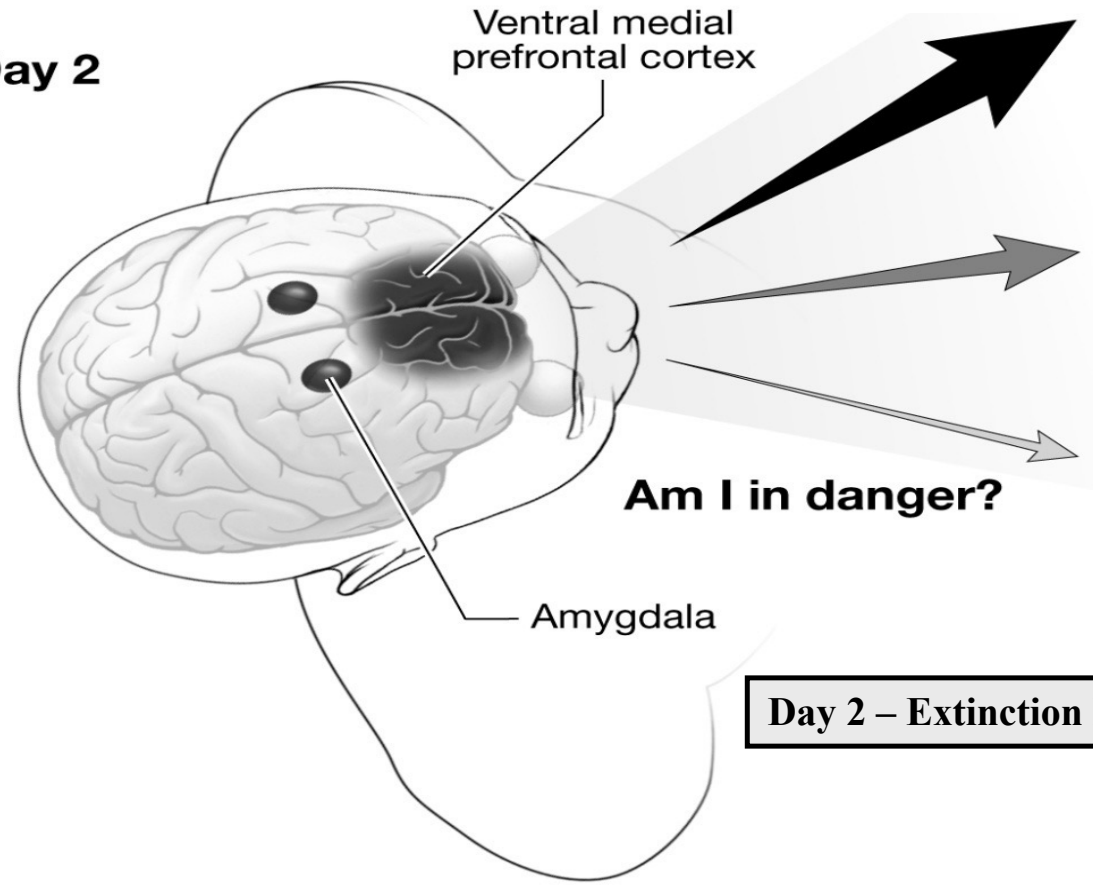


Lau et al. (2011)

Day 1 – Conditioning/Extinction

Day 15 - 400



Day 2 – Extinction Recall

Outline

- **Introduction**
- **Diagnostic Specificity**
- **Risk versus Disorder**
- **Novel Therapeutics**

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