

fMRI & Children

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

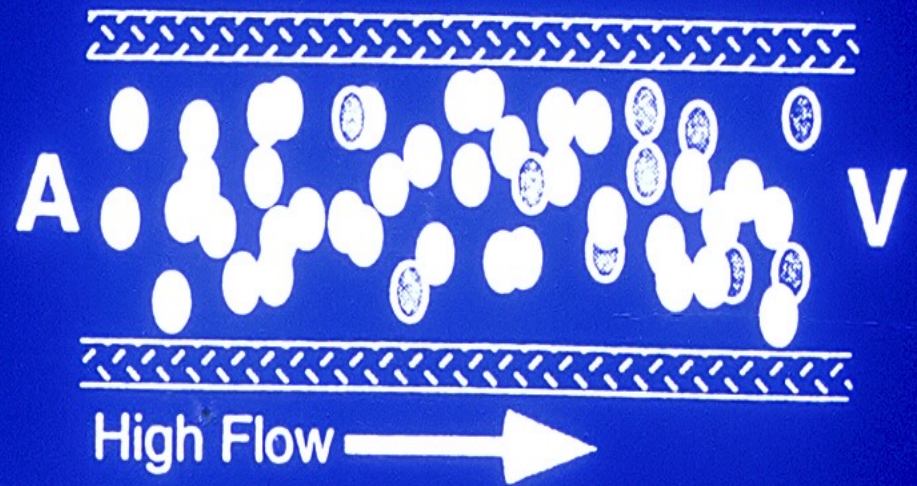
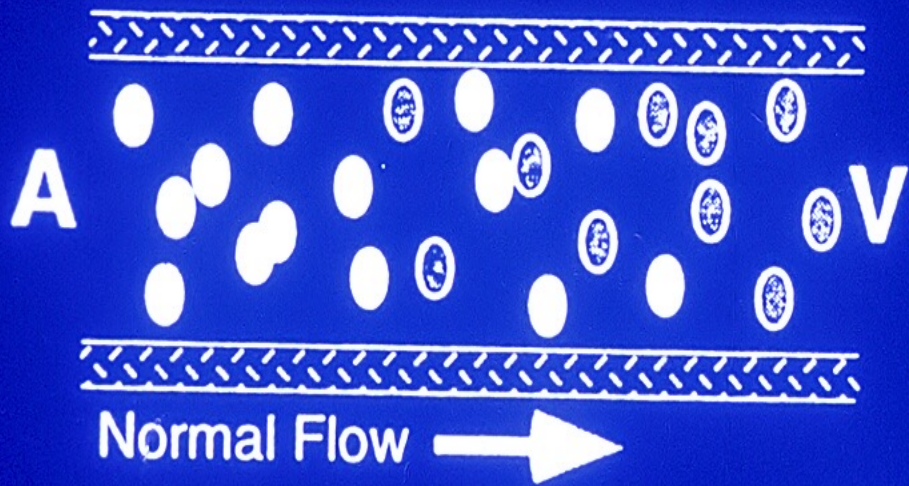
- **Introduction**
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Pediatric Mental Illnesses

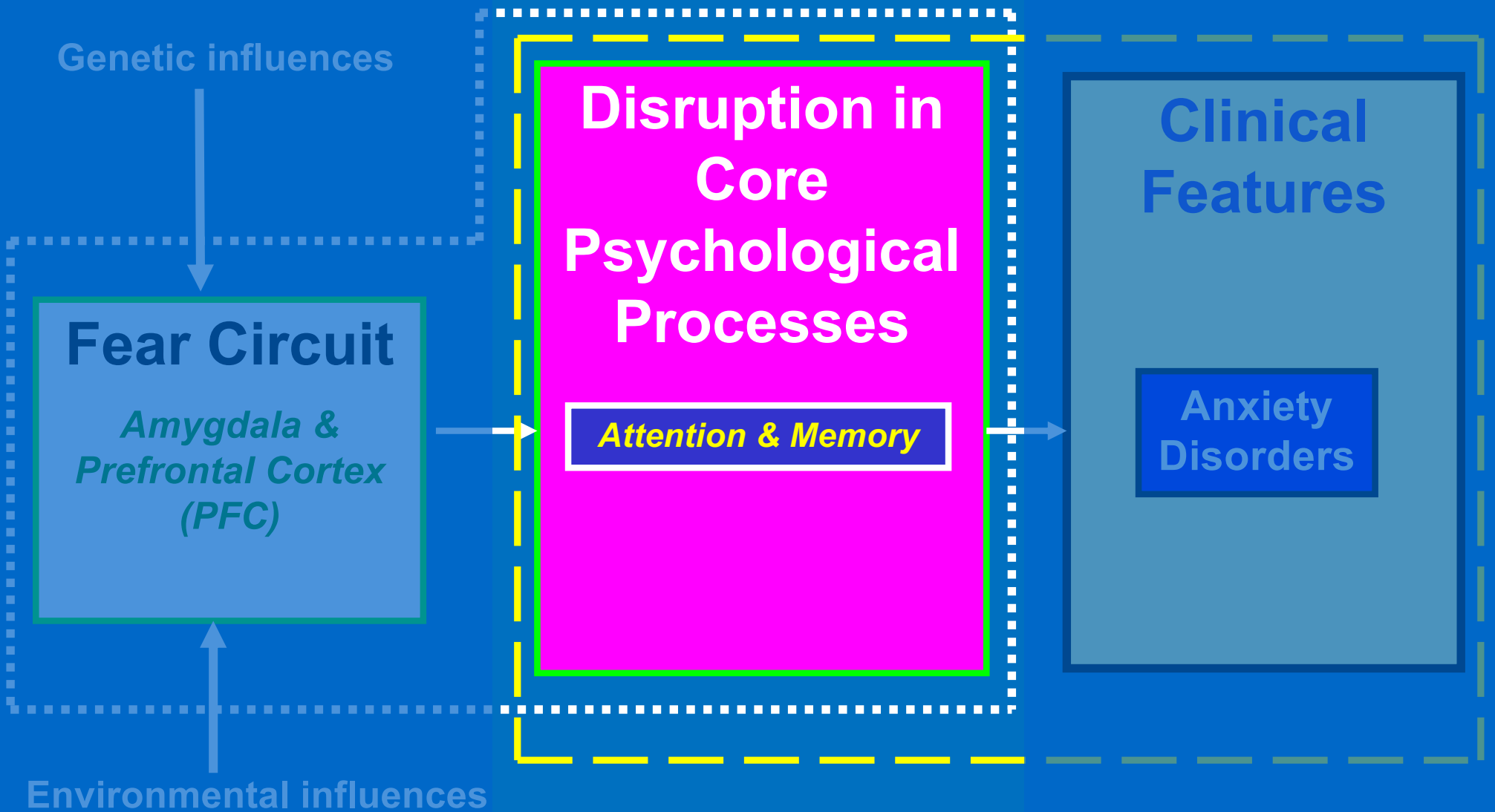
- **Extremely Common**
- **Usually Transient**
 - *But...predicts long-term problems*
- **Prediction, Therapeutics**

Pediatric Mental Illnesses

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



- Oxyhemoglobin
- Deoxyhemoglobin



A Focus on *Trajectories*

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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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AMY DAVIDSON

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



National Institute of Mental Health

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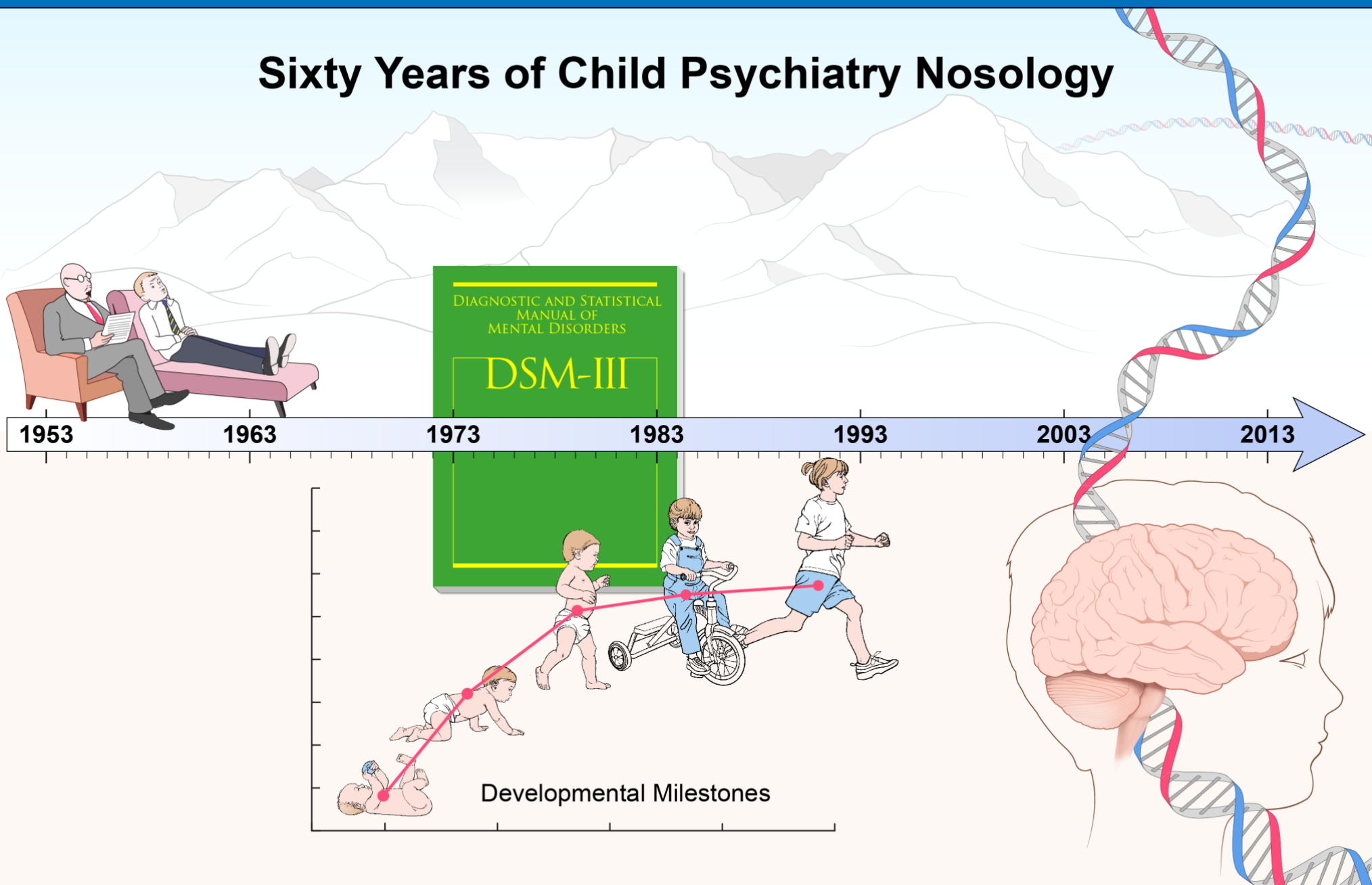
MY BLOG
Tom Insel, M.D.
NIMH Director

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Director's Blog

Sixty Years of Child Psychiatry Nosology



Diagnostic Specificity

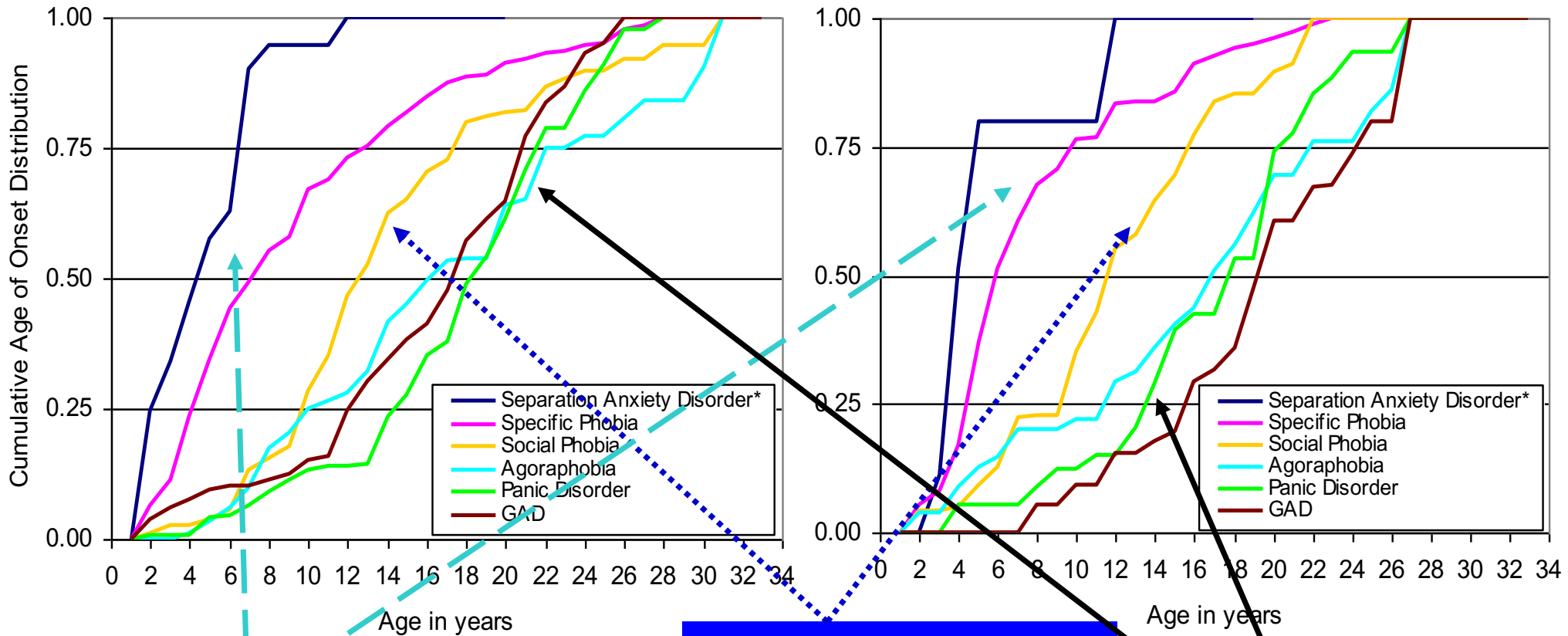
- Unique, stable patterns manifest
- Comorbidity is rampant
- Vexing questions on anxiety

Age of Onset of Specific Anxiety Disorders

Females

Specificity?

Males



Social Phobia

Separation Anxiety Disorder & Specific Phobia

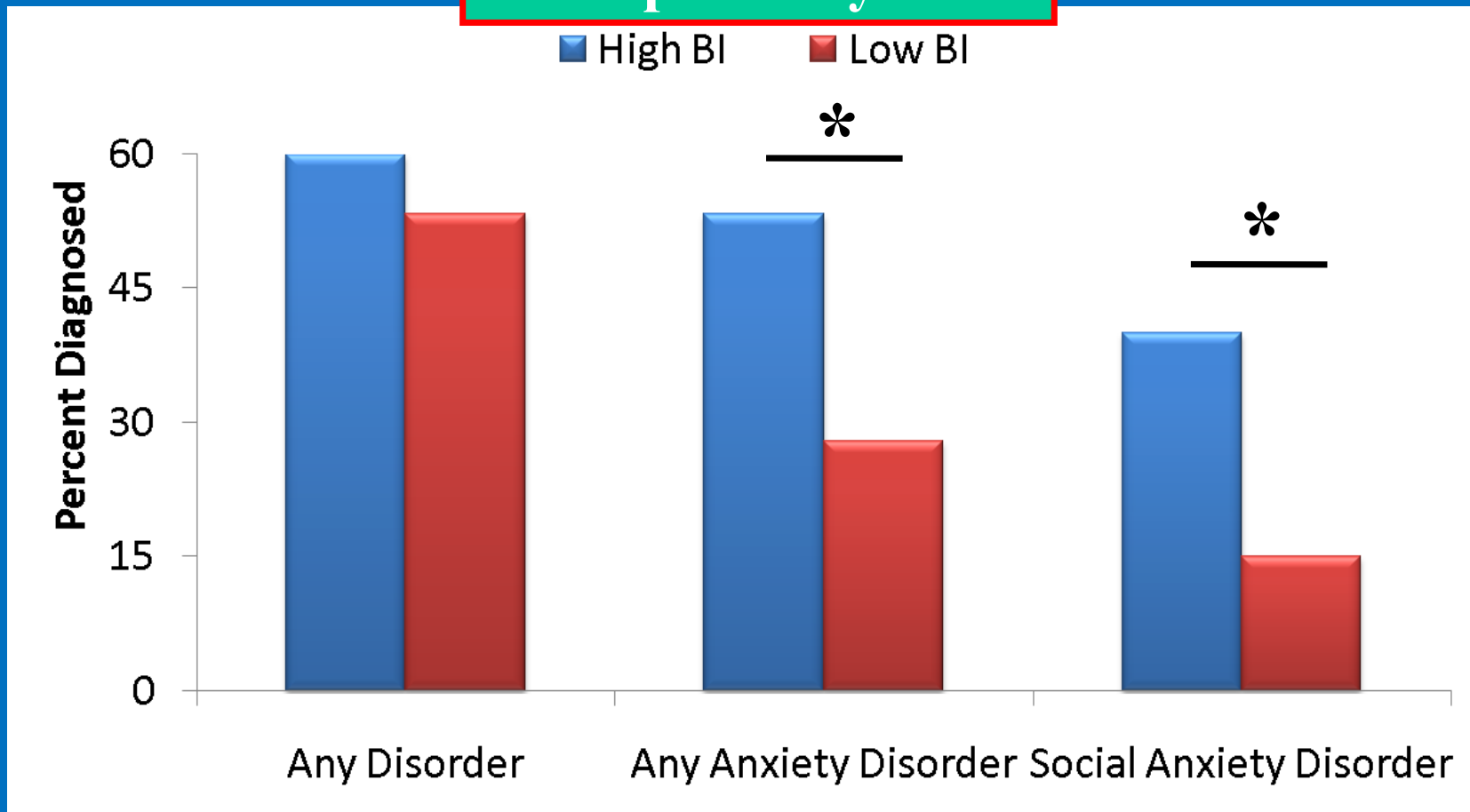
Panic Disorder/Agoraphobia & Generalized Anxiety Disorder

Behavioral Inhibition and Anxiety

Specificity?

Behavioral Inhibition and Anxiety

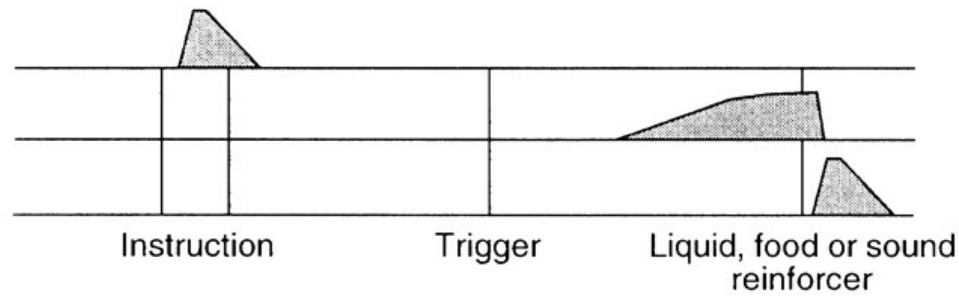
Specificity?



Chronis-Tuscano et al, 2009

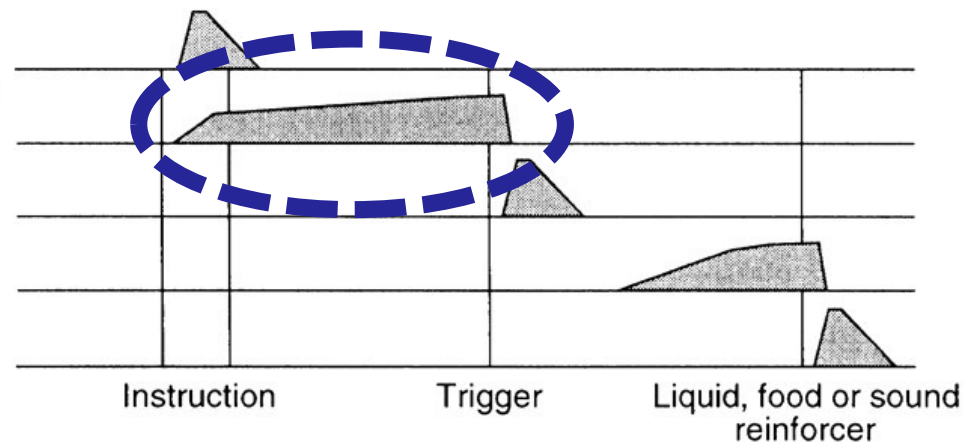
ORBITOFRONTAL CORTEX

Response to reward-predicting instruction
 Activation during expectation of reward
 Response to primary reward



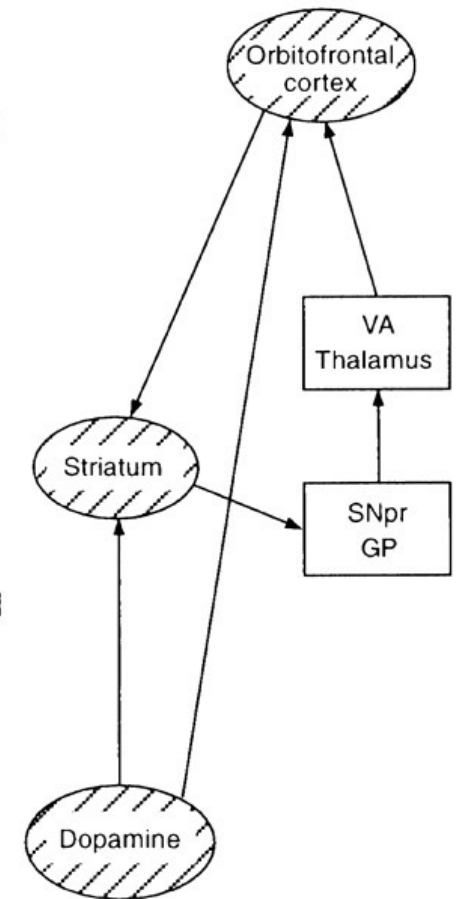
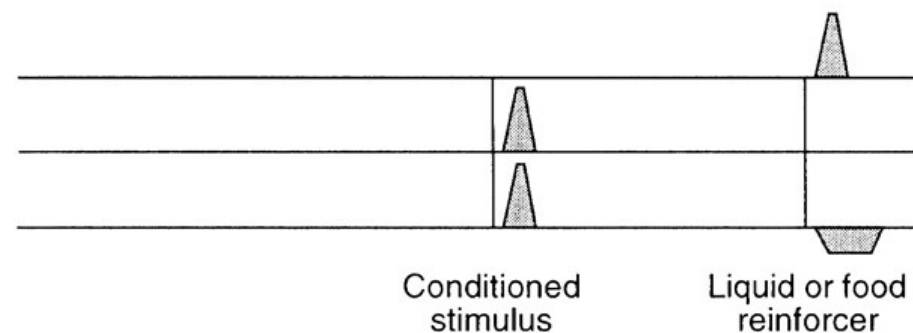
STRIATUM

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

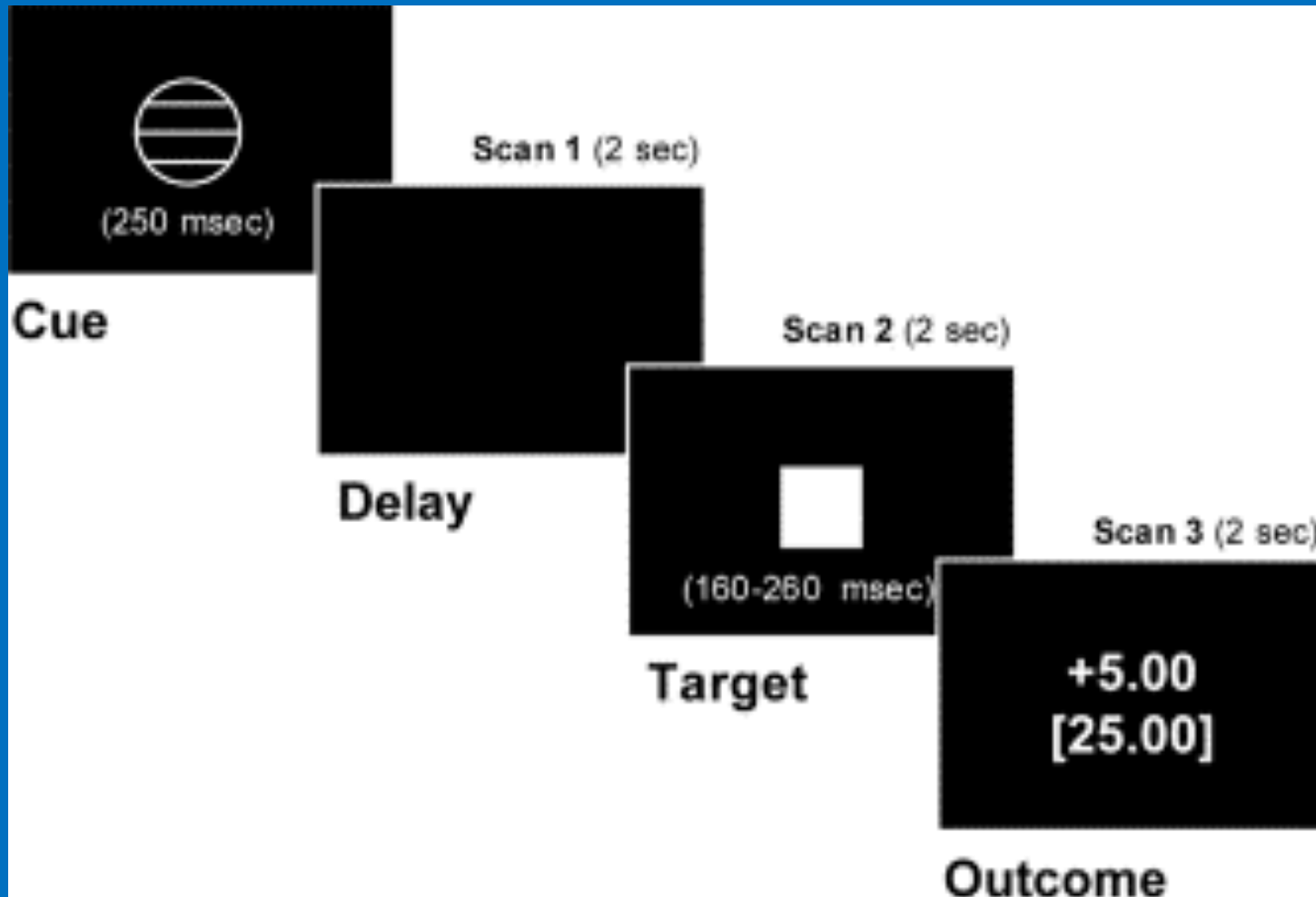


DOPAMINE NEURON

Response to unpredicted primary reward
 Response to reward-predicting stimulus
 Response to reward-predicting stimulus and omitted reward



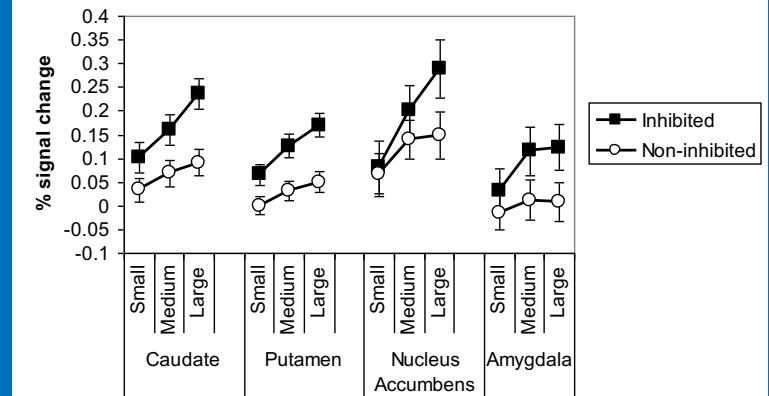
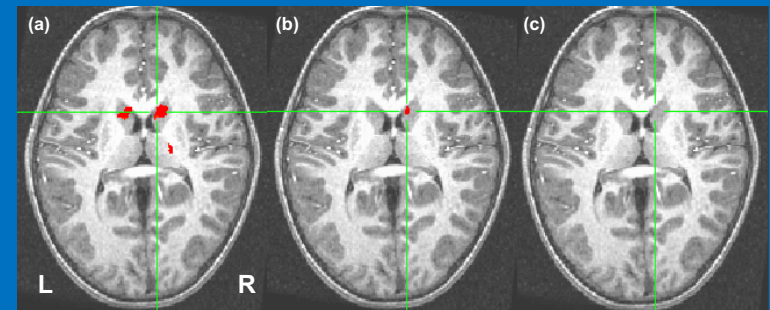
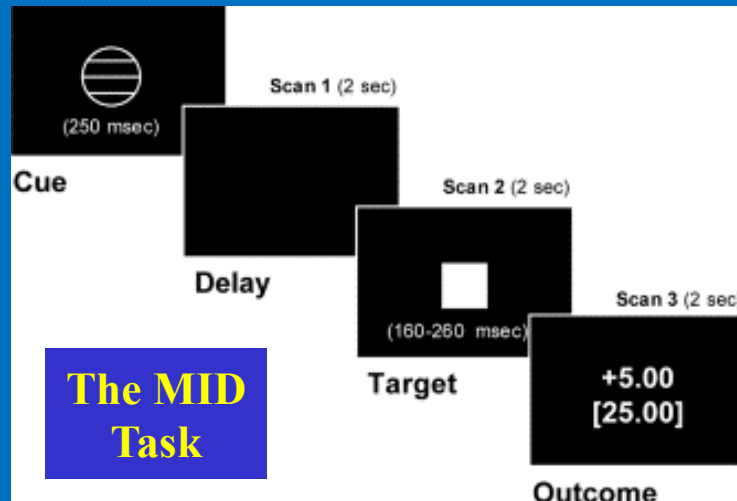
Assessing Reward Systems Function



BEHAVIORAL INHIBITION

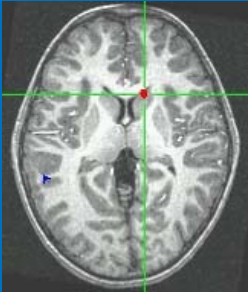
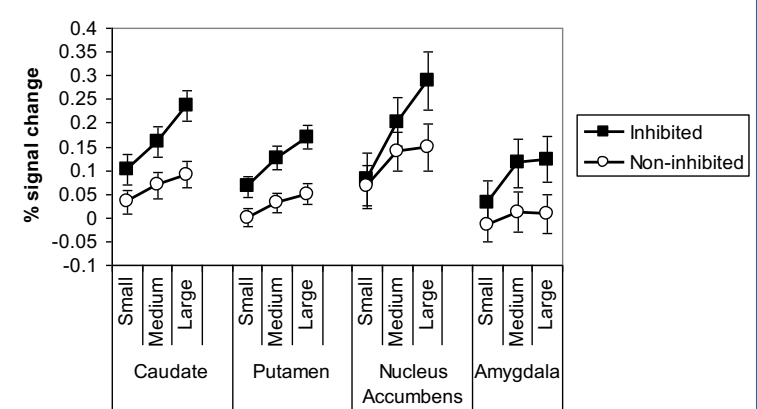
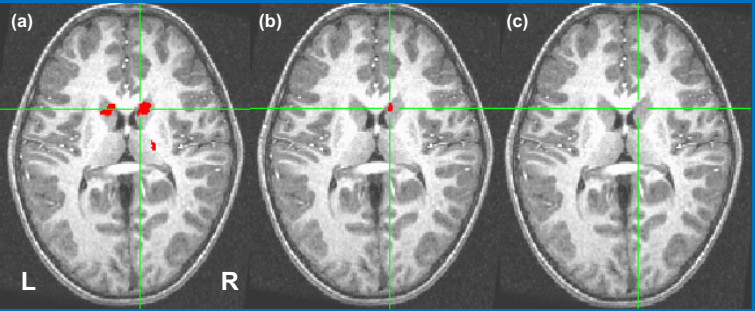
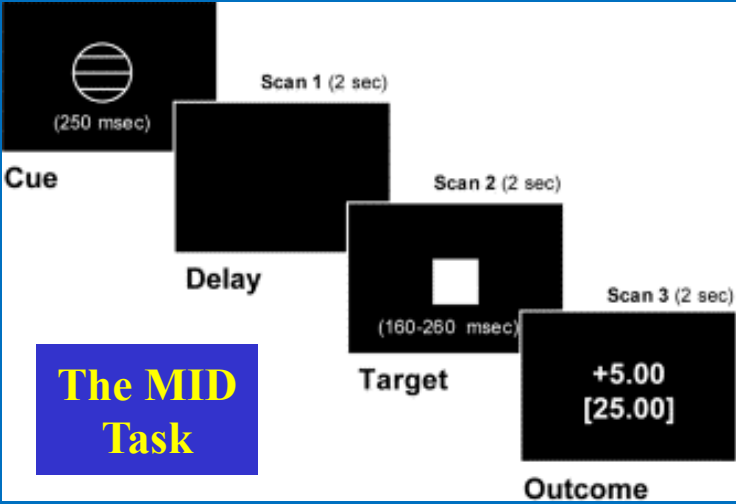
4 Months:	Recruitment and Selection
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17 Years:	Clinical Assessment, fMRI

Behavioral Inhibition, Anxiety, & Reward Processing

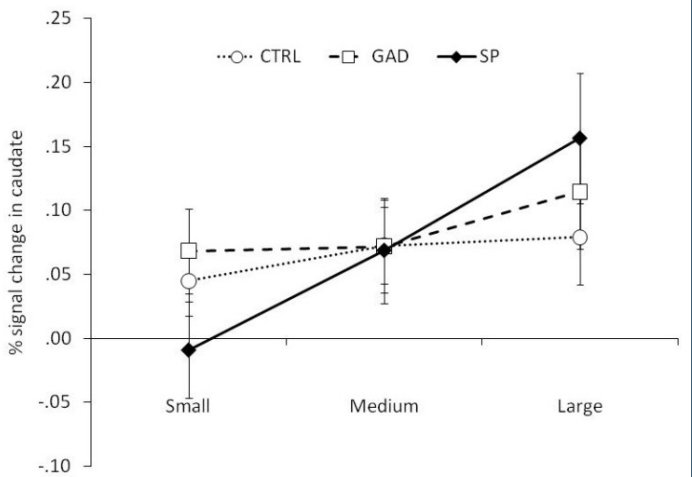


Behavioral Inhibition *Guyon et al. 2006*

Behavioral Inhibition, Anxiety, & Reward Processing



Anxiety *Guyer et al. 2012*



Behavioral Inhibition *Guyer et al. 2006*

Essay

Why Most Published Research Findings Are False

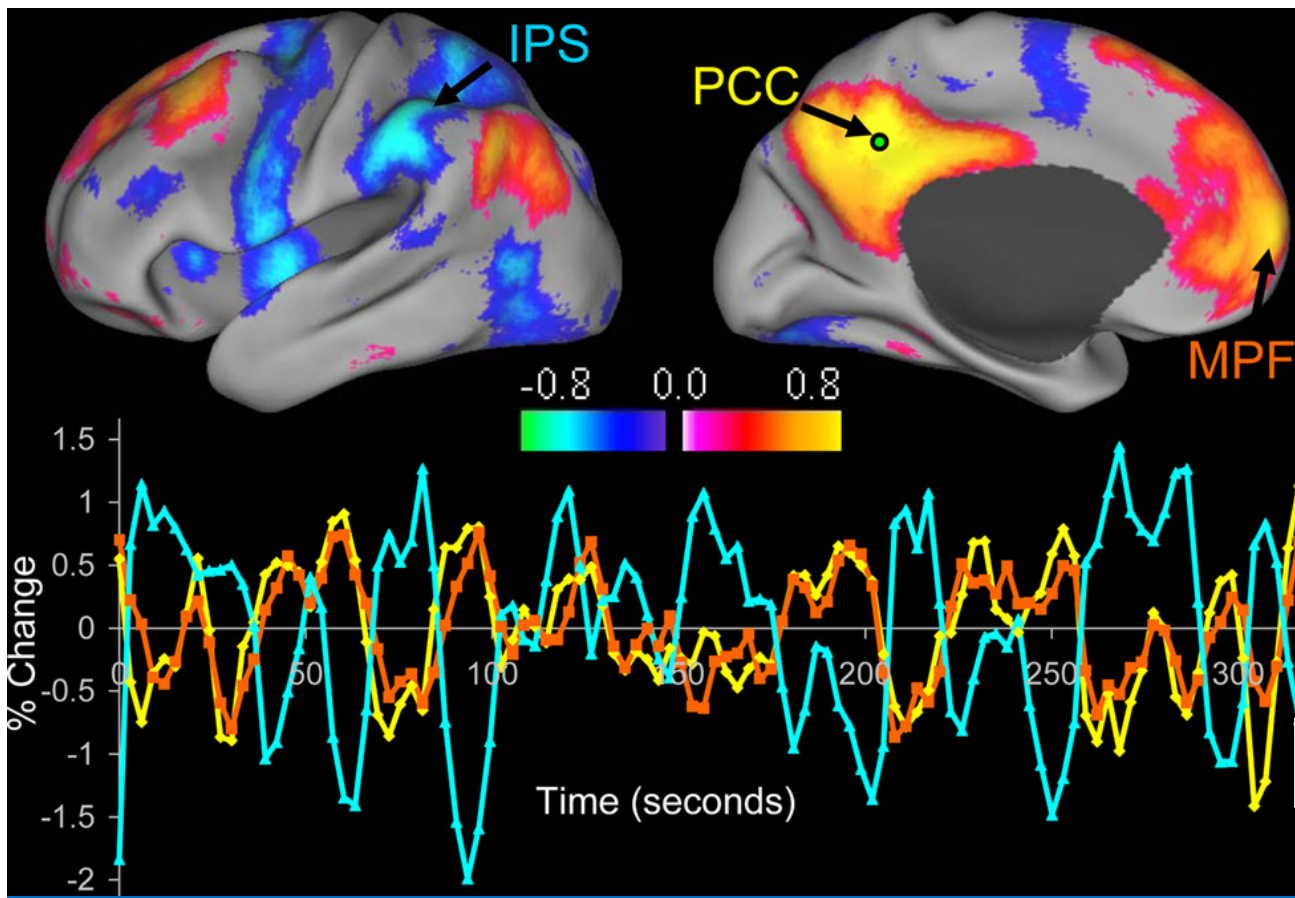
John P. A. Ioannidis

Contradicted and Initially Stronger Effects in Highly Cited Clinical Research

John P. A. Ioannidis, MD

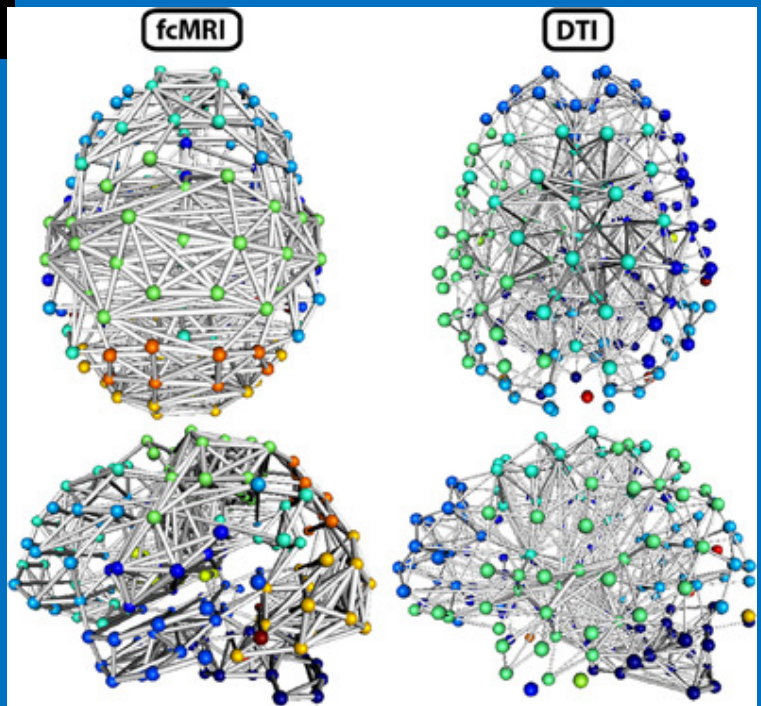
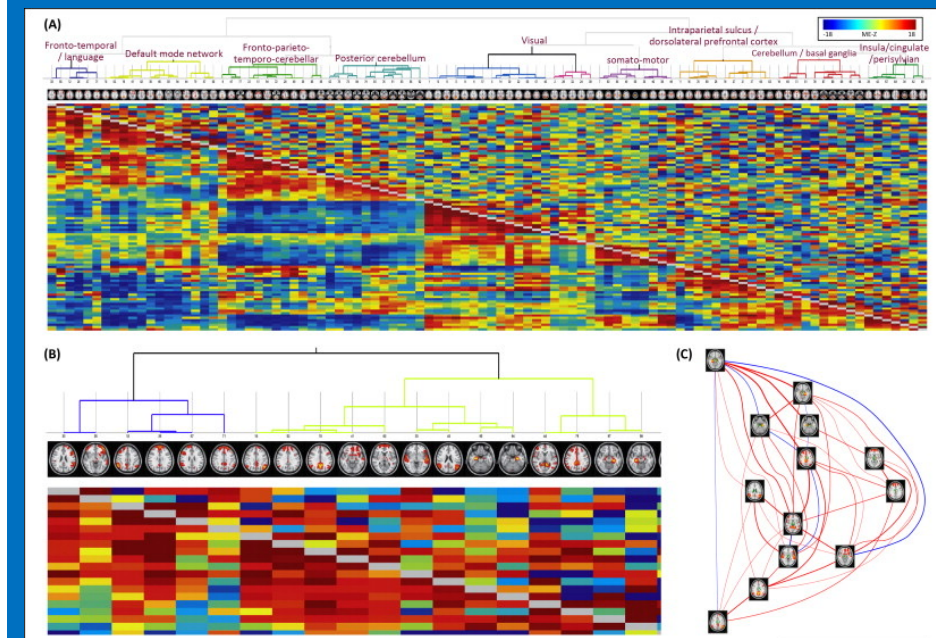
Excess Significance Bias in the Literature on Brain Volume Abnormalities

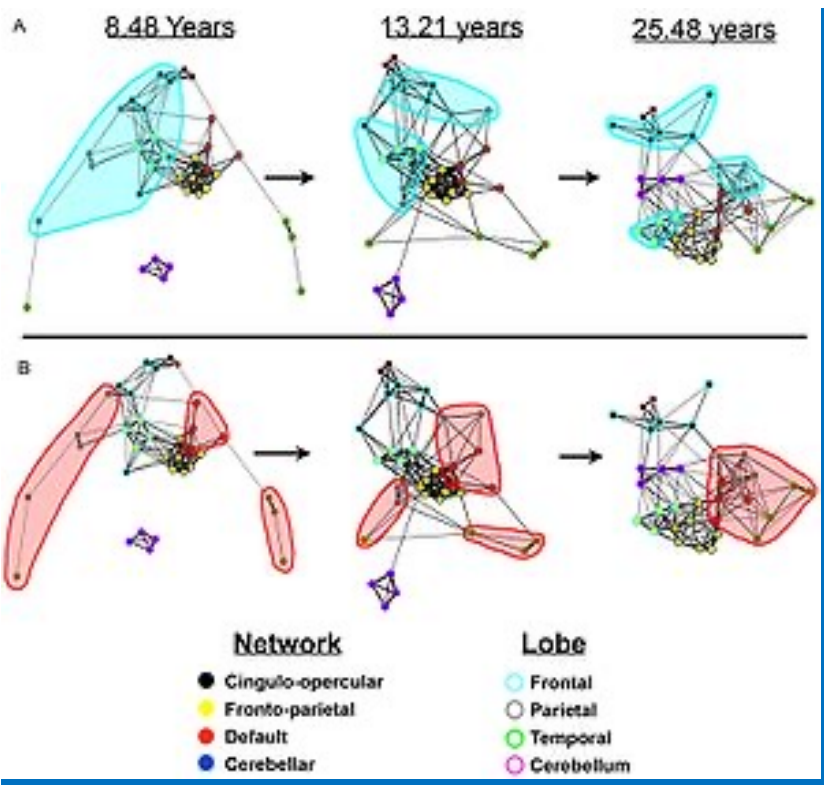
John P. A. Ioannidis, MD, DSc



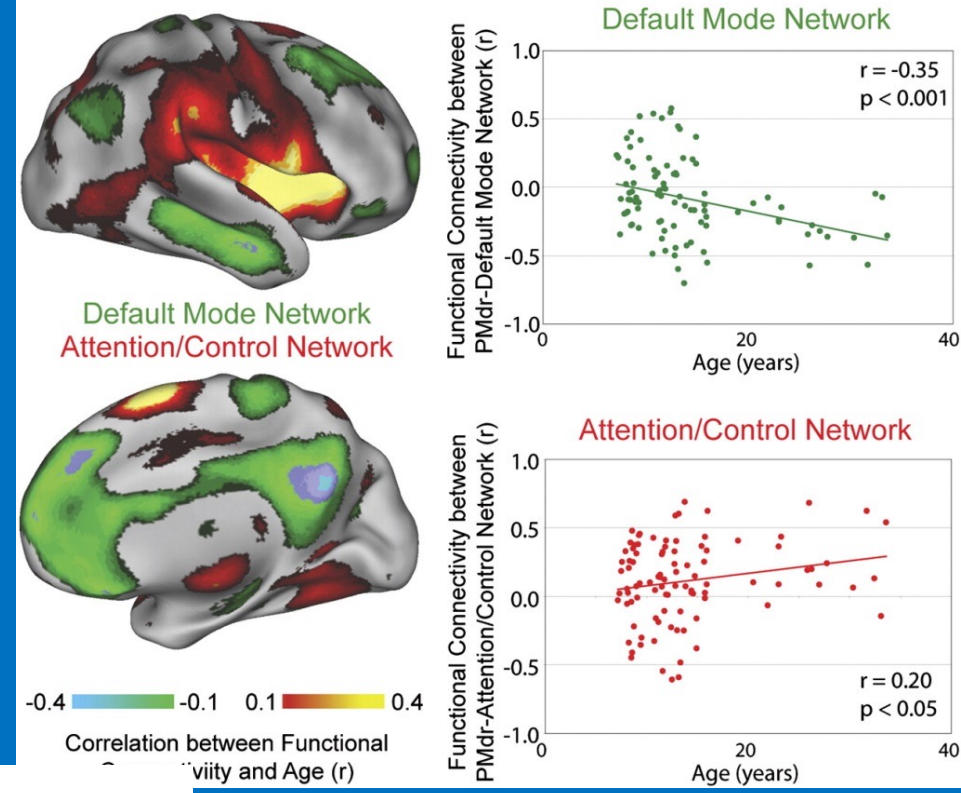
Biswal et al. 1995

Fair, Schlagger, Peterson & others



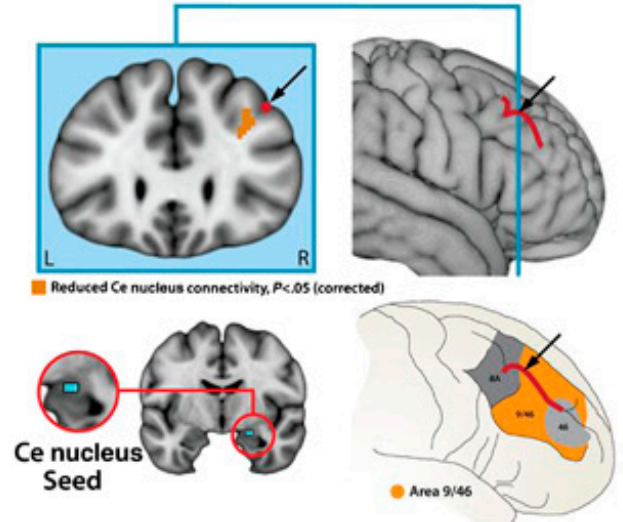


Functional Connectivity and Age in Typical Development

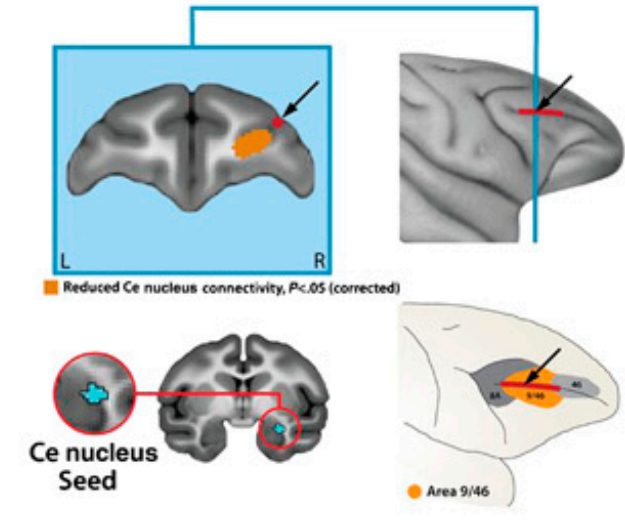


Homologous dIPFC subdivisions show decreased intrinsic connectivity with the Ce nucleus in anxious children and monkeys

a Children with anxiety disorders at rest



b Young monkeys with higher levels of AT under anesthesia



Fair, Schlagger, Peterson & others

Birn et al. 2014

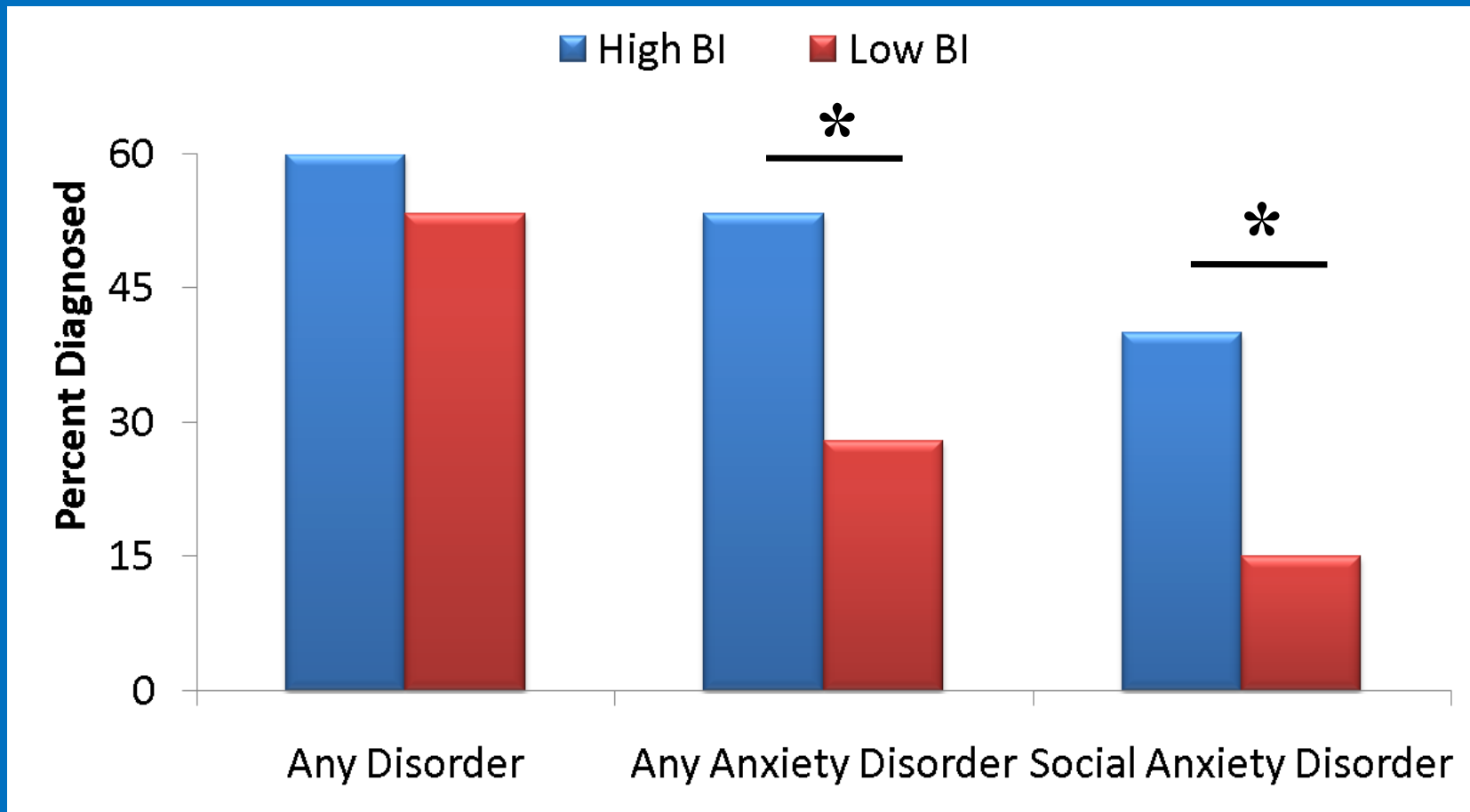
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Behavioral Inhibition and Anxiety



Chronis-Tuscano et al, 2009

**VISUAL
CORTEX**

VISUAL THALAMUS

AMYGDALA

HEART RATE



BLOOD PRESSURE



MUSCLE



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

The Dot-Probe Task



time

*



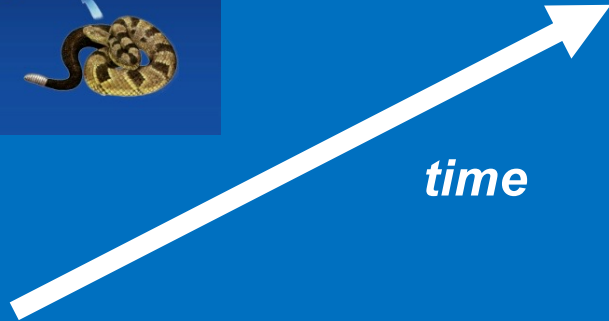
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Mogg & Bradley

Bar-Haim et al. (2007)

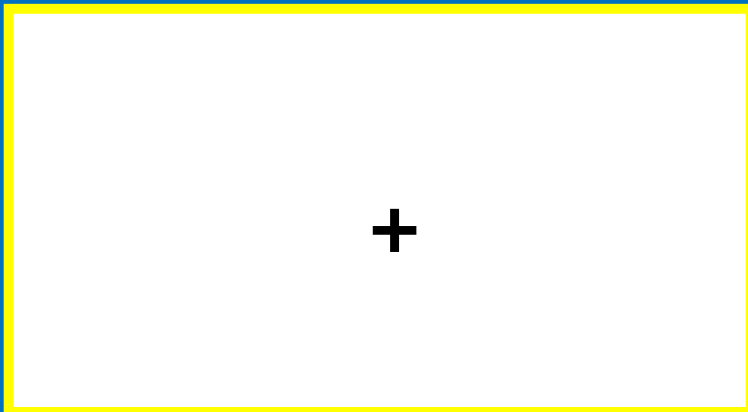
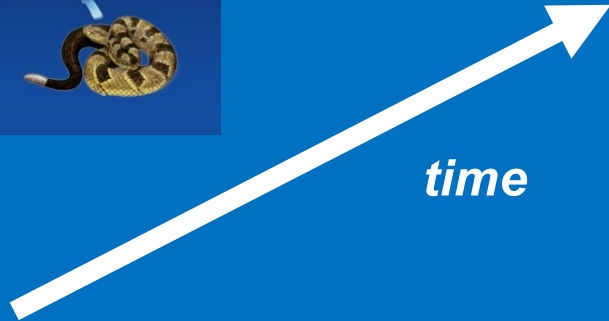
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The Dot-Probe Task



+

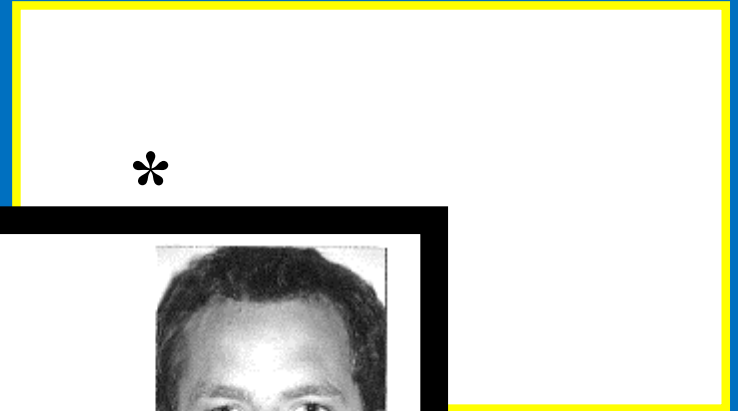
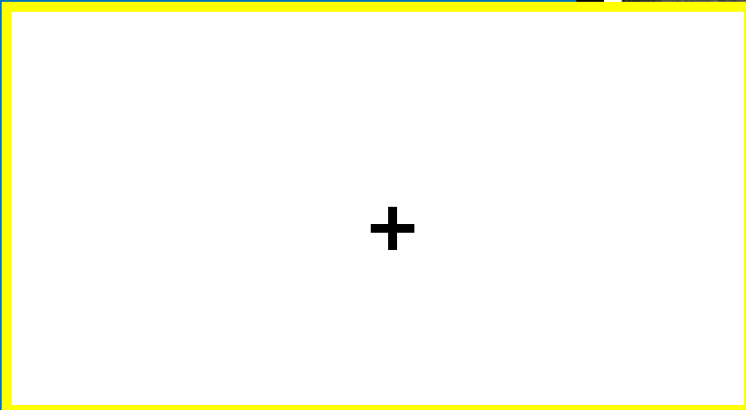
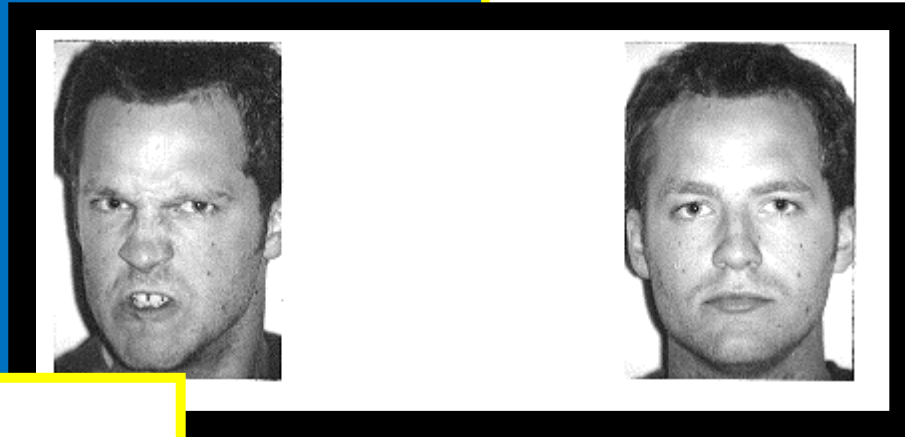
The Dot-Probe Task



The Dot-Probe Task



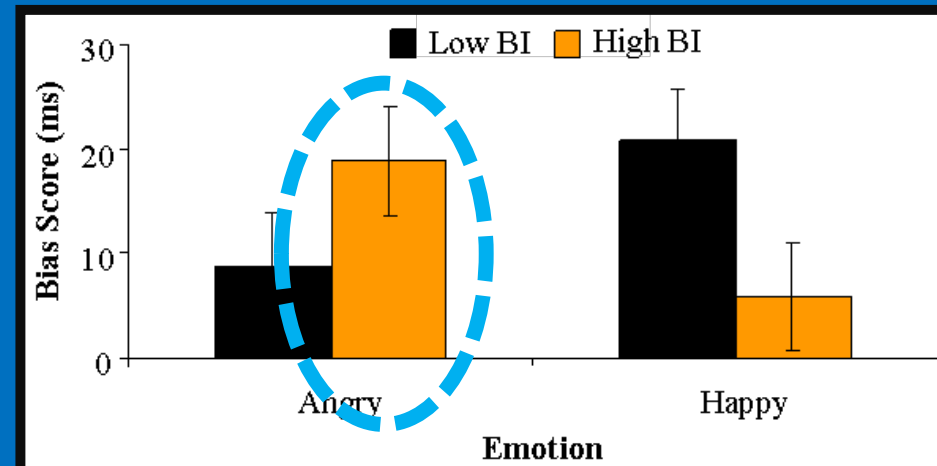
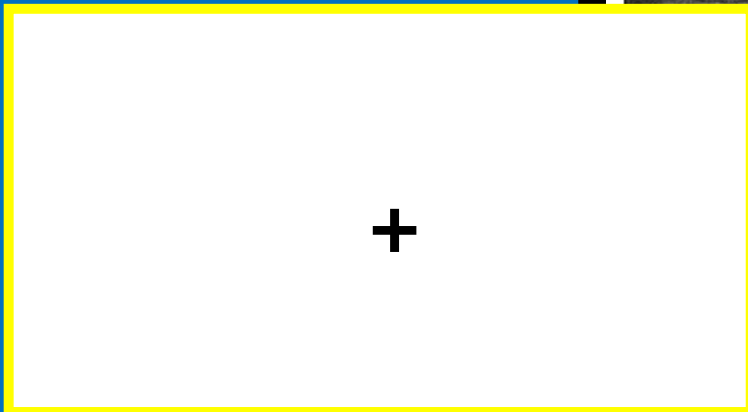
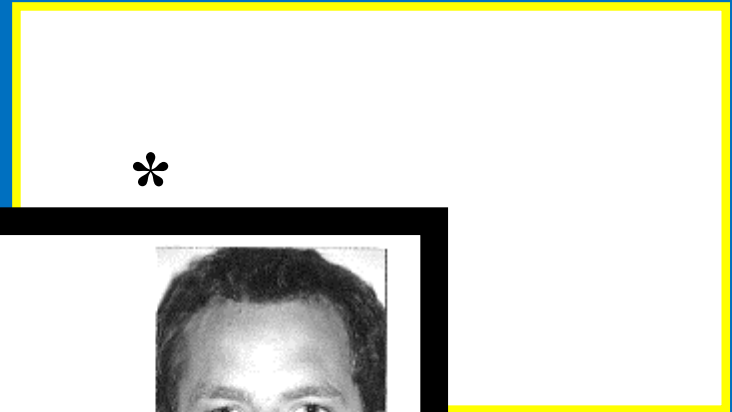
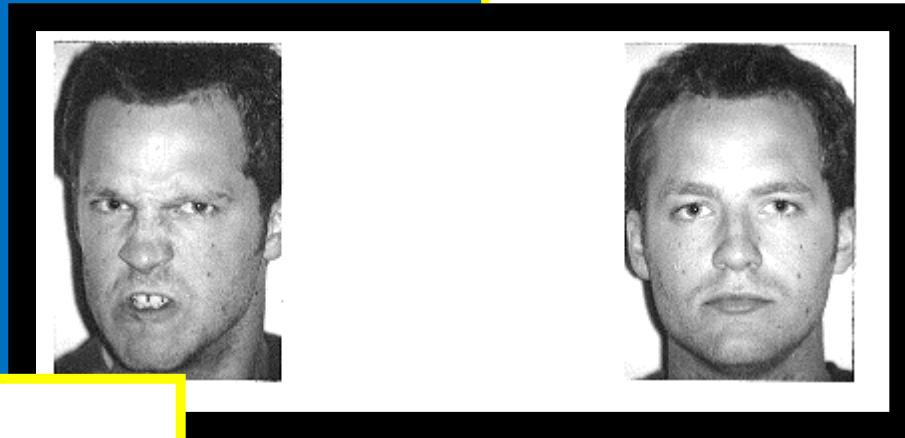
time



The Dot-Probe Task



time



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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***-assessment of attention

Fox et al. 2006

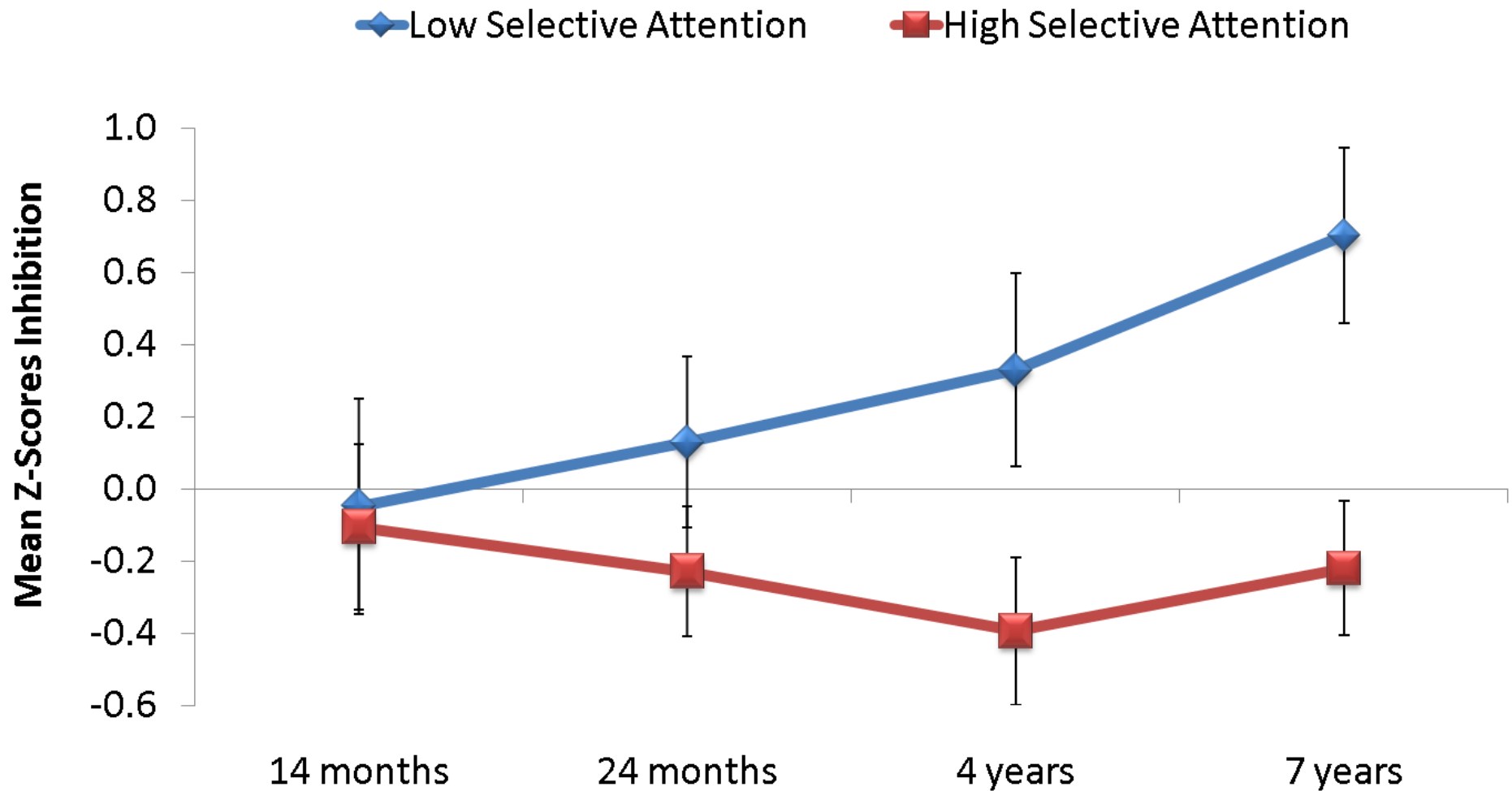
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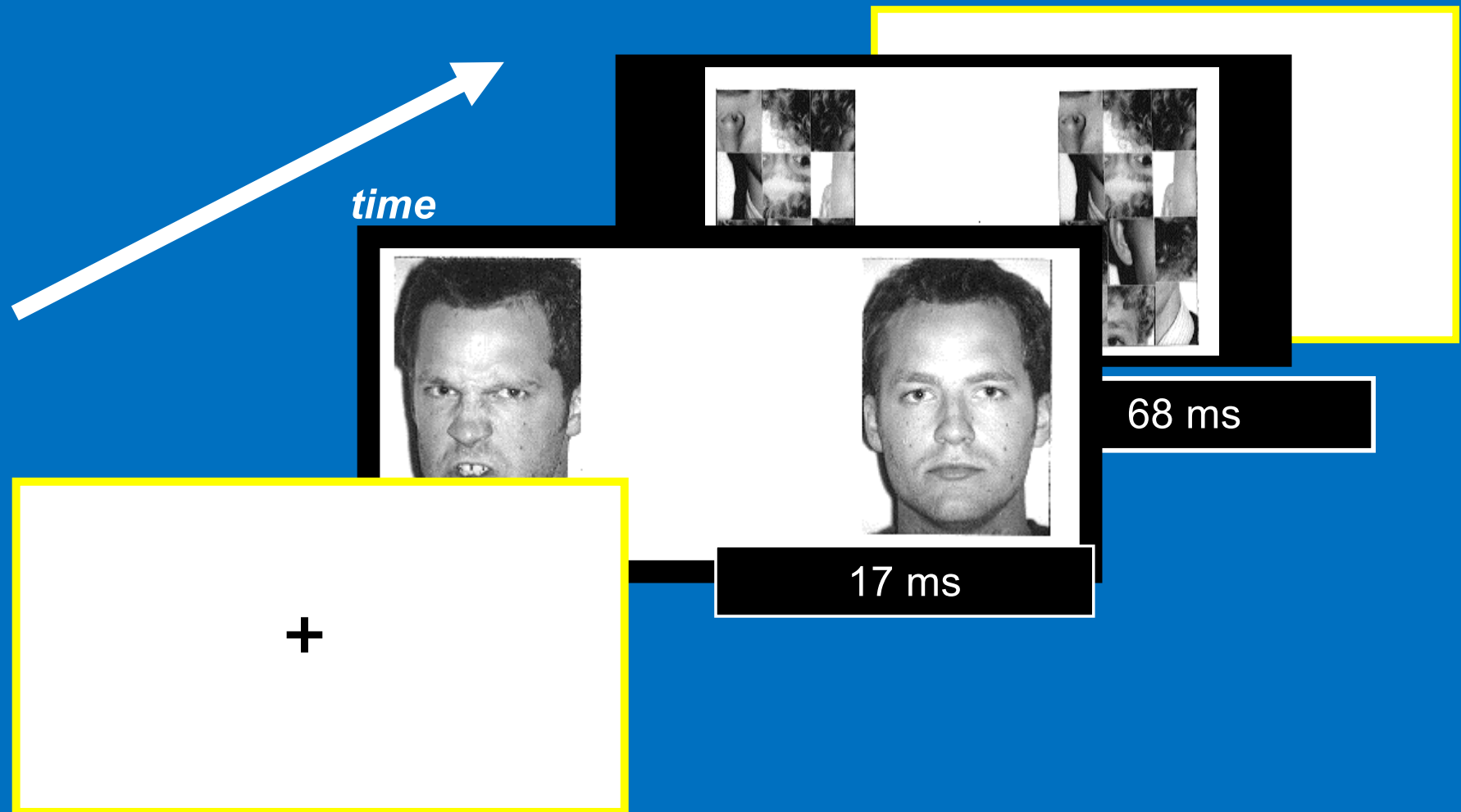
Fox et al. 2006

Persistent Anxiety Emerges Over Time

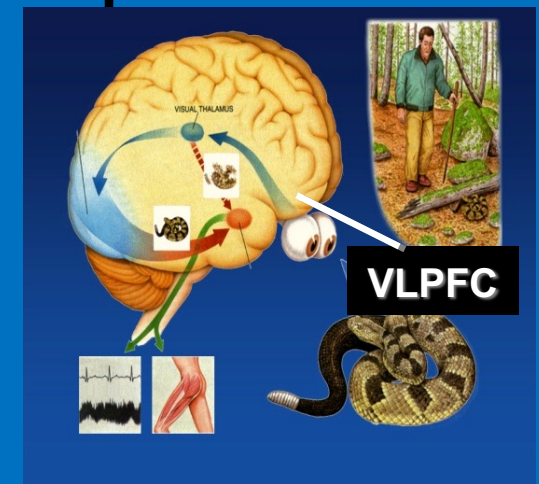


Perez-Edgar et al. 2010

The Dot-Probe Task



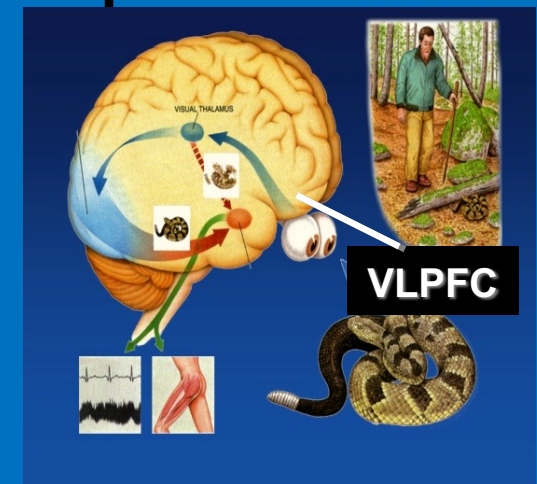
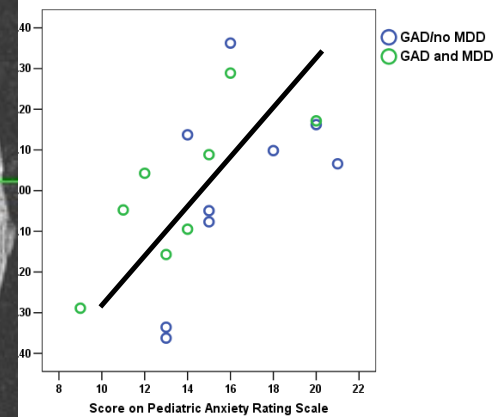
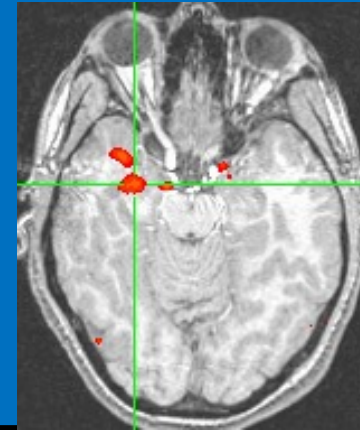
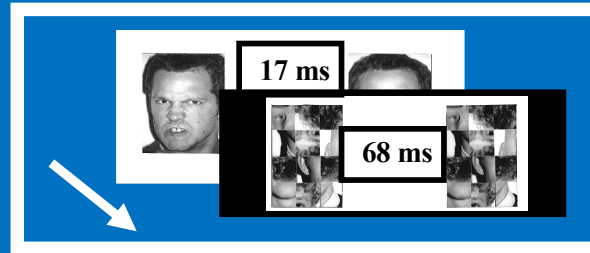
Attention, PFC-Amygdala-Circuitry, and Pediatric Anxiety



Monk et al. 2006, 2008

Attention, PFC-Amygdala-Circuitry, and Pediatric Anxiety

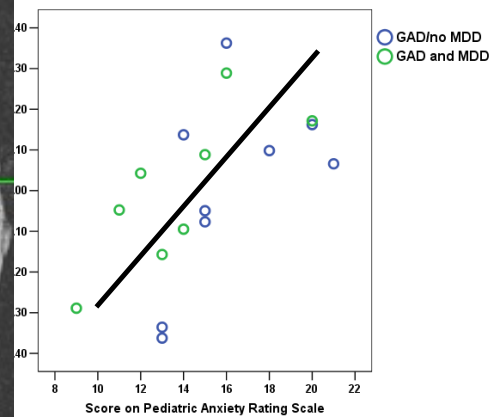
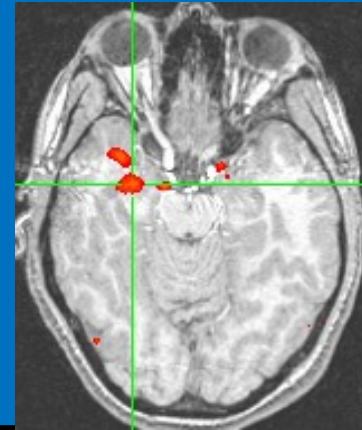
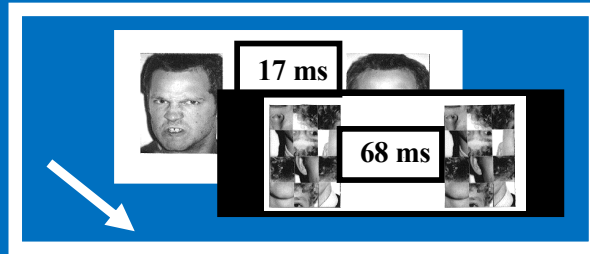
Brief Subliminal Threat: *Amygdala instantiates anxiety*



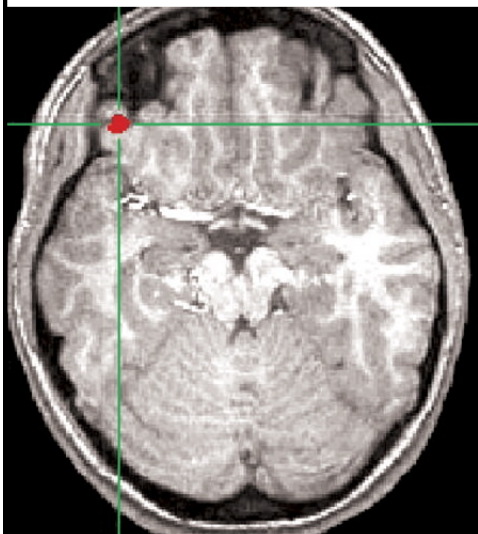
Monk et al. 2006, 2008

Attention, PFC-Amygdala-Circuitry, and Pediatric Anxiety

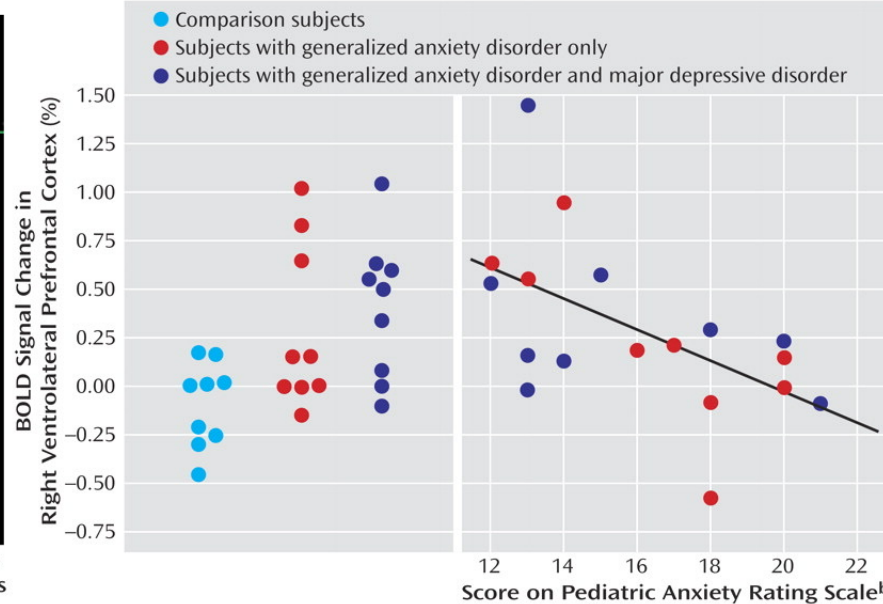
Brief Subliminal Threat: *Amygdala instantiates anxiety*



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

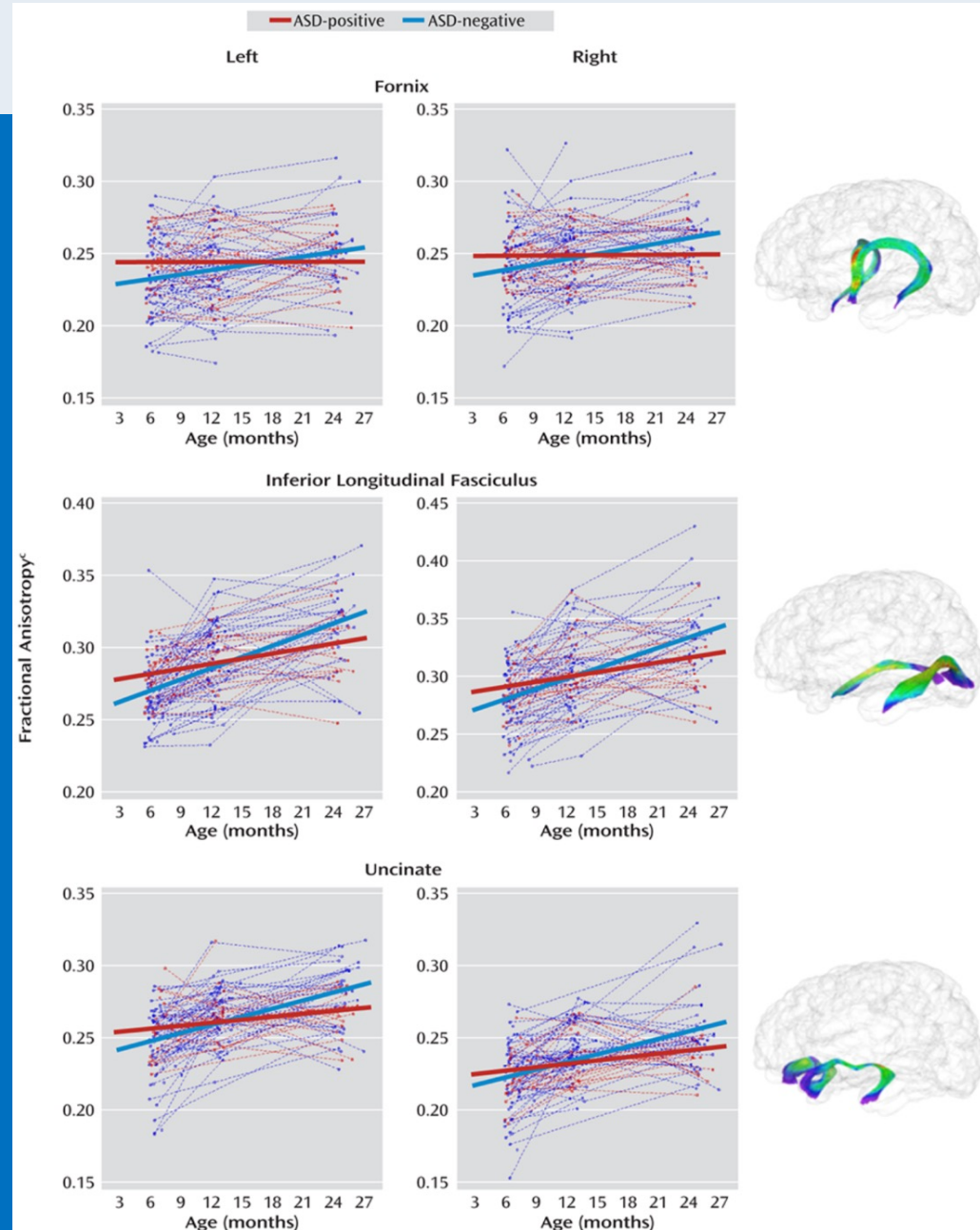
From: Differences in White Matter Fiber Tract Development Present From 6 to 24 Months in Infants With Autism

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



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Any Adolescent Anxiety Disorder & Any Adult Mood/Anxiety Disorder

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

Pine et al. 1998, 2001, 2002

Any Adolescent Anxiety Disorder & Any Adult Mood/Anxiety Disorder

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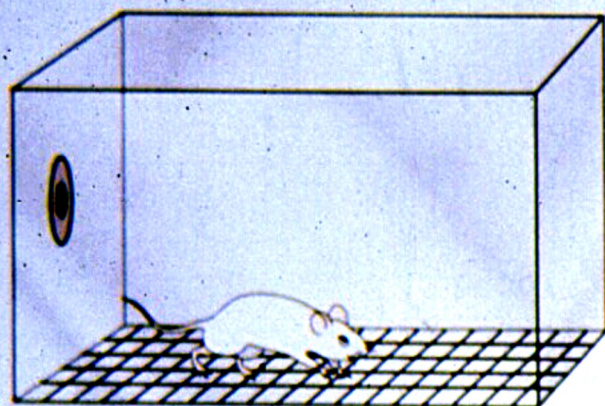
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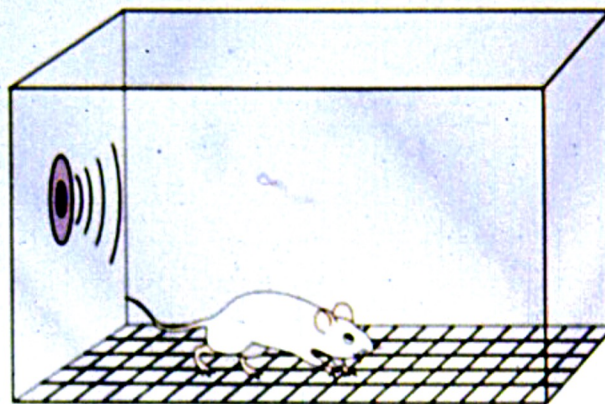
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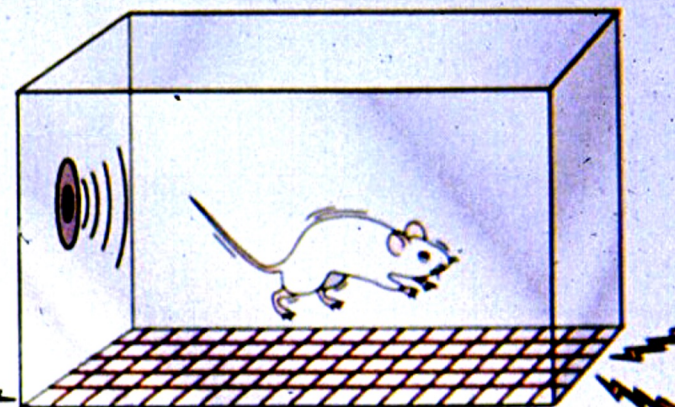
TRAINING



Exposure to context (2 min)

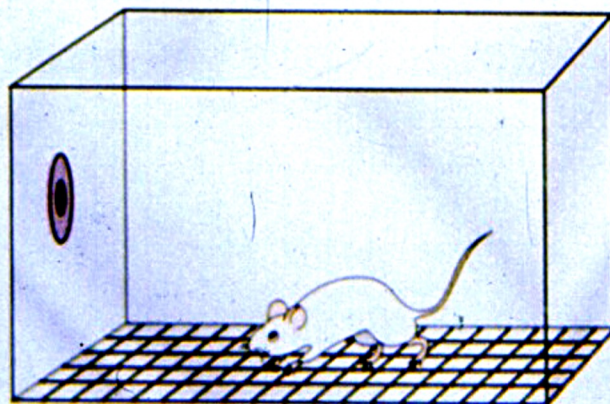


Onset of sound (CS: 30 s)



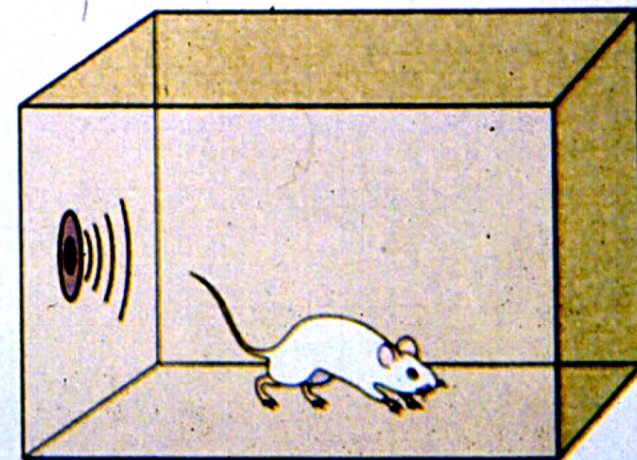
Onset of shock (US: 2 s)

TESTING: Context
Test at 1 hour
and 24 hours



Same context (5 min)

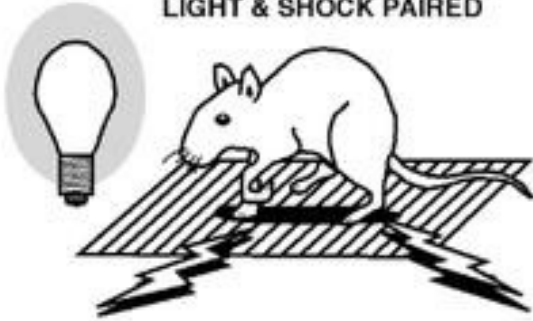
TESTING: Cued
Test at 1 hour
and 24 hours



Onset of sound (CS: 3 min)

A

**CONDITIONING:
LIGHT & SHOCK PAIRED**



**TESTING:
NOISE-ALONE
TRIALS**

Normal Startle
(In Dark)



**LIGHT/NOISE
TRIALS**

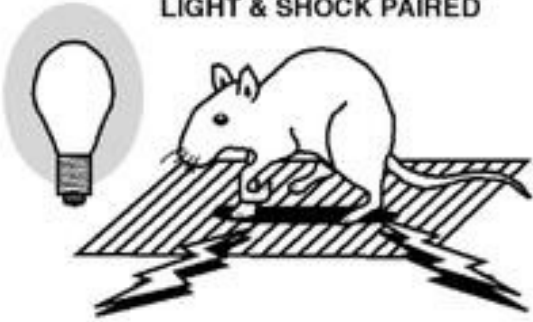
Potentiated Startle
(In Light)



Ressler & Davis 2003

A

CONDITIONING:
LIGHT & SHOCK PAIRED



TESTING:
NOISE-ALONE
TRIALS

Normal Startle
(In Dark)



LIGHT/NOISE
TRIALS

Potentiated Startle
(In Light)

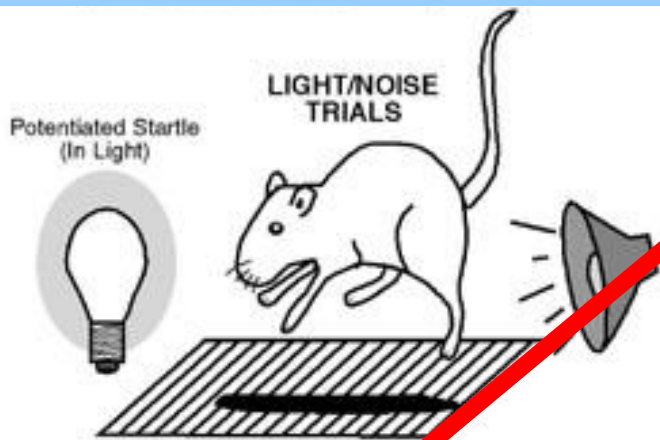
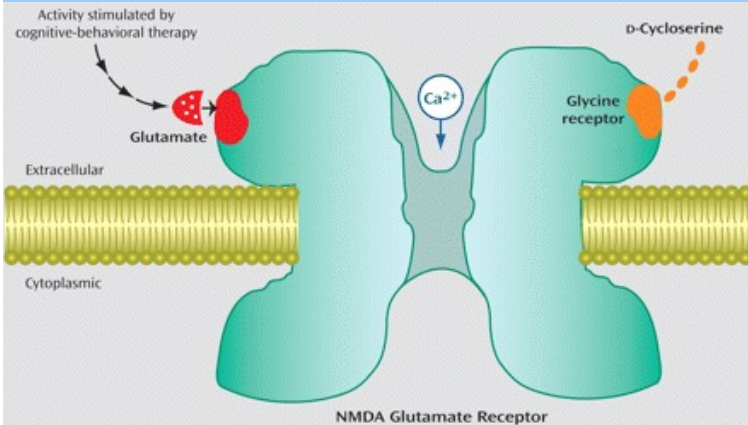


Extinction Recall: *Remembering the Boundary Between Danger and Safety*

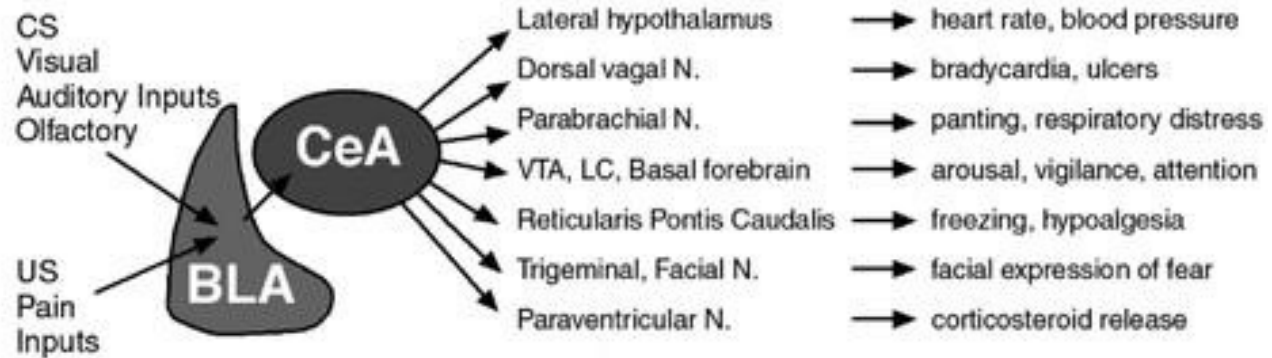
Ressler & Davis 2003

EXTINCTION

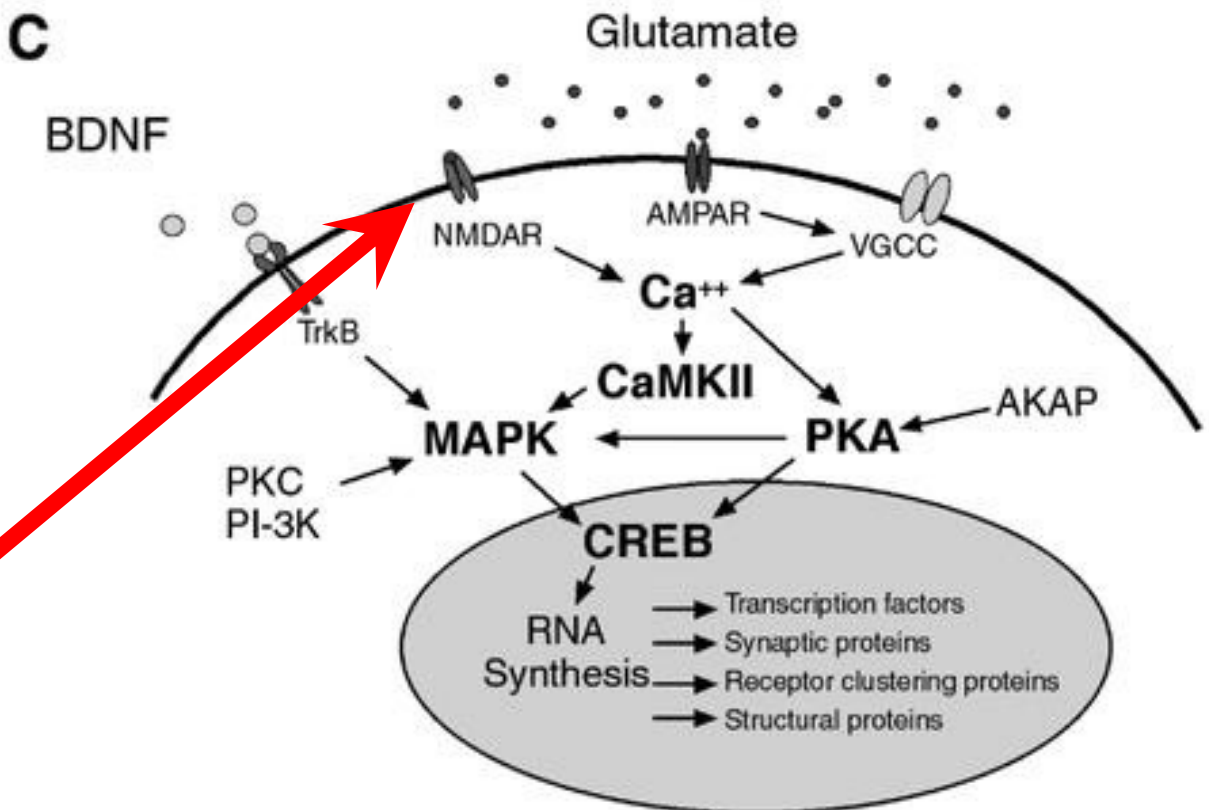
Insights on Therapeutics



B



C



NMDA manipulations?

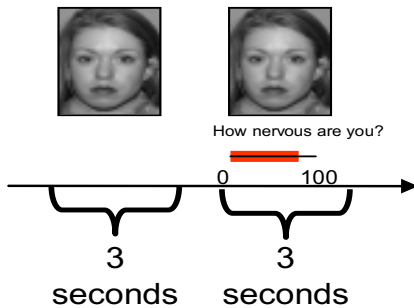
Ressler & Davis 2003

How do we study fear learning in youth?

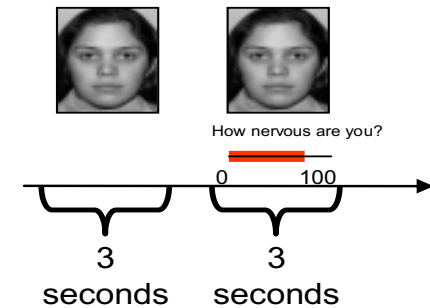


FACE-SCREAM CONDITIONING

CS MINUS



CS PLUS

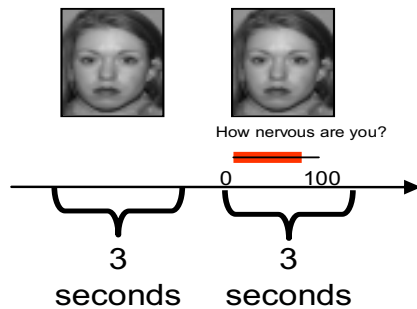


Conditioning of Fear Reactions:

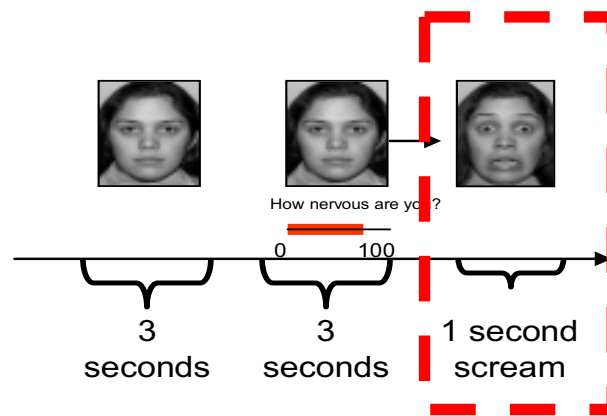
Neutral Face CS; Screaming Lady UCS

FACE-SCREAM CONDITIONING

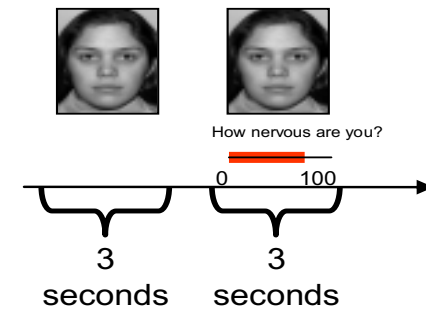
CS MINUS



CS PLUS (paired)



CS PLUS



Conditioning of Fear Reactions:

Neutral Face CS; Screaming Lady UCS

Pre-conditioning

Expt 1: 8 trials of each

Expt 2: 3 trials of each



How nervous are you?



How nervous are you?



Conditioning

Expt 1: 10 trials of each

Expt 2: 60 trials of each

CS+



How nervous are you?



Reinforced CS+



+ scream

80% (Expt 1)
50% (Expt 2)

20% (Expt 1)
50% (Expt 2)

How nervous are you?



CS-



How nervous are you?



Non-Reinforced CS+



How nervous are you?



Attention-State & Anxiety:

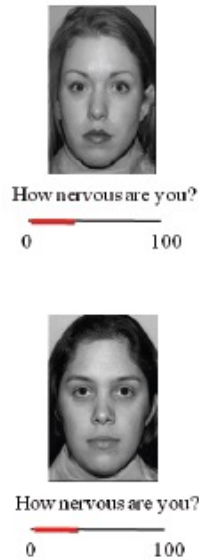
The importance of threat appraisal

Lau et al. (2011)

Pre-conditioning

Expt 1: 8 trials of each

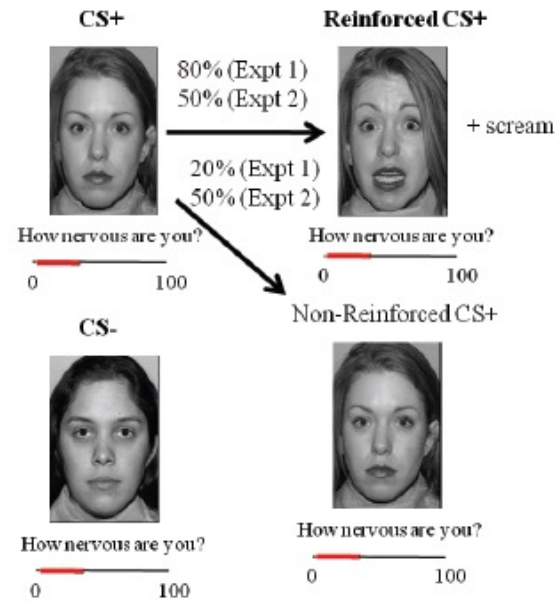
Expt 2: 3 trials of each



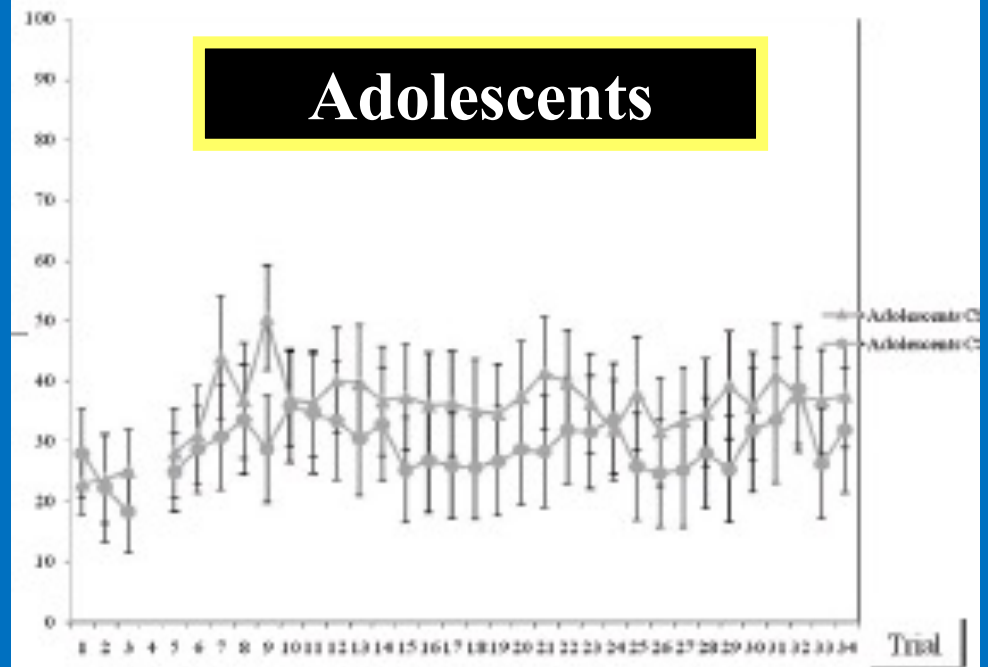
Conditioning

Expt 1: 10 trials of each

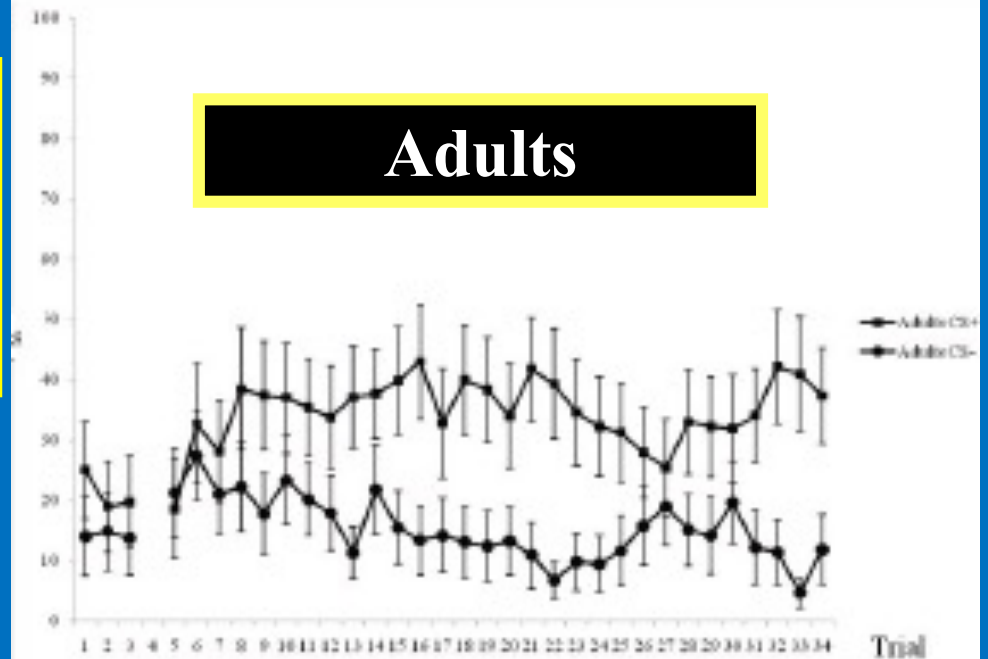
Expt 2: 60 trials of each



Adolescents



Adults

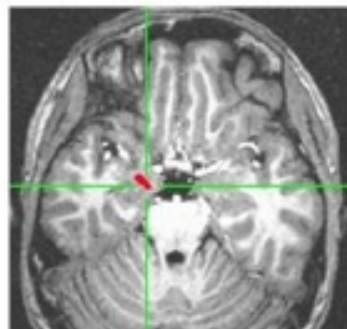
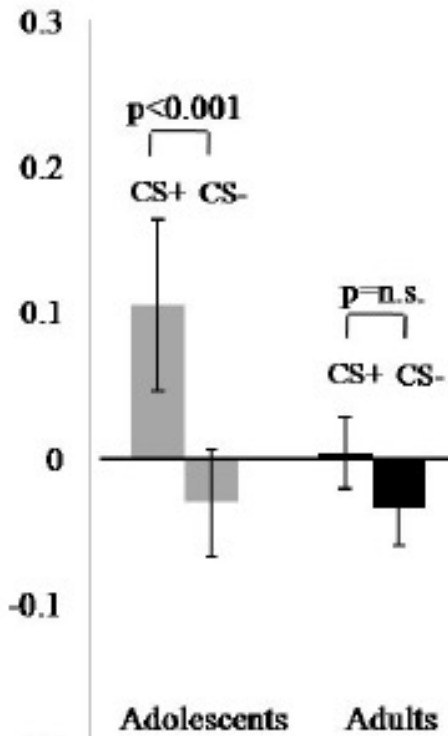


Attention-State & Anxiety:

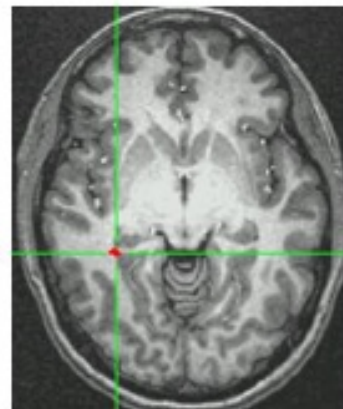
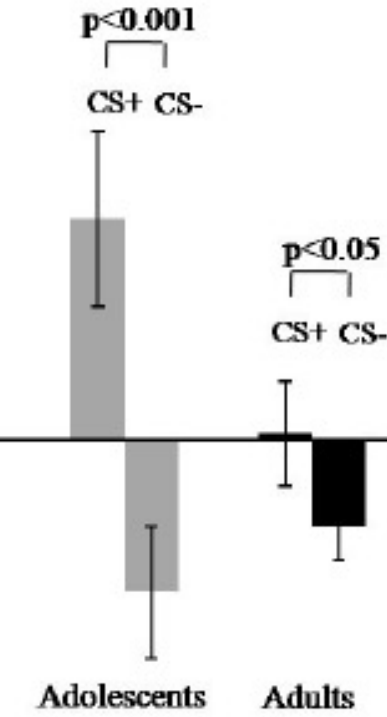
The importance of threat appraisal

Lau et al. (2011)

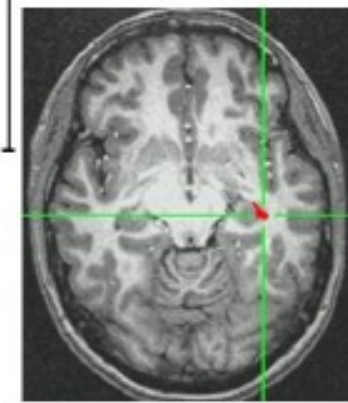
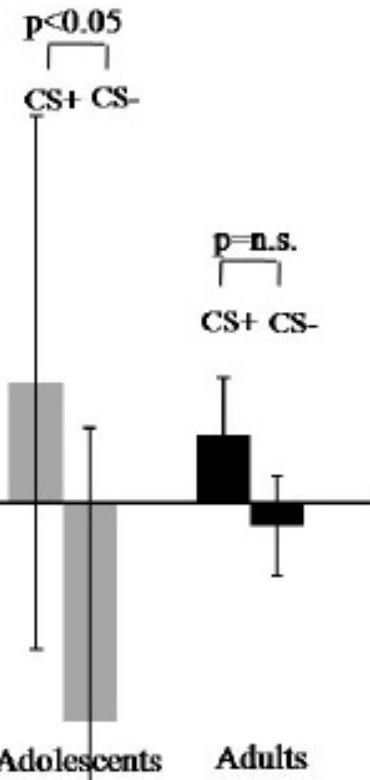
Right amygdala
(Talairach coordinates: 25 -2 -18)



Right hippocampus
(Talairach coordinates: 37 -19 -5)



Left hippocampus
(Talairach coordinates: -31 -36 -2)



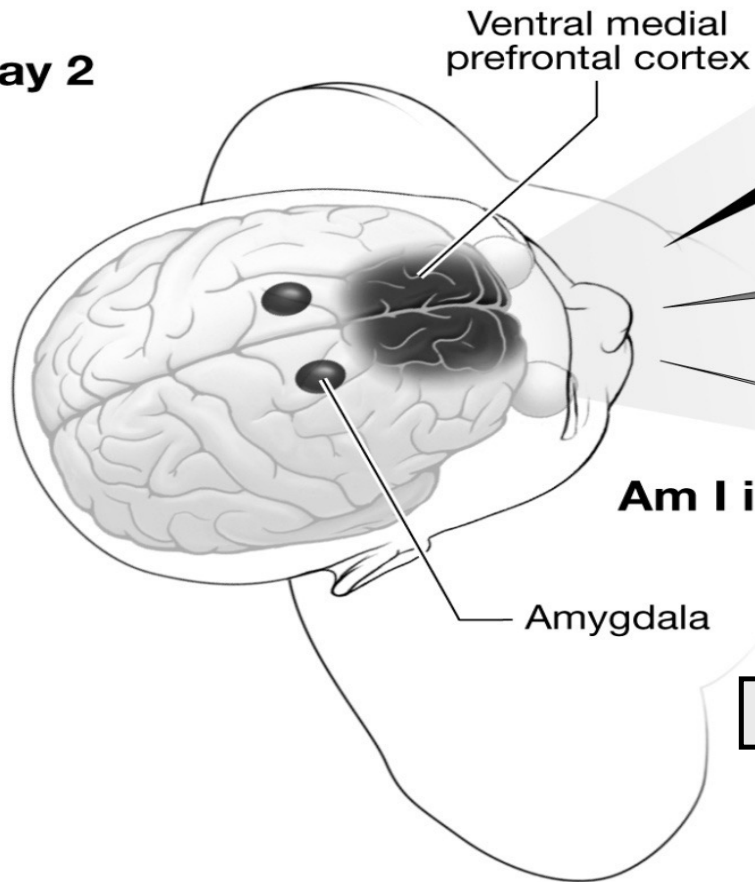
Lau et al. (2011)

Day 1 – Conditioning/Extinction

Day 1



Day 2

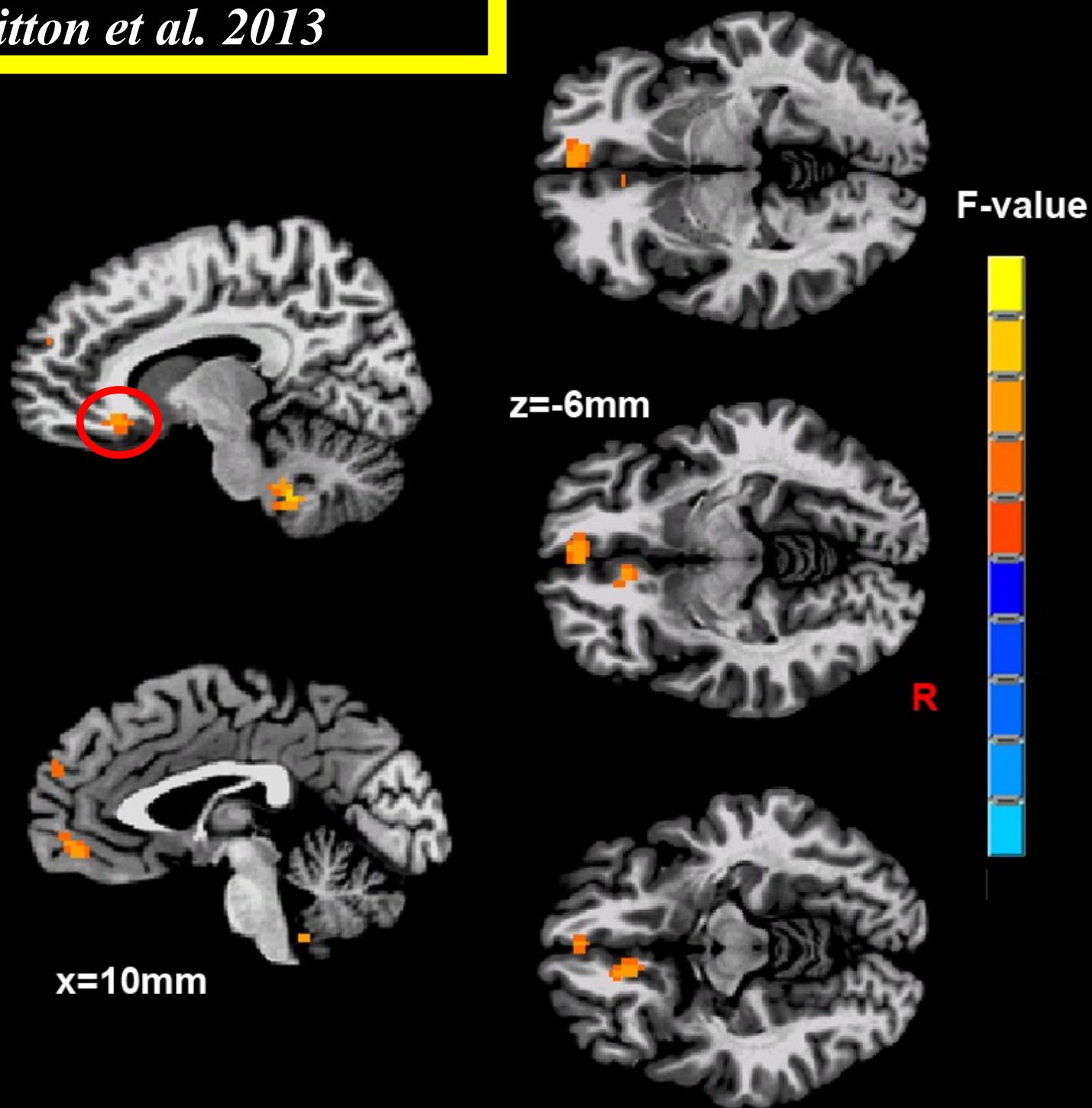


Day 15 - 400



Am I in danger?

Day 2 – Extinction Recall



Outline

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

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