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neuroscience CME

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## Perspectives in the Management of Anxiety Disorders

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## *Disclosures*



- **Grants:** National Institute of Mental Health (NIMH)
- **Honorariums:** CME Outfitters; Elsevier Inc.
- **Scientific Advisory Board:** Corcept Therapeutics
- **Stockholder, Equity Options:** Corcept Therapeutics
- **Patents:** Promoter sequences for corticotropin-releasing factor CRF2alpha and method of identifying agents that alter the activity of the promoter sequences: U.S. Patent issued on 07-04-06; patent #7071323, U.S. Patent issued on 05-12-09; patent #7,531,356. Promoter sequences for urocortin II and the use thereof: U.S. Patent issued on 08-08-06; patent #7087385. Promoter sequences for corticotropin-releasing factor binding protein and use thereof: U.S. Patent issued on 10-17-06; patent #7122650.

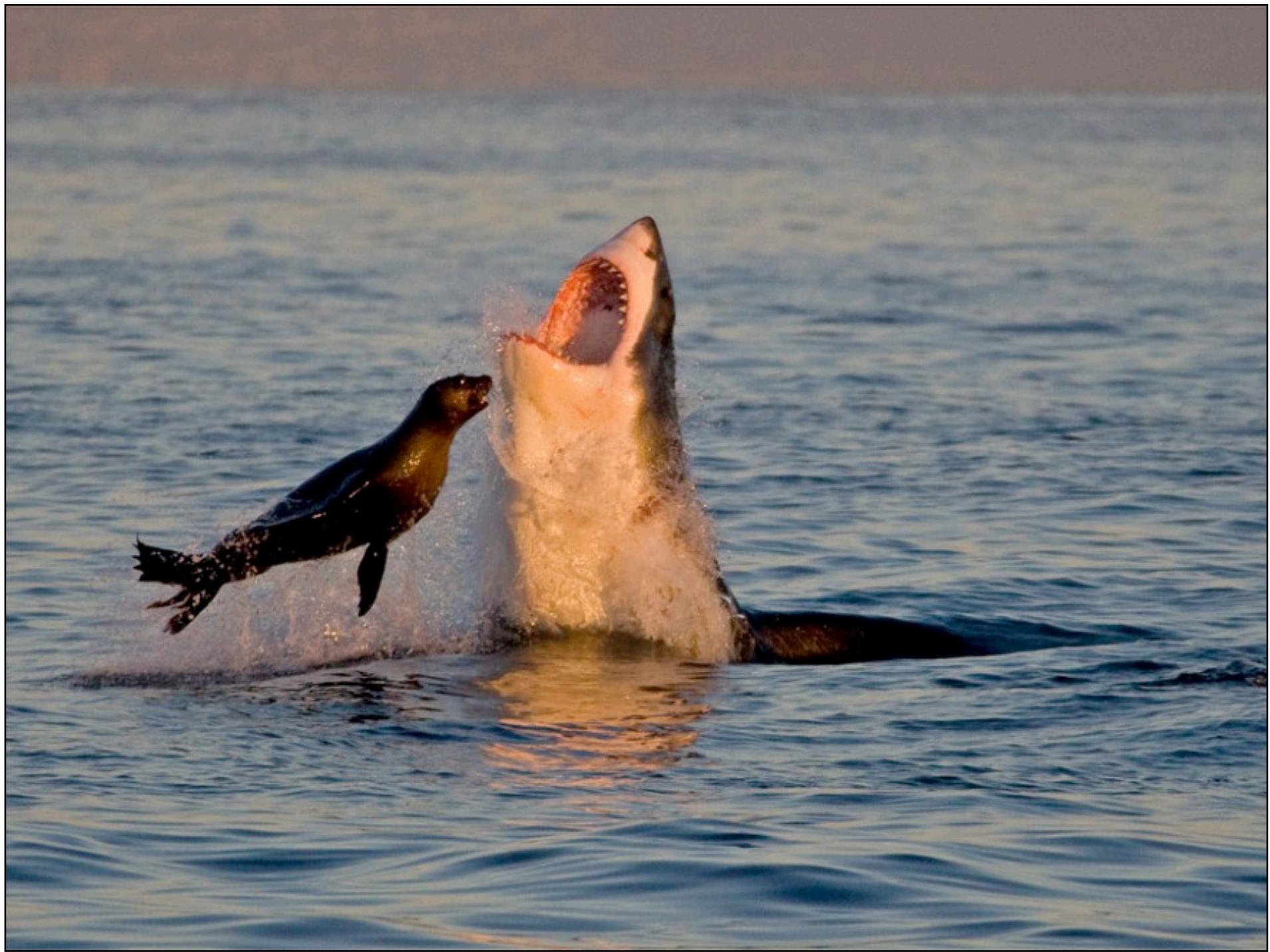


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## Learning Objective

Describe the neurobiology of the stress response and anxious temperament.



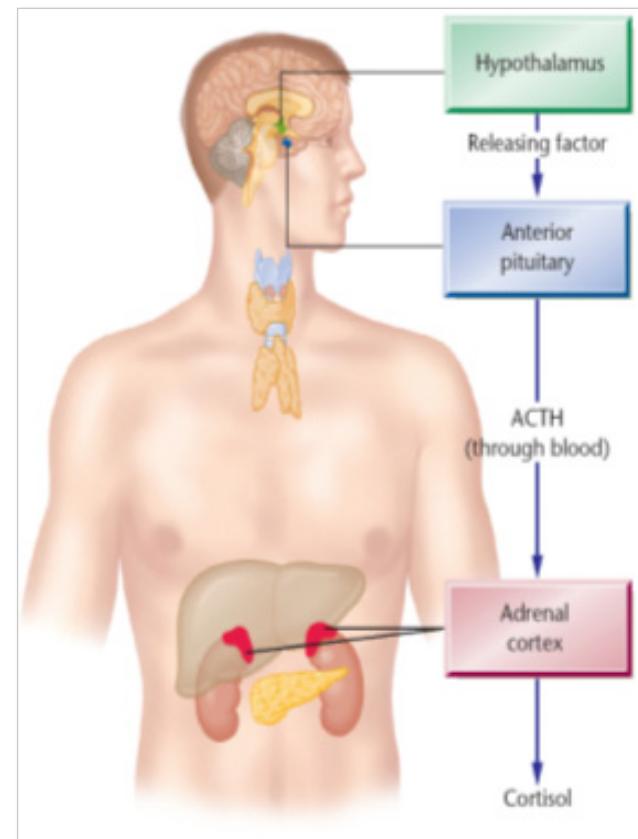




# Stress is a Whole Body Response and Cortisol is Key



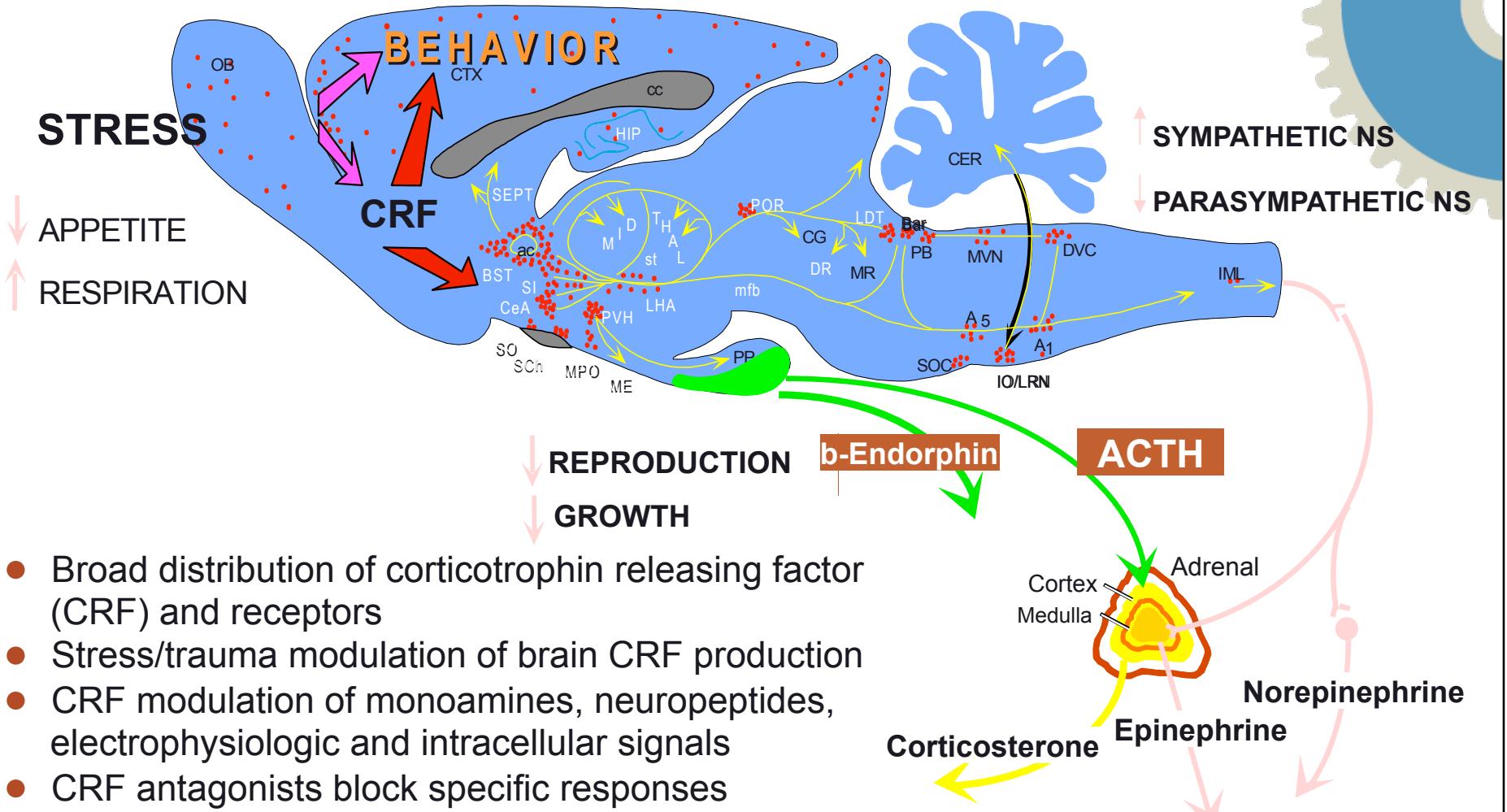
- Stress response is adaptive, helping us survive challenges.
- Chronically elevated cortisol results in greater likelihood of developing depression, hypertension, diabetes, heart disease, osteoporosis, immune problems and memory problems.



Jansen AS, et al. *Science*. 1995;270(5236):644-646. PMID: 7570024.

# Corticotrophin Releasing Hormone Integrates Stress Response

AROUSAL ANXIETY FEAR DEPRESSION



- Broad distribution of corticotrophin releasing factor (CRF) and receptors
- Stress/trauma modulation of brain CRF production
- CRF modulation of monoamines, neuropeptides, electrophysiologic and intracellular signals
- CRF antagonists block specific responses



**For survival we are wired to have universal responses to stress.**

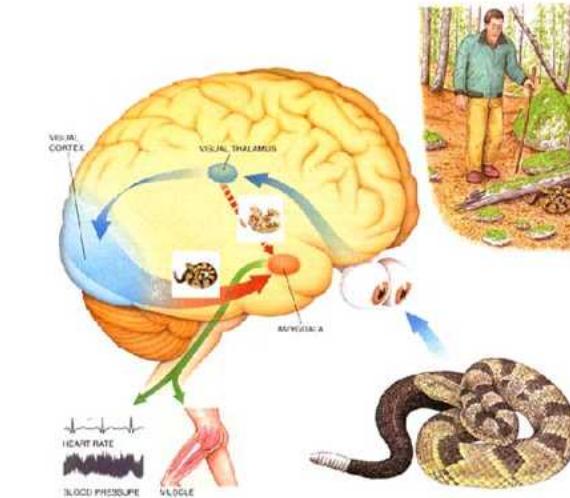
# We Get Vulnerability Genes From Our Parents and They Teach Us About Fear



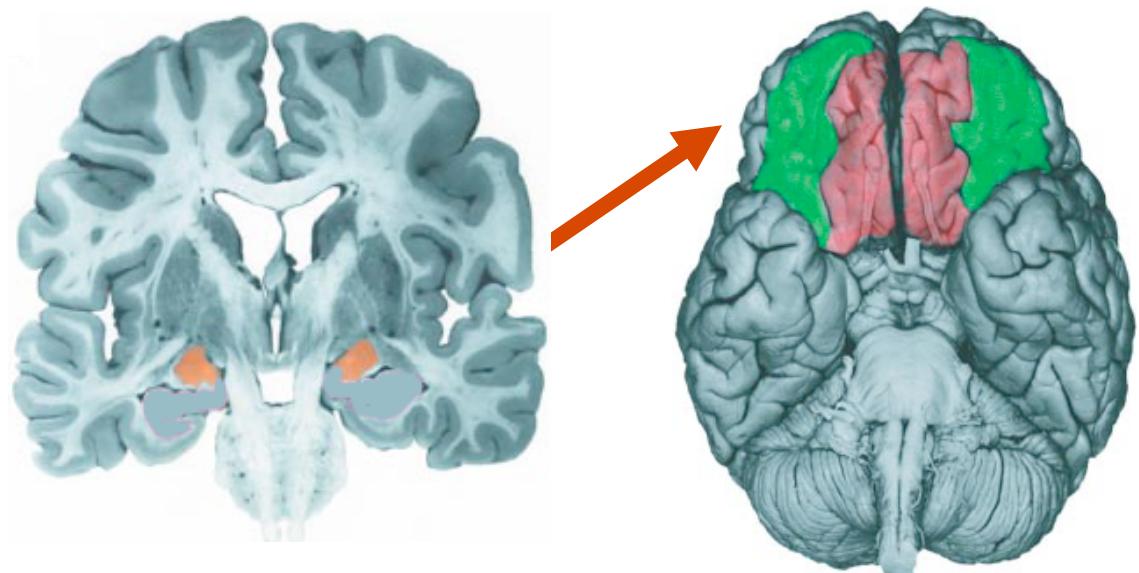
# Brain Systems Important In Stress, Resilience And Psychiatric Disorders



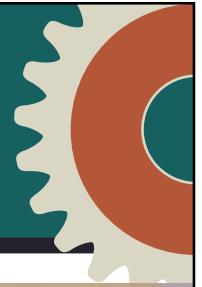
The prefrontal cortex regulates the amygdala



Cognitive therapy for anxiety and depression may work by strengthening the ability of the prefrontal cortex to regulate the amygdala



# Tess Struggles



**UWHealth**  
[uwhealth.org](http://uwhealth.org)

# Extreme Anxious Temperament as the Early Risk to Develop Anxiety and Depression



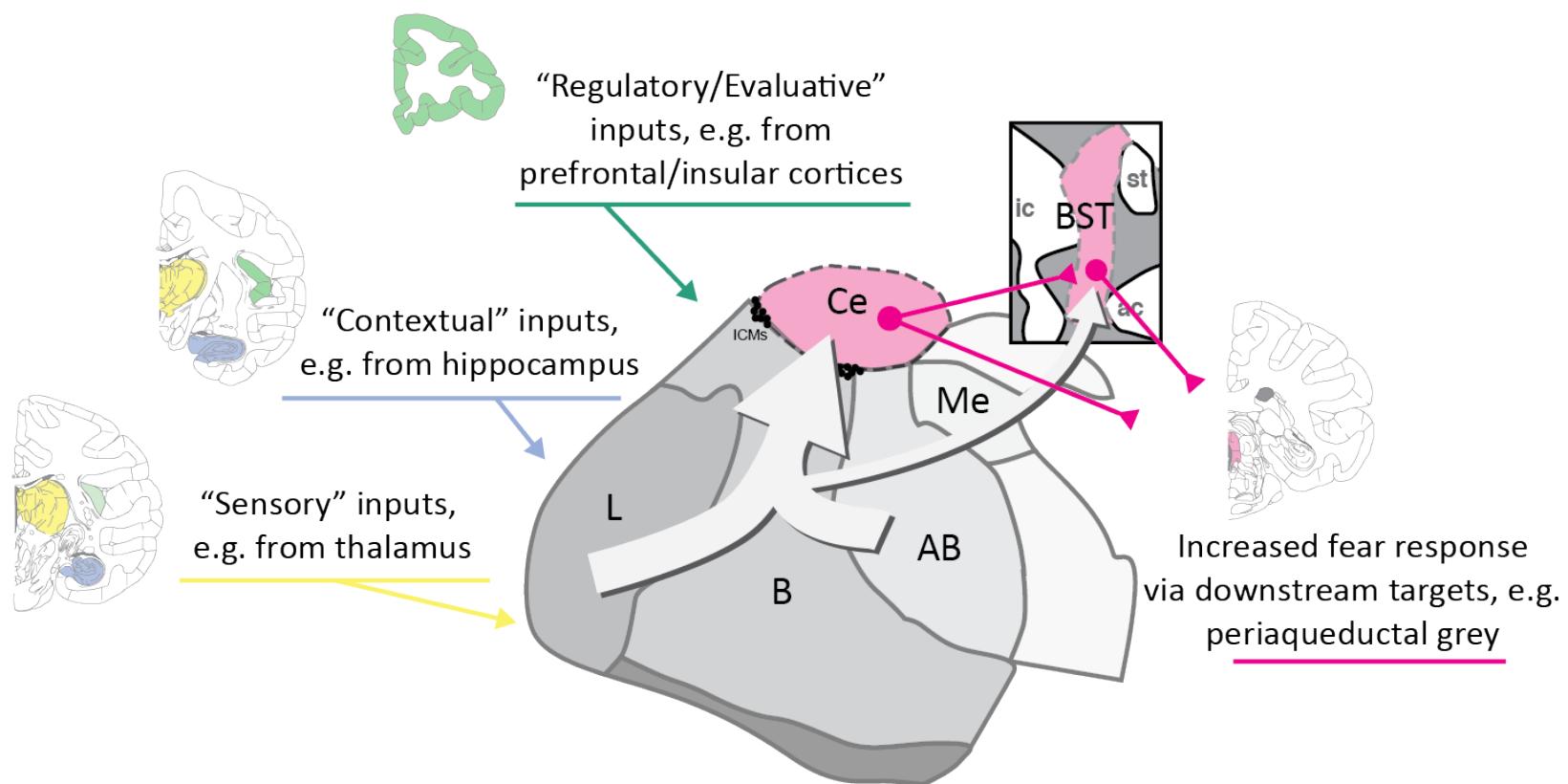
# Inhibited or Anxious Temperament (AT) is the Risk Phenotype



- Extreme behavioral inhibition to novel situations or strangers
- Predicts development of anxiety disorders, depression, and co-morbid drug abuse
- Greater than 7 fold risk to develop social anxiety disorder
- Can be identified early in life
- Inhibited monkeys and humans share behavioral and physiological features

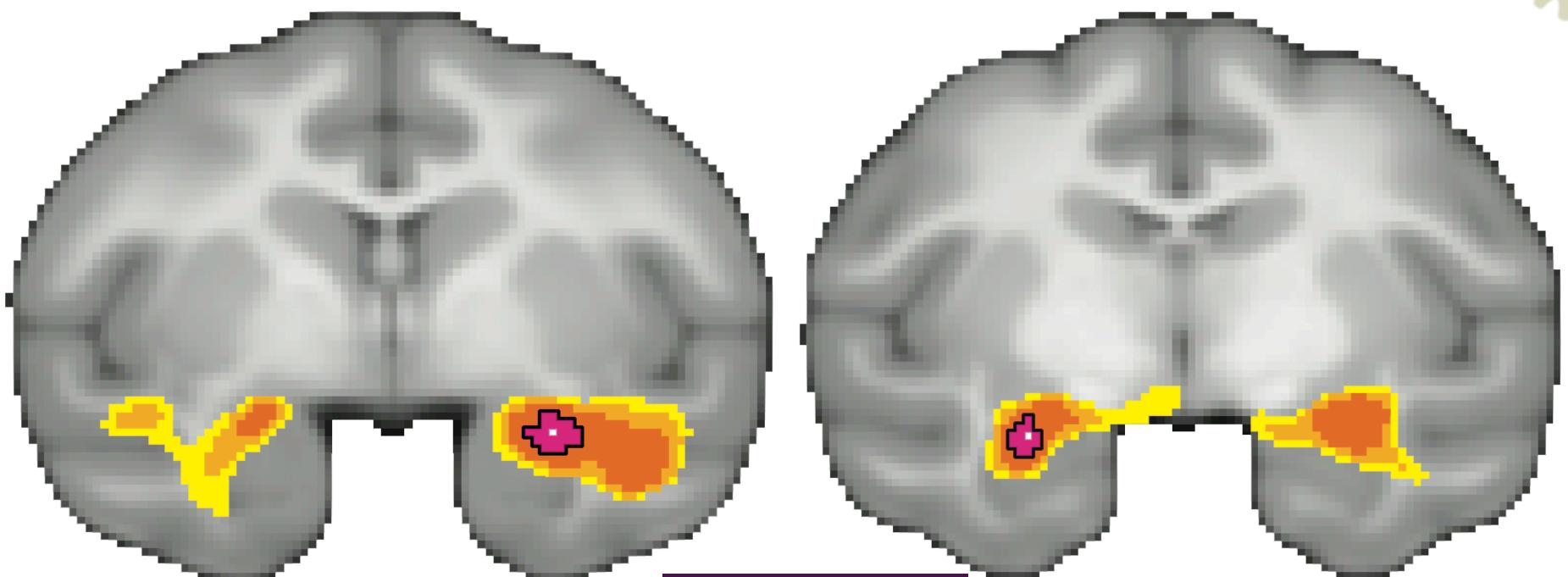


# Central Nucleus of the Amygdala at the Interface of Fear and Anxiety



# Regions Correlated with AT

238 Young Monkeys



Oler JA, et al. *Nature*.  
2010;466(7308):864-868.

Regions correlated with  
Anxious Temperament (AT)

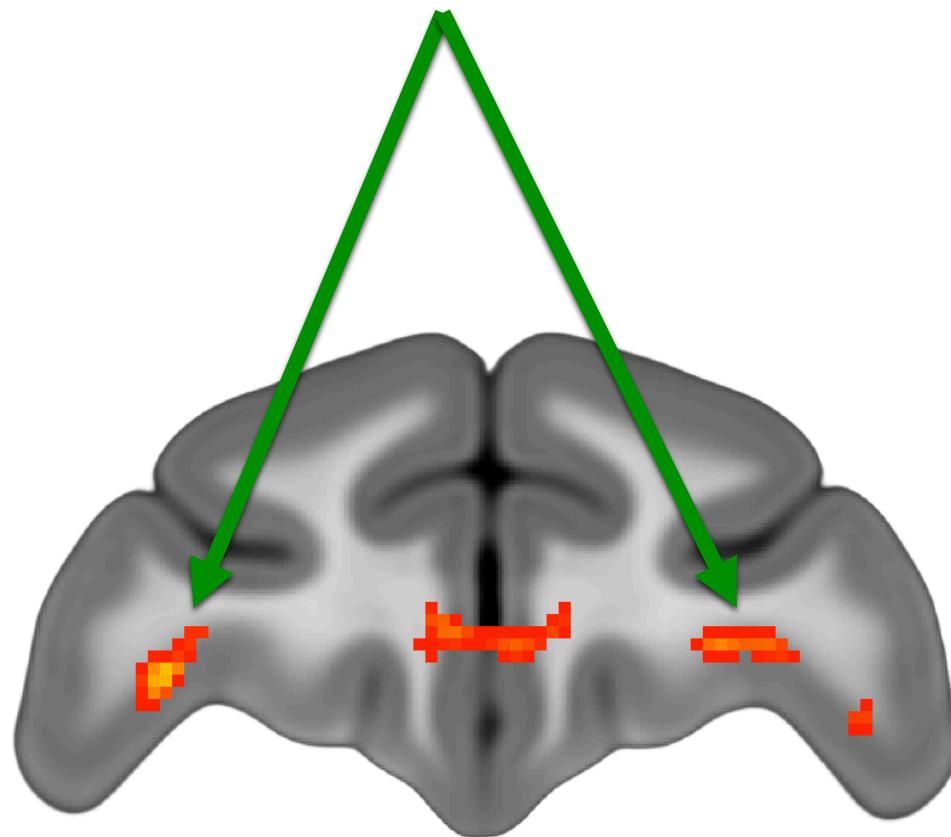
■ p<.05, corrected

■ p<.01, corrected

■ p<.001, corrected

■ Peak voxel correlated with  
AT within its 95% spatial  
confidence interval

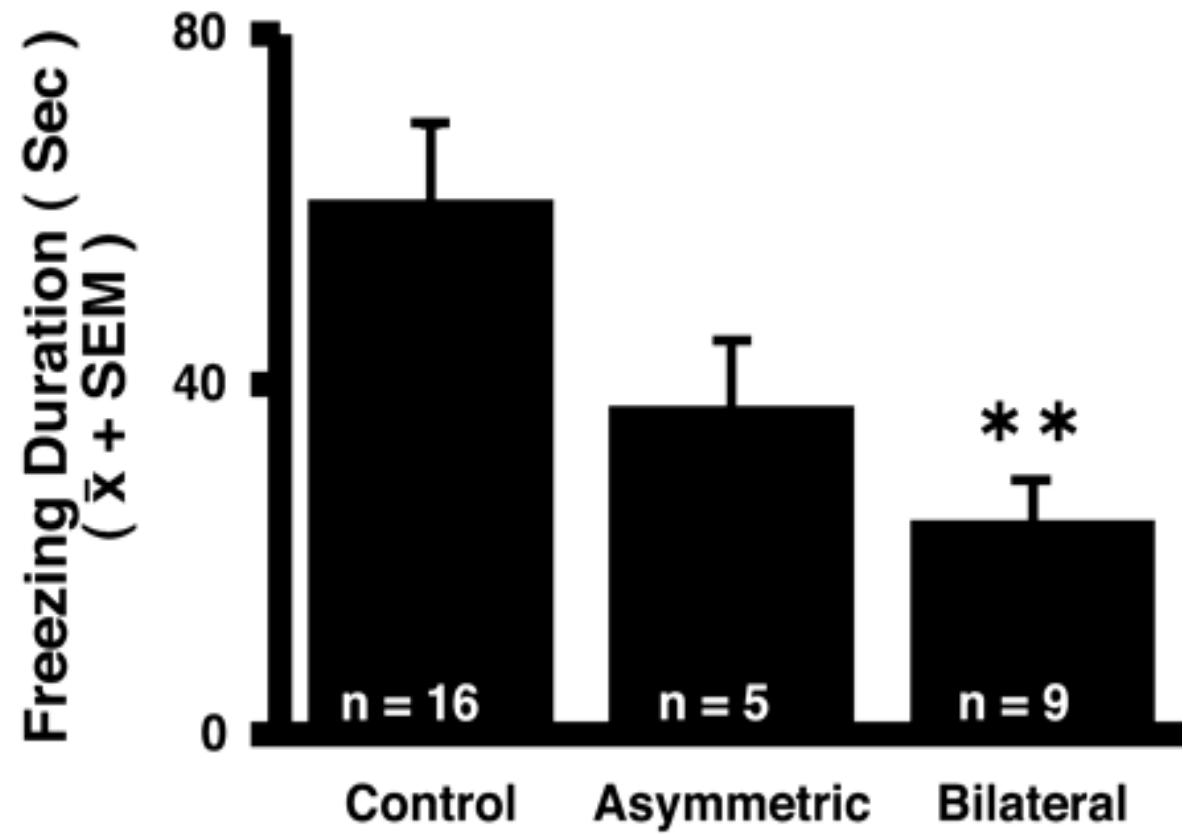
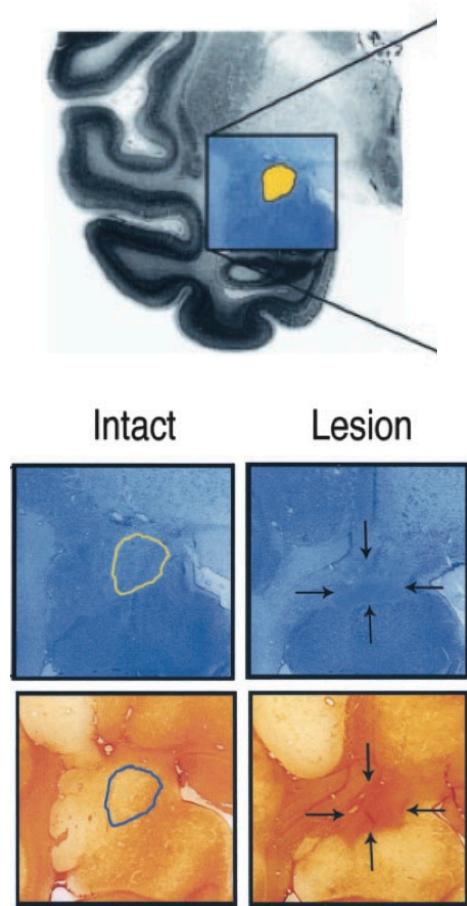
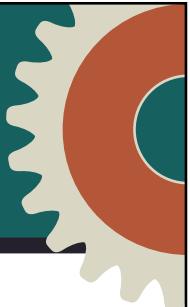
# Elaboration of AT Circuit (N = 592) OFC Metabolism Predicts Anxious Temperament (AT)



N = 592  
 $T > 5.0$

Kalin N, et al. Unpublished data.

# Central Nucleus of the Amygdala (CeA) Lesions Decrease Freezing



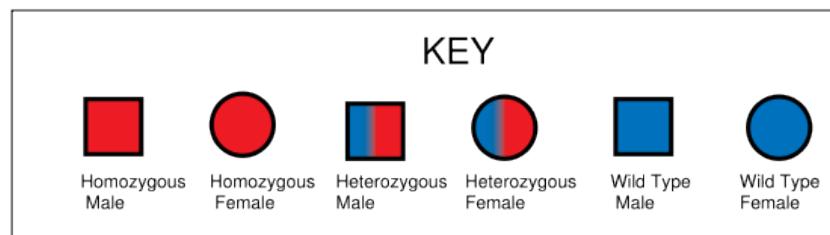
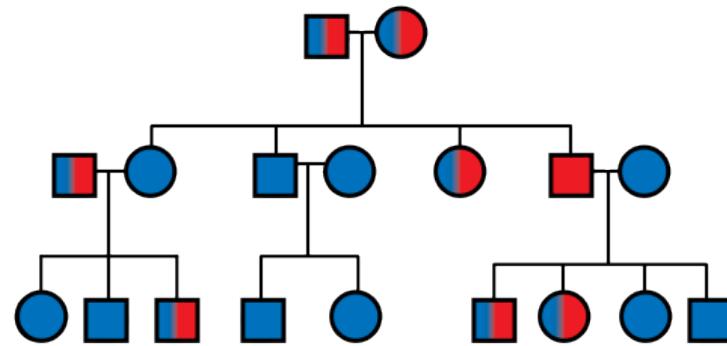
Kalin NH, et al. *J Neurosci*. 2004;24(24):5506-15. PMID: 15201323.

# AT Heritability



- Heritability estimate - variance that can be predicted by the family tree

AT was heritable in this sample of 238 individuals ( $h^2 = 0.36, p = 0.015$ )

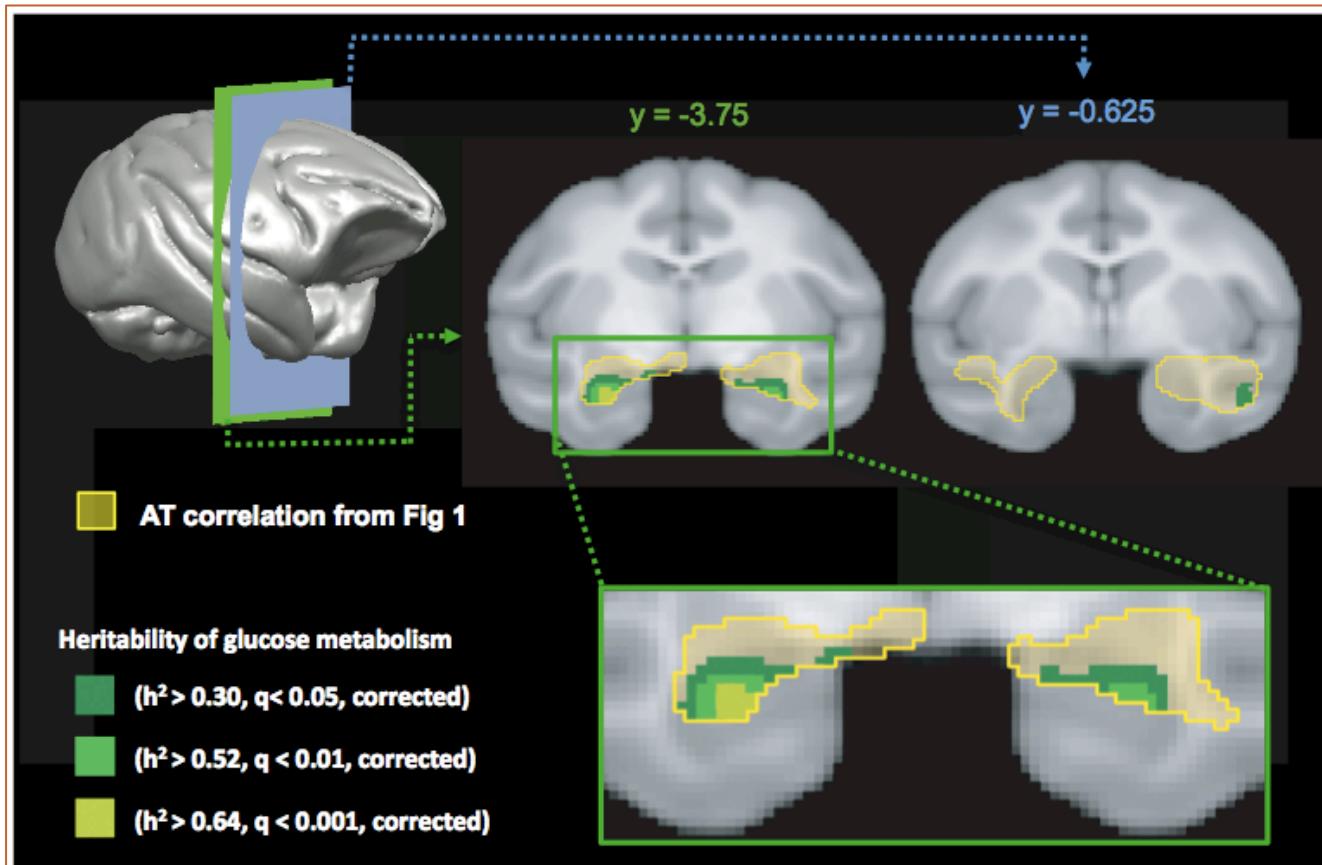


Oler JA, et al. *Nature*. 2010;466(7308):864-868. PMID: 20703306.

# Heritability of Glucose Metabolism in Hippocampus and Not Amygdala

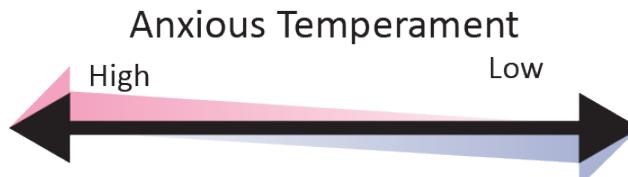


Voxelwise Analysis Within Regions Predictive of AT



Oler JA, et al. *Nature*. 2010;466(7308):864-868. PMID: 20703306.

**a) Disrupted gene expression pathways in AT lead to disrupted neuroplastic processes**

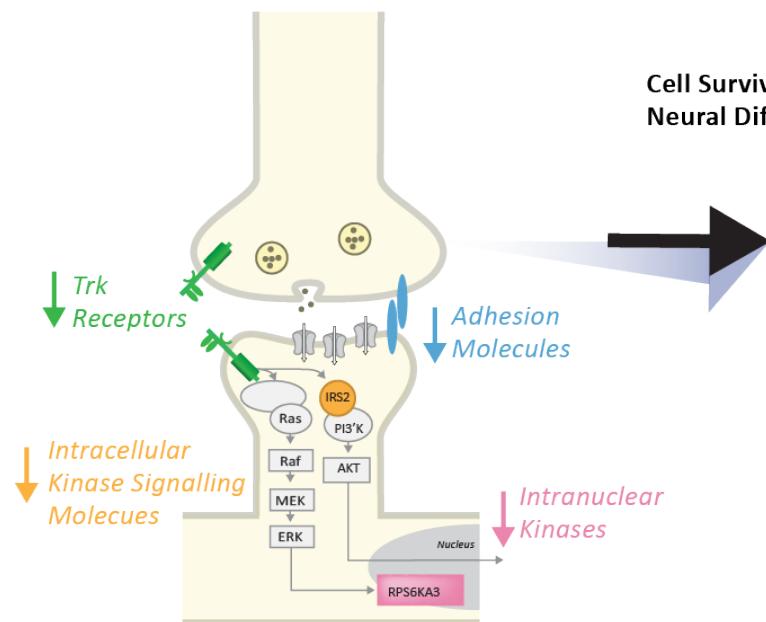


**Decreased Neuroplasticity in AT-regions**

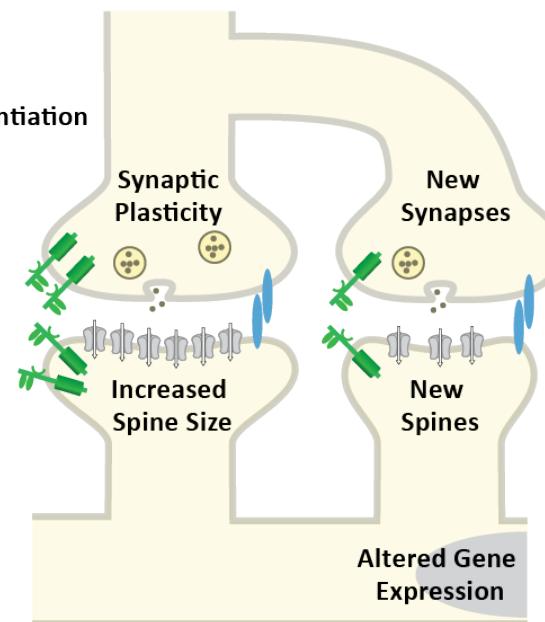
**Increased Neuroplasticity in AT-regions**



**b) Mechanisms of decreased neuroplasticity**



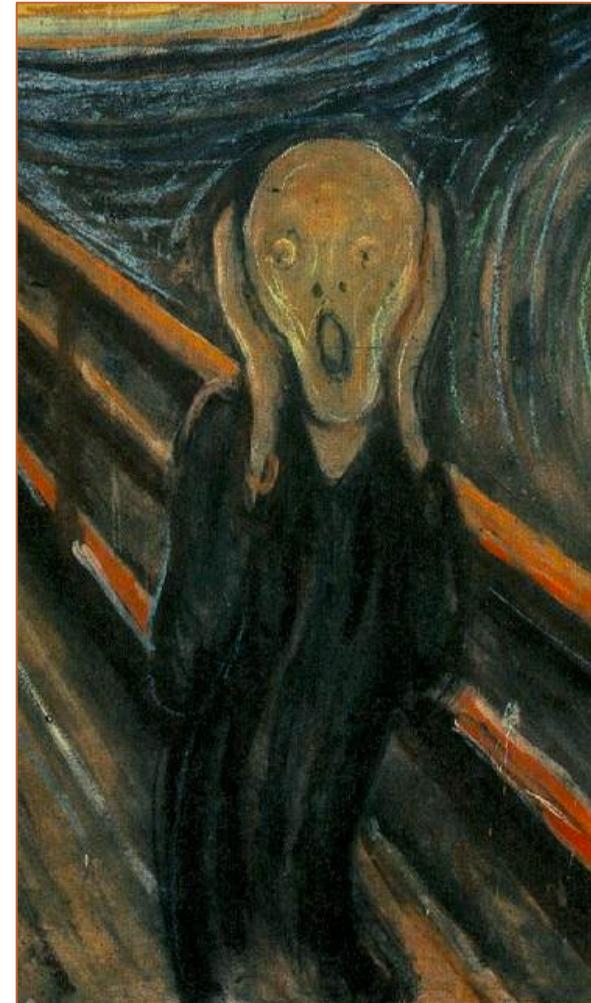
**c) Function of increased neuroplasticity**



# Anxiety Disorders



- Among the most common psychiatric disorders
- Highly comorbid with other psychiatric disorders and medical conditions
- Can become chronic and disabling
- Frequently start in early childhood



# Childhood Anxiety Disorders Imaging Study



- Preadolescent children age 8-12
- Anxiety disorder
  - At least one of the following: generalized anxiety, social phobia, separation anxiety, anxiety NOS
  - Comorbid: another anxiety disorder, major depression, ADHD, oppositional-defiant disorder
  - Unmedicated
- Healthy control

Kalin N, et al. Unpublished data.

# Demographics and Clinical Characteristics

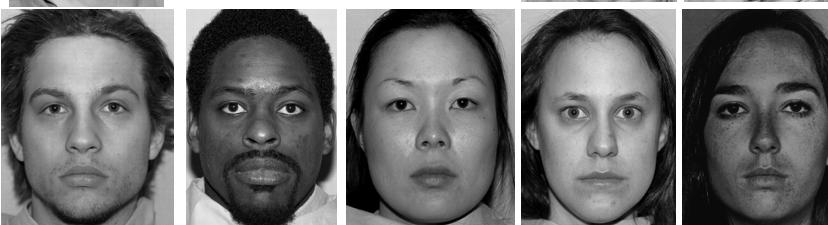
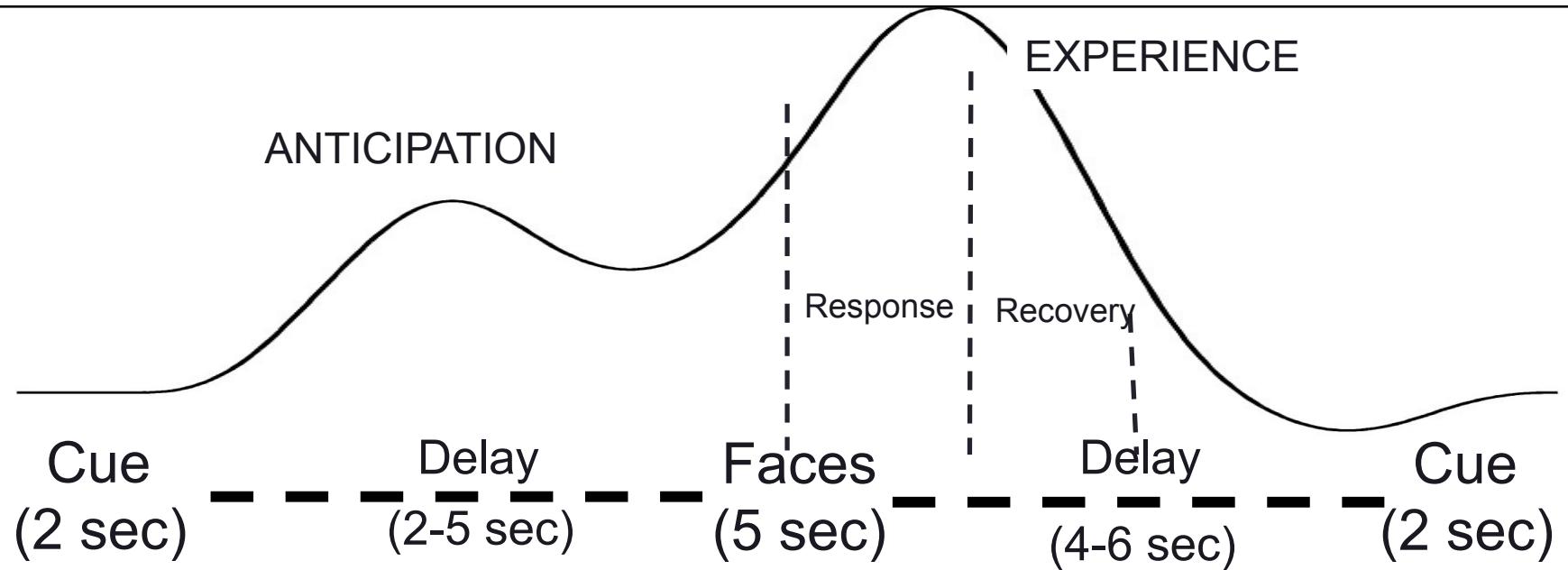


	Anxiety (n = 20)	Control (n = 20)
Age, mean (SD)	9.79 (1.27)	9.85 (1.09)
Sex, M/F	10/10	12/8
Parent SCARED Total, mean (SD)*	24.42 (14.17)	4.74 (4.85)
Child Depression Inventory (CDI)*, t score, mean (SD)	49.37 (12.28)	40.58 (5.19)

Kalin N, et al. Unpublished data.



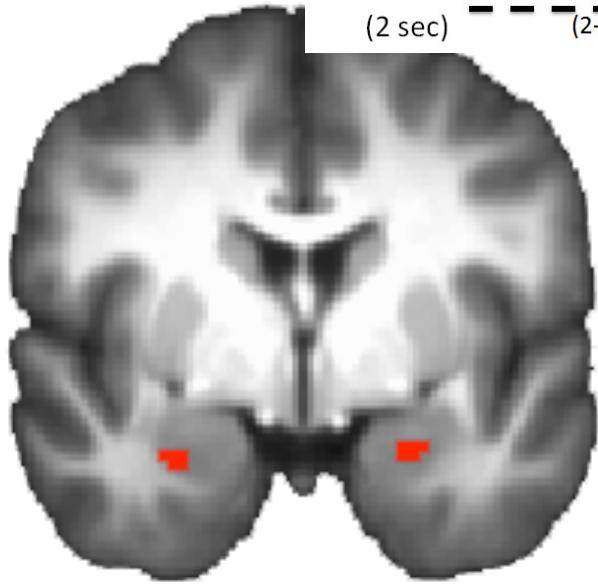
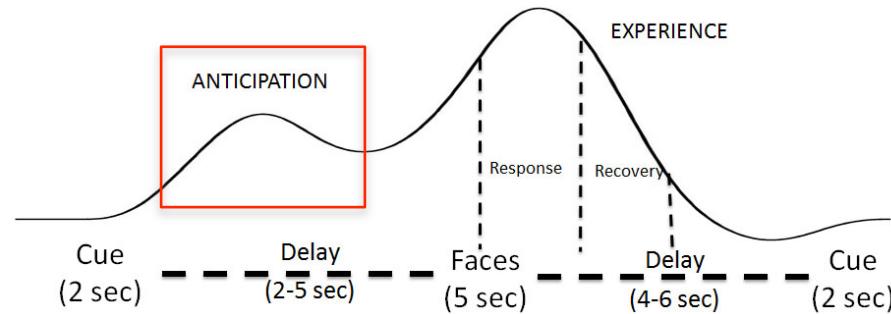
# **Brain Activation in Preadolescents: Altered Response to Uncertainty and Failure of Amygdala to Recovery in Anxiety Patients**



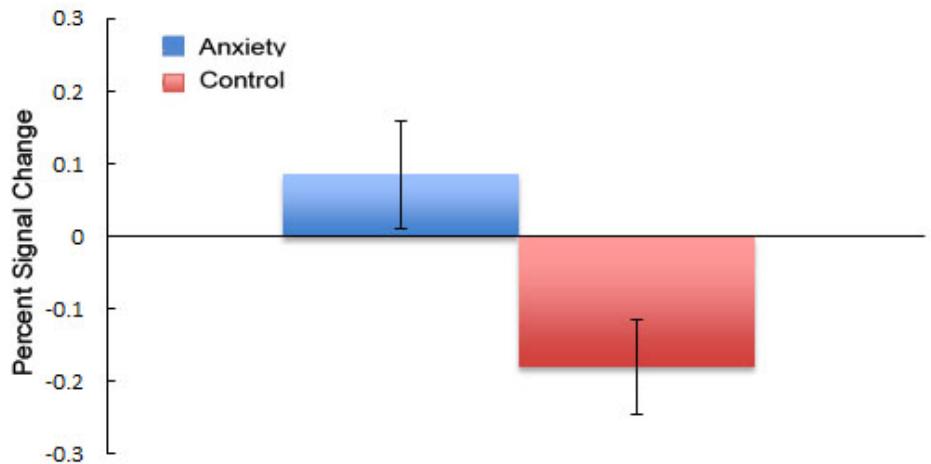
Neutral or Fear (equally likely)



# Uncertainty Also Increases Ventral Amygdala Activity in Anxious Children

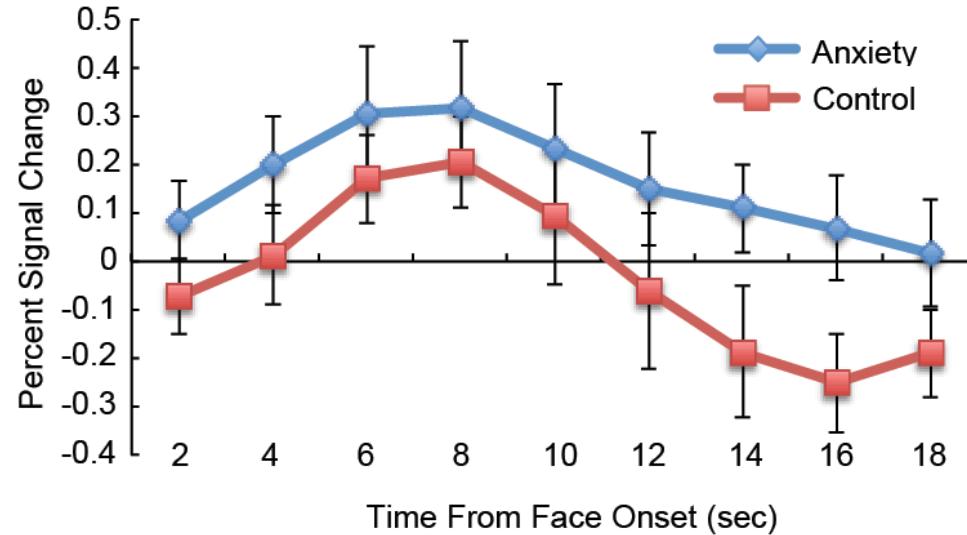
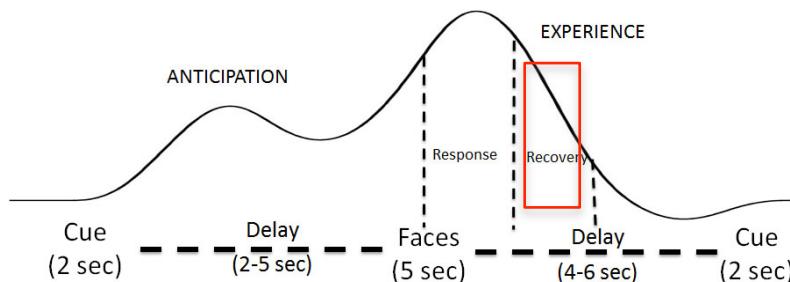


Ambiguous Cue - Negative Cue



Ambiguous Cue minus Negative Cue  
Anxiety minus Control N = 20/group  
 $p < .05$  cluster corrected for amygdala volume  
Kalin N, et al. Unpublished data.

# Sustained Amygdala Response – Failure To Recover – In Anxious Children



Recovery controlling for reactivity, AUC  
Fear Faces Anxiety minus Control  
N = 20/group  
 $p < .05$  corrected for amygdala volume  
Kalin N, et al. Unpublished data.

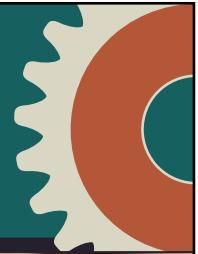
# DSM-5 Anxiety Disorders



- Separation anxiety disorder
- Selective mutism
- Specific Phobia-specify stimulus type
- Social Anxiety-specify performance only
- Panic disorder
- Agoraphobia (irrespective of panic disorder)
- Generalized anxiety disorder
- Substance/Medication-Induced
- Anxiety disorder due to another medical condition

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. 5th ed. 2013.

# Treatment of Childhood and Adolescent Anxiety Disorders



# CBT, Sertraline, or Combination in Childhood Anxiety



- RCT, N = 488, ages 7-17
- Primary diagnosis: SAD, GAD, social phobia
- 14 sessions of CBT or sertraline (up to 200mg/d), combination or PBO over 12 wks
- Improvement measured with CGI
- PBO = 23%, Sert = 54.9%, CBT = 59.7%, combo = 80.7% ( $p < .001$ )
- Both CBT and sertraline reduced severity of anxiety in children with anxiety disorders, the combination was superior to either alone

Wakup JT, et al. *N Engl J Med.* 2008;259(26):2753-2766. PMID: PMC270284.

# Sertraline Treatment of Children and Adolescents with PTSD



- Aim was to evaluate efficacy and safety of sertraline in children and adolescents who meet DSM-IV criteria for PTSD
- 10 week, double-blind, PBO-controlled trial
- N = 131, ages 6-17, sertraline dose (50-200mg/d)
- Efficacy measured using UCLA PTSD-I scores
- Sertraline was found to be safe but did not demonstrate efficacy when compared to PBO over 10- week trial

Robb AS, et al. *J Child Adolesc Psychopharm*. 2010;20(6):463-471.

# Clinical Response and Risk for Reported Suicide Ideation and Suicide Attempts in Pediatric Antidepressant Treatment



- Aim was to assess the risk of reported suicidal ideation/suicide attempt in children and adolescents with OCD, MDD and non-OCD anxiety disorders
- Meta-analysis of 24 PBO-controlled trials including 4400 children and adolescents
- Relative to PBO antidepressants are effective in MDD, OCD and non-OCD disorders
- Benefits appear to be much greater than risk for suicidal ideation/attempt across indications although it varies as a function of indication, age, chronicity and study conditions.

Bridge JA, et al. JAMA. 2007;297(15):1683.

# Generalized Anxiety Disorder



- Life time prevalence 5-6%
- Most prevalent anxiety disorder in primary care
- Lifetime comorbidity of 90%; especially depression
- SSRIs and SNRIs are effective
- Benzodiazepines are effective – 70% response
- Buspirone (azapirone) – partial agonism of 5-HT1a receptors
- Other approaches – mirtazapine, bupropion, hydroxyzine, pregabalin, quetiapine
- CBT may have sustained benefits

Baldwin DS, et al. *Curr Top Behav Neurosci*. 2010;2:453-67. PMID: 21309121.

David D and Davidson, JR 2013 in Essentials of Clinical Psychopharmacology, Ed. Schatzberg and Nemeroff.

# Panic Disorder Pharmacological Treatment



- SSRIs – paroxetine, fluoxetine, and sertraline FDA approved
- SNRIs – venlafaxine FDA approved
- Sensitive to activating effects – start w low doses or also prescribe low dose benzodiazepine
- Benzodiazepines are highly effective – alprazolam and clonazepam (careful w use in elderly)
- Some anticonvulsants - gabapentin

David D and Davidson, JR 2013 in Essentials of Clinical Psychopharmacology, Ed. Schatzberg and Nemeroff.

# Social Anxiety Disorder (Social Phobia)



- Life time prevalence 12%
- Generalized and non generalized
- SSRIs first line, SNRIs
- Beta-blockers and benzodiazepines are acutely useful for non generalized
- Anticonvulsants – gabapentin (900-3600 mg/d) and pregabalin (600mg/d)
- CBT and group therapy

David D and Davidson, JR 2013 in Essentials of Clinical Psychopharmacology, Ed. Schatzberg and Nemeroff.

# Post Traumatic Stress Disorder



- Life time prevalence approx 7%
- High levels of comorbidity – depression and drug abuse
- SSRIs and SNRIs
- Benzodiazepines decrease hyperarousal but do not likely help core symptoms
- Anticonvulsants?
- Atypicals as augmentors; quetiapine for monotherapy
- Alpha-1 antagonists – prazosin (up to 15mg/d) decrease nightmares, improve sleep and global improvement
- CBT – exposure as a key feature

Ursano RJ, et al. *Am J Psychiatry*. 2004;161(11 Suppl):3-31. PMID: 15617511

David D and Davidson, JR 2013 in *Essentials of Clinical Psychopharmacology*, Ed. Schatzberg and Nemeroff.

# Acute Stress Disorder



- PTSD prevention strategies
  - Beta blockade - as a Initial Pitman study (2002) positive; more recent study (Stein 2007) not positive
  - Benzodiazepines reduce acute distress but not preventive
  - Hydrocortisone in medically ill patients may be helpful

Ursano RJ, et al. *Am J Psychiatry*. 2004;161(11 Suppl):3-31. PMID: 15617511.

David D and Davidson, JR 2013 in *Essentials of Clinical Psychopharmacology*, Ed. Schatzberg and Nemeroff.

# Obsessive Compulsive Disorder Monotherapy



- SSRIs first line
- Fluvoxamine, fluoxetine, sertraline, and paroxetine FDA approved
- Clomipramine, fluvoxamine, fluoxetine, and sertraline are effective in children
- Frequently need higher doses and longer duration of treatment
- Generally treatment should be long term

American Psychiatric Association. 2013. <http://psychiatryonline.org/content.aspx>  
David D and Davidson, JR 2013 in Essentials of Clinical Psychopharmacology, Ed.  
Schatzberg and Nemeroff.

# Obsessive Compulsive Disorder Augmentation Strategies



- Comorbidity is common; treat the comorbid condition
- Up to 60% have at least partial response to SSRIs; relapse is common
- Methods to increase plasma levels of SSRI (IV CMI)
- Atypical antipsychotics, clonazepam
- CBT: Exposure with response prevention  
→ (Edna Foa, U Penn)

American Psychiatric Association. 2013. <http://psychiatryonline.org/content.aspx>  
David D and Davidson, JR 2013 in Essentials of Clinical Psychopharmacology, Ed. Schatzberg and Nemeroff.

# General Recommendations: Psychosocial Interventions



- Efficacy of psychotherapy and pharmacology are generally similar
- Evidence based approaches by appropriately trained therapist
- Prolonged treatment usually required
- Self-help – books and internet for milder sx
- Doesn't have to be *either or* – combination of both psychotherapy and pharmacotherapy are frequently the most effective

Adapted from, Baldwin DS, et al. *J Psychopharmacol*. 2014 May;28(5):403-439.  
PMID: 24713617

# Clinical Connections



- Anxiety disorders is one of the most common psychiatric disorders
  - Highly comorbid with other psychiatric disorders and medical conditions
  - Frequently start in early childhood
- Studies in children demonstrate that anxious temperament is an important risk factor for the later development of anxiety disorders, depression and comorbid substance abuse.



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## Questions & Answers