

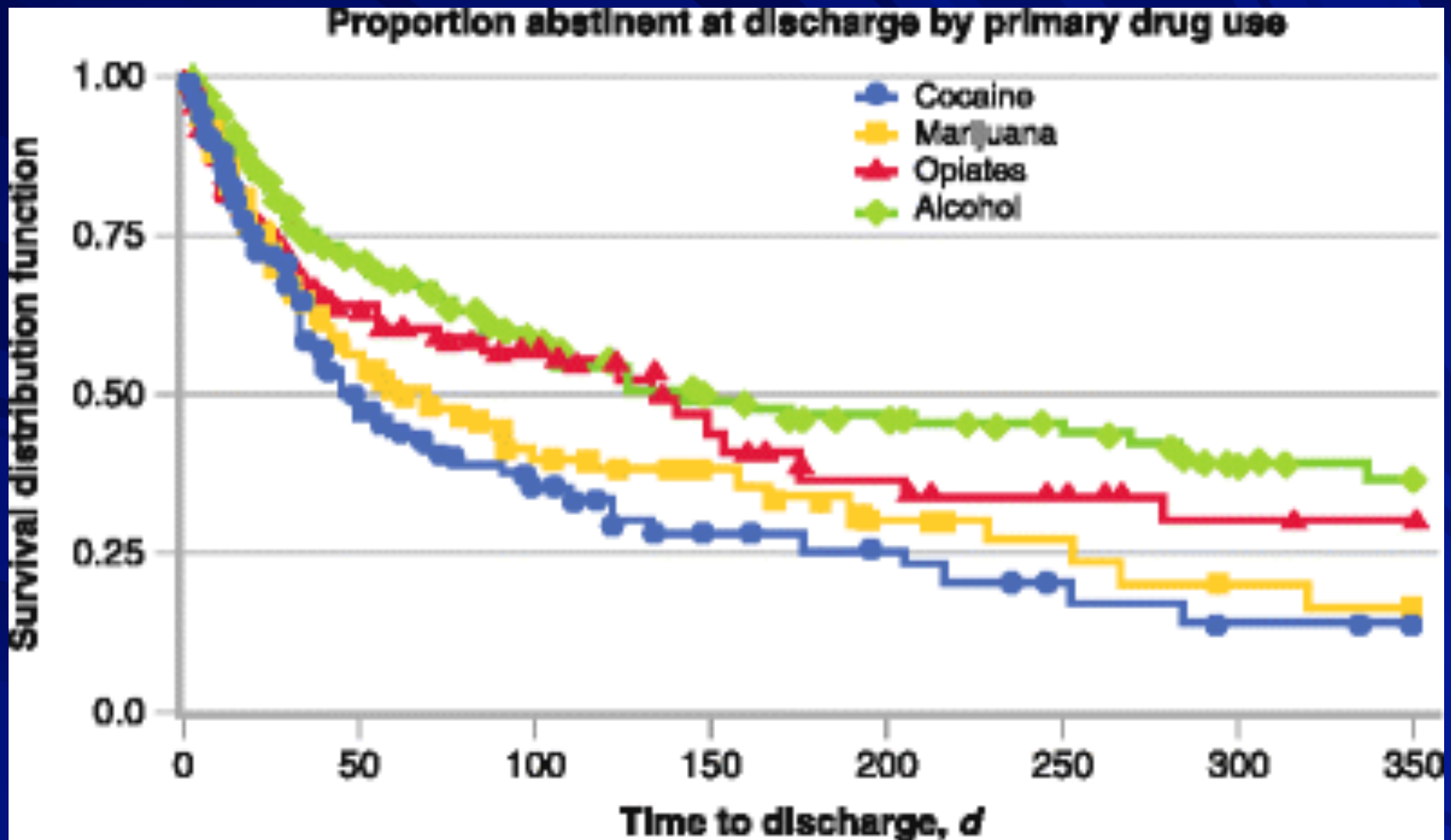


# Alcohol, Stress and the Brain: Effects on Alcohol Relapse and Recovery

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Data from 878 outpatients classified on the basis of primary drug of abuse (cocaine, marijuana, opioid, alcohol). Survival distribution function is shown on the y axis, which represents the proportion of patients surviving relapse and remaining abstinent during the assessment period of 350 days shown on the x axis

# How Can We Understand Alcohol Relapse and Recovery?

## MAJOR CHALLENGE:

- Relapse is a highly common phenomena!
- Multiple relapse precipitants: stressors, negative moods, boredom, drug related stimuli (people, places and things) and temptations.
- What leads to a specific lapse or relapses across episodes of recovery may be different in the same individual and of course be different across individuals.

# Why Focus on Understanding Alcohol Relapse and Recovery?

## POTENTIAL BENEFITS:

- **Identify biomarkers of alcohol relapse:**  
Develop and validate measures that drive alcohol relapse and jeopardize recovery.
- **Personalized Medicine:**
  - Use those biomarkers to identify those most at risk for relapse and treatment failure
  - Develop specific treatments to reverse those effects and help those most susceptible to high alcohol relapse risk and to jeopardizing recovery.

# Chronic Alcohol-related Changes Associated with Early Recovery

## Behavioral/Mood Changes

- Alcohol Craving – reactivity to alcohol related stimuli
- Increased stress, anxiety, and irritability
- Sleep problems
- Cognitive Problems

## Brain Atrophy:

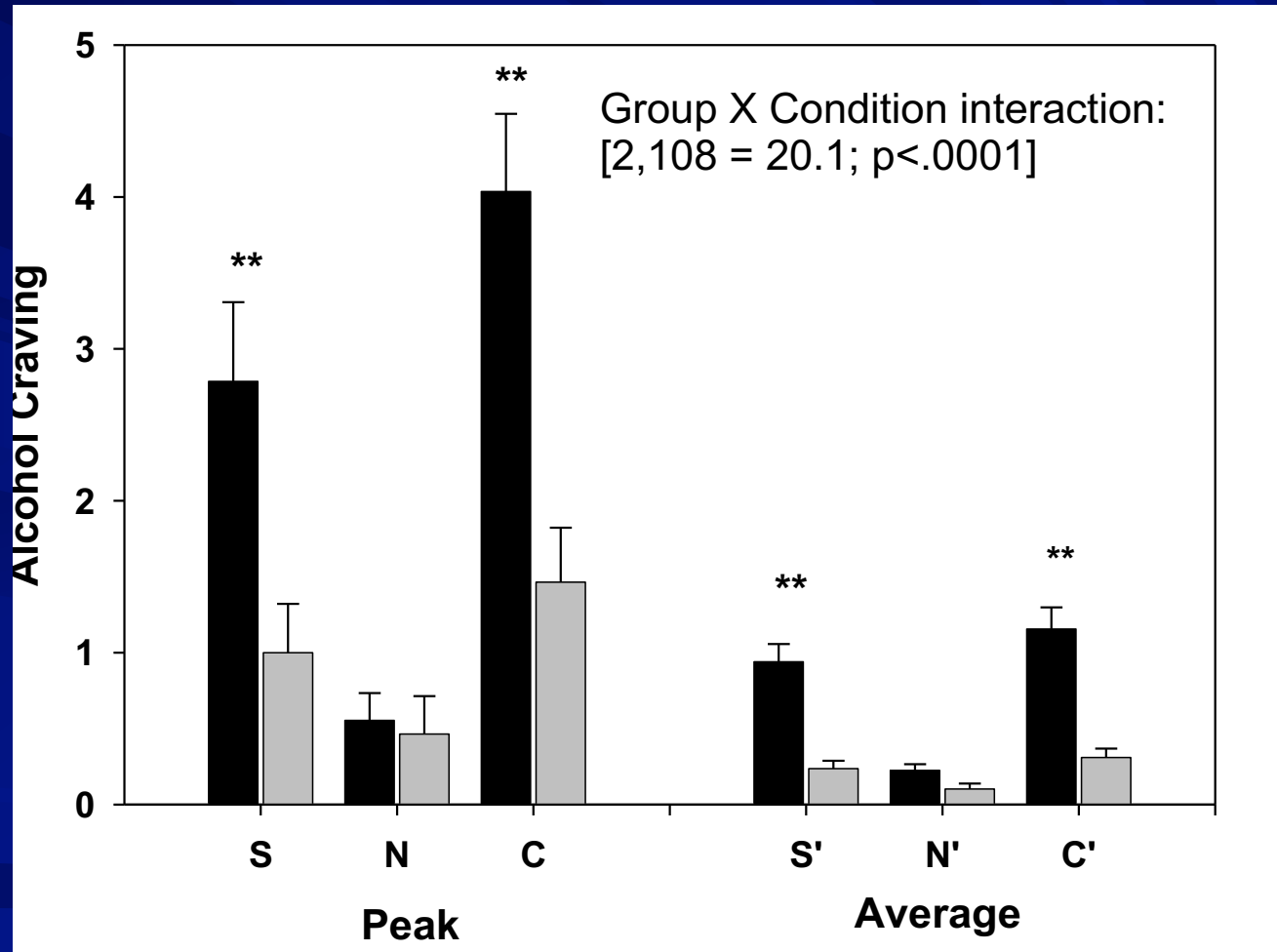
- Change in gray and white volume, brain proteins

## Altered Stress Neurobiology

- Alterations in CRF-HPA axis function
- High sympathetic arousal and lower parasympathetic tone
- Noradrenergic dysregulation
- Decreased activity of D2 receptors
- Decreased responsiveness of the frontal cortex; lower GABA

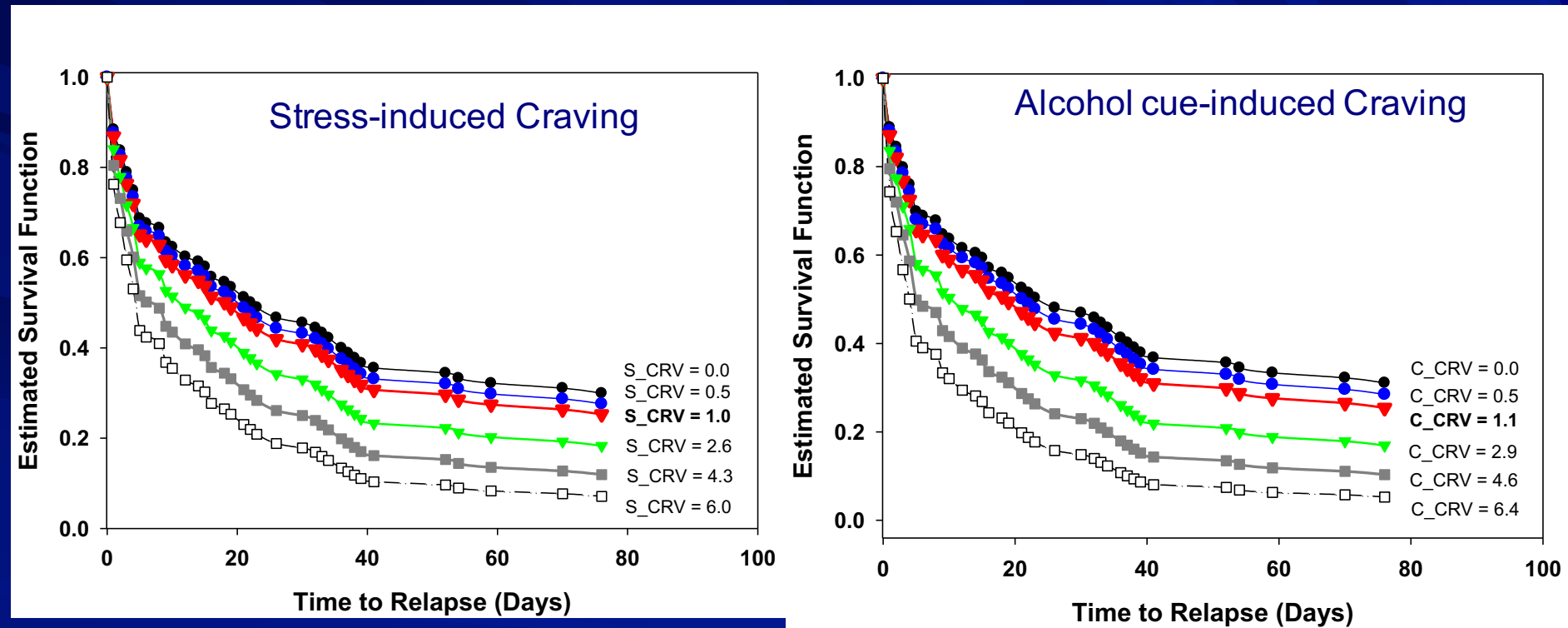


# Enhanced Alcohol Craving in 4-week Abstinent Alcoholics



*Black bars: AD patients; Grey bars: SD Controls*

# Higher Stress-Induced and Cue-Induced Alcohol Craving is Predictive of Time to Alcohol Relapse During Follow-up

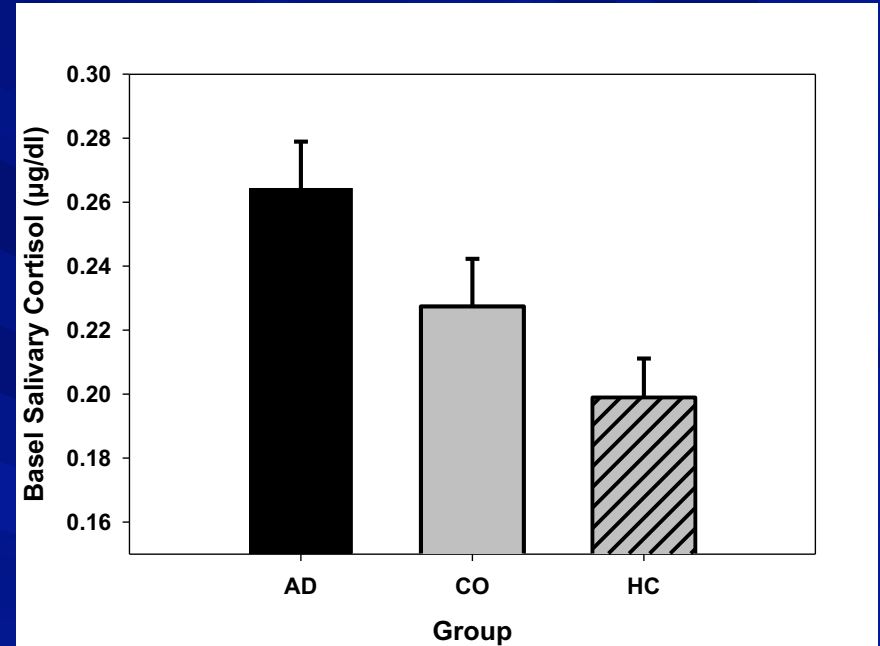
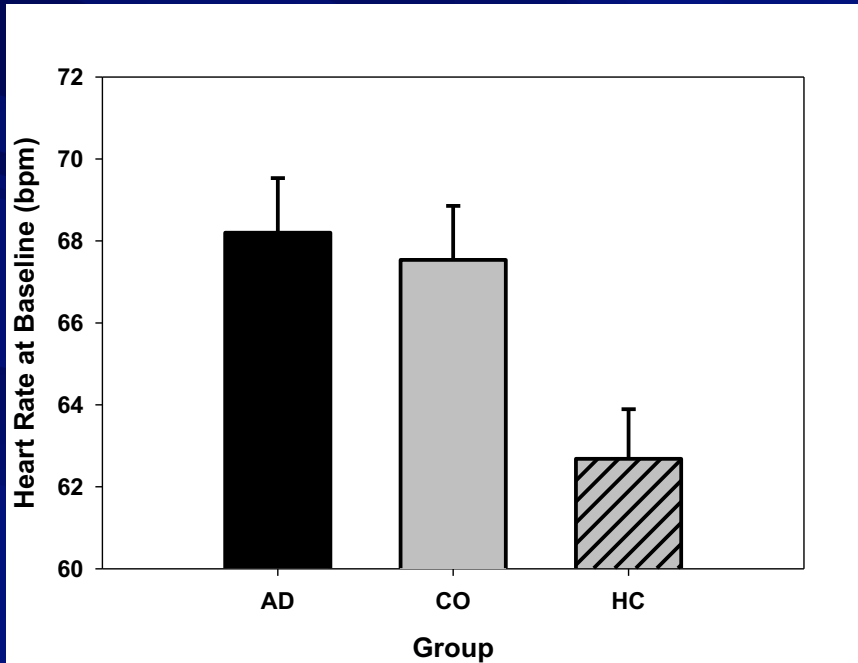


Cox Proportional Hazards Regression: Stress-induced alcohol craving ( $X^2=4.86$   $p<.03$ ; HR: 1.16) and alcohol cue-induced craving ( $X^2=5.75$ ,  $p<.02$ ; HR: 1.18) were each predictive of time to alcohol relapse.

Sinha et al., *Archives of General Psychiatry*, 2011



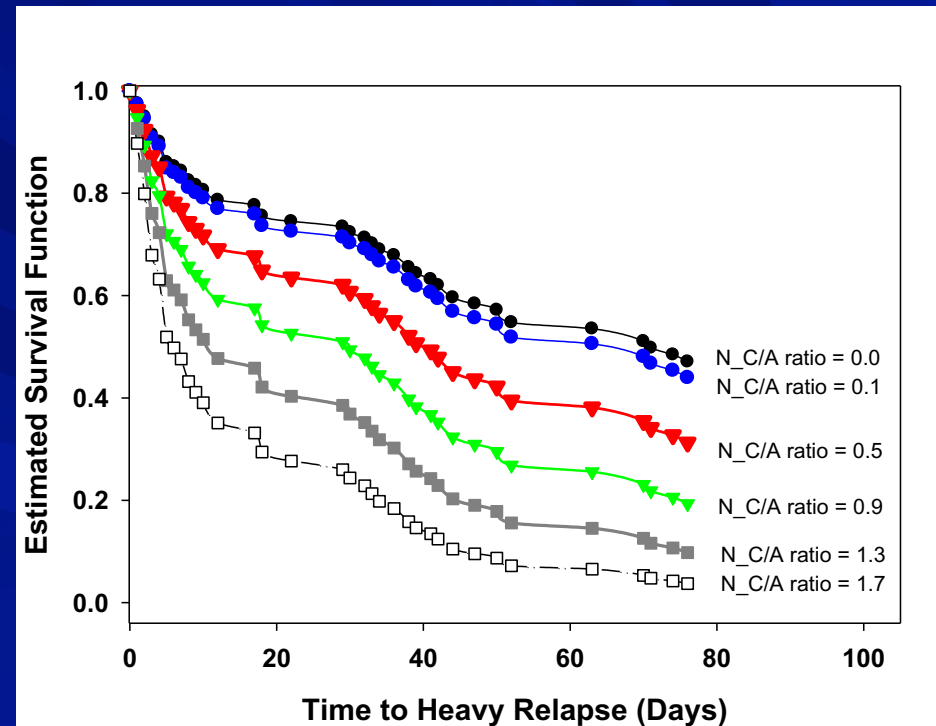
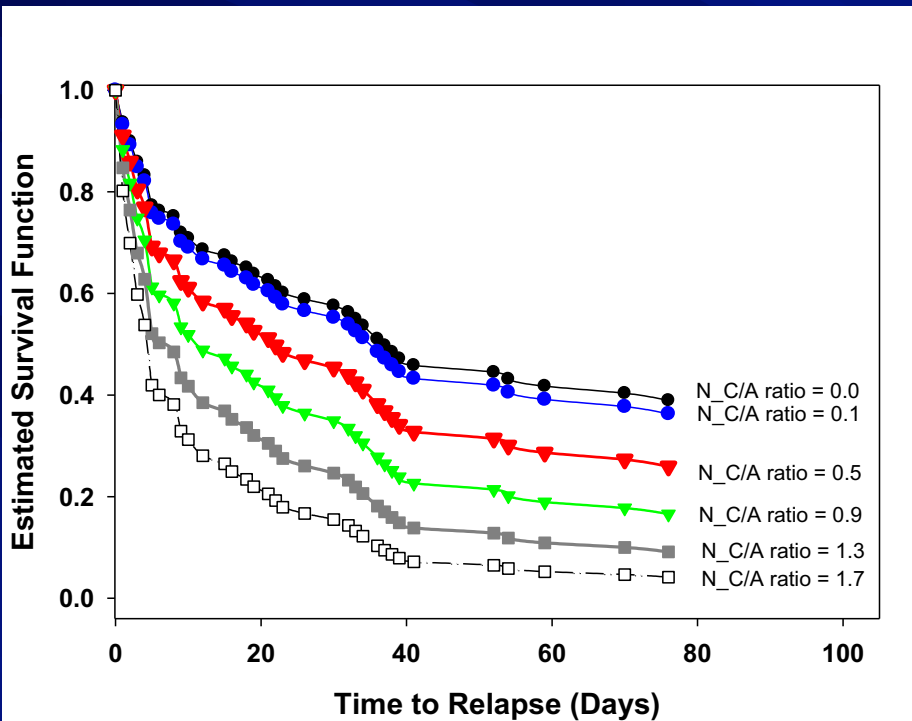
# Altered Stress Physiology: Abstinent Patients vs. Controls



*Heart rate: AD=Coc>HC ( $p<.01$ ); Cortisol: AD>HC ( $p<.03$ )*

*data combined across studies (Fox et al., 2007; Sinha et al., 2009; summarized in Sinha, Addiction Biology, 2009)*

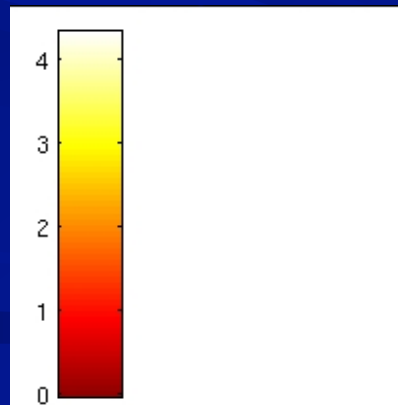
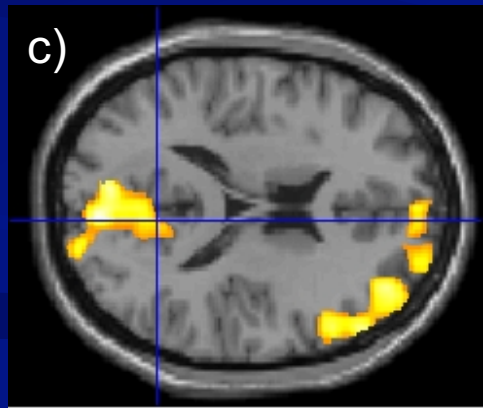
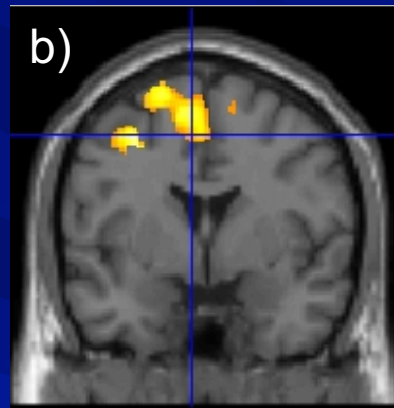
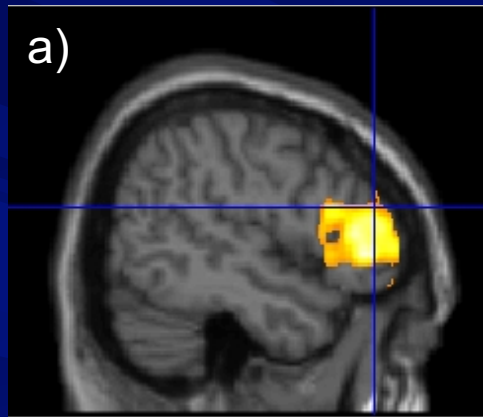
# Higher Neutral State the Cort/ACTH AUC Ratio (adrenal sensitivity), Greater the Likelihood of Relapse



Cox Proportional Hazards Regression: Cort/ACTH ratio during neutral ( $X^2=7.24$ ,  $p<.007$ ; HR: 2.16) and stress exposure ( $X^2=5.37$ ,  $p<.02$ ; HR: 1.62) were predictive of time to alcohol relapse.

Sinha et al., Archives of General Psychiatry, 2011

# Smaller gray matter volume in abstinent alcoholics vs Controls ( $p < .01$ FWE corrected)



## Patient vs. Controls:

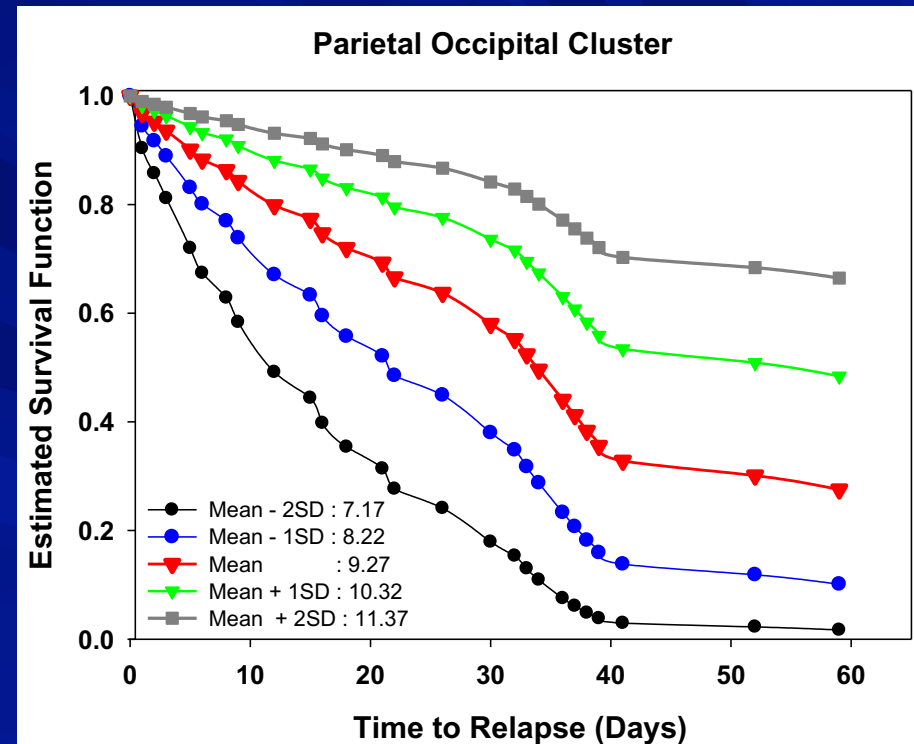
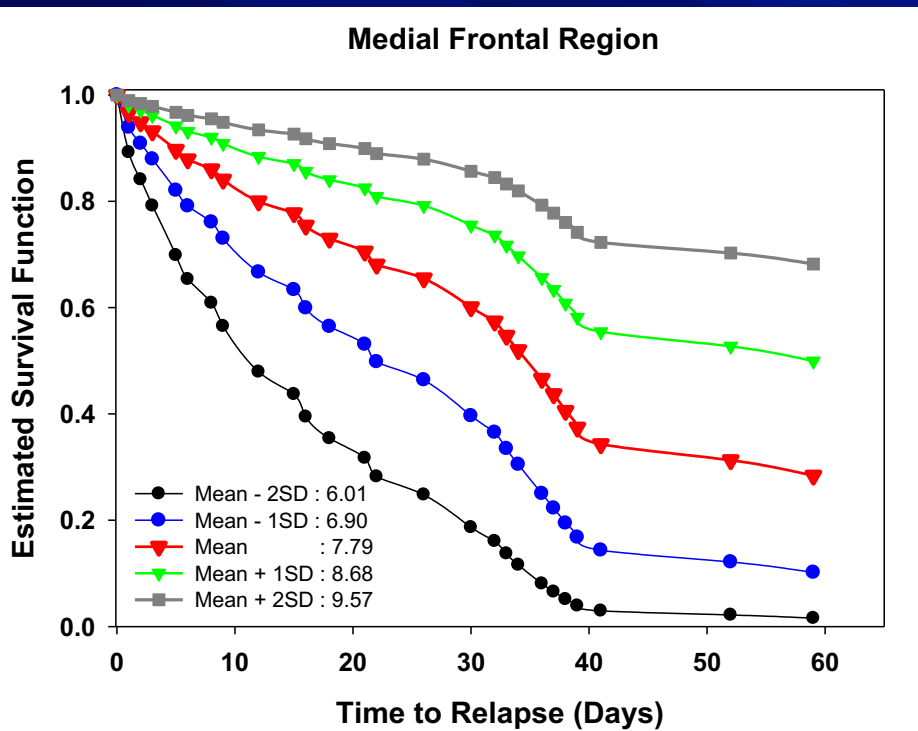
- a) Lateral frontal region
- b) Medial frontal regions  
(BA 24, SMA region 6)
- c) Parietal – occipital  
region

Whole brain voxel based morphometry (VBM),  
controlling for age, sex, total intracranial volume

*Rando et al., American J of  
Psychiatry, 2011*

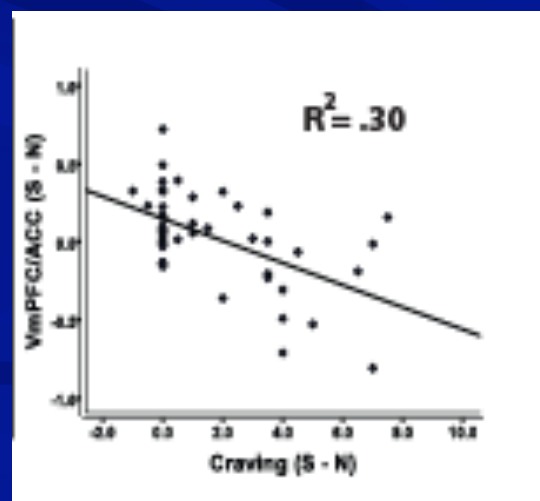
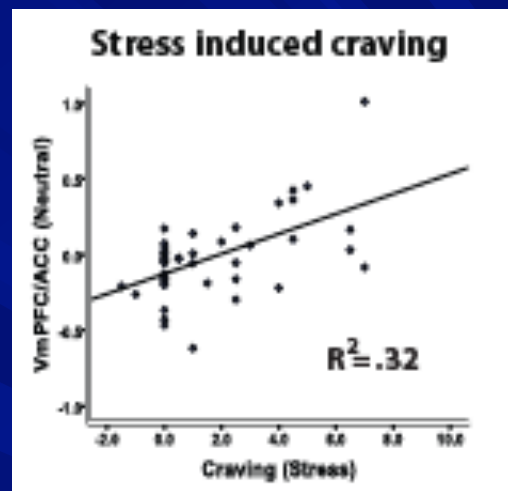
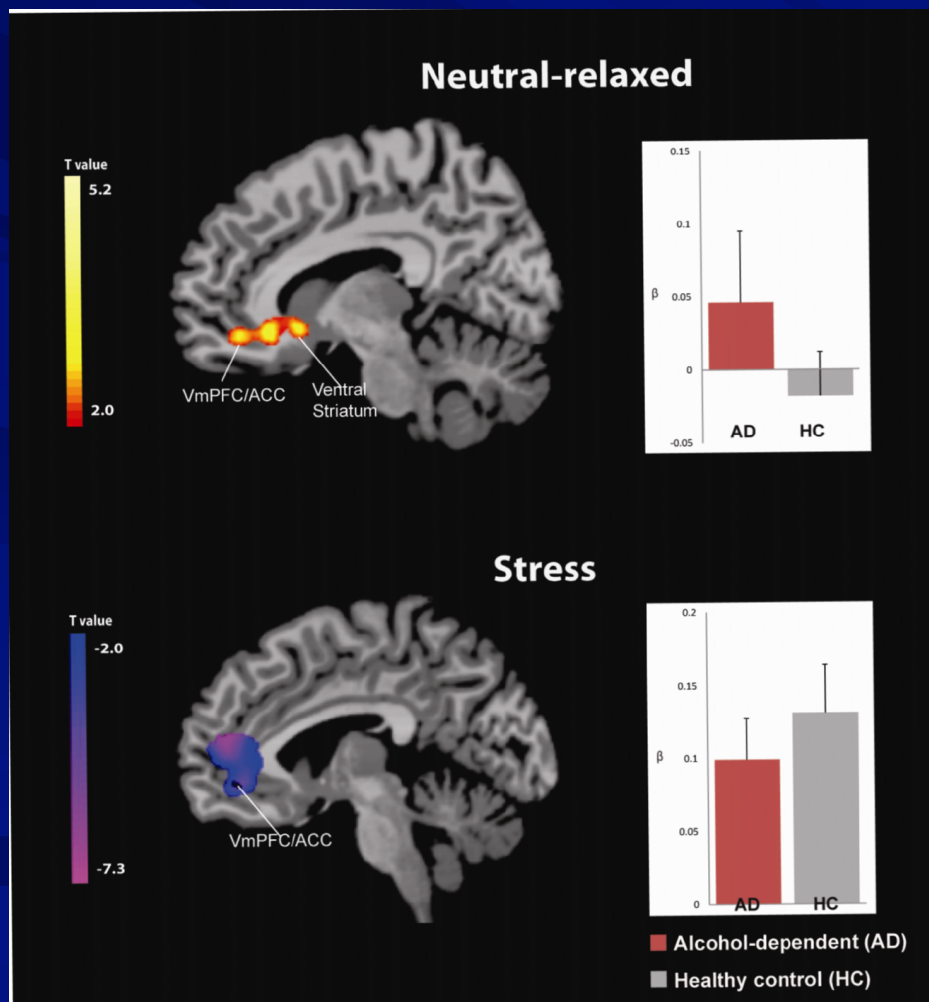
# Smaller GMV is Predictive of Future Alcohol Relapse in Abstinent Alcoholics

(Rando et al., Am J of Psychiatry, 2011)

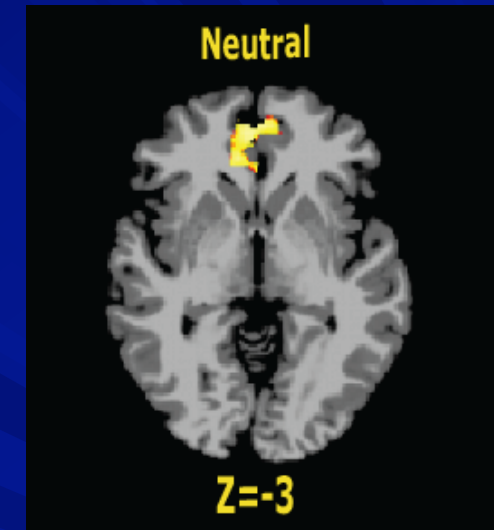
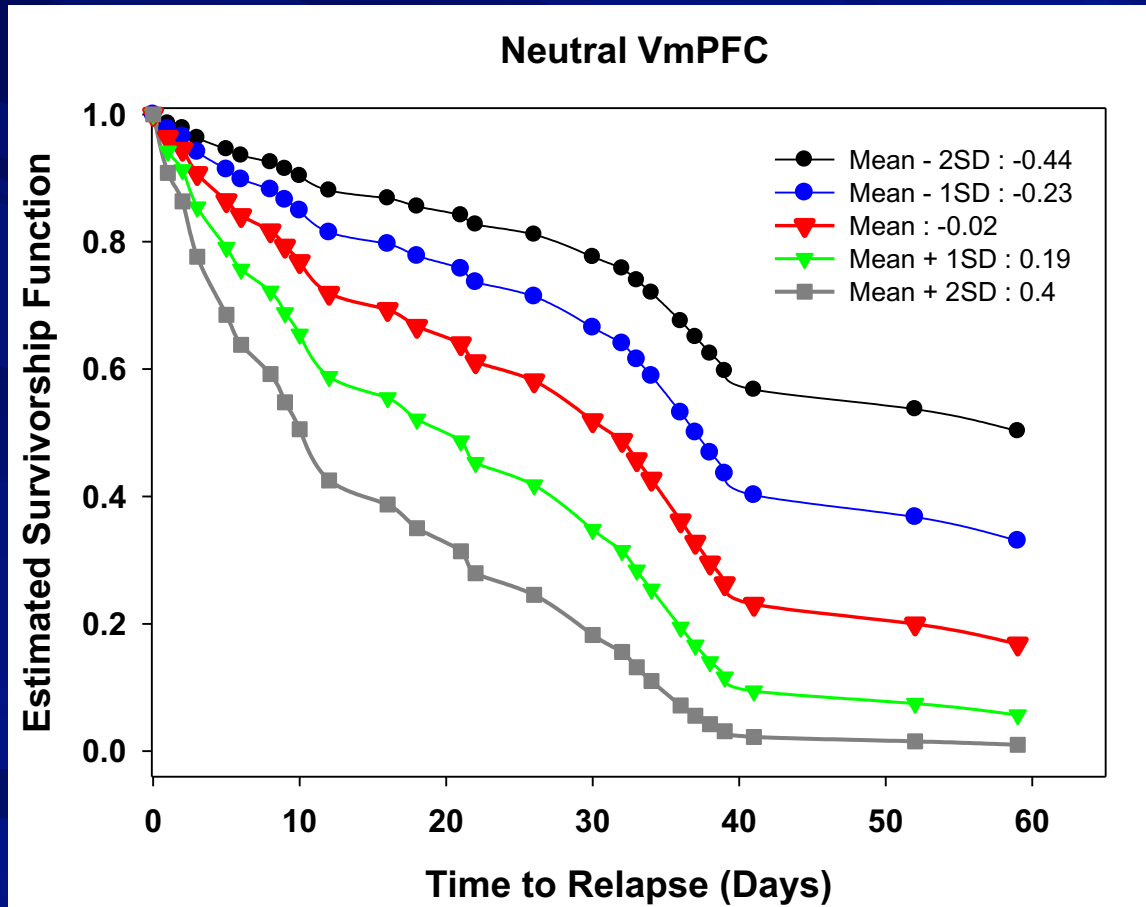


Estimated survival risk functions for specific gray matter volume values for mean (in red) and at +/-1 and +/-2 SD above and below the mean for, (a) the medial frontal cluster ( $X^2 = 6.97$ ,  $p < .008$ , HR = .51, CI = .31-.84) and, (b) the parietal-occipital cluster ( $X^2 = 6.90$ ,  $p < .009$ , HR = .57, CI = .38 -.87).

# Disrupted Neural Response to Stress and Relaxed Scenarios in Recovering Alcoholics (AD)s versus Controls (HC) ( $p < .01$ WBC)



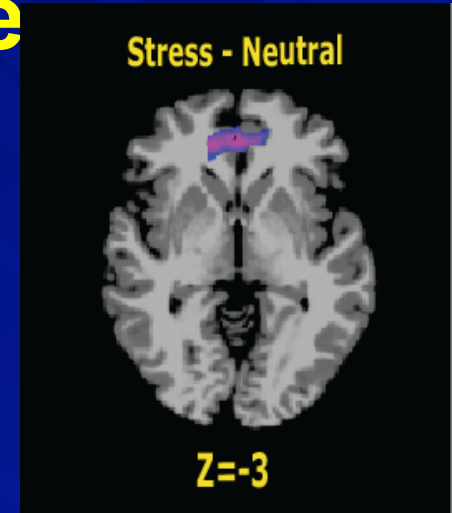
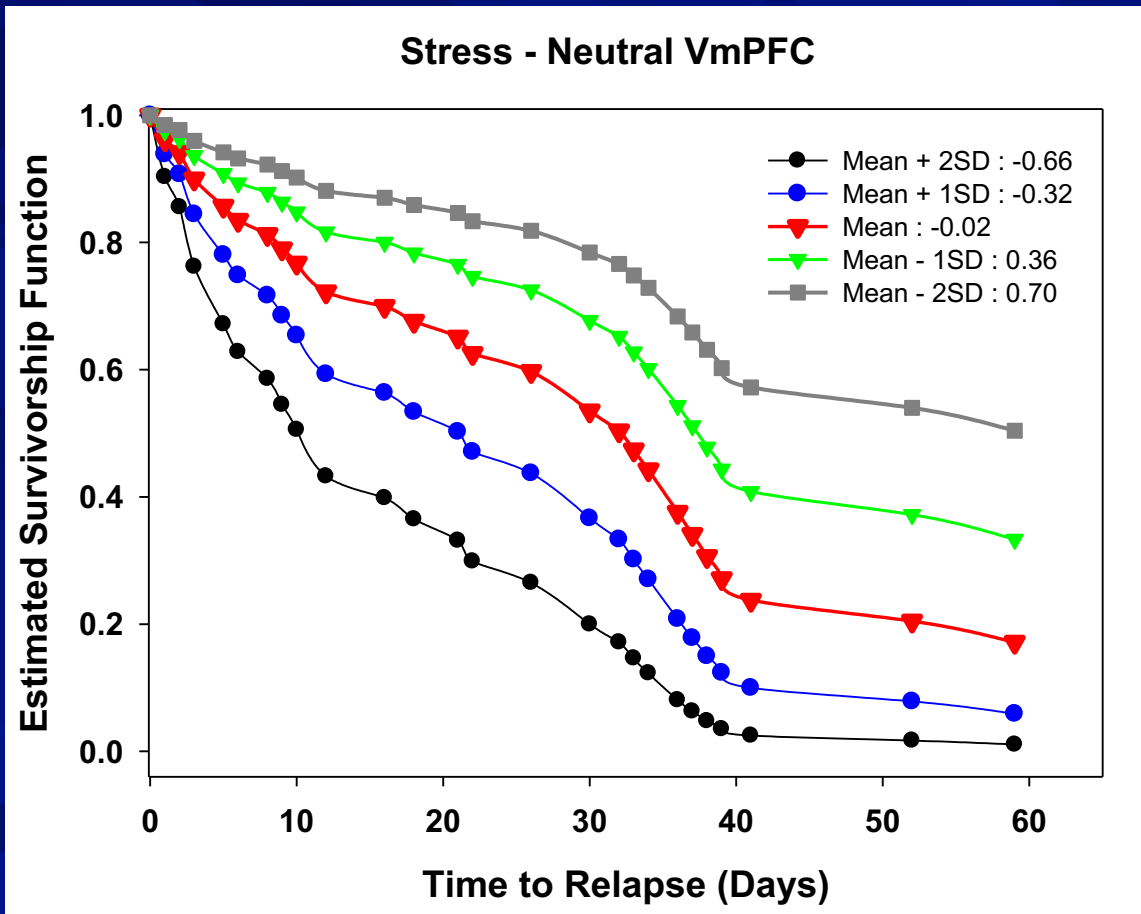
# Greater mPFC activity during neutral relaxed state predicts shorter time to future alcohol relapse



Greater relapse risk with less deactivation in the medial PFC, shown at specific percent signal change values

Cox Proportional Hazards Regression Model:  $X^2=8.4$ ,  $p<.002$ , HR:6.6; (6.6 times greater likelihood of relapse) (controlling for craving and years of alcohol use)

# Blunted stress-related medial pre-frontal activity predicts shorter time to alcohol relapse



Greater relapse risk with blunted stress-related activity in the medial PFC, shown at specific percent signal change values

Cox Proportional Hazards Regression Model:  $X^2=5.16$ ,  $p<.02$ , HR: 0.25 (75% increased likelihood of relapse)

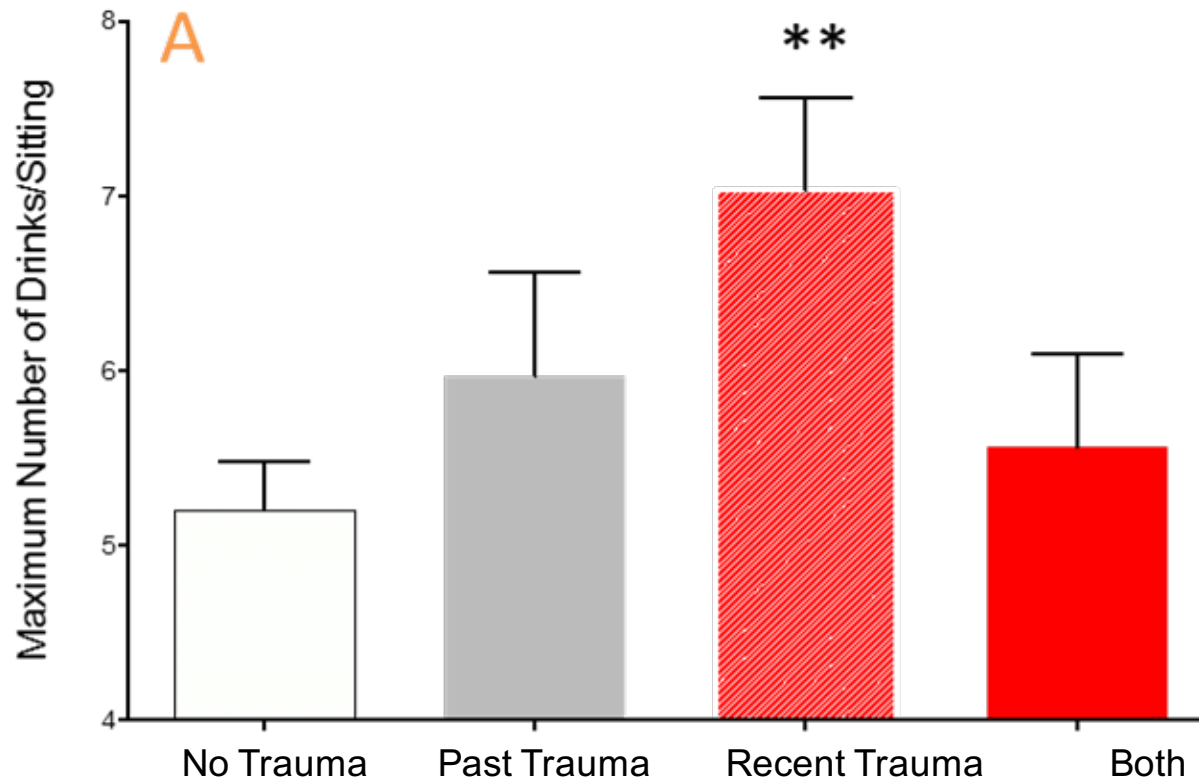
Seo et al., *JAMA Psychiatry* (2013)

# Jeopardizing Recovery: The Alcohol Relapse Risk Phenotype

- The Psychobiological and Neural Response Profile of Relapse Risk:
  - Increased anxiety and provoked alcohol craving
  - High cortisol/ACTH ratio and altered stress endocrine responses (NPY , BDNF and anandamide)
  - Hyperresponsive brain during neutral relaxed state associated with greater anxiety and alcohol craving and blunted PFC response with stress.
  - Smaller gray matter volume in medial frontal and posterior regions



# Effect of Past and Recent Trauma on Alcohol Intake



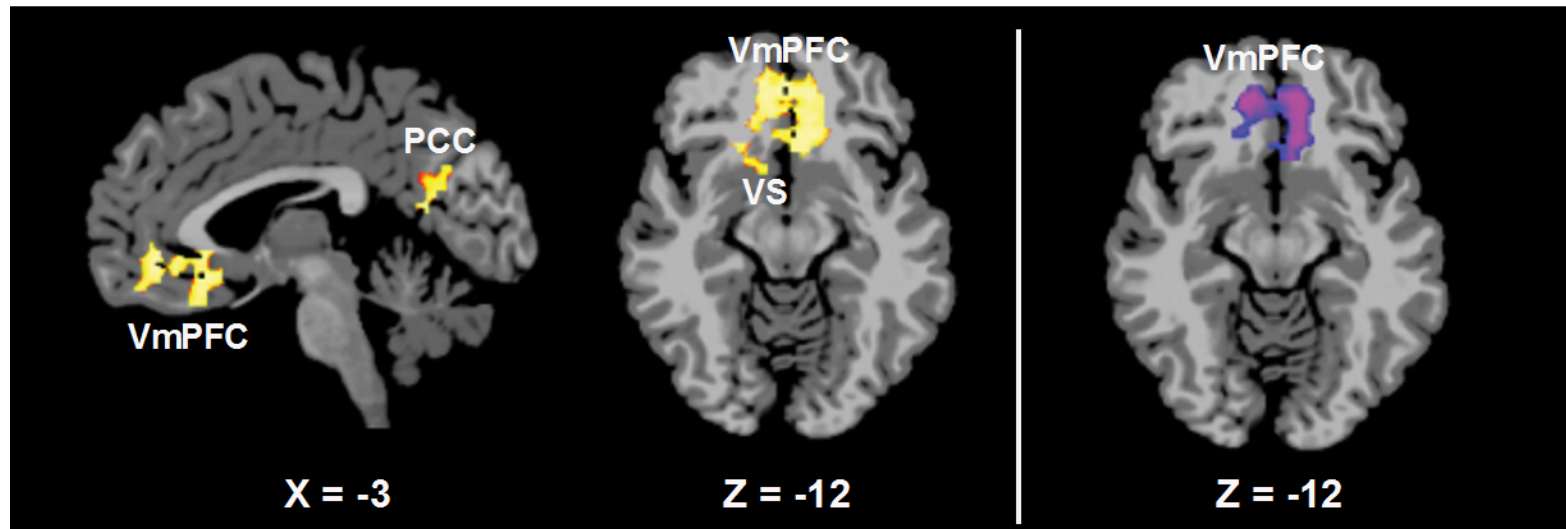
\*\*p<.01;

Large Adult Community Sample (N=847) - comprehensively assessed for Past and Recent Trauma and Alcohol Intake

# Effects of Recent Trauma on Brain Activation During Neutral and Stress

During Neutral/Relaxing State

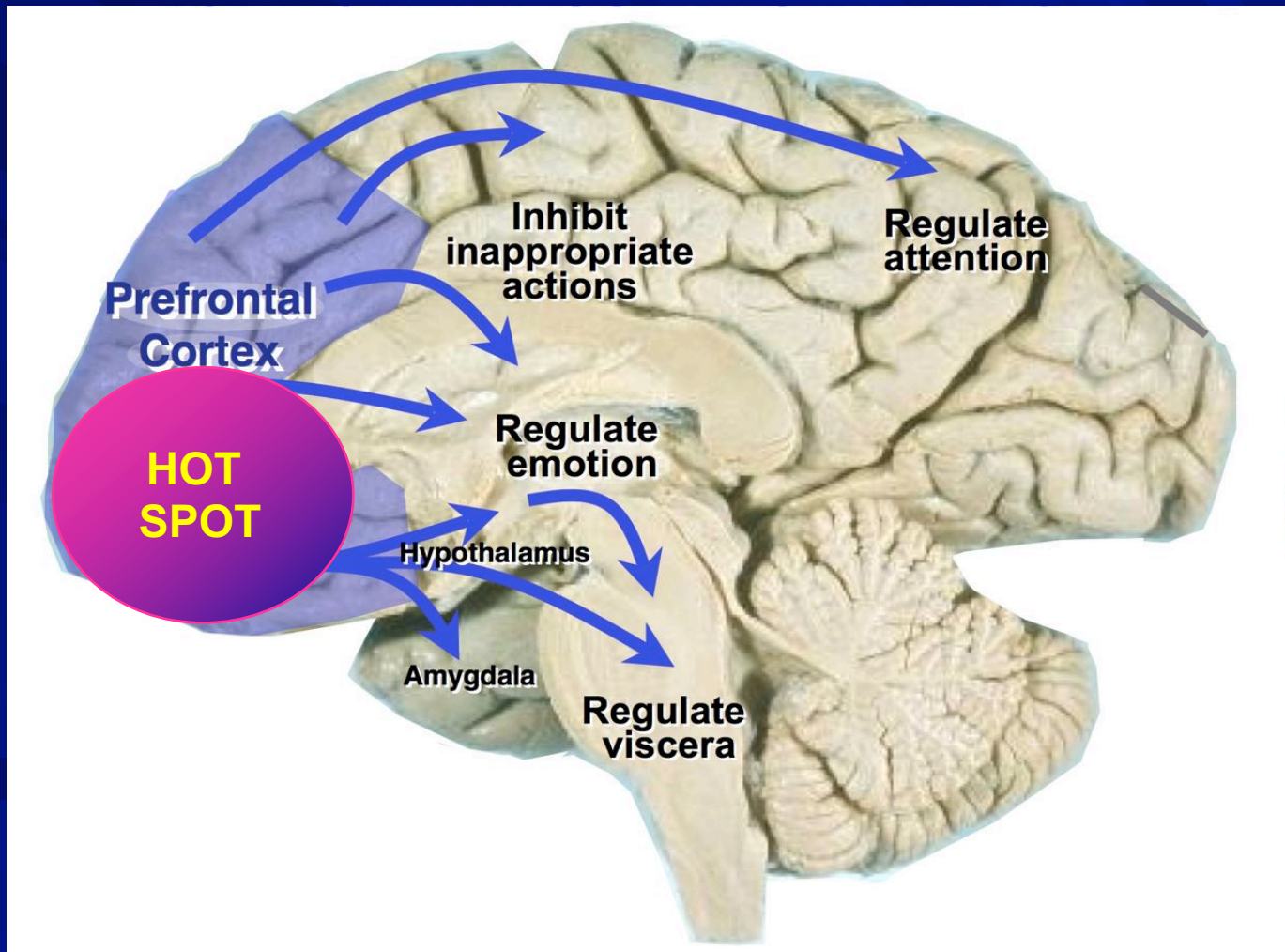
Stress - Neutral



Significant correlation between number of recent traumatic events and neutral relaxed condition increased activation in the ventromedial prefrontal cortex (VmPFC), anterior cingulate cortex (ACC), ventral striatum (VS), posterior cingulate cortex and precuneus regions, and decreased VmPFC/ACC response during stress was correlated with frequency of recent stress/trauma events (Whole brain corrected,  $p < 0.05$ ).

*Hermes, Sinha et al., ACNP 2015*

# Prefrontal Control of Stress, Craving and Behavior



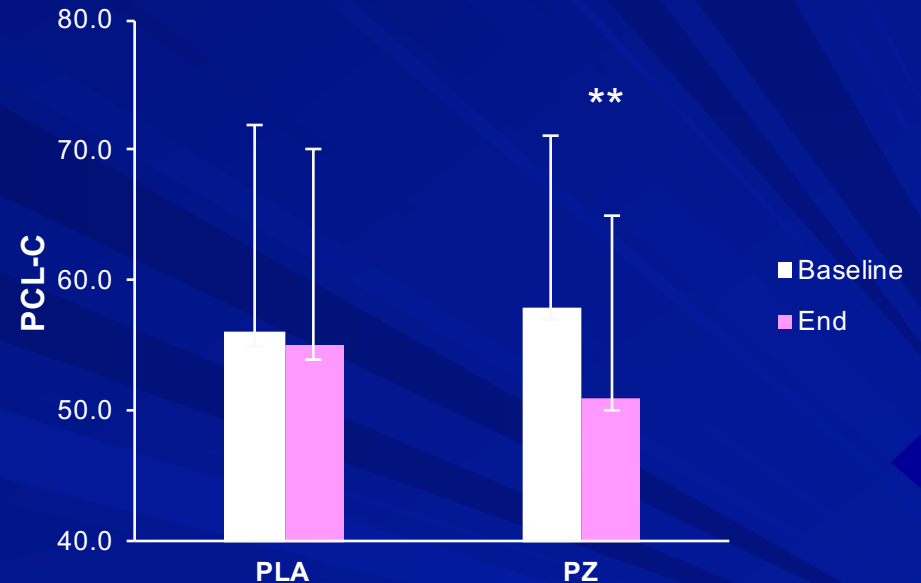
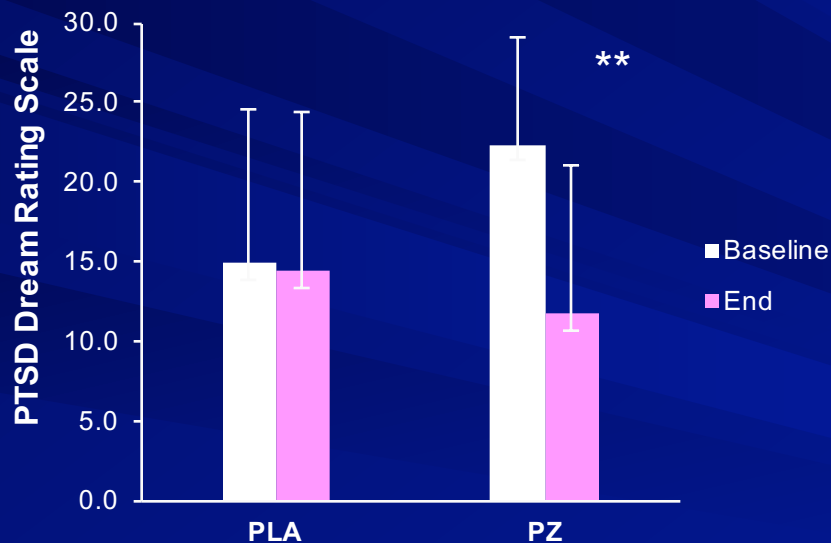
■ ***Can we reverse the effects of chronic alcohol and trauma to improve recovery outcomes?***

– **Medications**

– **Behavioral Strategies**

– **Adjunct wellness strategies**

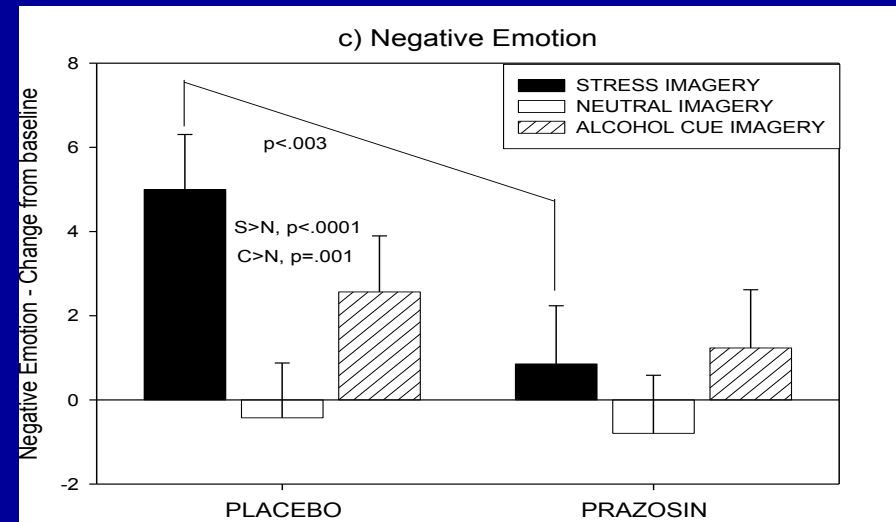
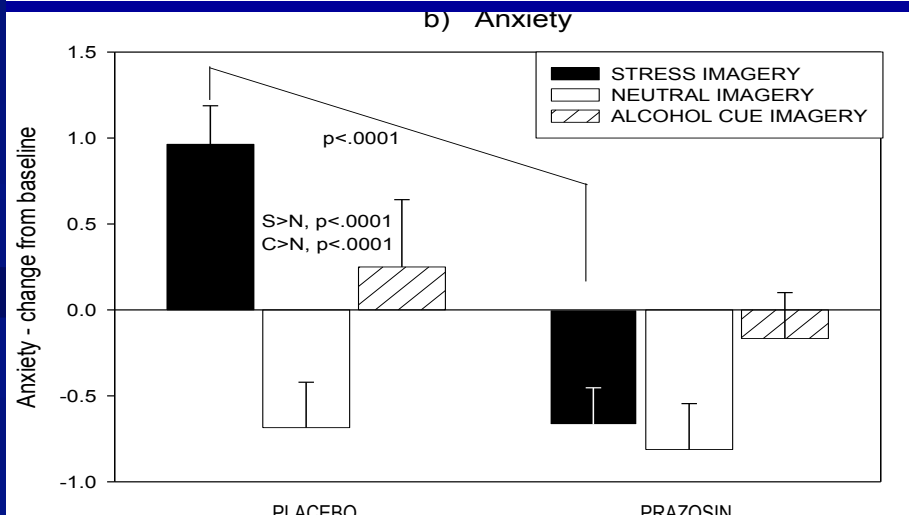
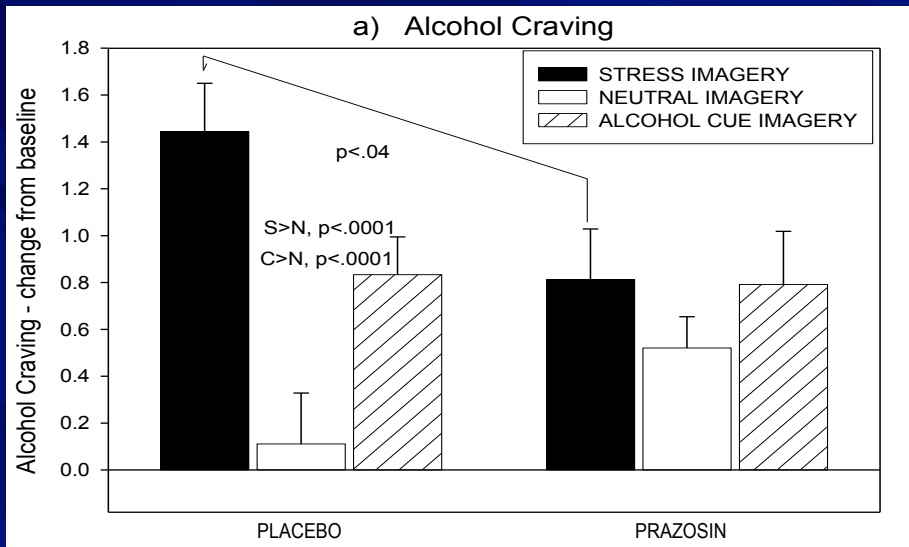
# Prazosin Improves Dream Ratings and Decreases PTSD Clinical Symptoms



\*\* p < .05; PLA: PLACEBO; PZ: PRAZOSIN

Taylor, Raskind et al., Biological Psychiatry, 2008

# Prazosin decreases stress-induced alcohol craving, anxiety and negative emotions in the laboratory (N=17)



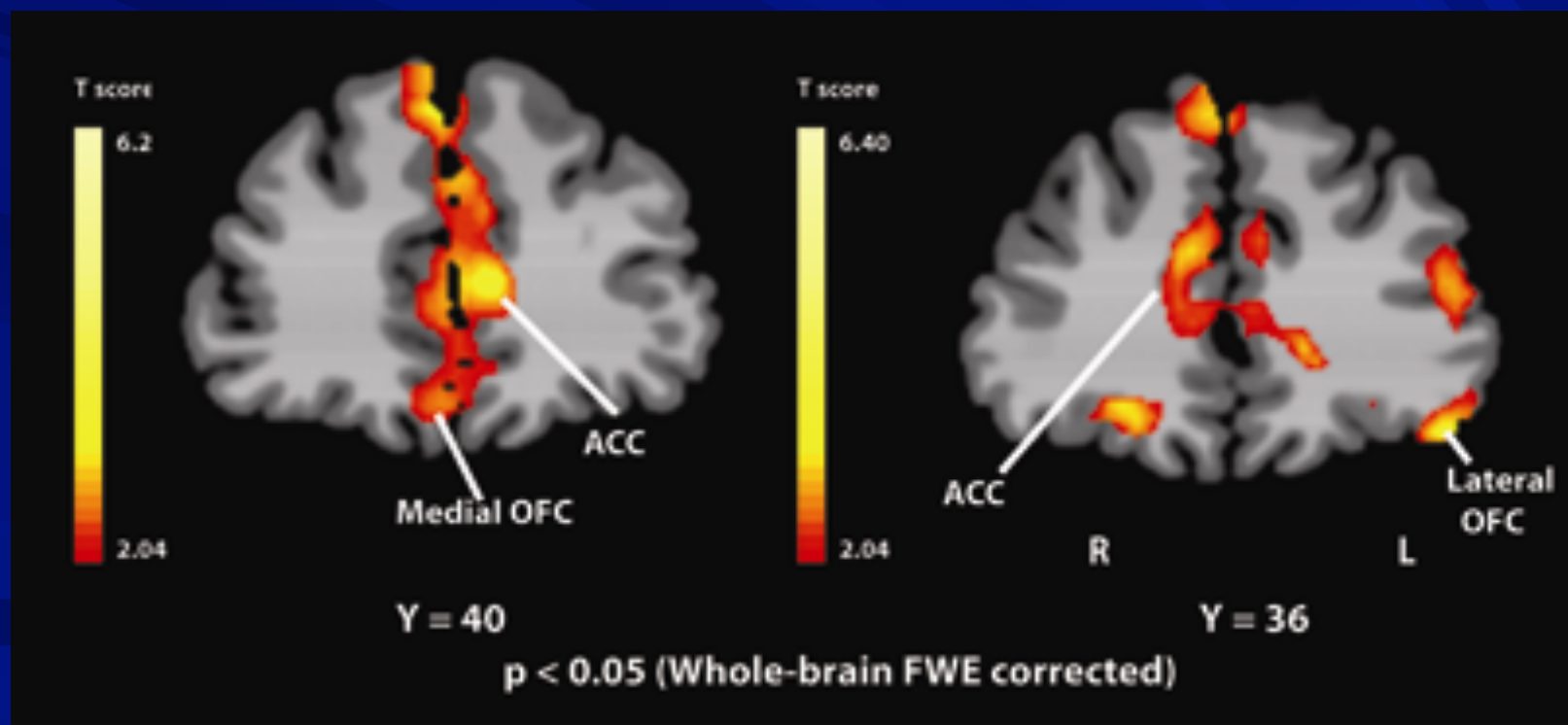
Fox et al., Alcoholism: Clinical and Experimental Research (2011)

# Prazosin normalizes prefrontal activation during stress and cue exposure in alcohol dependent patients (N=14)

## PRAZOSIN – PLACEBO

(A) Drug Cue

(B) Stress



Sinha Lab: Preliminary data: unpublished

# In Conclusion

- **Specific blood and brain biomarkers of alcohol relapse:** These have been identified and now we are working to validate these biomarkers.
- **Personalized Medicine Goal 1:** Identify those are most vulnerable at treatment entry or during early recovery
- **Personalized Medicine Goal 2:** Developing specific treatments to reverse chronic alcohol and trauma brain effects to help those most susceptible to high alcohol relapse risk and to jeopardizing recovery.



# Acknowledgements

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