

Tackling Hard Problems

Neuroscience, Treatment, & Anxiety



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NIMH
National Institute
of Mental Health

Disclosures: Conflicts

Sources of Research Support

National Institute of Mental Health

Roles in DSM-5, RDoC

Role in cognitive training research

My perspective

Paid Editorial Relationship

Am J Psychiatry– Deputy Editor

Consulting Relationships

None

Stock Equity (>\$10,000)

None

Speaker's Bureau

None

Outline

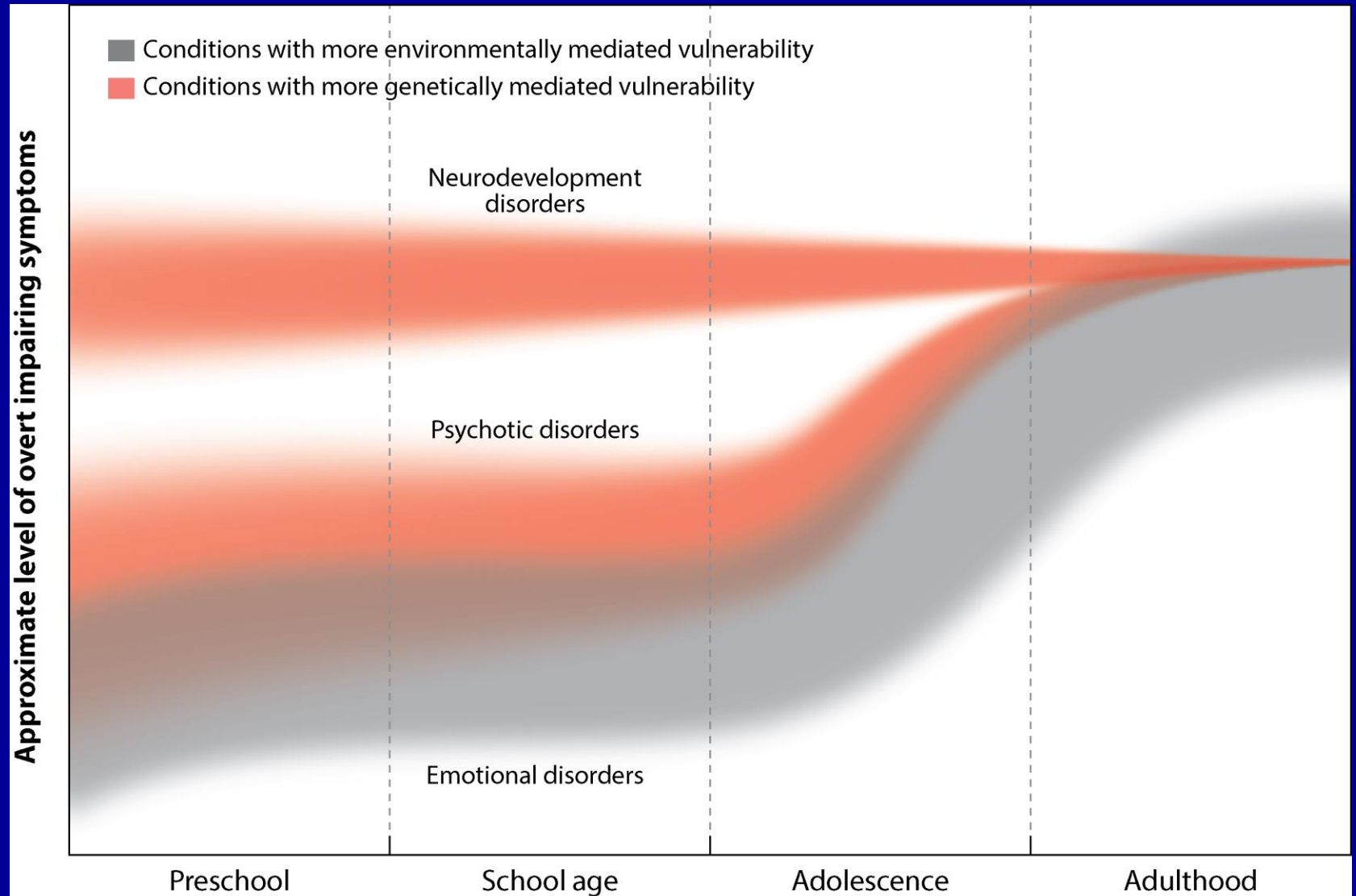
- **Overview**
- **Two Systems Theory**
- **Reflections**

Outline

- **Overview**
- **Two Systems Theory**
- **Reflections**

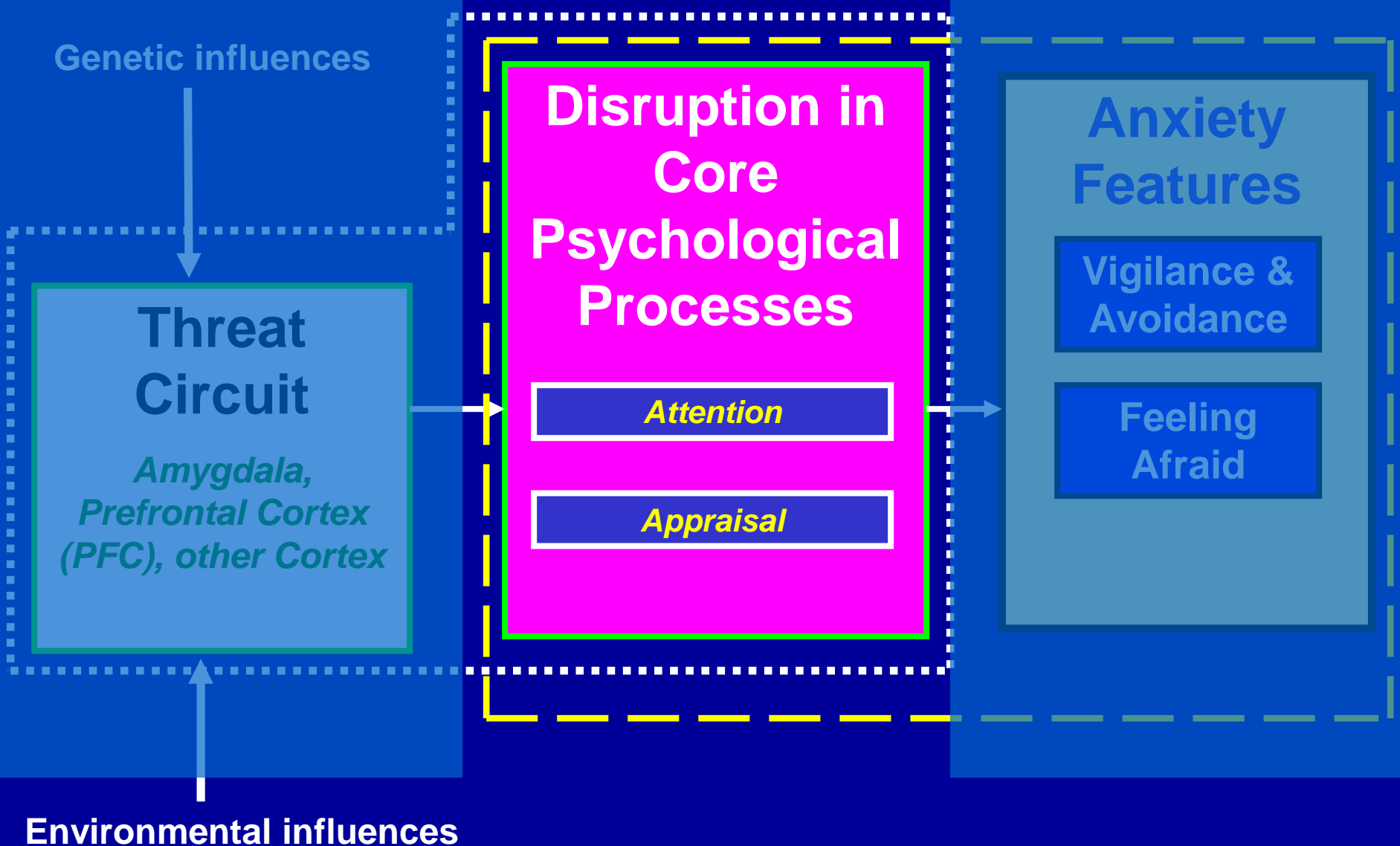
Research Goals

- **Use neuroscience for clinical means**
- **Anxiety as a good starting point**
- **Areas generating key questions:**
 - *Developmental change in symptoms*
 - *Differences between risk & disorder*
 - *Understanding and improving treatment*

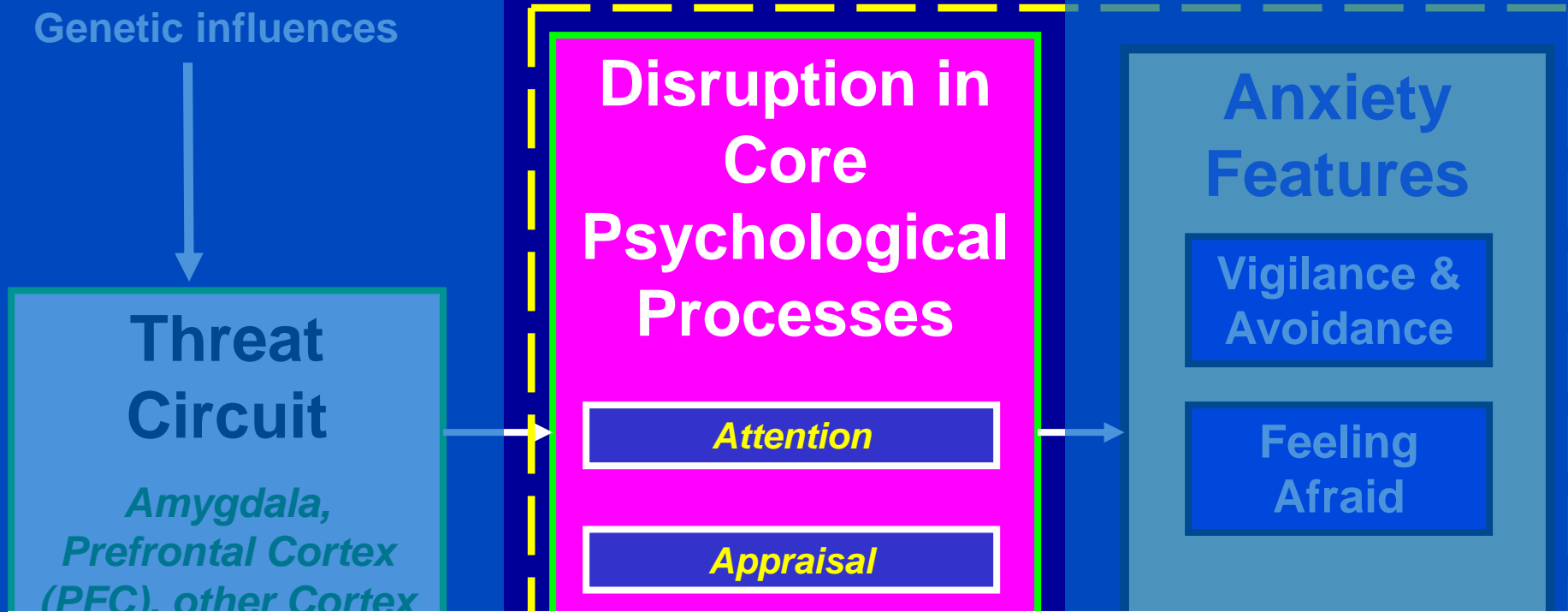


Pine DS, Fox NA. 2015.

Annu. Rev. Psychol. 66:459–85



Sweet spot: *behaviors bridging basic and clinical work*

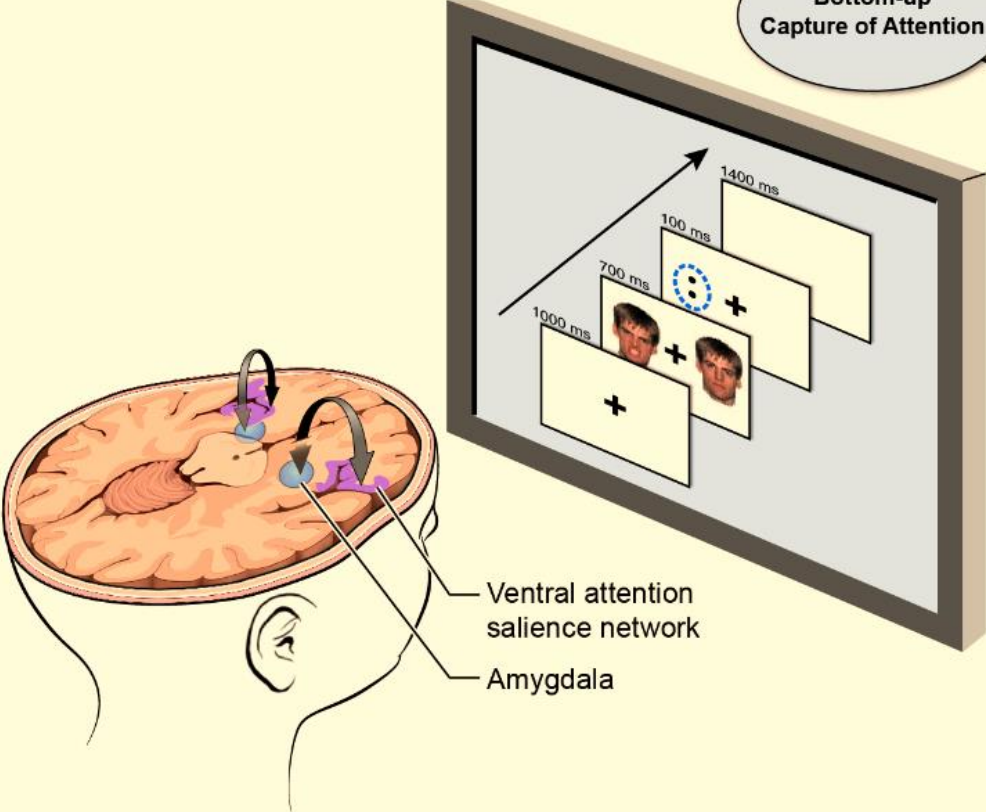
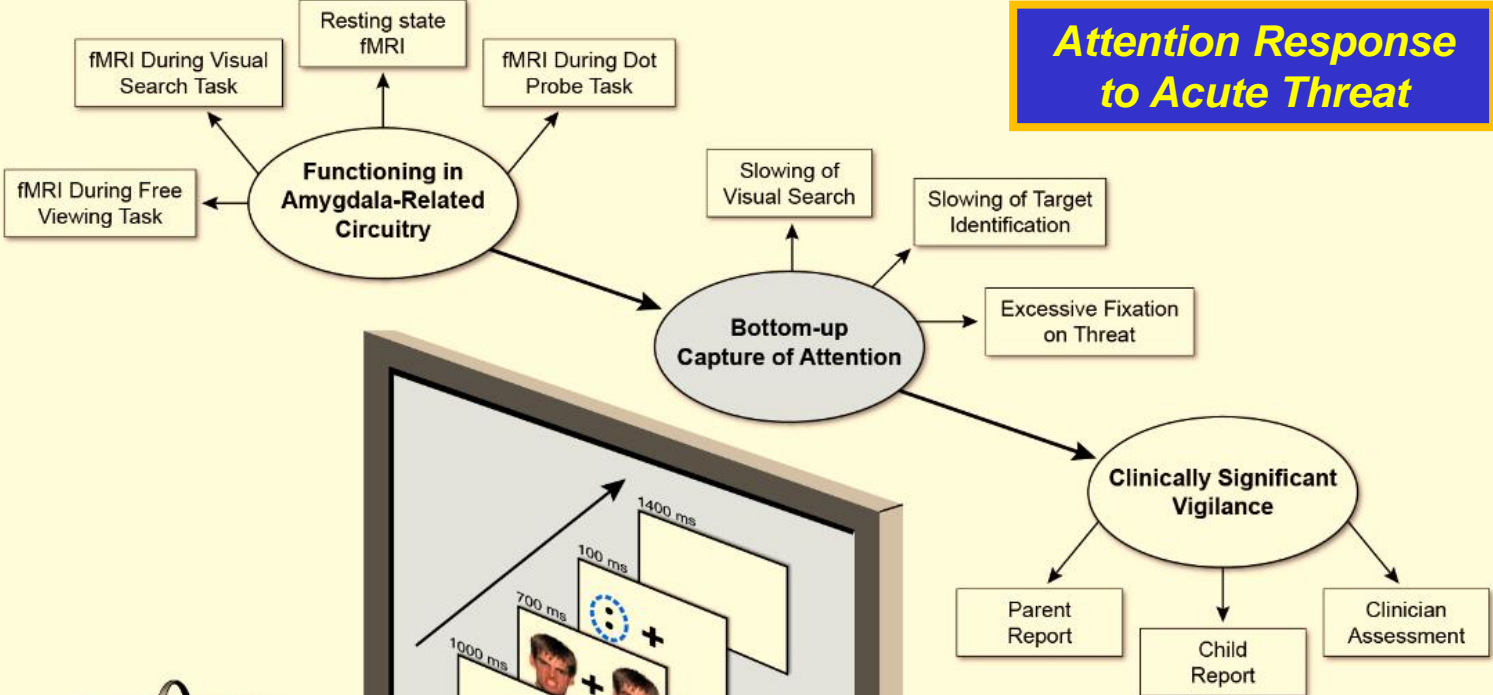


Overarching Conceptualization:

- 1. “Disorders” composed of distinct components*
- 2. Level of Analysis: brain-mind-symptom*
- 3. Nature of perturbation differs across components*

Addressing Measurement Problems

Attention Response to Acute Threat



Pine (2017)

Outline

- **Overview**
- **Two Systems Theory**
An example of successful reduction?
- **Reflections**

Using Neuroscience to Help Understand Fear and Anxiety: A Two-System Framework

Am J Psychiatry 2016;

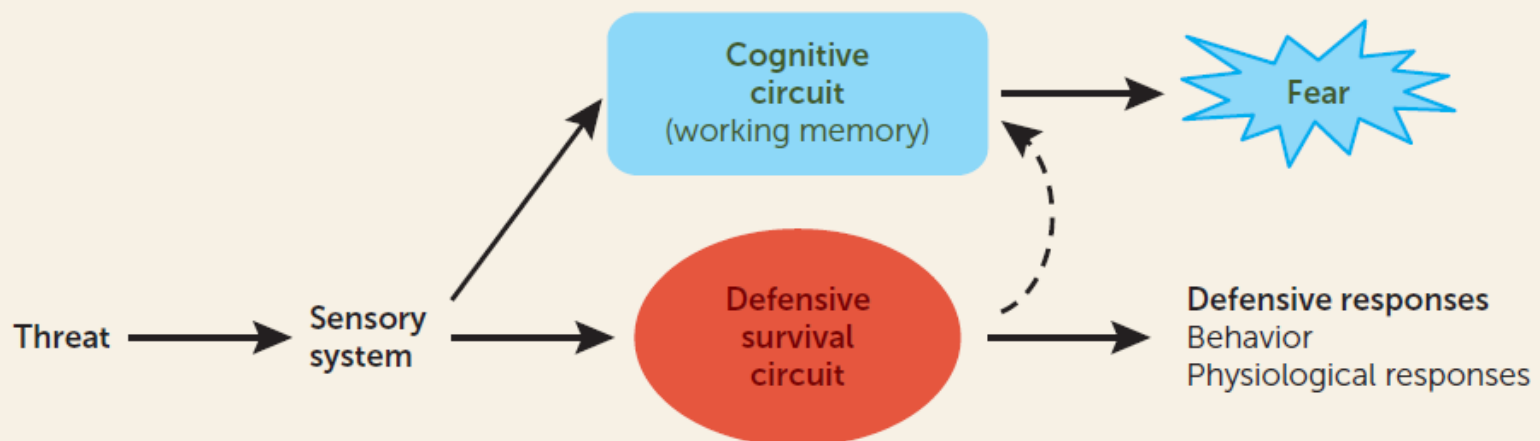
Joseph E. LeDoux, Ph.D., Daniel S. Pine, M.D.

REVIEWS AND OVERVIEWS

A. The "Fear Center" Model



B. The Two-System Model



Defensive-Survival Circuit

Defensive-Survival Circuit

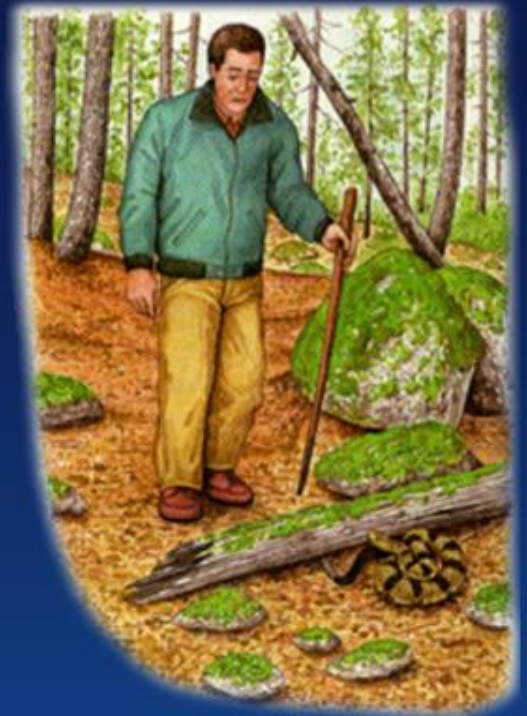
Overarching Conceptualization:

- 1. High Cross-Species Similarity*
- 2. High Similarity Across Development*
- 3. Perturbation: context-inappropriate deployment of an adaptive brain-mind reaction*

VISUAL
CORTEX

VISUAL THALAMUS

AMYGDALA



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



Cross-Species Conservation

CONGRUENT

INCONGRUENT

NEUTRAL



Context Inappropriate:

- 1. In real danger, all show effect*
- 2. Anxiety show in safe contexts*

CONGRUENT

INCONGRUENT

NEUTRAL

n=54 Anxious (ANX)
n=51 Healthy (HV)

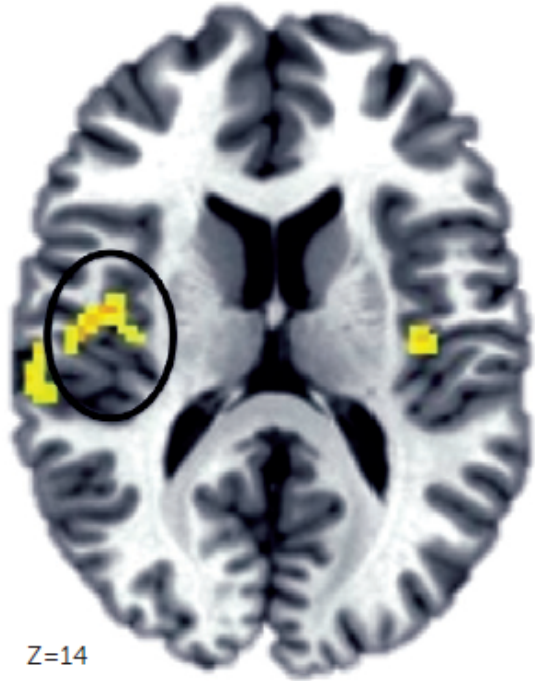


Linking Three Levels:

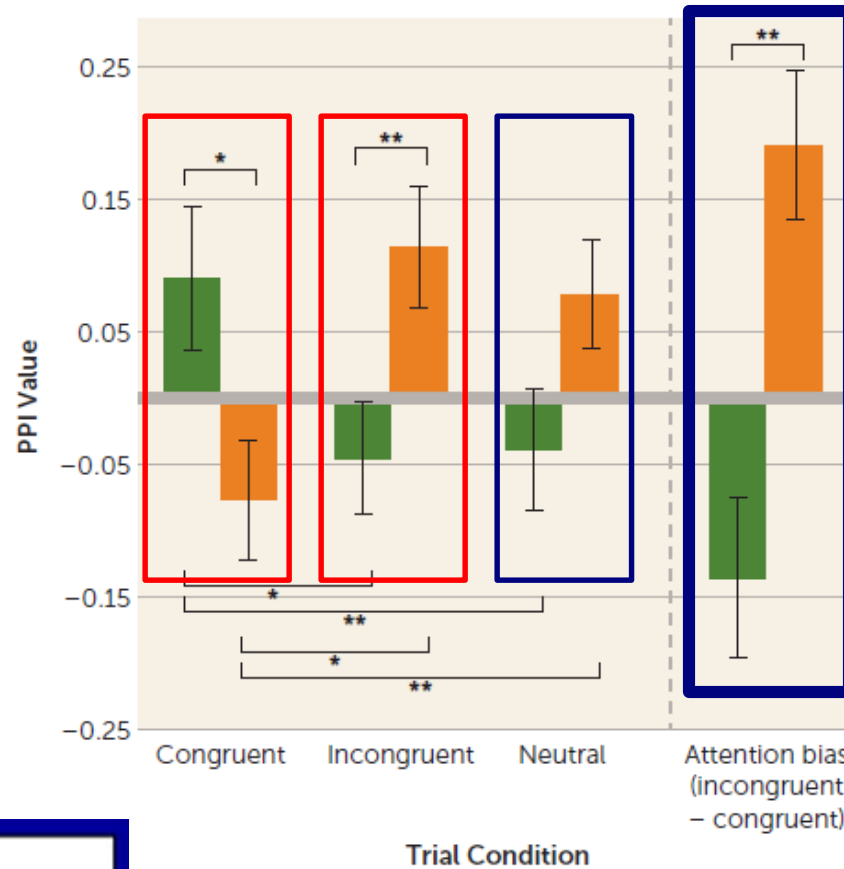
Brain-Mind-Disorder

	ANX	HV
% Female	61	57
Age (years)	12.12 (3)	12.74 (2)
IQ	110 (16)	112 (12)
SCARED-C	29 (14)	6 (6)
SCARED-P	31 (12)	4 (6)
STAI-trait	39 (7)	27 (5)

Amygdala-Insula Connectivity Across Event Types



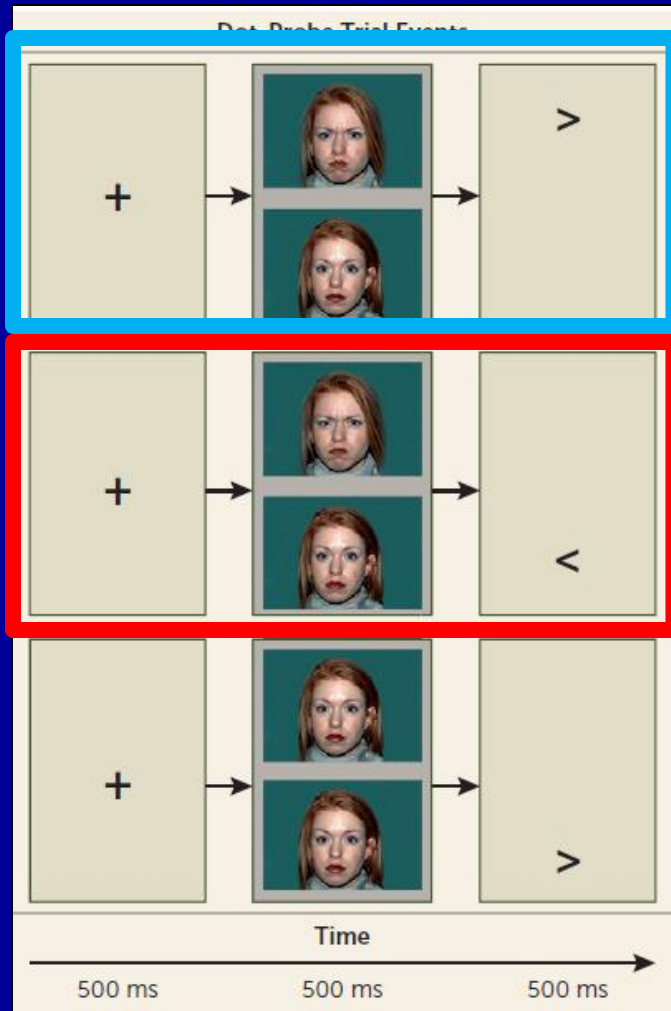
Map displayed at $p < .005$ threshold



Inappropriate Deployment of Amygdala-PFC Connectivity

	ANX	HV
% Female	61	57
Age (years)	12.12 (3)	12.74 (2)
IQ	110 (16)	112 (12)
SCARED-C	29 (14)	6 (6)
SCARED-P	31 (12)	4 (6)
STAI-trait	39 (7)	27 (5)

Attention Bias Modification Therapy (ABMT)



Successful reduction:

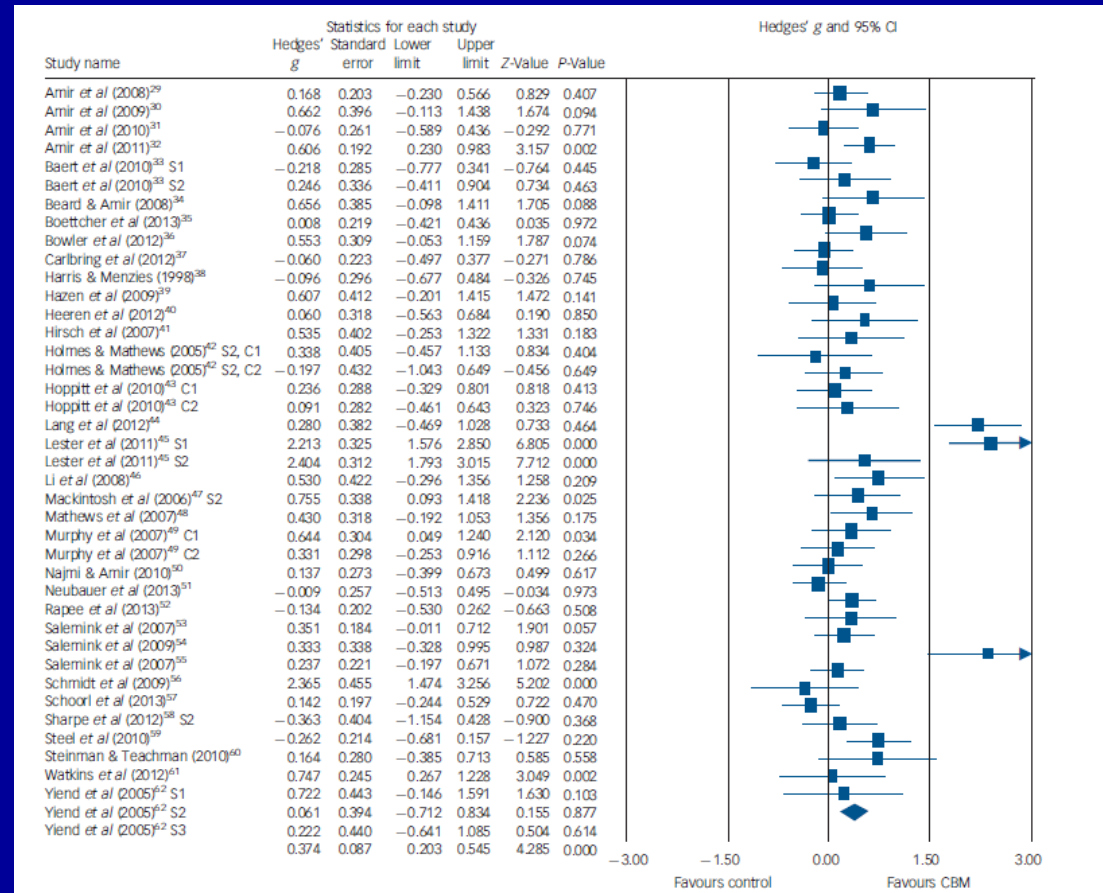
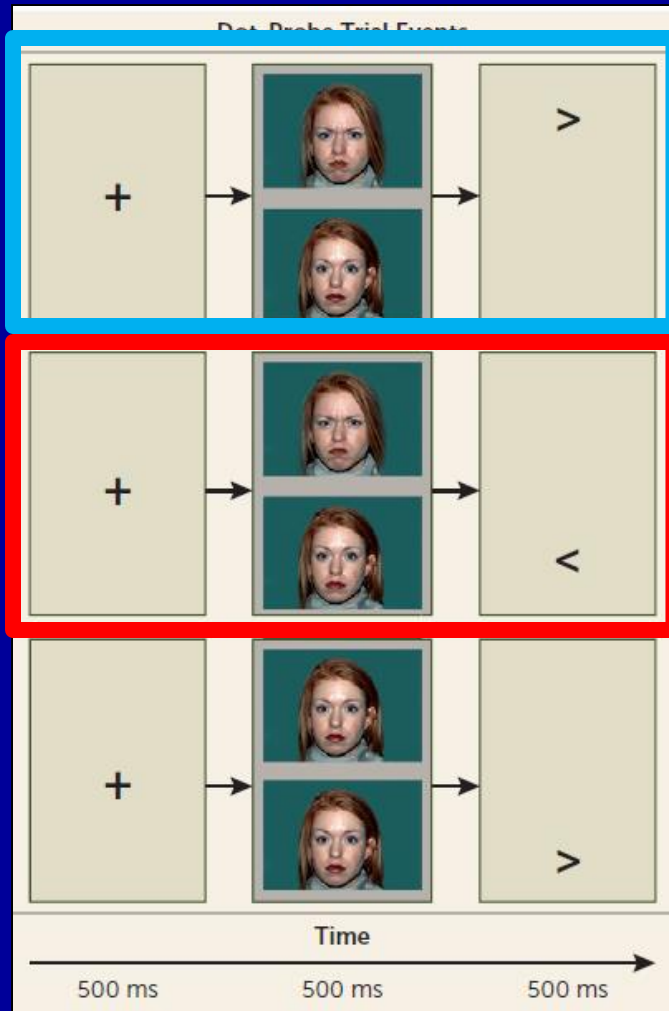
- *New treatment*
- *Targets mind*
- *Link to brain function*

Linking Three Levels:

Brain-Mind-Disorder

Training of Attention

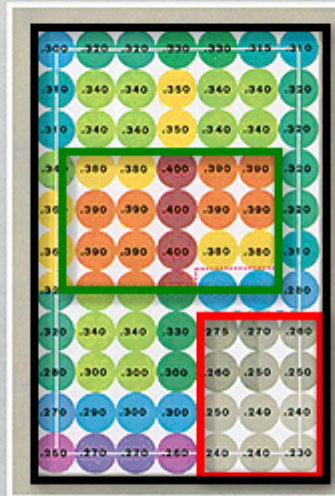
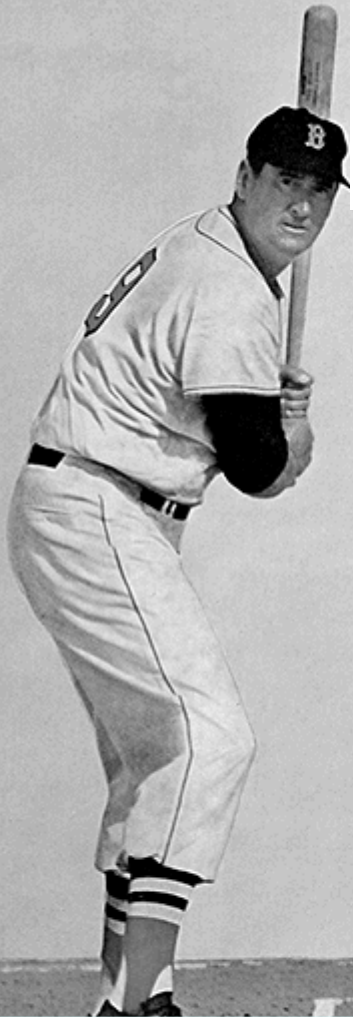
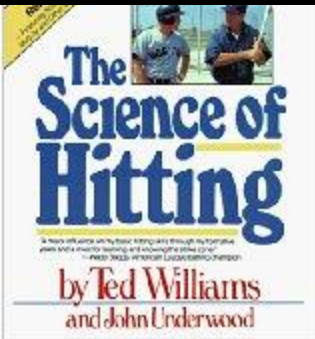
Attention Bias Modification Therapy (ABMT)



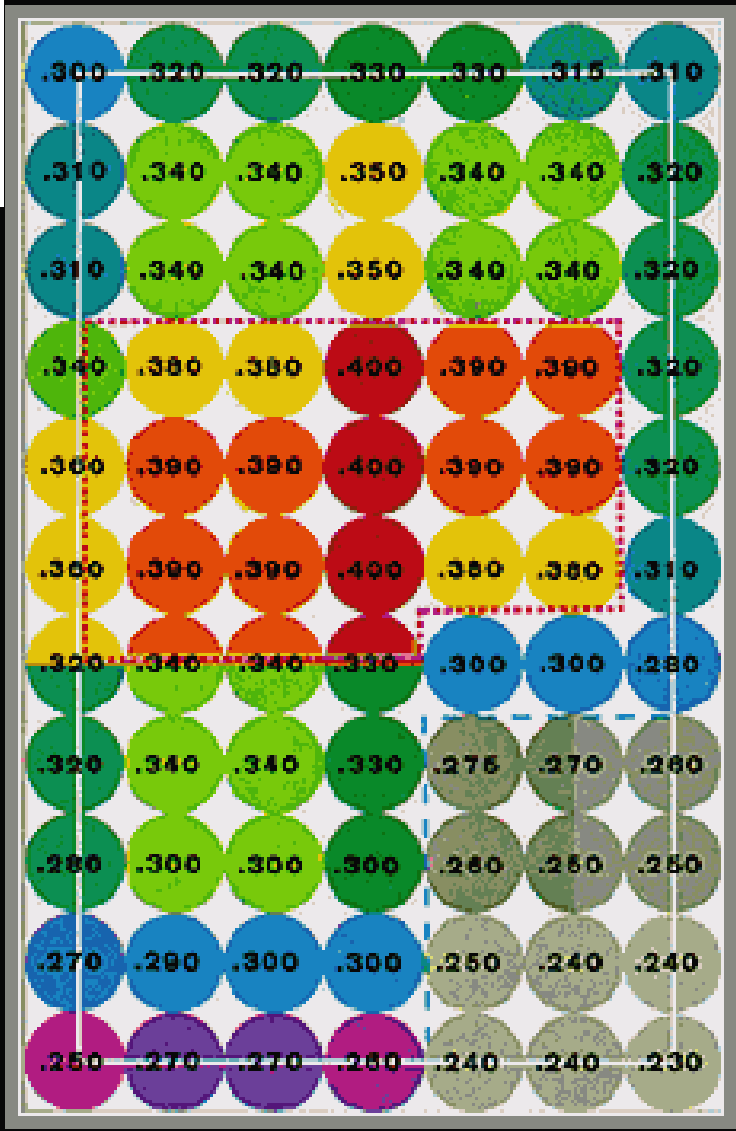
Training of Attention

Cristea et al. 2015

Treating Two Components



CBT-Defensive Actions



ABMT-Defensive Reactions

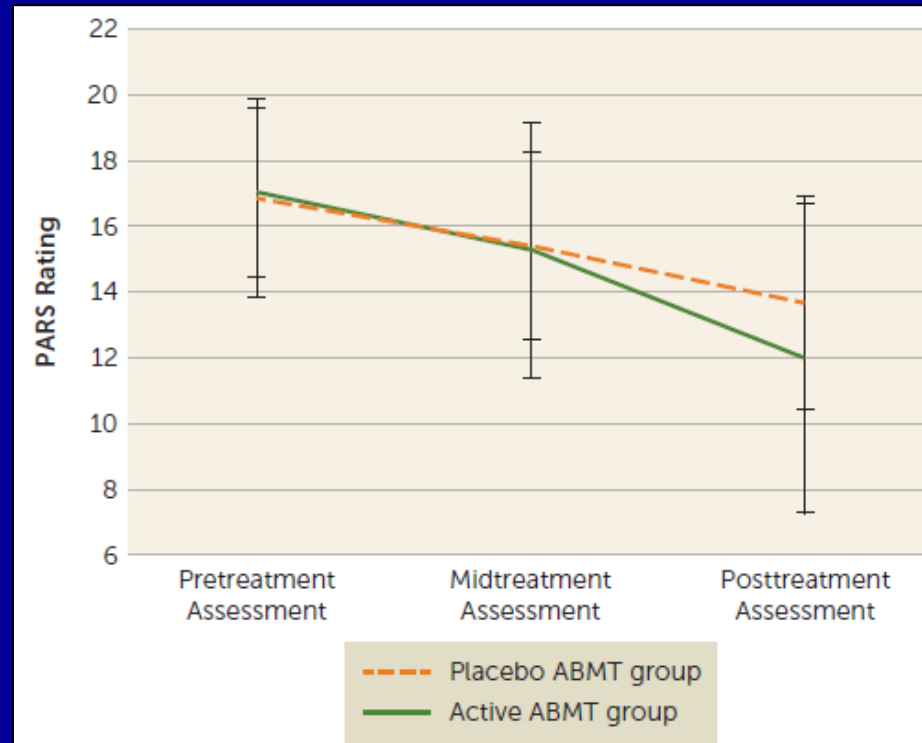
72 patients randomized to active or placebo ABMT

All patients receive CBT

Attention Bias Modification
Training (ABMT):
*Adapt Dot Probe to Implicitly
Alter Threat Reactions*

Less Post-Treatment Anxiety in
Active than Placebo Condition

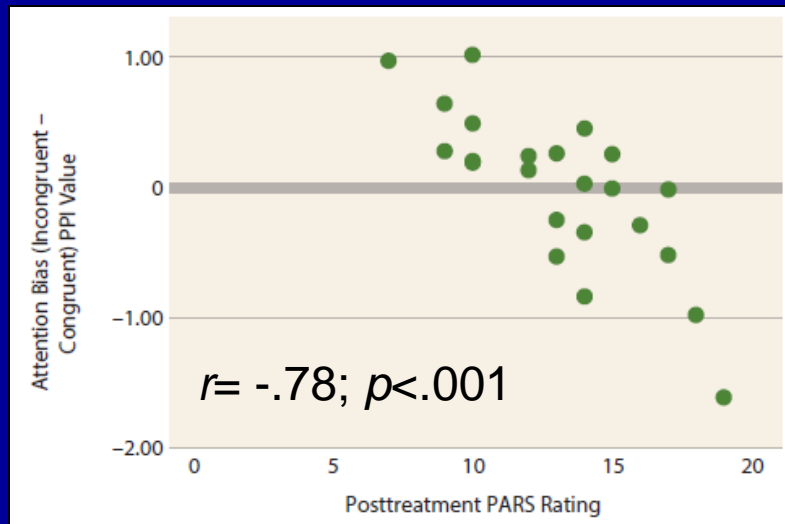
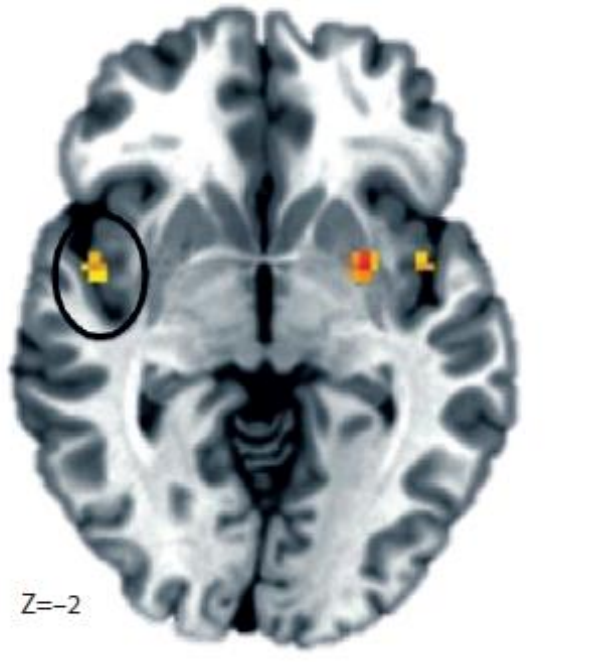
Effect Size=0.45
 $t = 1.9; p = 0.06$



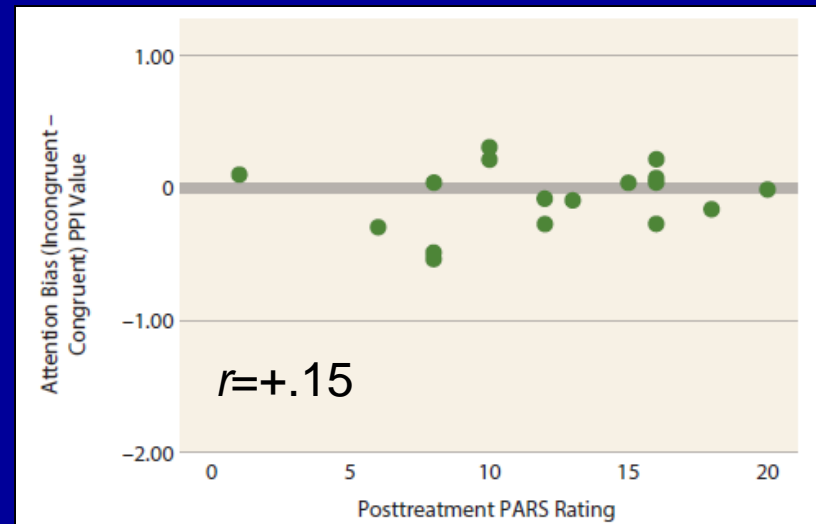
ABMT-Specific Treatment Outcome

PPI Analysis: *fMRI Connectivity at Baseline Group [active vs. placebo]-by- Δ PARS-by-Event Type*

Figure Displayed at $p < 0.005$ Threshold
n=40 (22 placebo, 18 active)



CBT + PLACEBO ABMT



CBT + ACTIVE ABMT

Defensive-Survival Circuit

Overarching Conceptualization:

- 1. High Cross-Species Similarity*
- 2. High Similarity Across Development*
- 3. Perturbation: context-inappropriate deployment of an adaptive brain-mind reaction*

Cognitive (appraisal?) Circuit

Overarching Conceptualization:

- 1. Low Cross-Species Similarity*
- 2. Low Similarity Across Development*
- 3. Perturbation: poorly understood*

Diagnosis of Anxiety

- **Self-Report of Distress**
- **Model of Consciousness**

Self-Report & Development

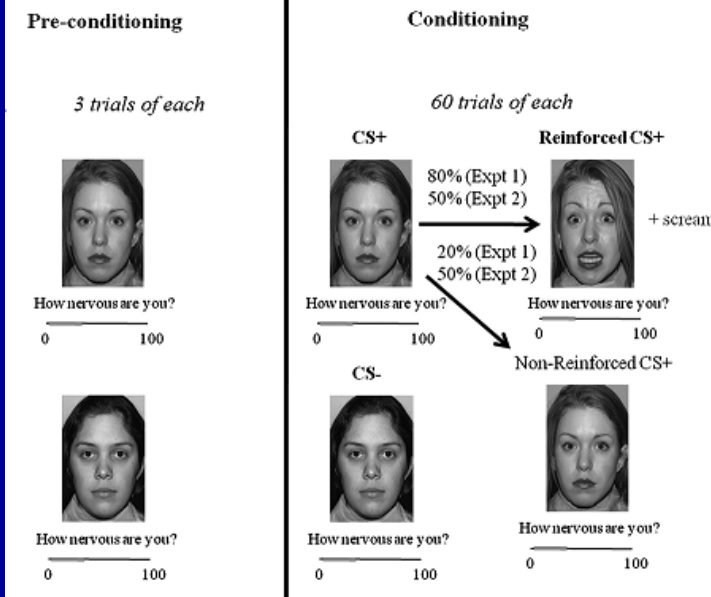
1. **Reliability increases with age**
2. **Concept of “self” also changes**
3. **Accuracy increases with age**

Diagnosis of Anxiety

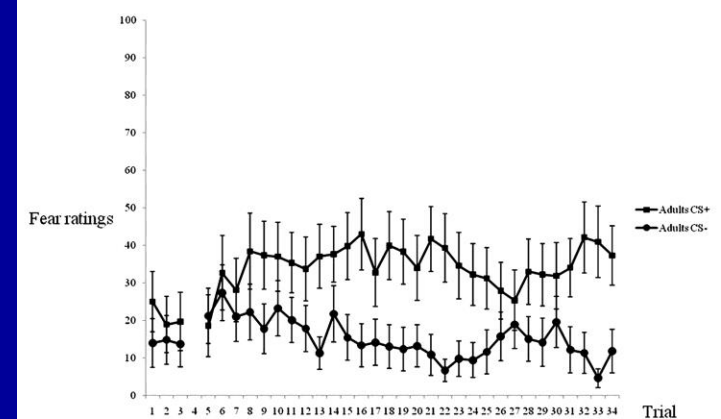
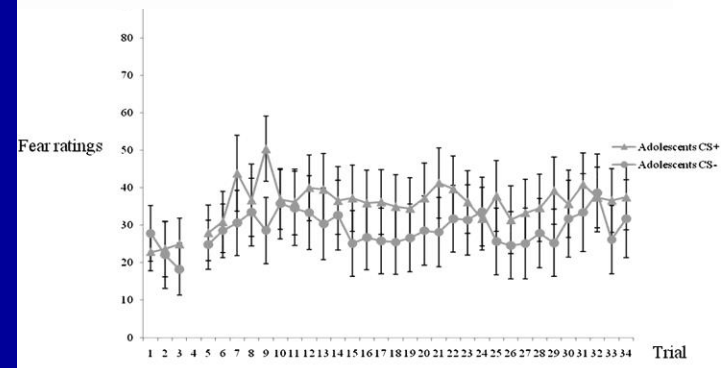
- **Self-Report of Distress**
- **Model of Consciousness**

Self-Report & Development

1. Reliability increases with age
2. Concept of “self” also changes
3. Accuracy increases with age
4. May relate to dlPFC maturation

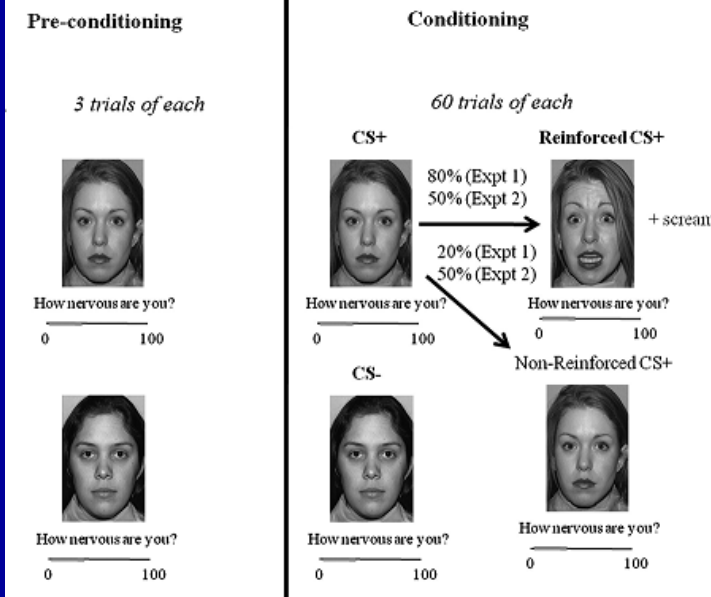


Jennifer Y. Lau et al. PNAS 2011;108:11:4500-4505

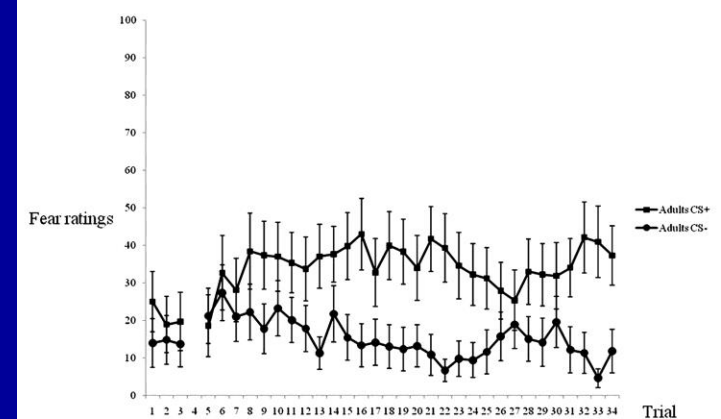
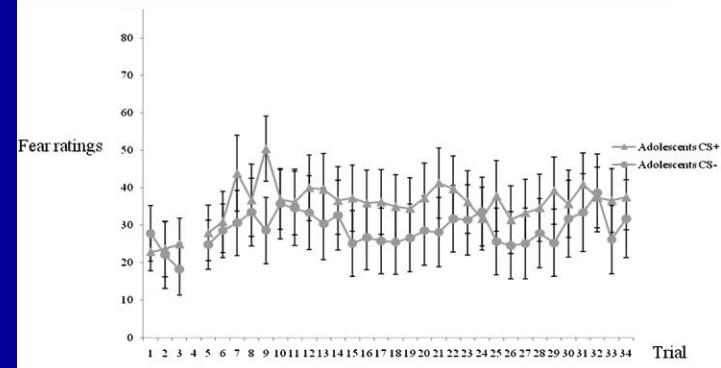


Self-Report & Development

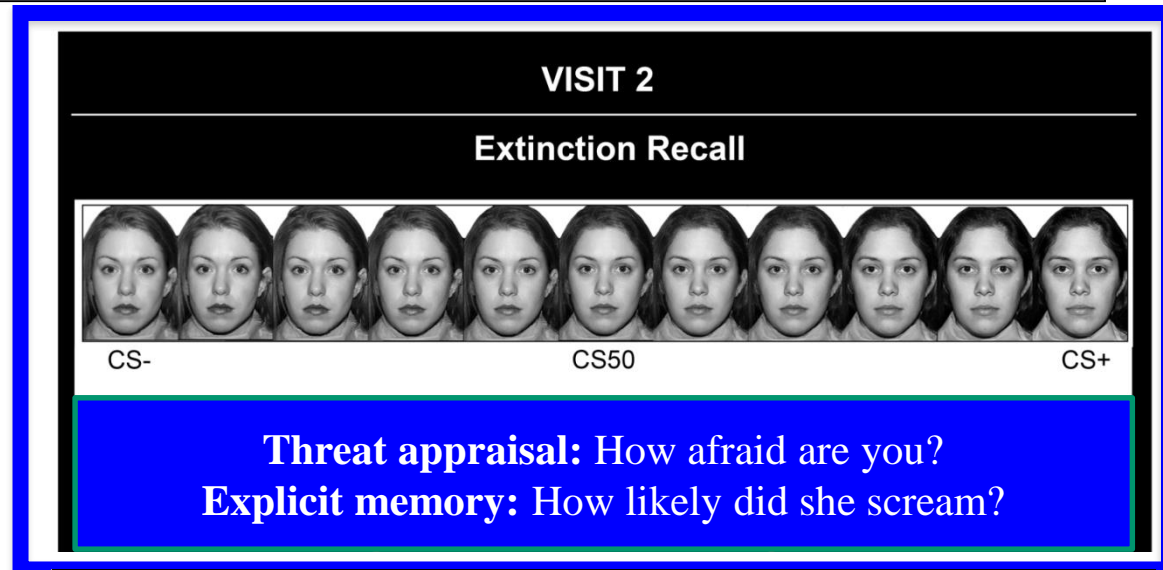
1. Reliability increases with age
2. Concept of “self” also changes
3. Accuracy increases with age
4. May relate to dlPFC maturation
5. Brain-Mind-Symptom & development?



Jennifer Y. Lau et al. PNAS 2011;108:11:4500-4505



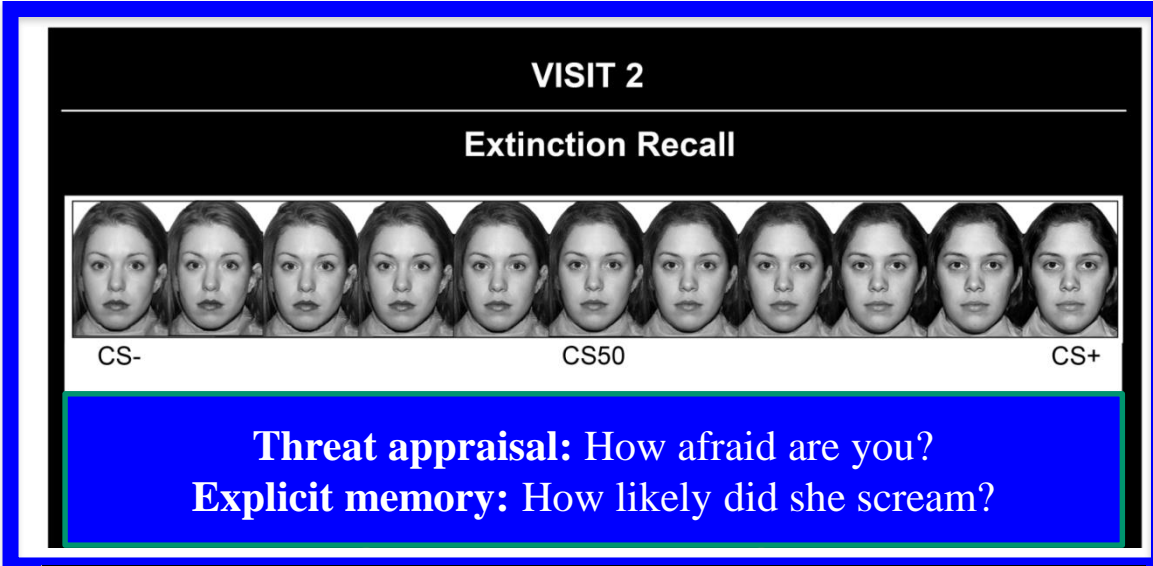
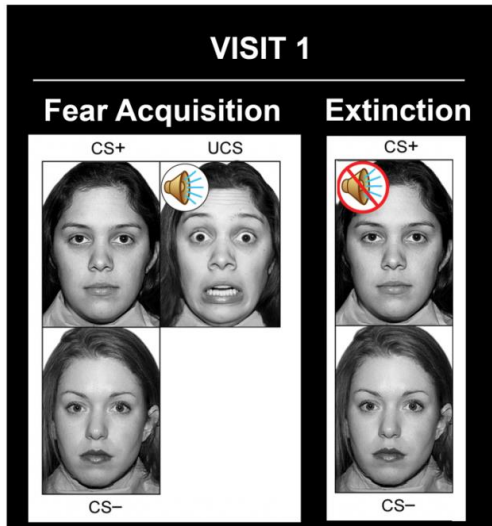
Extinction recall fMRI



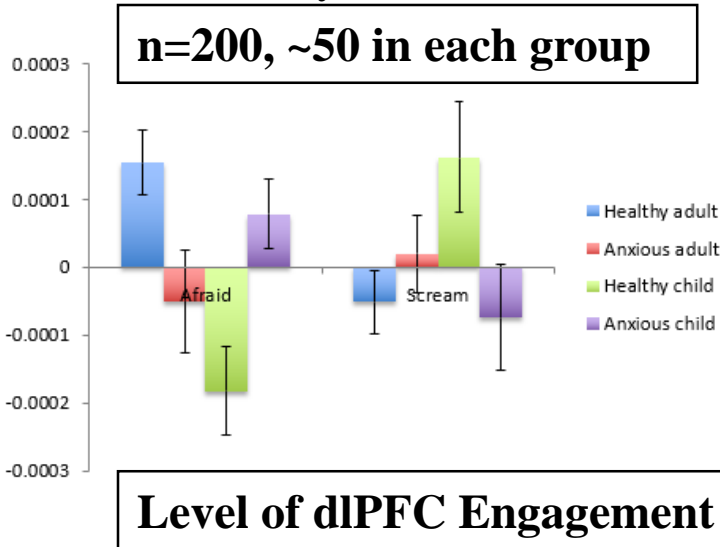
Visit 1: Conditioning; Extinction
Visit 2 (20 days later): Recall



Extinction recall fMRI



Visit 1: Conditioning; Extinction
 Visit 2 (20 days later): Recall



Outline

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Progress in Brain Imaging?

- **Old Problems**

- *Disorder definitions do not match brain components*
- *Work insufficiently critical, overly broad*

- **Solutions**

- *Tightly link brain to narrow, component behaviors*
- *Expect no larger than medium effects*
- *Leverage treatment to test falsifiable ideas*

- **New Problems**

- *Clinical problems involve subjective distress*
- *How deeply to pursue consciousness?*

Outline

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- **Reflections**

Collaborators

NIMH-SDAN

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