

EARLY BRAIN &
BIOLOGICAL
DEVELOPMENT:
A SCIENCE IN
SOCIETY SYMPOSIUM

FROM BENCH TO BEDSIDE: WHAT WE LEARNED ABOUT TEMPERAMENT AND ANXIETY AND HOW WE HAVE APPLIED THAT TO INTERVENTION

Nathan A. Fox, Ph.D.
Distinguished University Professor
University of Maryland



Outline of Talk Today

- Setting the Context: Behavioral Inhibition and risk for psychopathology
- Continuity and discontinuity in the temperament of behavioral inhibition
- Two cognitive processes that moderate behavioral inhibition over time
 - Attention Bias to Threat
 - Cognitive Control
 - Making attention work: Developing Interventions

Setting the Context of the Talk

- Behavioral Inhibition-a temperament in which children display heightened reactions to novelty or unfamiliarity, vigilance, social withdrawal
- Linked to ANS physiological reactivity and heightened amygdala activation to threat



Behavioral Inhibition

Reactions of an inhibited child to novelty include:

- Becomes quiet and watchful
- Ceases current activity
- Retreats from unfamiliarity
- Refuses to engage in interaction



What are the characteristics of children with Behavioral Inhibition

- Behavioral
 - Low self esteem
 - Poor peer relationships
 - Victims of bullying
- Physiological
 - Elevated morning cortisol levels
 - Enhanced autonomic reactivity
 - Enhanced startle responses



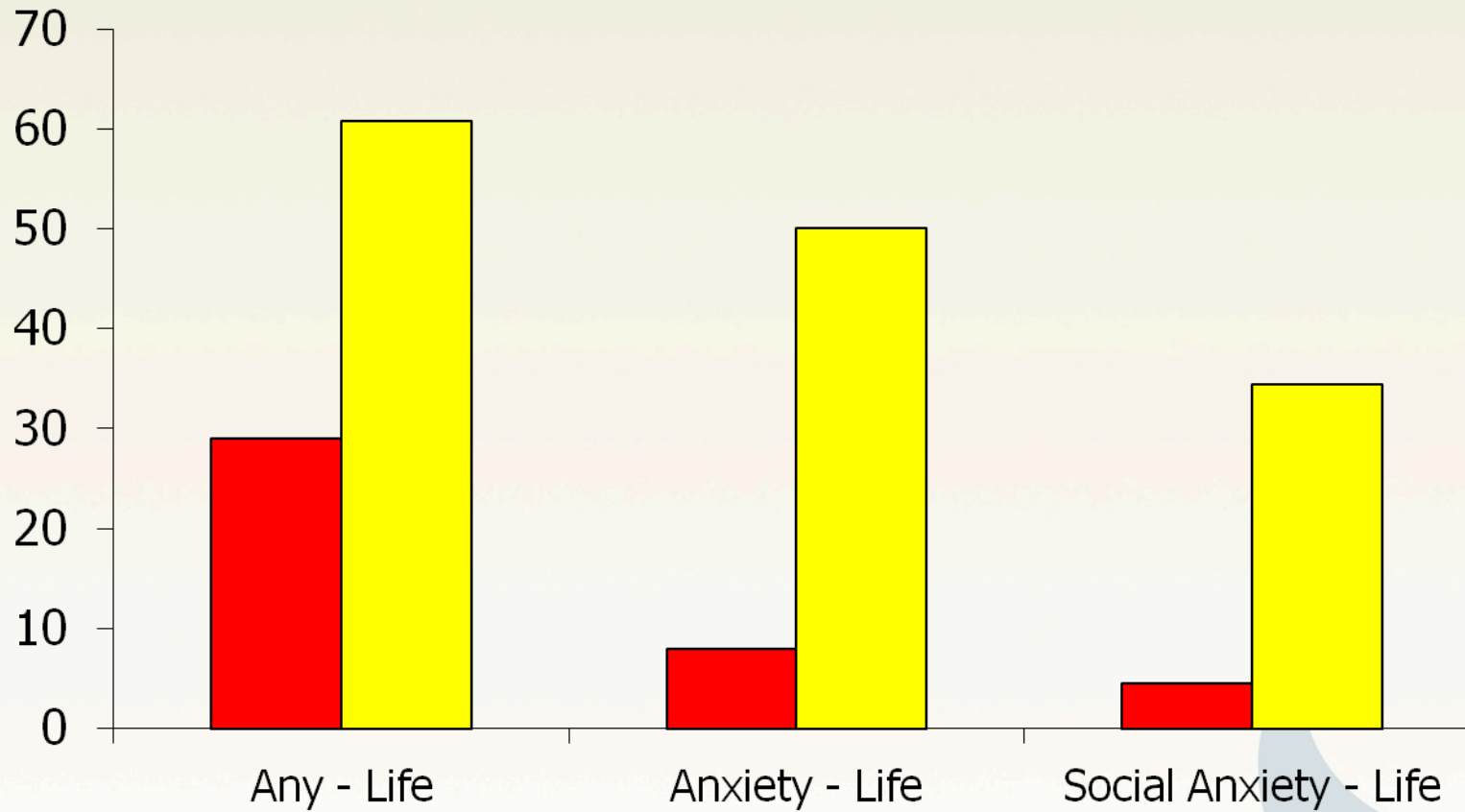
Continuity of Behavioral Inhibition

- Evidence for continuity throughout infancy, toddlerhood, childhood, and adolescence
- In fact, children who display continuous BI over childhood are more likely to display anxiety disorders as adolescents (Degnan & Fox, 2007)
- Also evidence for discontinuity (Degnan & Fox, 2007)
 - Selected samples: over 1/3 of BI children show discontinuity



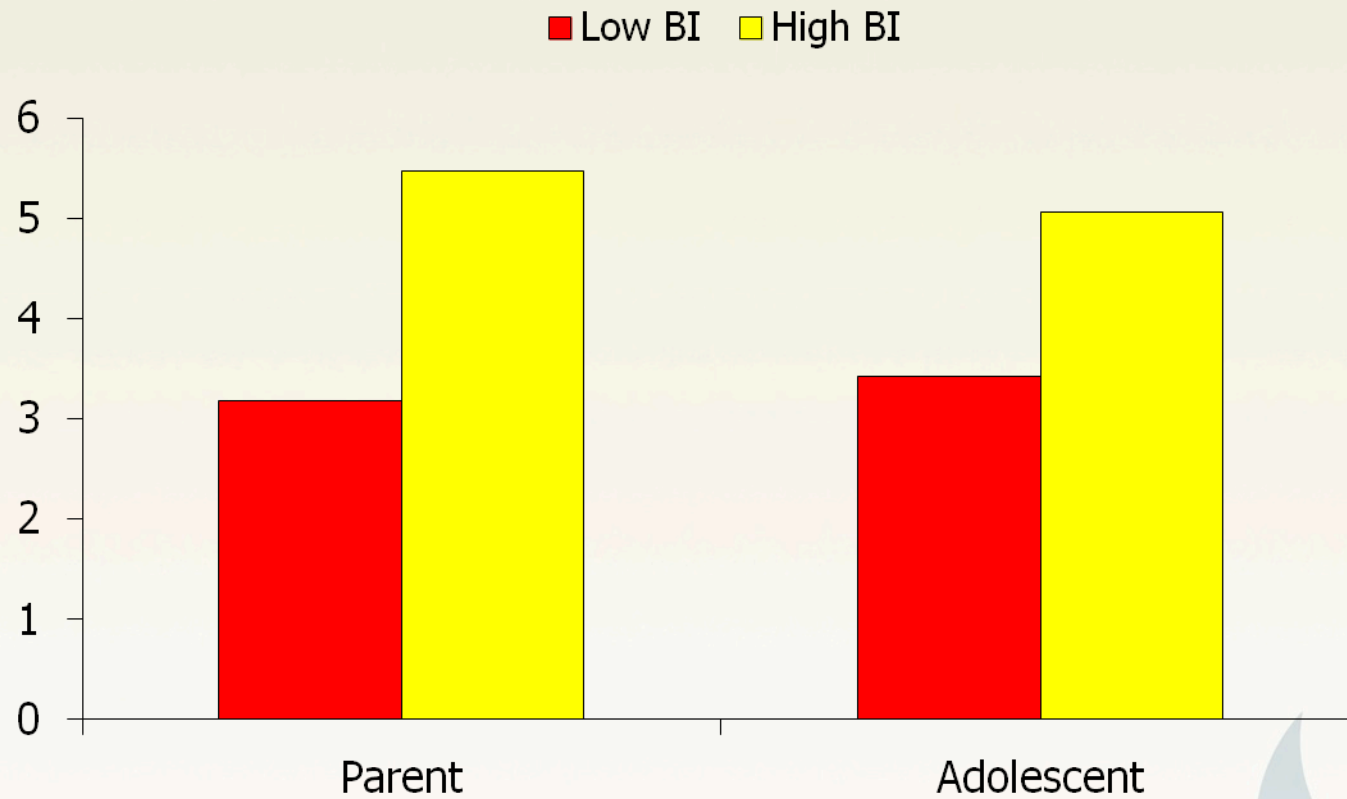
% with DSM-IV Diagnosis by Stable Temperament During Infancy/Early Childhood

■ Low BI ■ High BI



Chronis-Tuscano, et al 2009, *JAACAP*

SCARED Social Anxiety by Stable Temperament in Infancy/Early Childhood



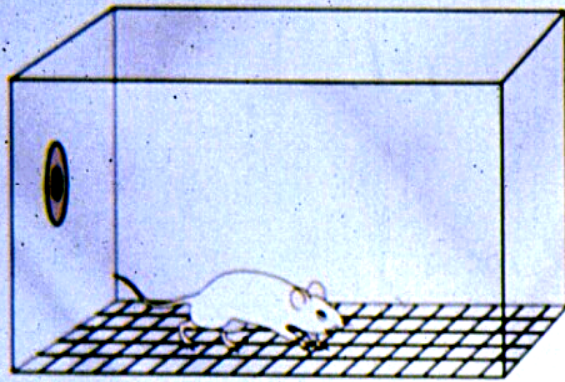
Chronis-Tuscano, et al 2009, *JAACAP*

Amygdala Model of Behavioral Inhibition

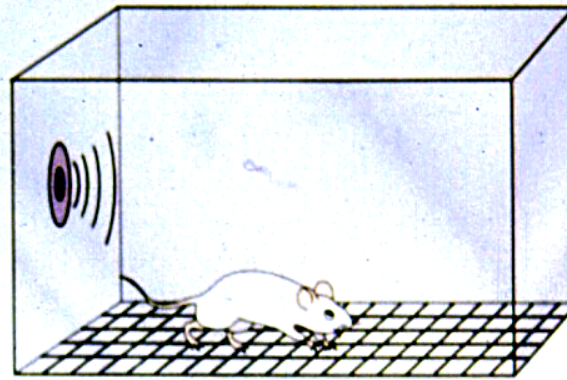
- A neural system underlying conditioned and unconditioned states of fear
- Based upon work of LeDoux and Davis
- Amygdala model applied to behavioral inhibition (Kagan, 1992; Fox, Henderson, & Marshall, 1998)



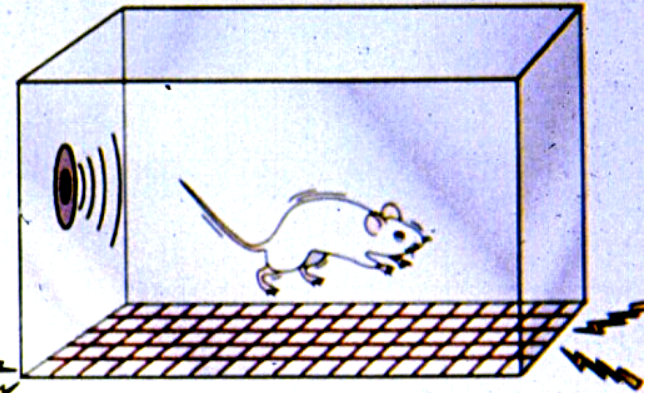
TRAINING



Exposure to context (2 min)

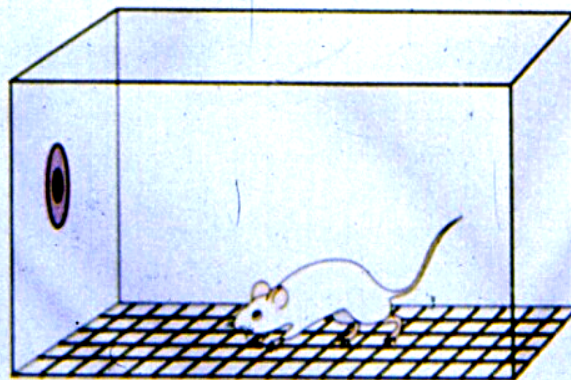


Onset of sound (CS: 30 s)



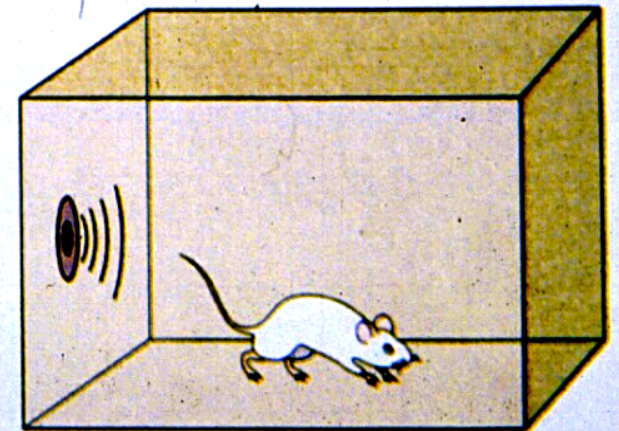
Onset of shock (US: 2 s)

TESTING: Context
Test at 1 hour
and 24 hours



Same context (5 min)

TESTING: Cued
Test at 1 hour
and 24 hours

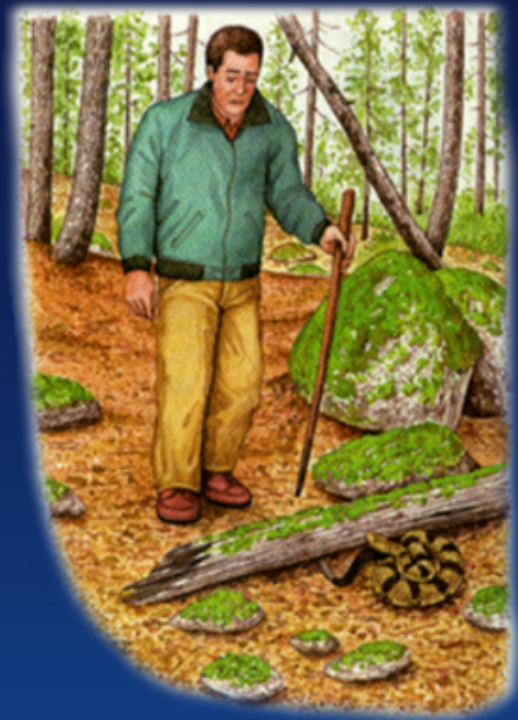


Onset of sound (CS: 3 min)

VISUAL
CORTEX

VISUAL THALAMUS

AMYGDALA



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

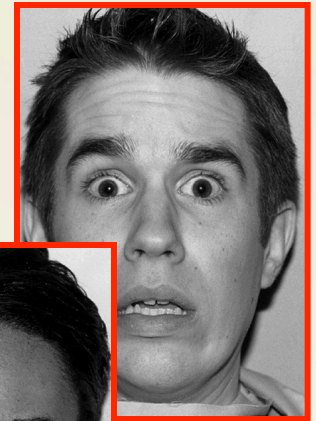
Face rating task

How hostile?

How afraid are you?

How wide is the nose?

Just look at the faces.



EVENT-RELATED SUBTRACTION PARADIGM



MINUS



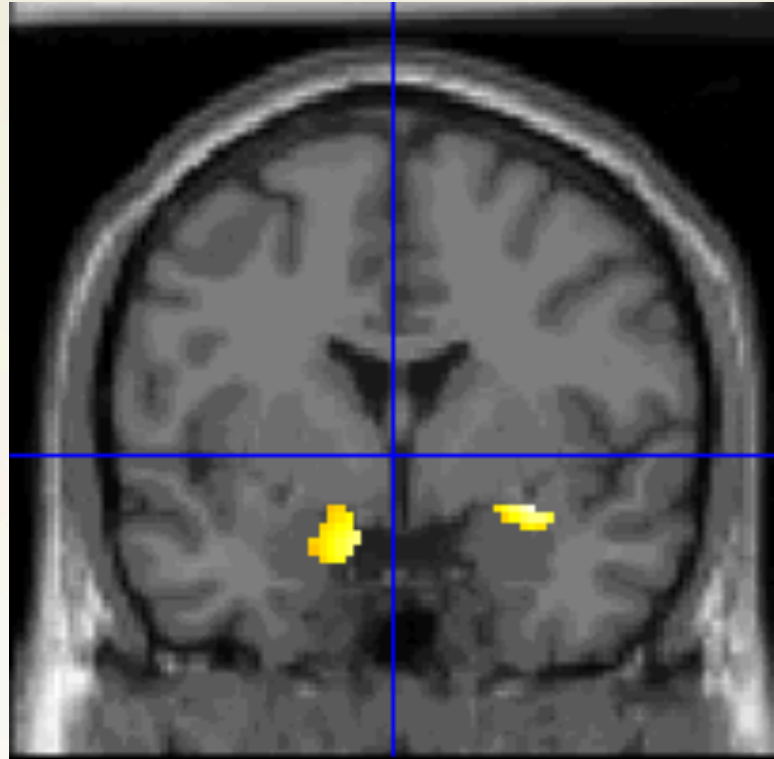
How afraid are you?

Attention toward internal state
Emotional expression

Passive viewing

Emotional expression

Adolescents Characterized in Infancy with Behavioral Inhibition Display Amygdala Activation to Fear Faces



Perez-Edgar, et al (2007) *Neuroimage*

What are the moderators of child temperament (Behavioral Inhibition) ?

- That contribute to continuity in BI over development
- That contribute to the emergence of anxiety disorders within the BI population
- Two cognitive processes
 - Attention bias to threat
 - Cognitive control

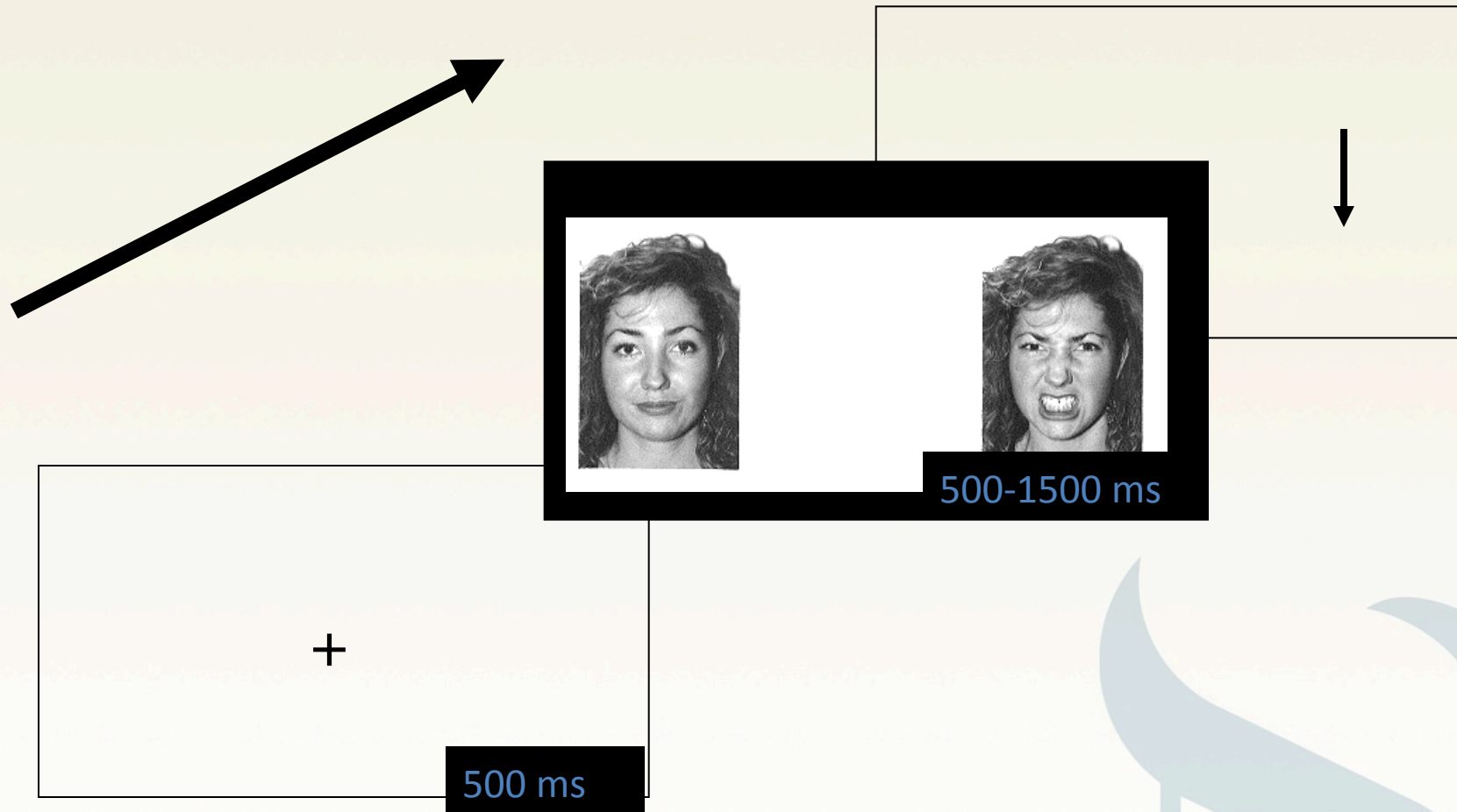


Measuring Attention Bias to Threat: Visual Probe Task

- Task has been used with both normal and clinical populations
- Bias scores show attention patterns
 - Vigilance: Positive Score
 - Avoidance: Negative Score



Visual Probe Task



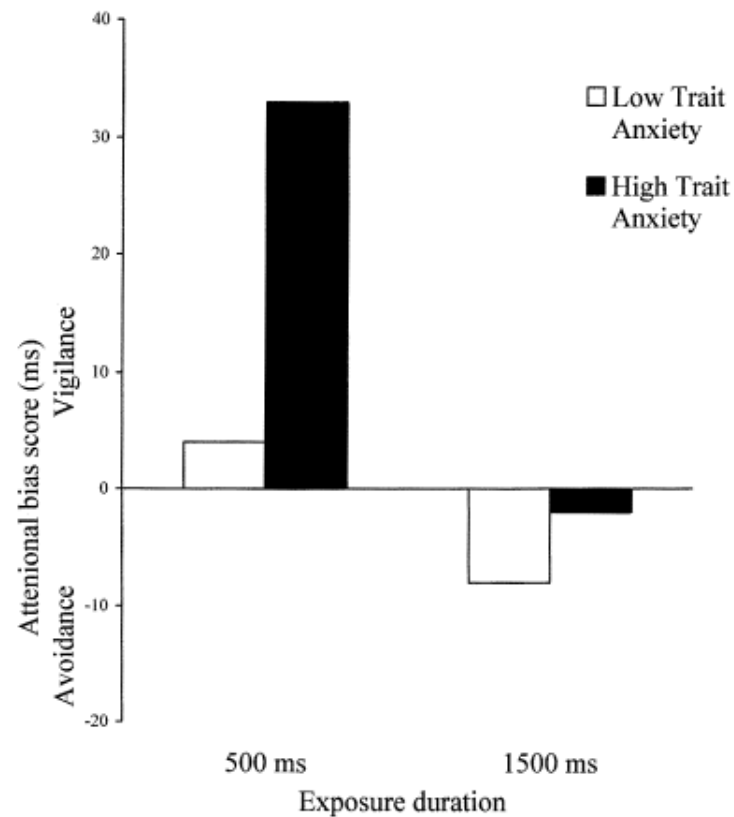
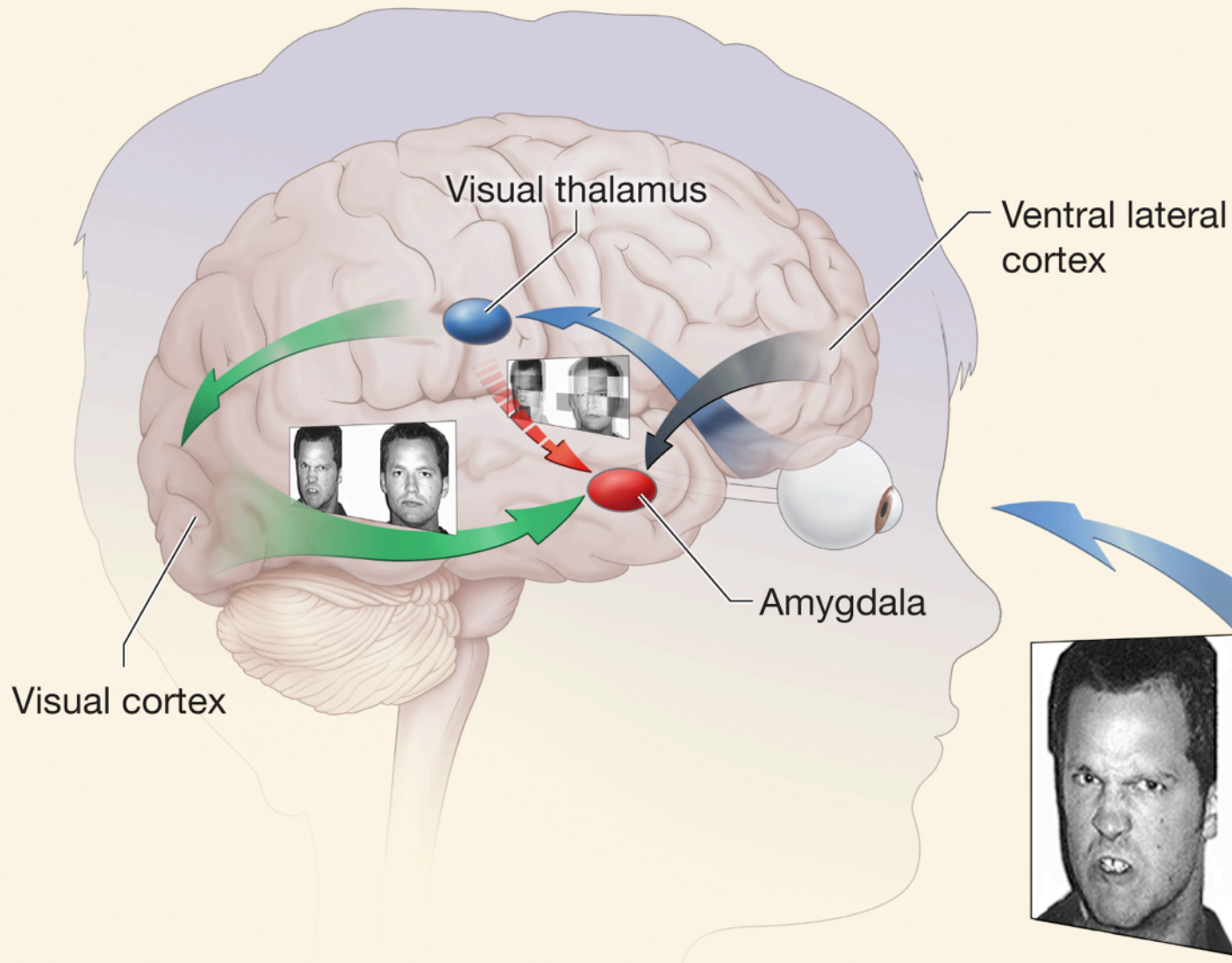


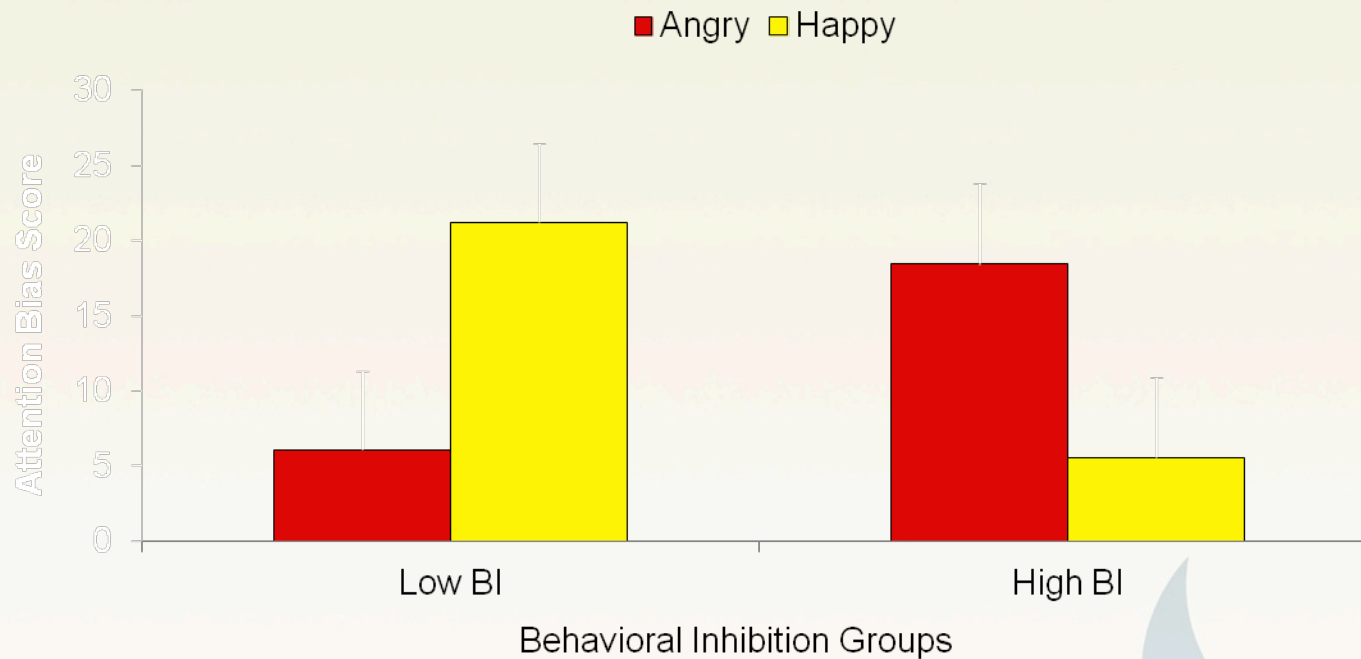
Figure 1. Mean attentional bias scores (in ms) for high threat scenes, relative to nonthreat scenes, in high and low trait anxiety groups.

Adapted from Mogg, Bradley, Miles & Dixon (2004).



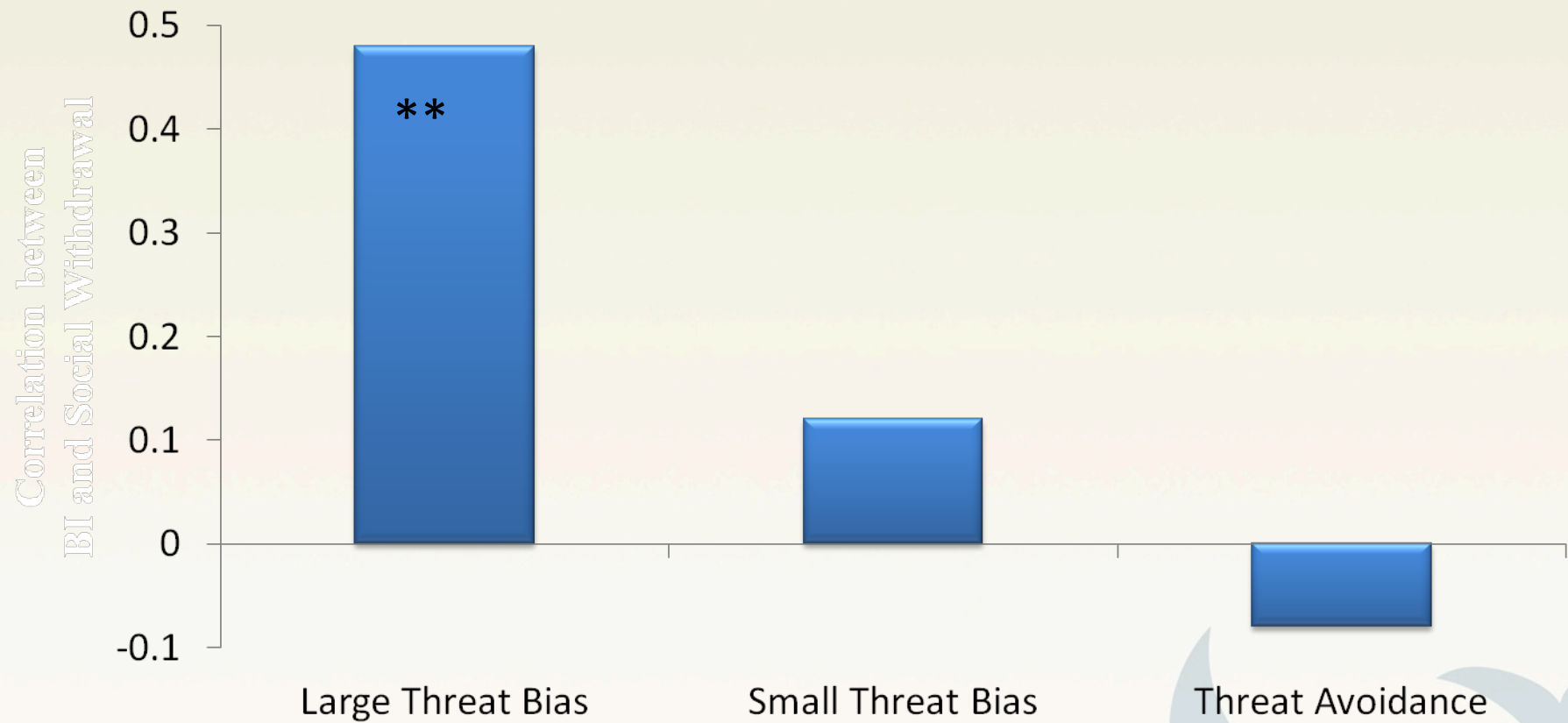
The circuitry of attention bias in pediatric anxiety and Behavioural Inhibition

Attention Bias to Threat and Behavioral Inhibition in Adolescence



Perez-Edgar et al, (2010) *Emotion*

Link between Attention Bias and Social Withdrawal



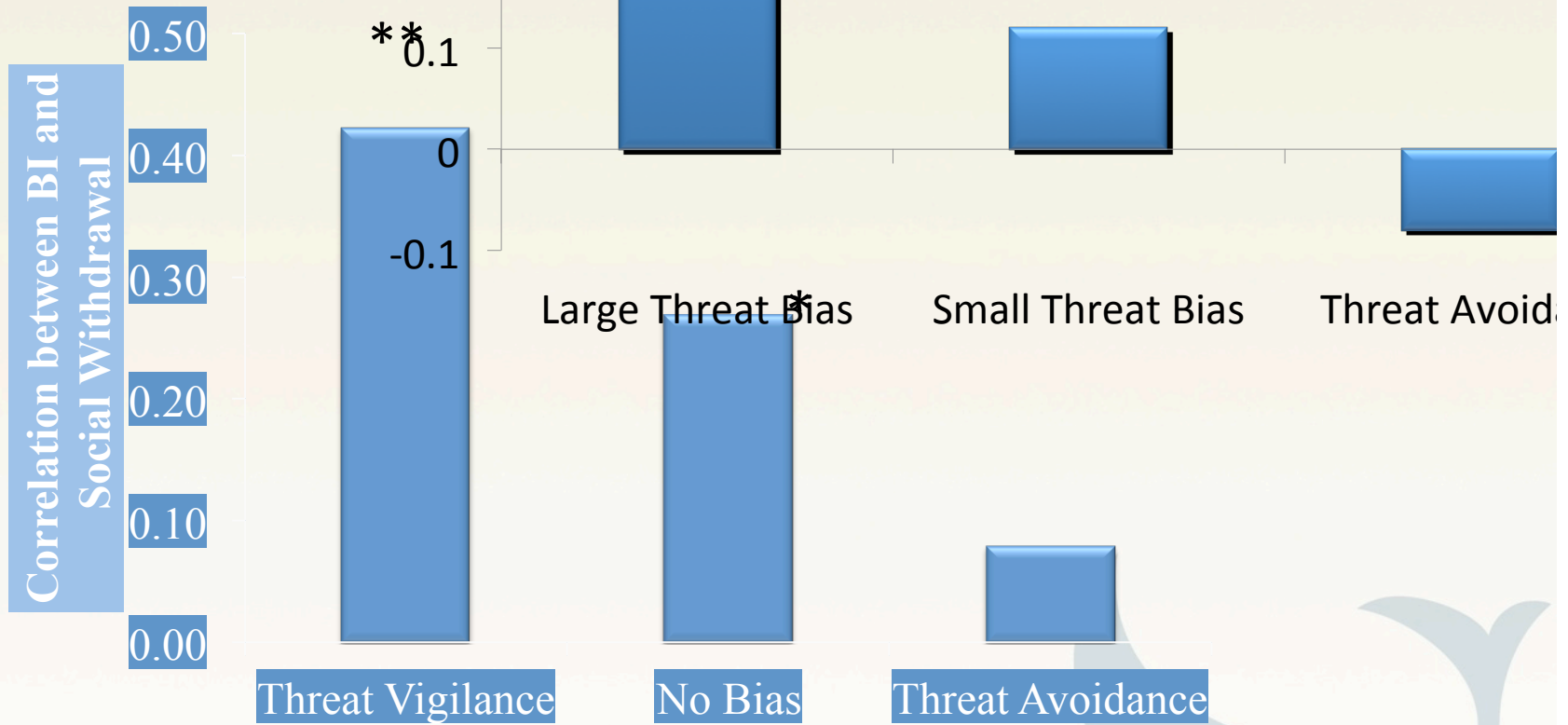
Perez-Edgar et al, 2010, Emotion

Linking Attention Bias to Threat to Social Withdrawal/Anxious Symptoms in Cohort 2

- At age 5 the Dot Probe was administered
- Behavioral and Questionnaire measures of social withdrawal/anxious symptoms were acquired



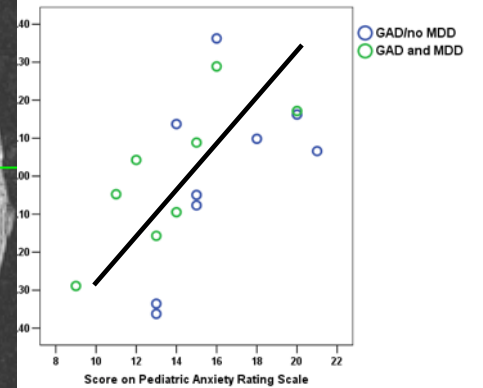
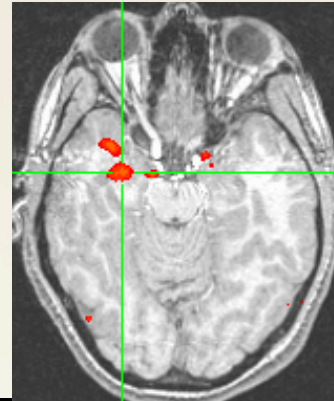
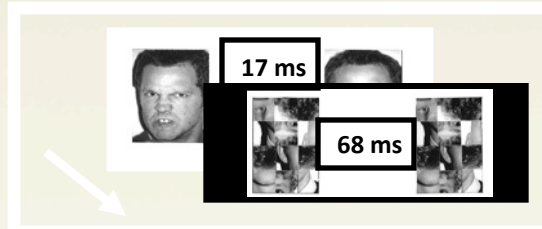
Link between Attention Bias and Social Withdrawal



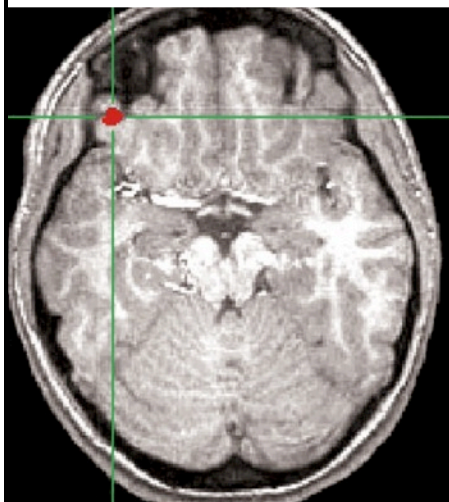
Perez-Edgar et al, 2011, JACP

Attention, PFC-Amygdala-Circuitry, and Pediatric Anxiety

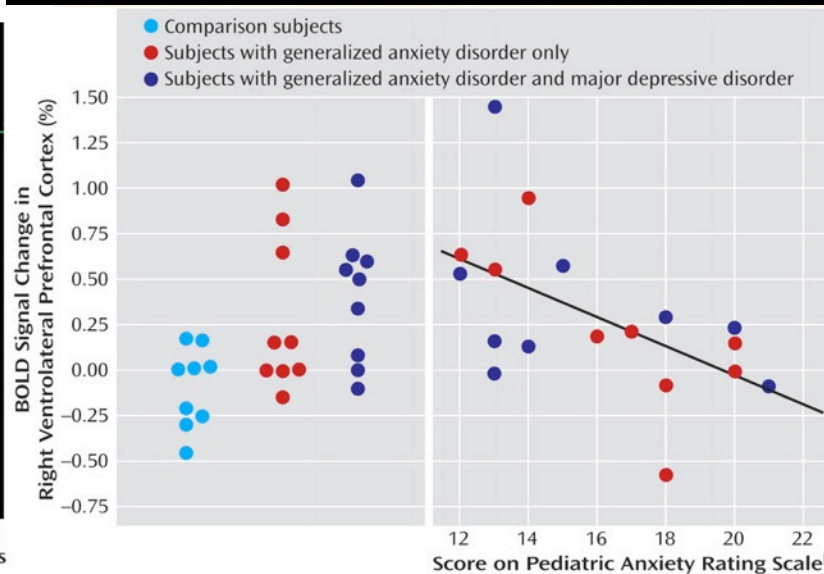
Brief Subliminal Threat: Amygdala instantiates anxiety



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

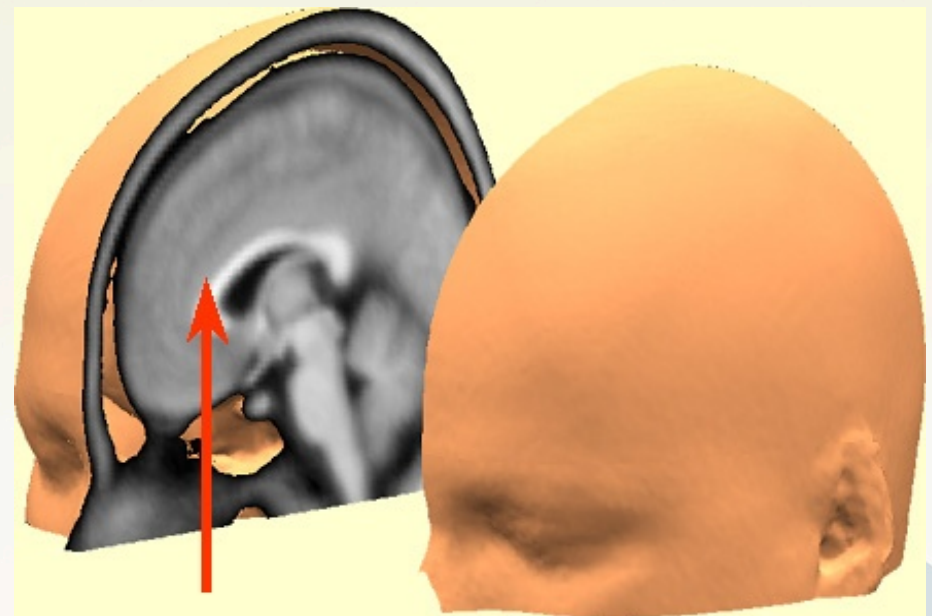
Error monitoring and Temperament

- A second cognitive process involved in temperament and anxiety
- Error monitoring---observing your own performance



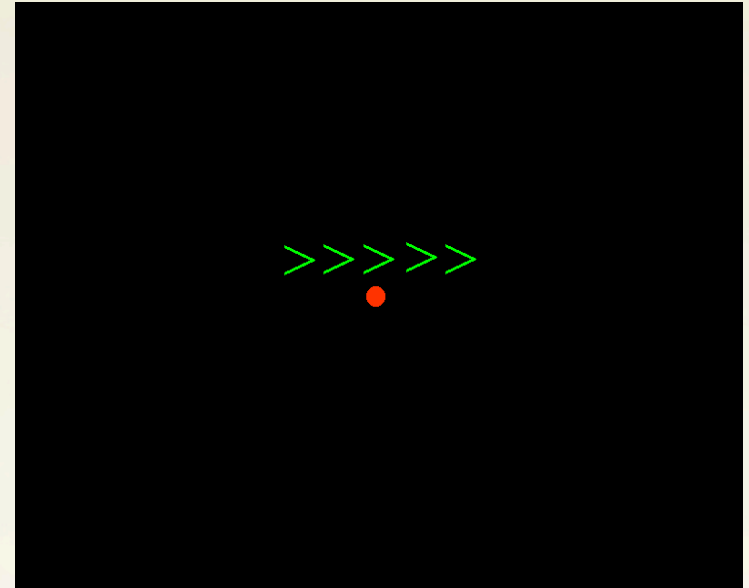
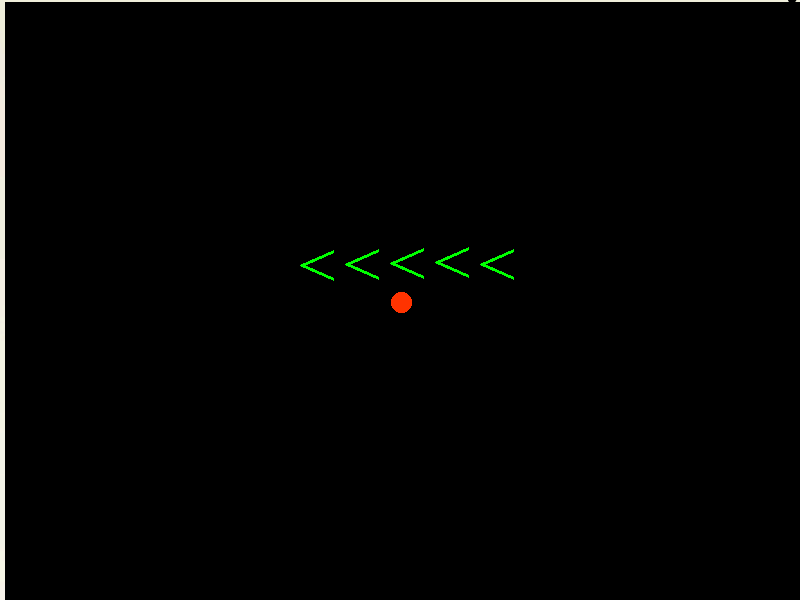
Neural generator of Error monitoring

- Anterior Cingulate Cortex (ACC)

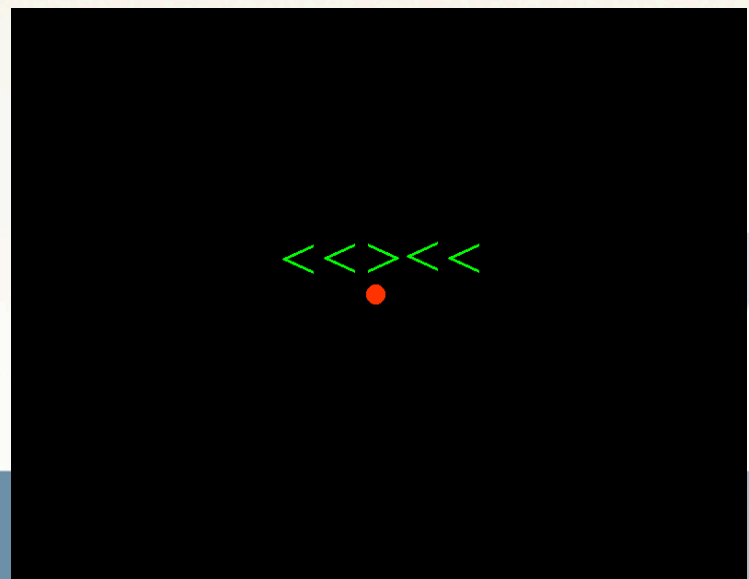
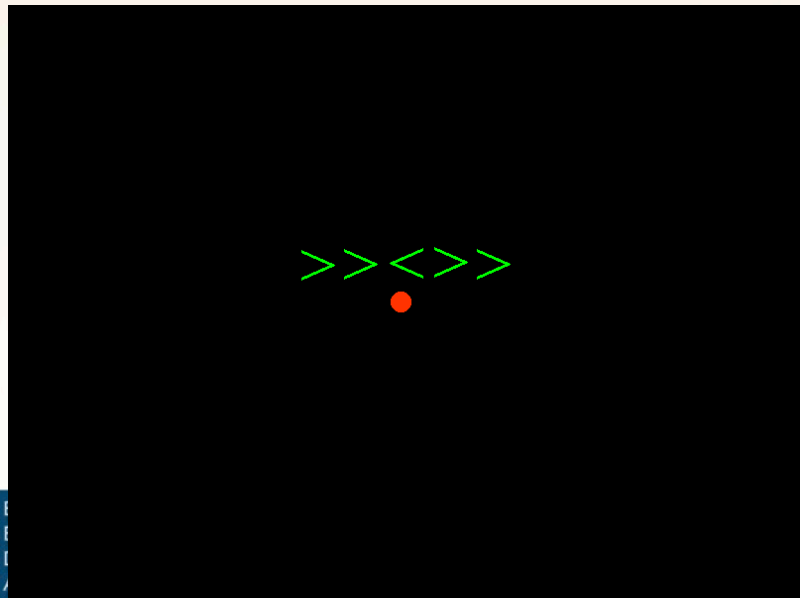


Gehring Lab- <http://www-personal.umich.edu/~wgehring/lab/Learn.html>

Compatible Trials (n=144)



Incompatible Trials (n=144)



Behavioral Measures of Error Monitoring

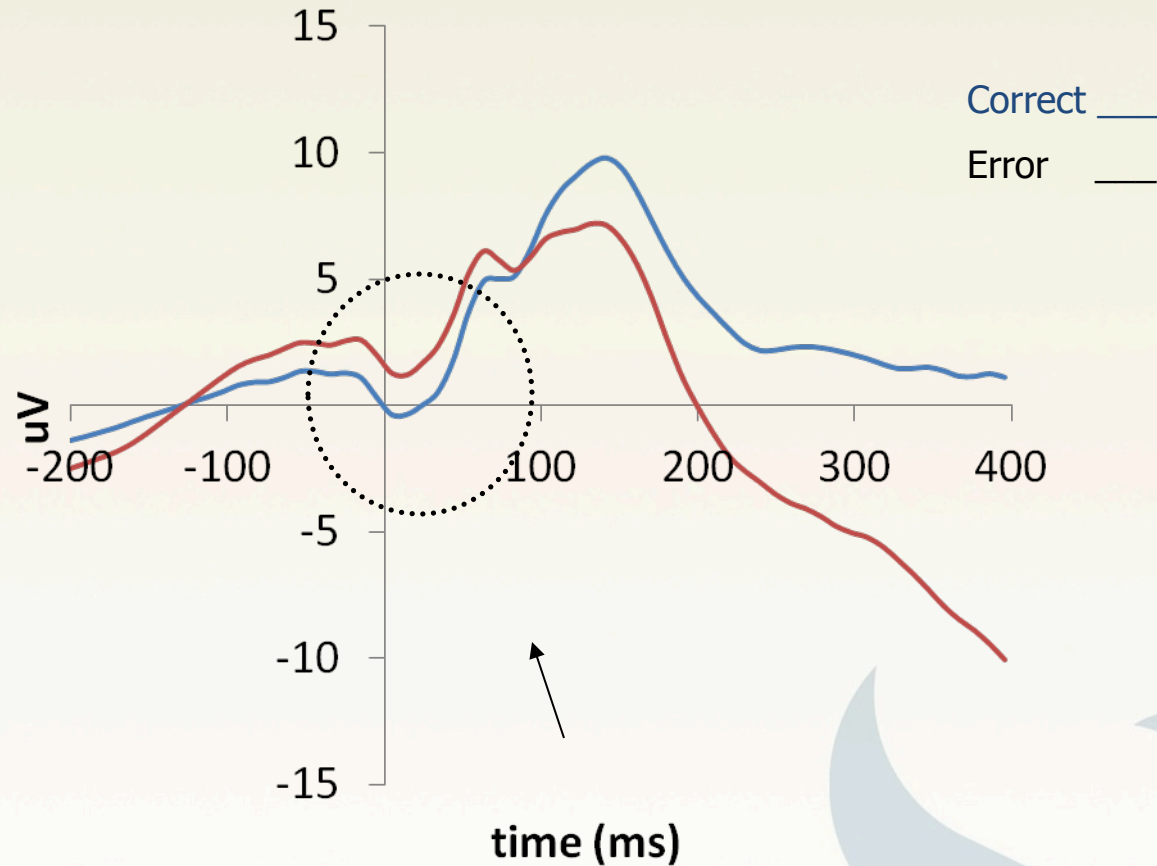
- Self-correction of errors (Rabbitt, 1966)
 - presence/absence of self-correction
 - latency to implement self-correction



Measuring Error Monitoring in the Brain

- Error-related Negativity: **ERN**

(Falkenstein et al., 1990; Gehring et al., 1993)



(Henderson, 2003)

Flanker Task: Letters Version

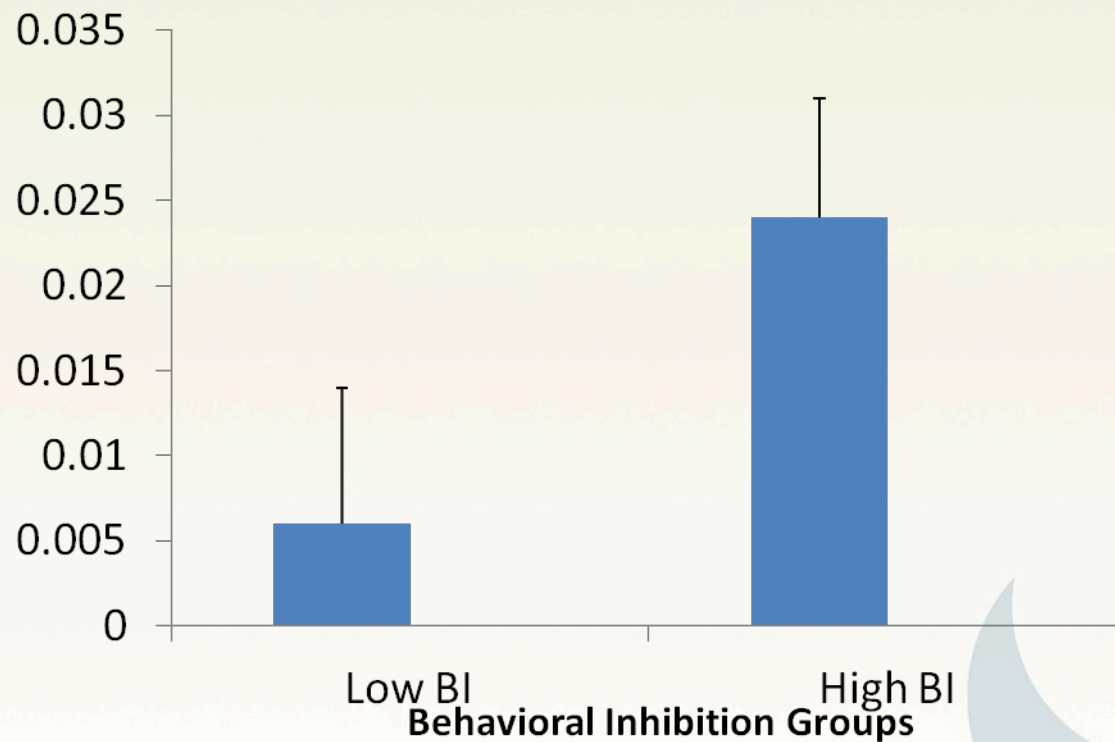
HHHHH

HHSHH

SSSSS

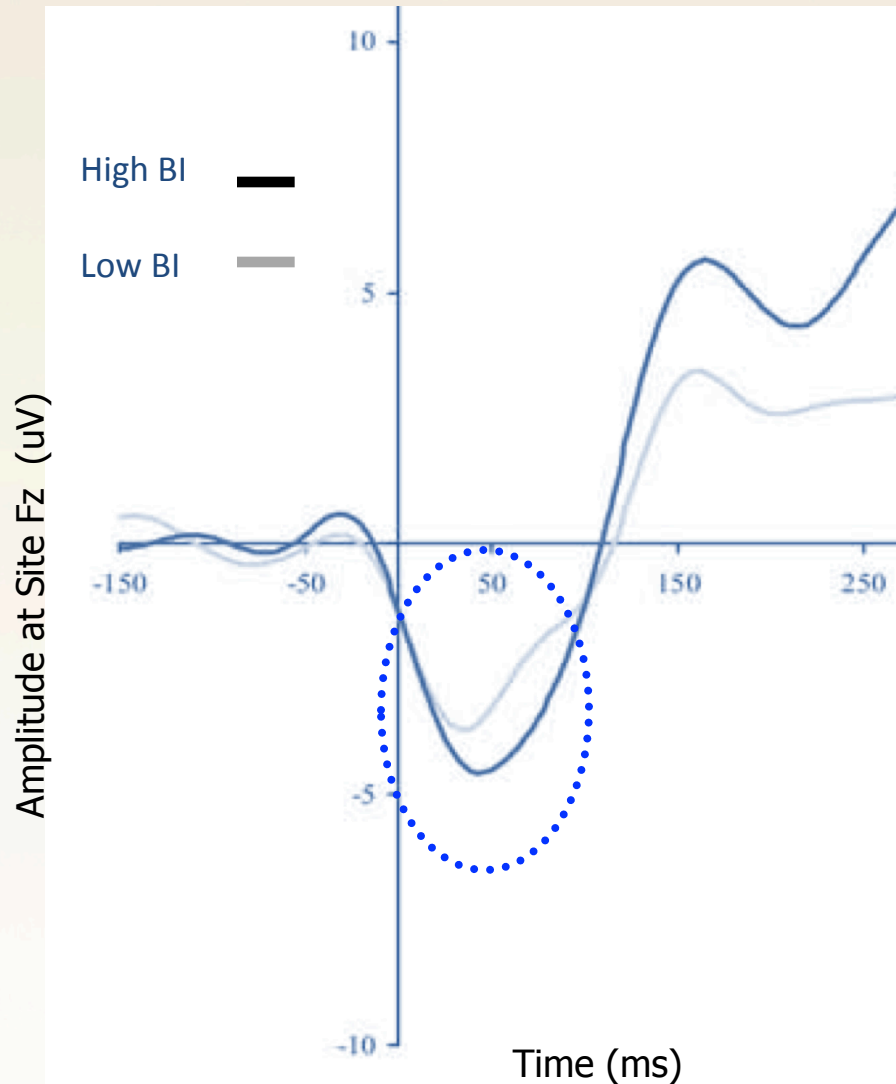
SSHSS

Error Monitoring and Behavioral Inhibition in Adolescence



McDermott et al, 2009, *Biological Psychiatry*

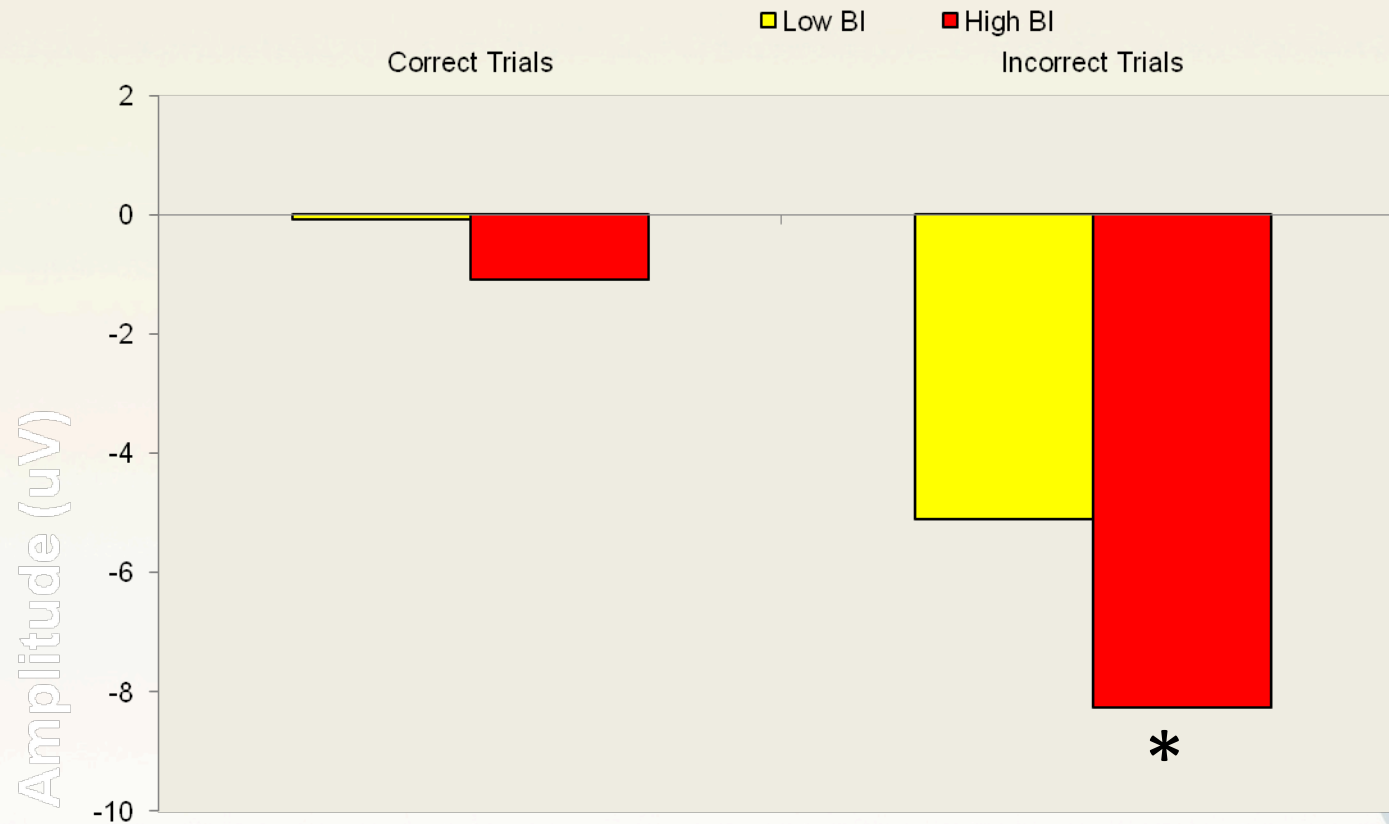
Behavioral Inhibition and Error Monitoring



- Highly inhibited adolescents display enhanced monitoring as indexed by the ERN

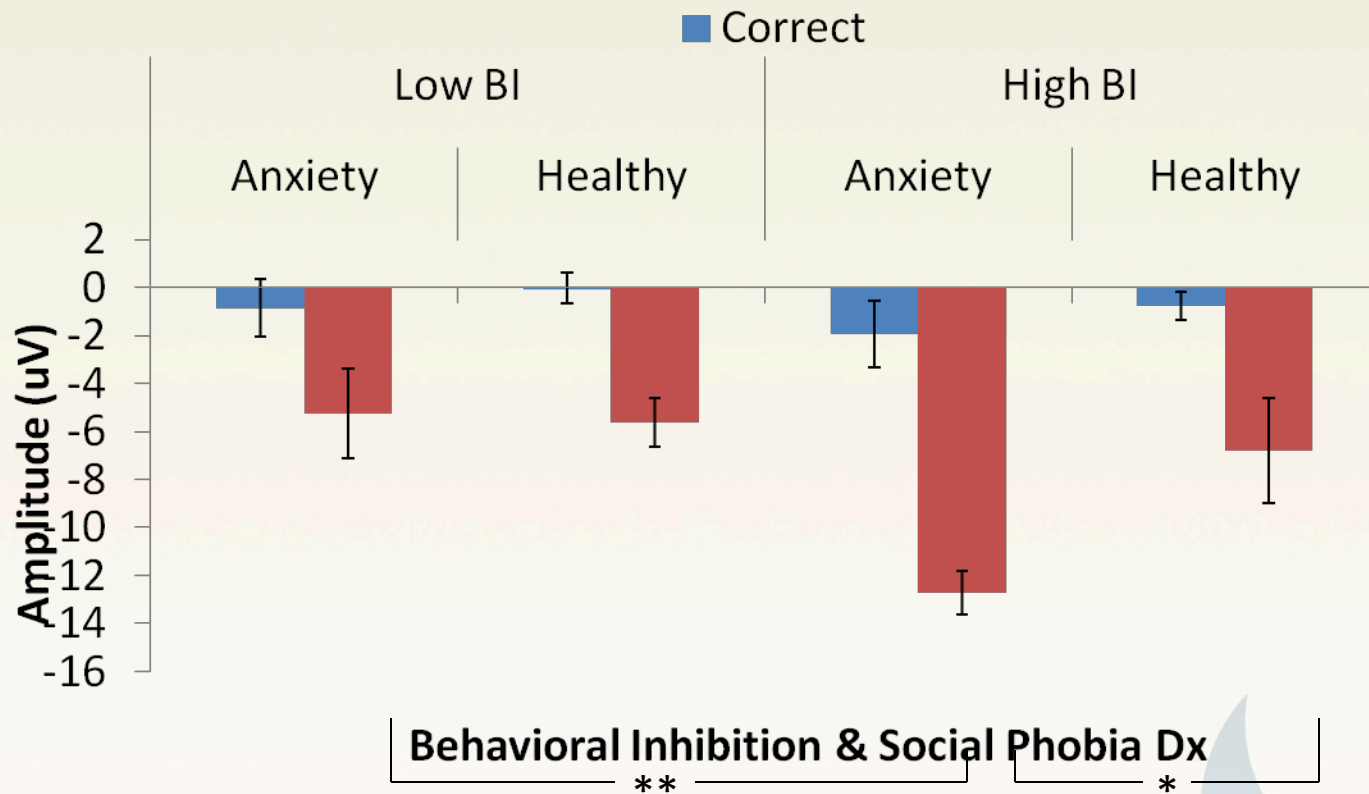
McDermott et al., (2009) Biological Psychiatry

Behavioral Inhibition predicting ERN Response



McDermott, et al, 2009 *Biological Psychiatry*

ERN Response, Behavioral Inhibition and Social Phobia in Adolescence



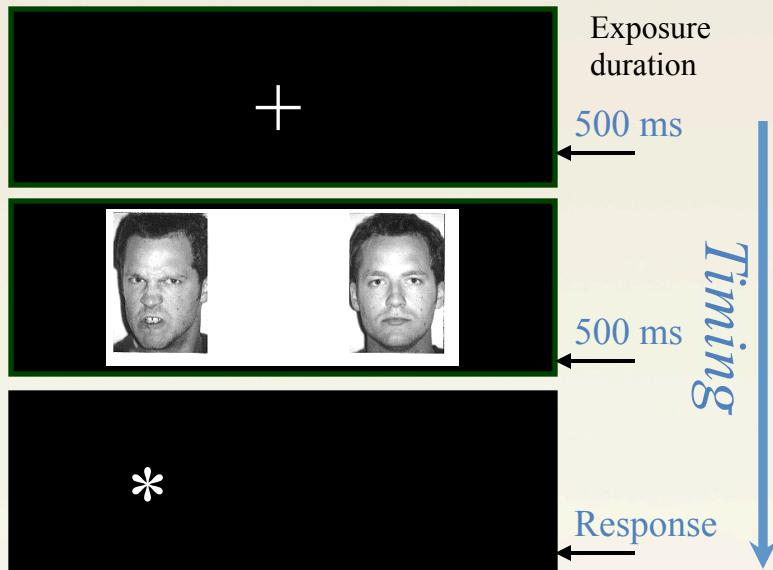
McDermott, et al, 2009 *Biological Psychiatry*

Using what we have learned about attention to design interventions for pediatric anxiety

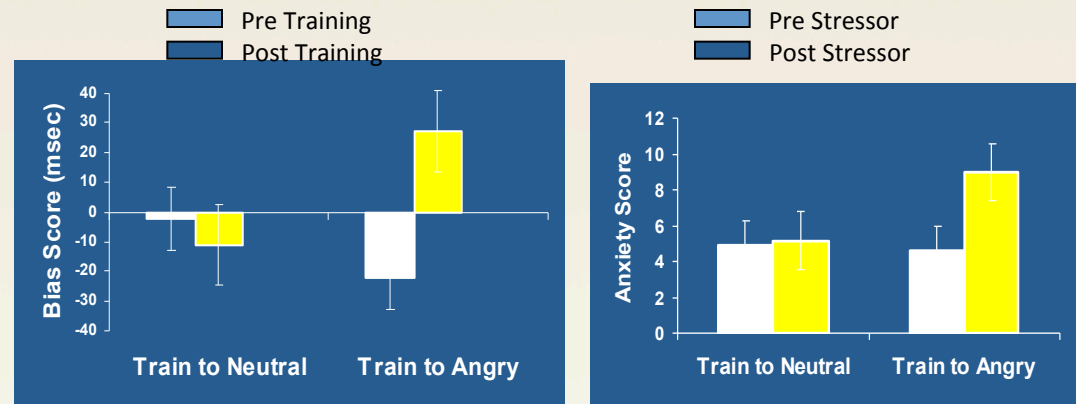
- We know that adults and children with anxiety display an attention bias to threat
- We also know that children with the temperament of behavioral inhibition display this same pattern of attention
- And bias to threat is associated with greater symptoms in behaviorally inhibited children



a. Events in Dot Probe Experimental Trials

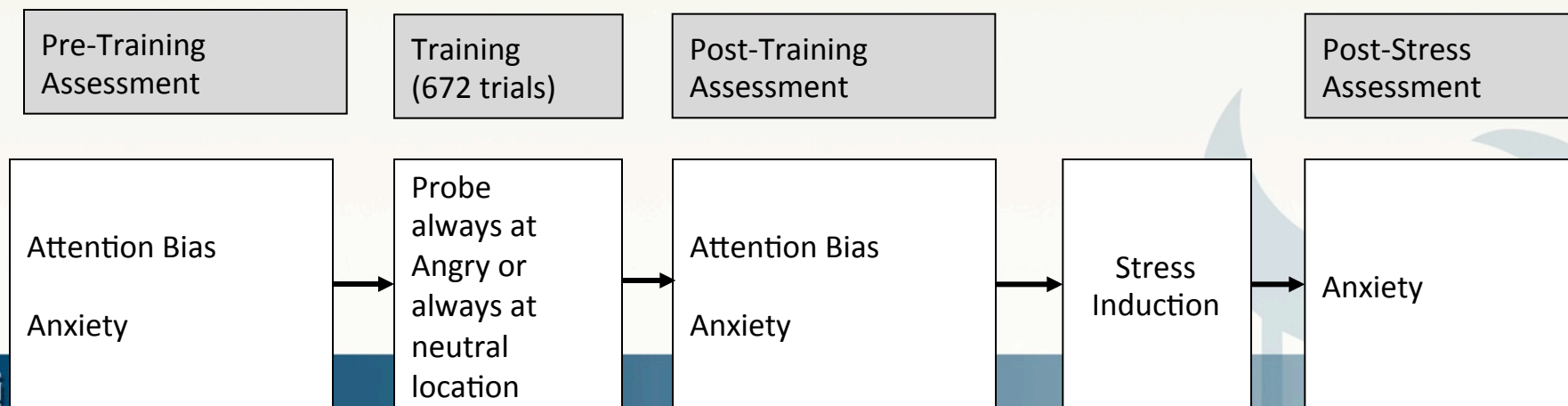


c. Training and Anxiety Patterns



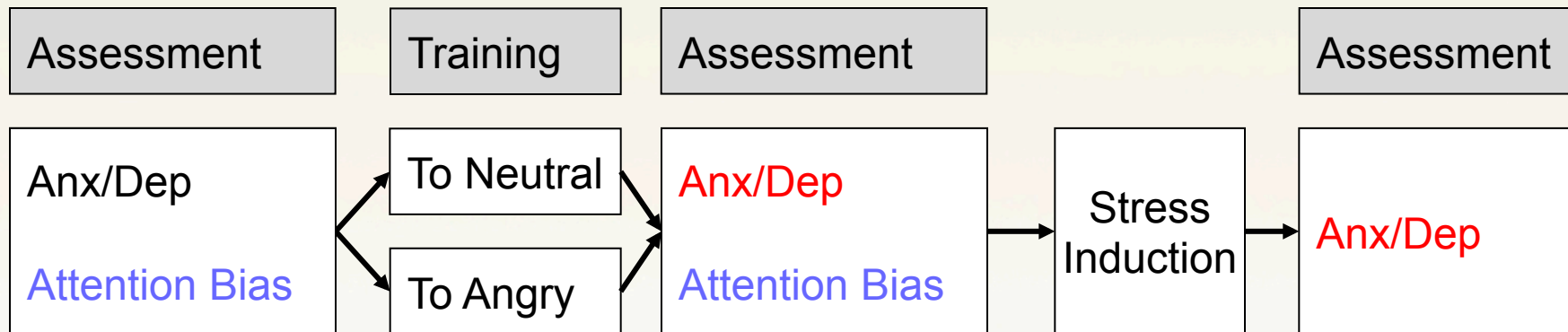
Increased attention toward threat in nonanxious children following training to attend to angry faces (left); Increased anxiety in these children following stress induction.

b. Events in a Training Experiment – Testing for Causality of Threat Bias in Anxiety

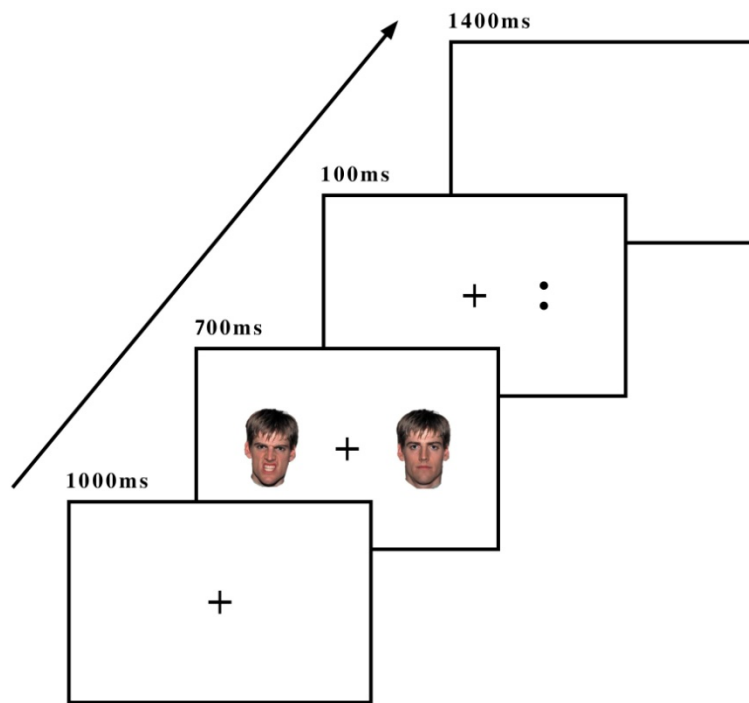


The MacLeod Design –testing the causal nature of attention bias

(MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002; Mathews & MacLeod, 2002)

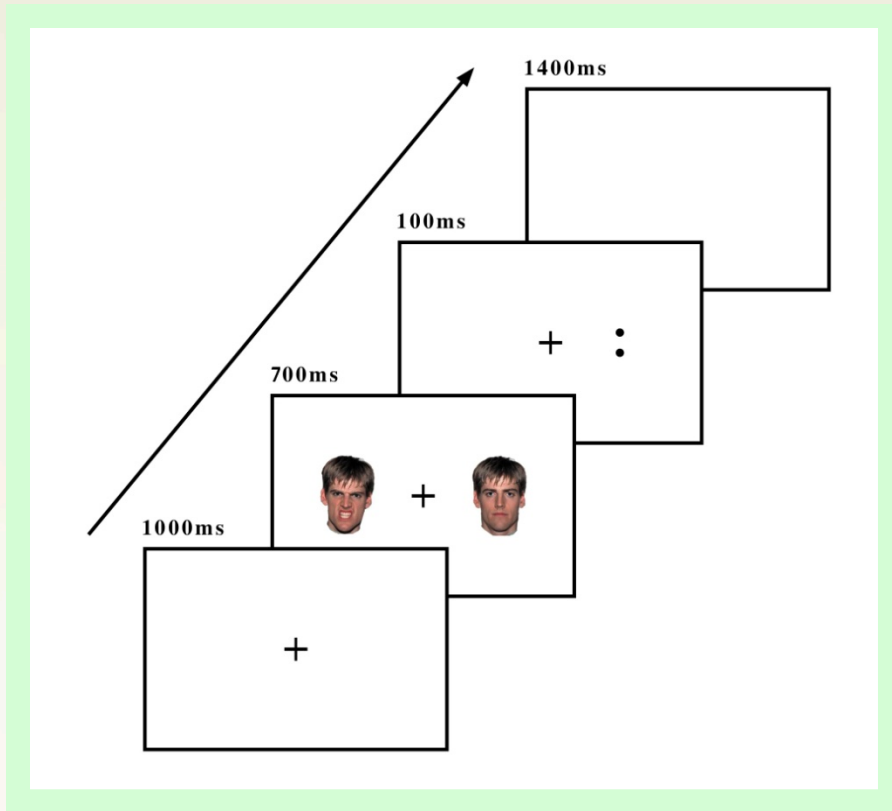


Manipulating Attention Bias—training attention bias to threat in children

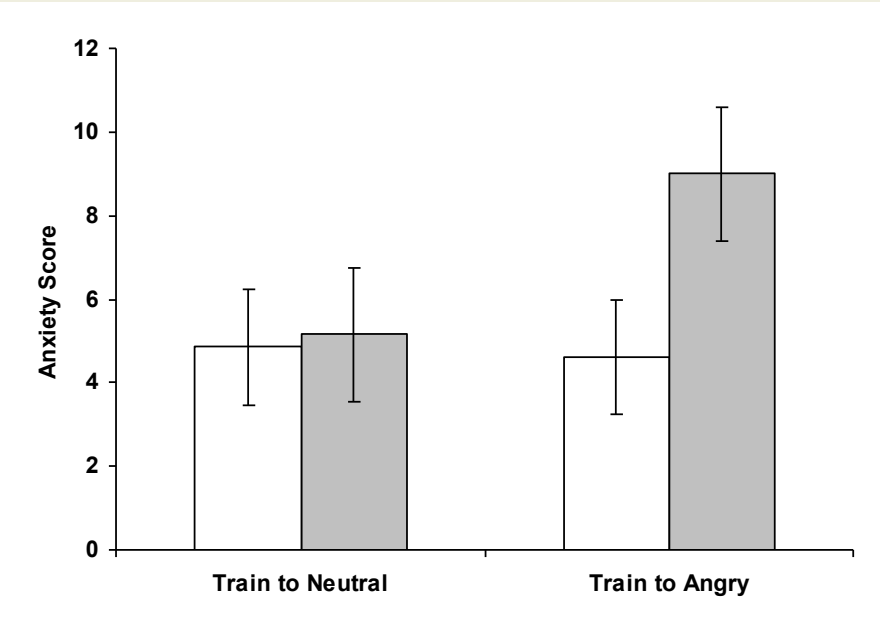


Training of Attention

Manipulating Attention Bias



Training of Attention



Altered Response to Stress

Eldara, Ricona, & Bar-Haim 2008

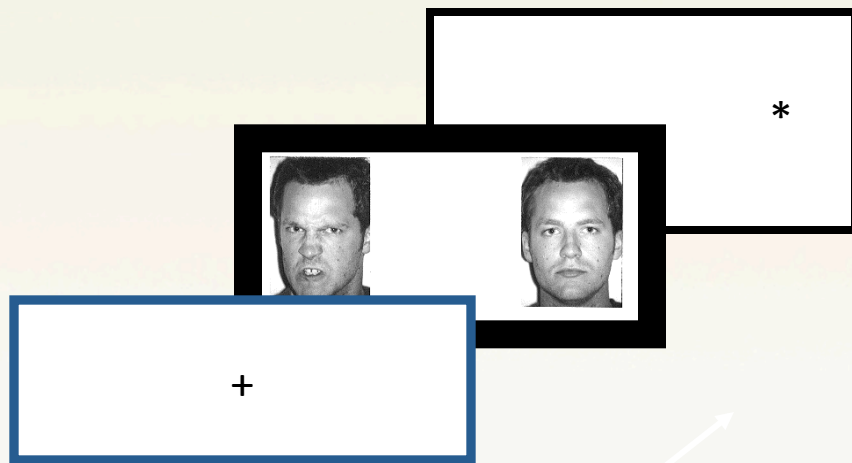
Is a bias towards threat always associated with threat and anxiety?

- How reliable is the dot probe as a measure of stress and threat?
- Can the bias be manipulated by environmental influences?
- What is the relation between direction of bias and anxiety and stress?

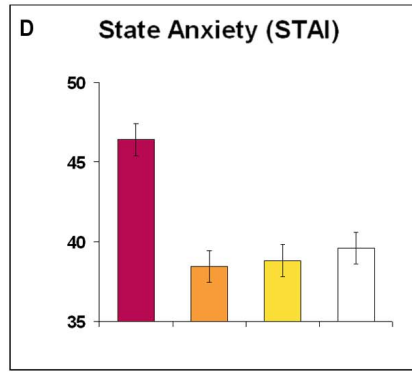
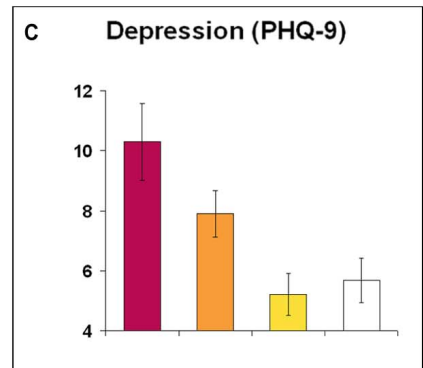
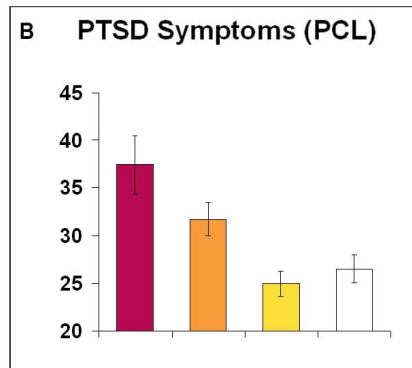
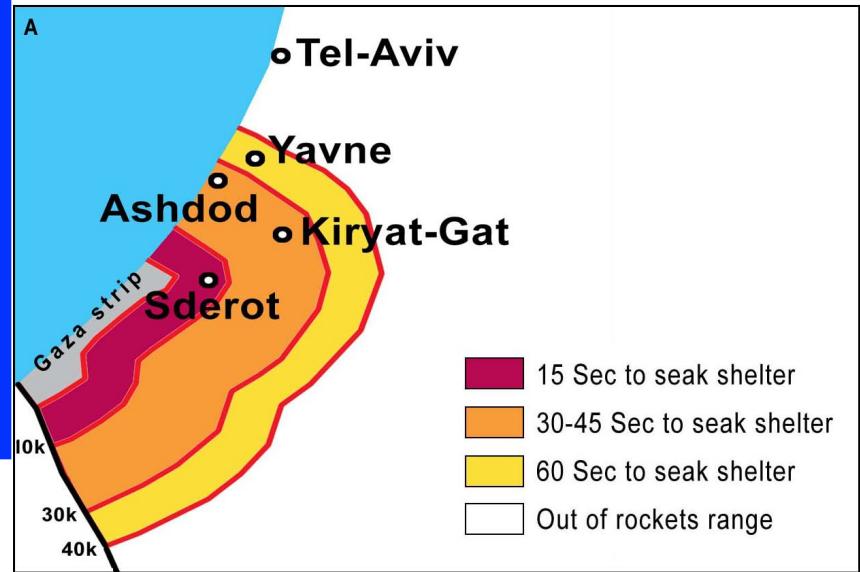


Attention Orienting and Threat

Influence by State and Trait Anxiety Factors

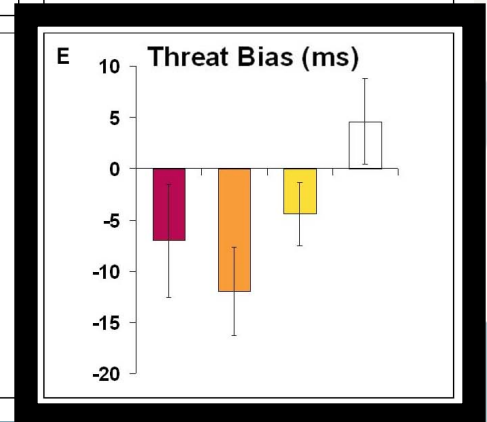
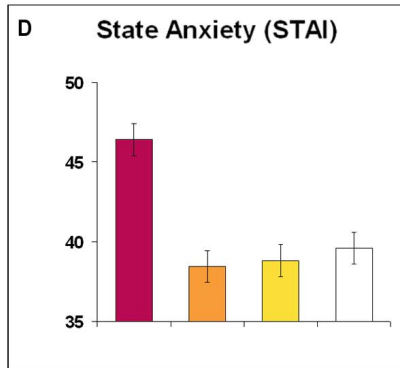
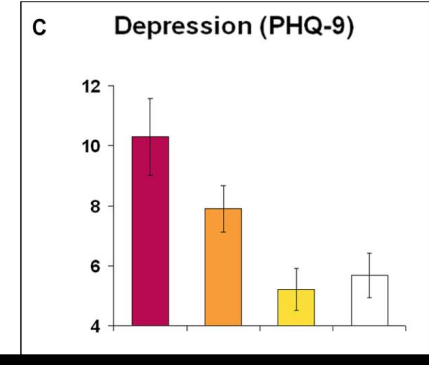
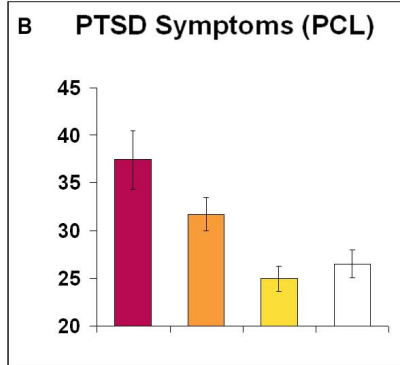
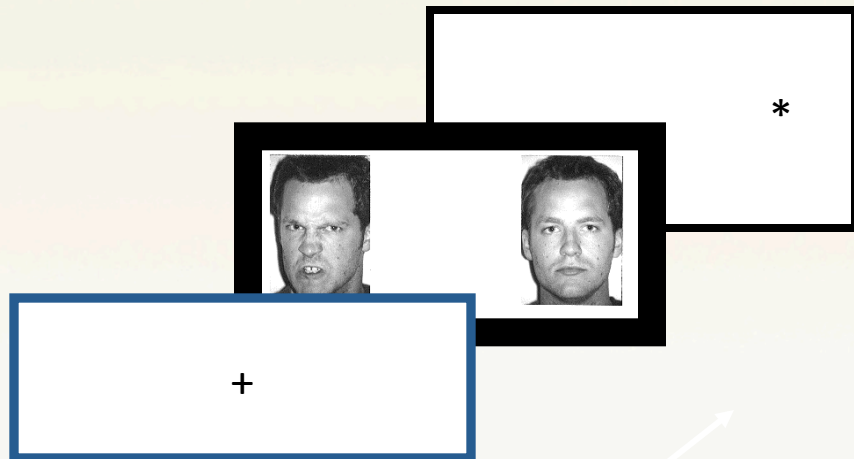
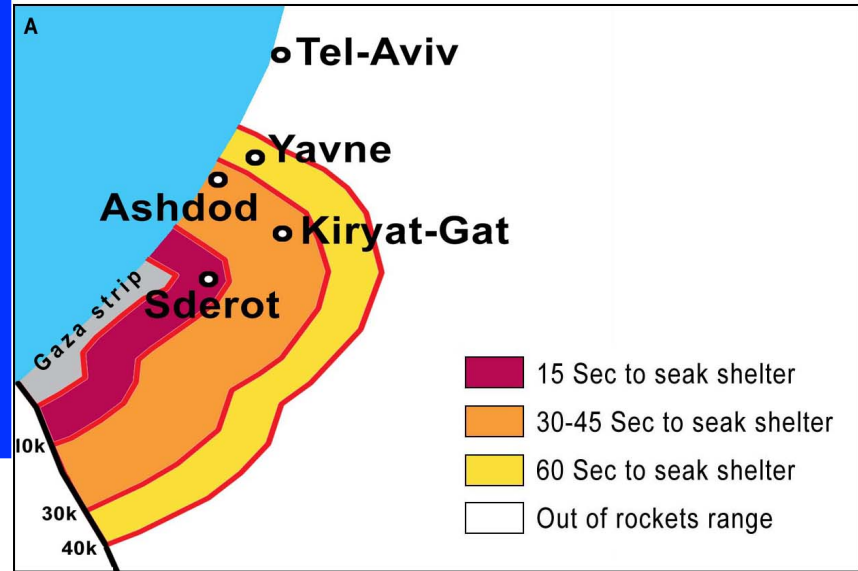


Bar-Haim et al. 2010



Attention Orienting and Threat

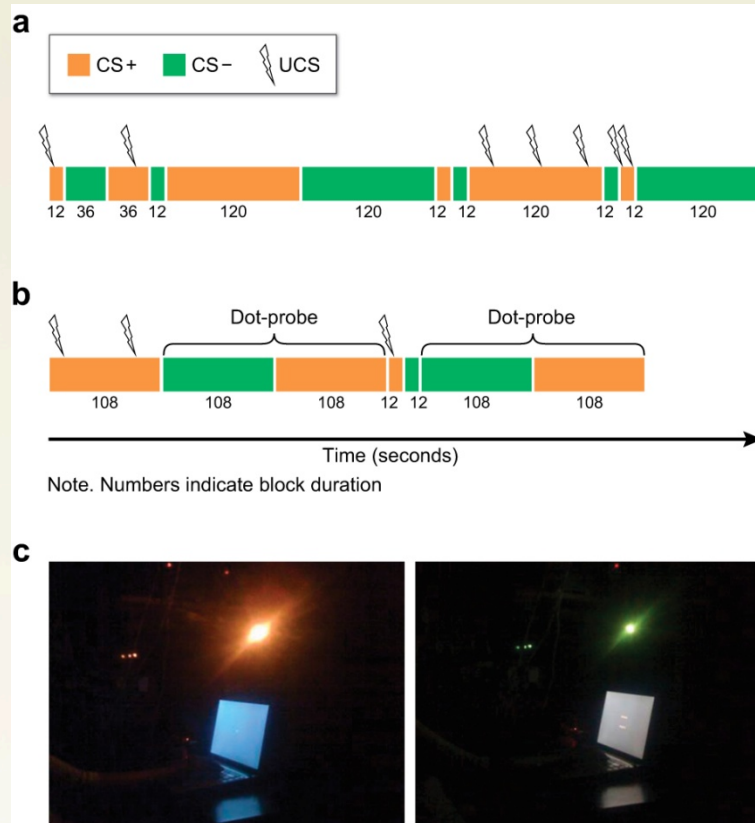
Influence by State and Trait Anxiety Factors



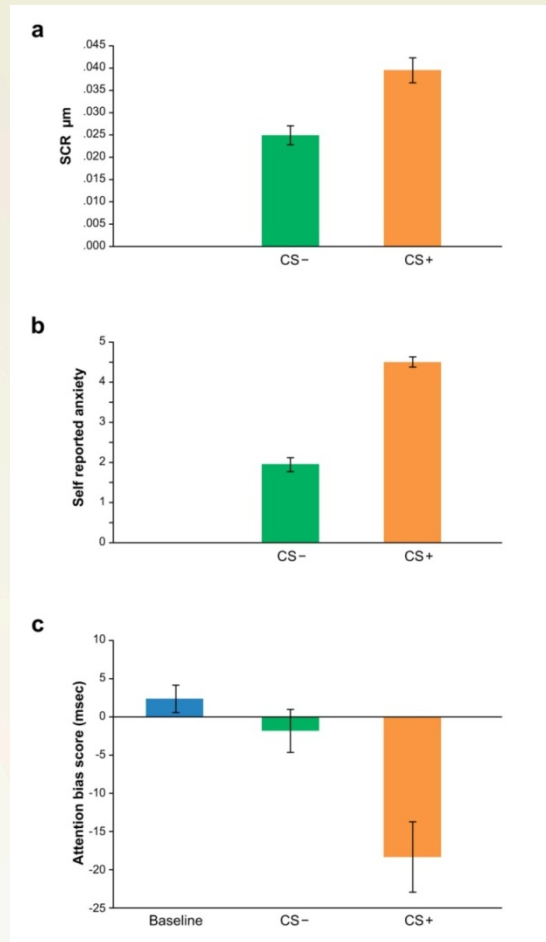
Bar-Haim et al. 2010

- Can we experimentally induce bias away from threat?
- Used threat of shock (undergraduates)
- Completed context fear conditioning and then examined bias
- Does bias predict response to stress?
- Examined combat soldiers threat bias and their PTSD after exposure to combat





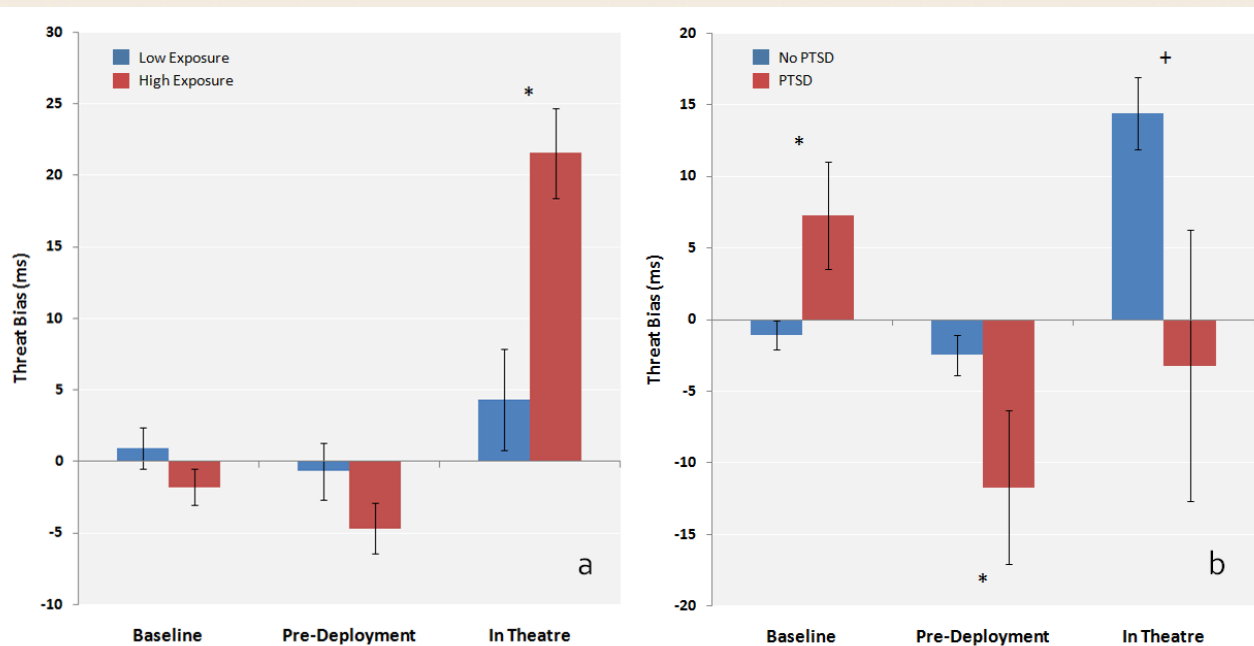
Instructed fear conditioning; (b) The experimental phase; (c) Dangerous and safe contextual cues



(a) SCR onset levels; (b) Self reported of anxiety levels across the experimental blocks; (c) Attention bias scores across blocks. Means and Standard errors.

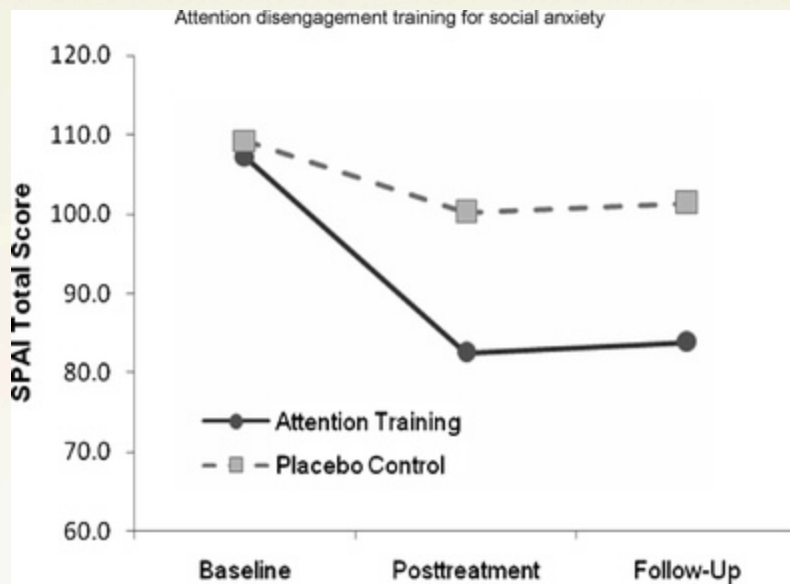
- Can we experimentally induce bias away from threat?
- Used threat of shock (undergraduates)
- Completed context fear conditioning and then examined bias
- **Does bias predict response to stress?**
- **Examined combat soldiers threat bias and their PTSD after exposure to combat**





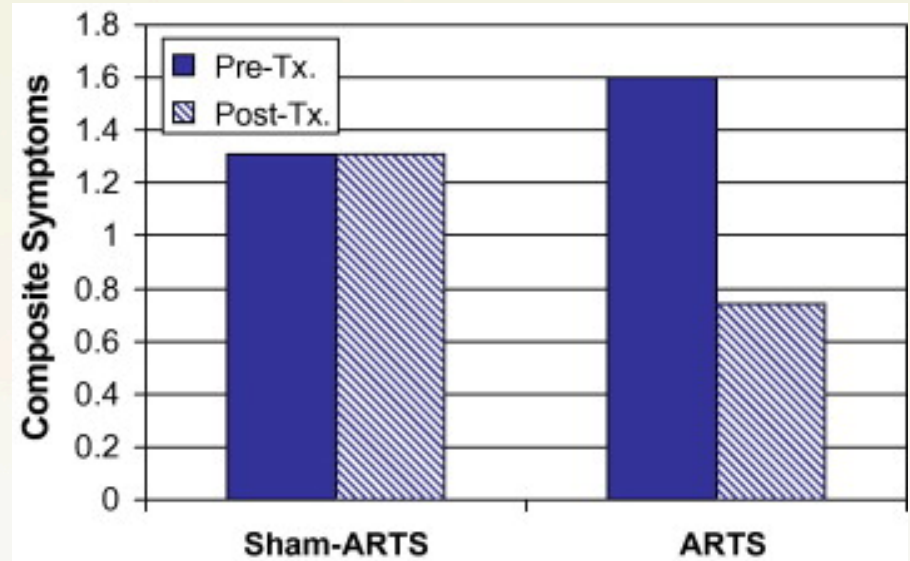
Means and standard error bars for (a) the effect of combat exposure on threat vigilance as a function of time in the deployment cycle, and (b) changes over time in threat related attention bias as a function of status of PTSD symptoms during deployment (clinical cutoff yes/no).

Clinical Trials in Adult Anxiety



Changes in SPAI in n=36 patients with Social Phobia

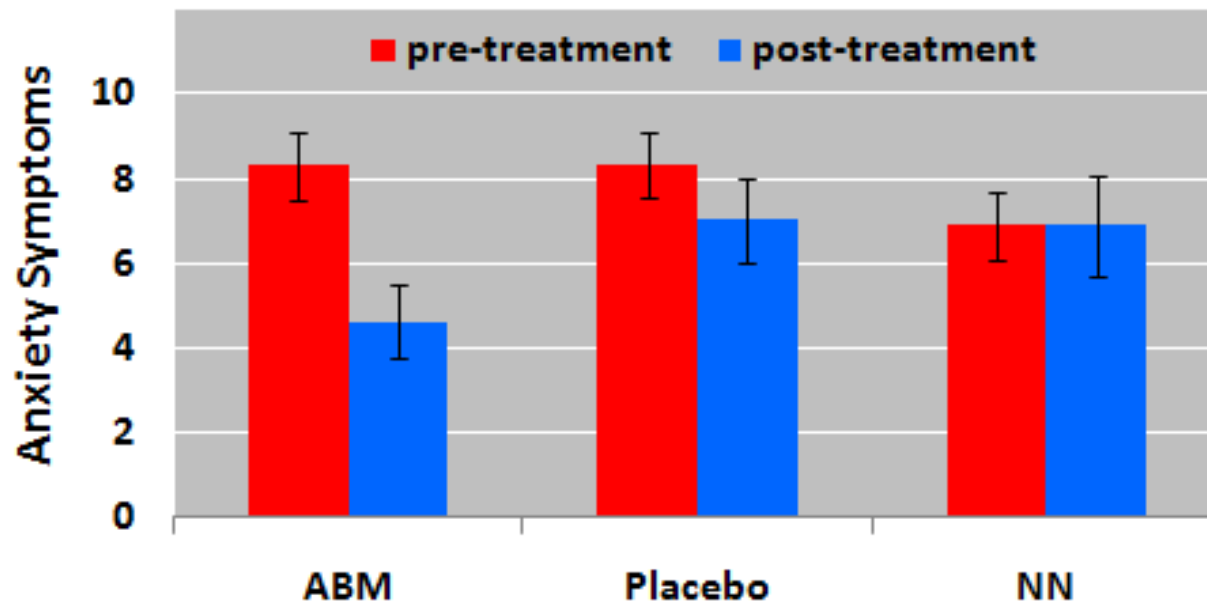
Schmidt et al. (2009)



Changes in Clinical Distress in n=24 Students with "Pathological Worry"

Hazen et al. (2008)

Results of randomized trial of attention bias modification with 10-14 year old socially anxious children



Eldar, Fox, Pine, & Bar-Haim (in press) American Journal of Psychiatry

What accounts for the emergence and stability of anxiety amongst Behaviorally Inhibited children ?

- Cognitive control processes appear to act differently as moderators of adaptive behavior based upon the temperament of the child
- Important to note that at in the case of the temperamentally BI children these represent about 15% of population
- Differences in cognitive cognitive control processes that emerge early in childhood
 - Attention processes
 - Bias to threat
 - Error monitoring



What are the next steps for developing interventions

- Need for attention training studies with children with anxiety disorders
- These studies should include contrasts with current available therapies including pharmacology and CBT



Thanks to my collaborators

- Daniel Pine, NIMH
- Monique Ernst, NIMH
- Koraly Perez-Edgar, Penn State
- Heather Henderson, Univ. of Miami
- Peter Marshall, Temple Univ.
- Yair Bar-Haim, Tel-Aviv Univ.
- Amie Hane, Williams College
- Jen McDermott, Univ. of Massachusetts, Amherst
- Chris Monk, Univ of Michigan
- Current members of the Child Development Lab
 - Kate Degnan, Ph.D.
 - Ayelet Lahat, Ph.D.
 - Connie Lamm, Ph.D.
 - Bethany Reeb, Ph.D.
 - Ross Vanderwert
 - Sarah Helfinstein
 - Lauren White
 - Jenna Suway

Thanks to

- NICHD, R37HD17899
- NIMH, R01 MH 55789



And Thanks for your attention

