

Stress and Cardiovascular Function: Implications for Risk and Resilience

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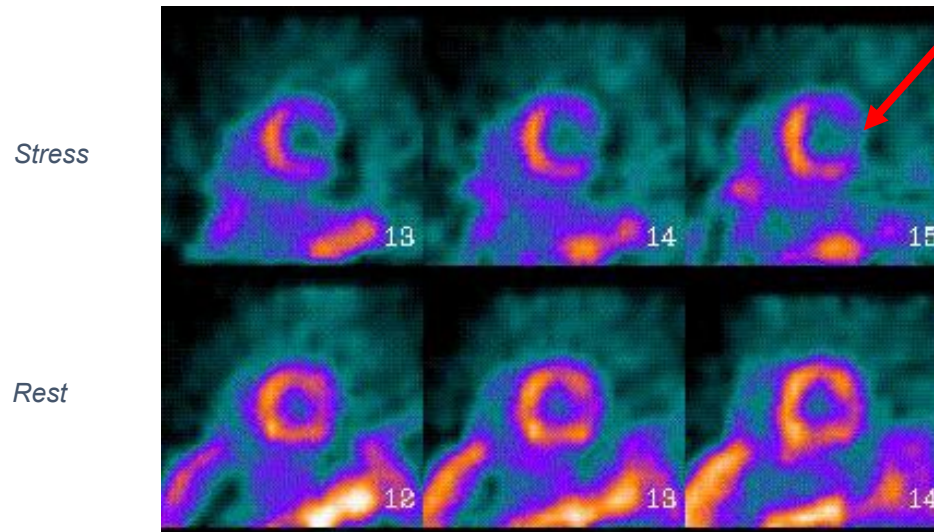
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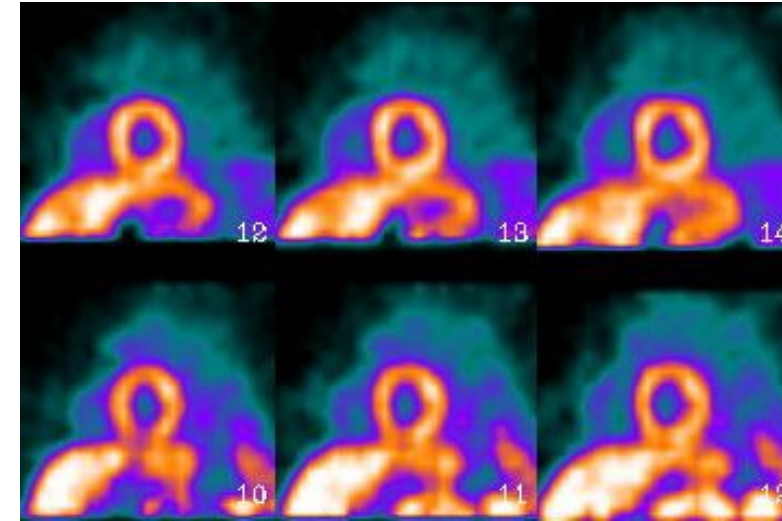
U.S. Department of Veterans Affairs

Atlanta VA Medical Center

Myocardial Perfusion Imaging in Twins With and Without Posttraumatic Stress Disorder (PTSD)



Twin with subclinical ischemia

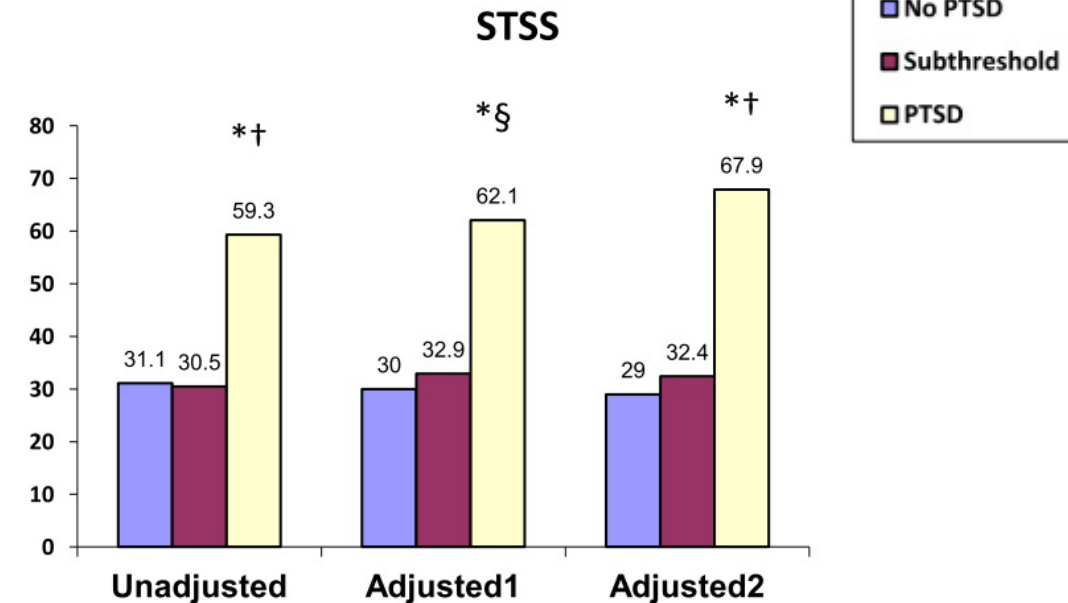


Twin without subclinical ischemia

Myocardial perfusion measured with PET [N -13] ammonia in twins with and without PTSD (N=281) at rest and with adenosine stress;

*STSS=Stress Total Severity Score; * p <.01*

adjusted1=sociodemographic factors; adjusted2=depression, alcohol



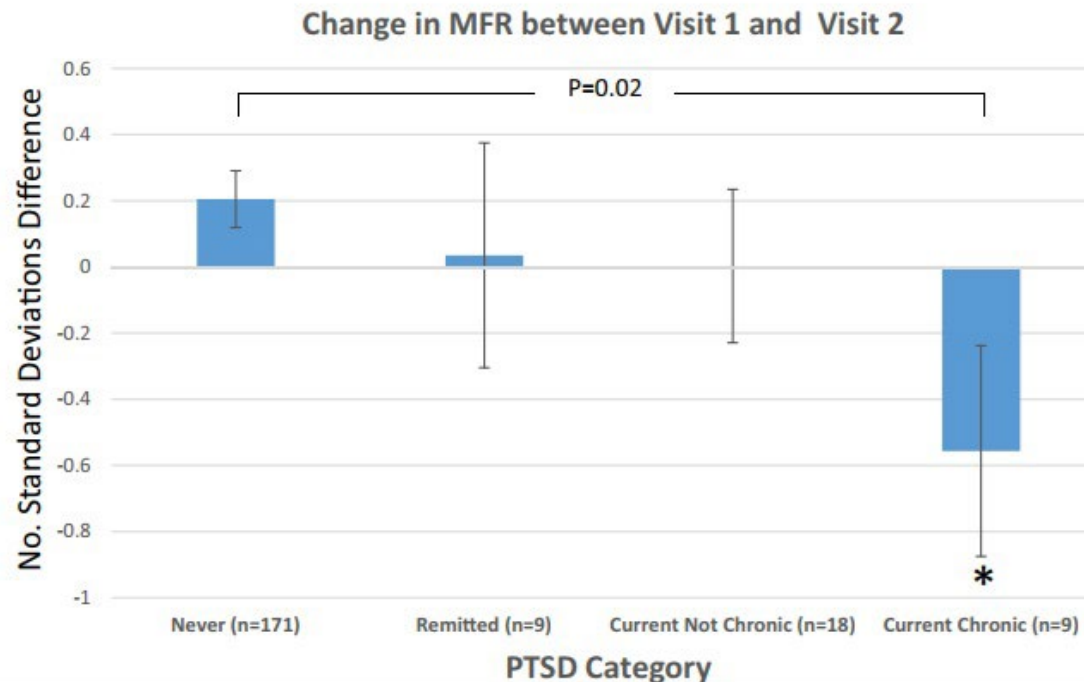
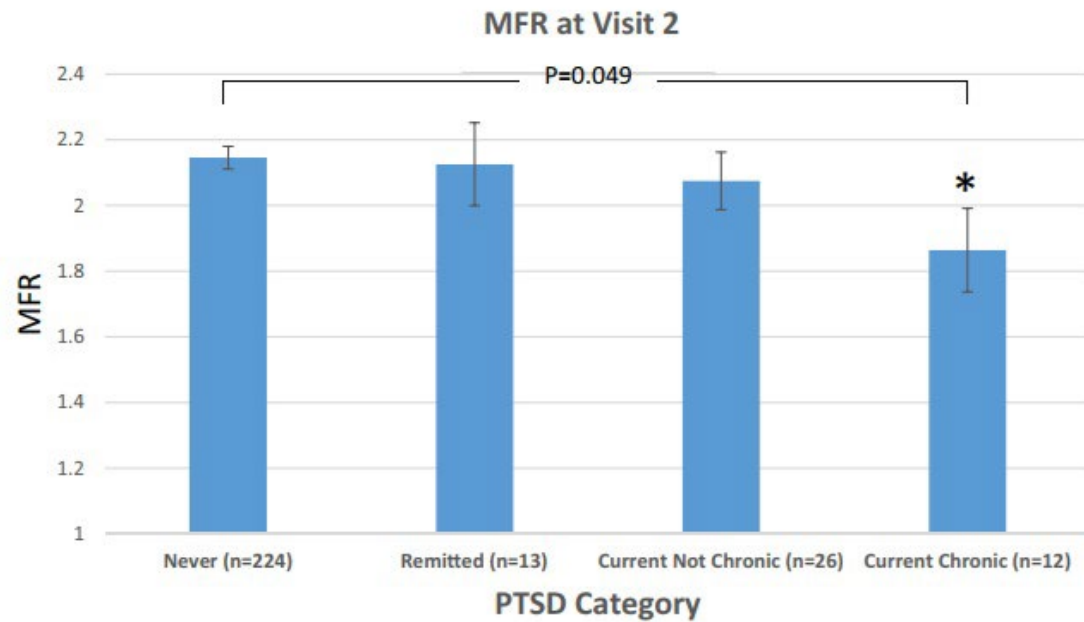
Decreased Myocardial Flow Reserve (MFR) in Chronic PTSD

275 Vietnam Era twins with visits 7 years apart

PET [N-13]ammonia with rest and pharmacologic stress

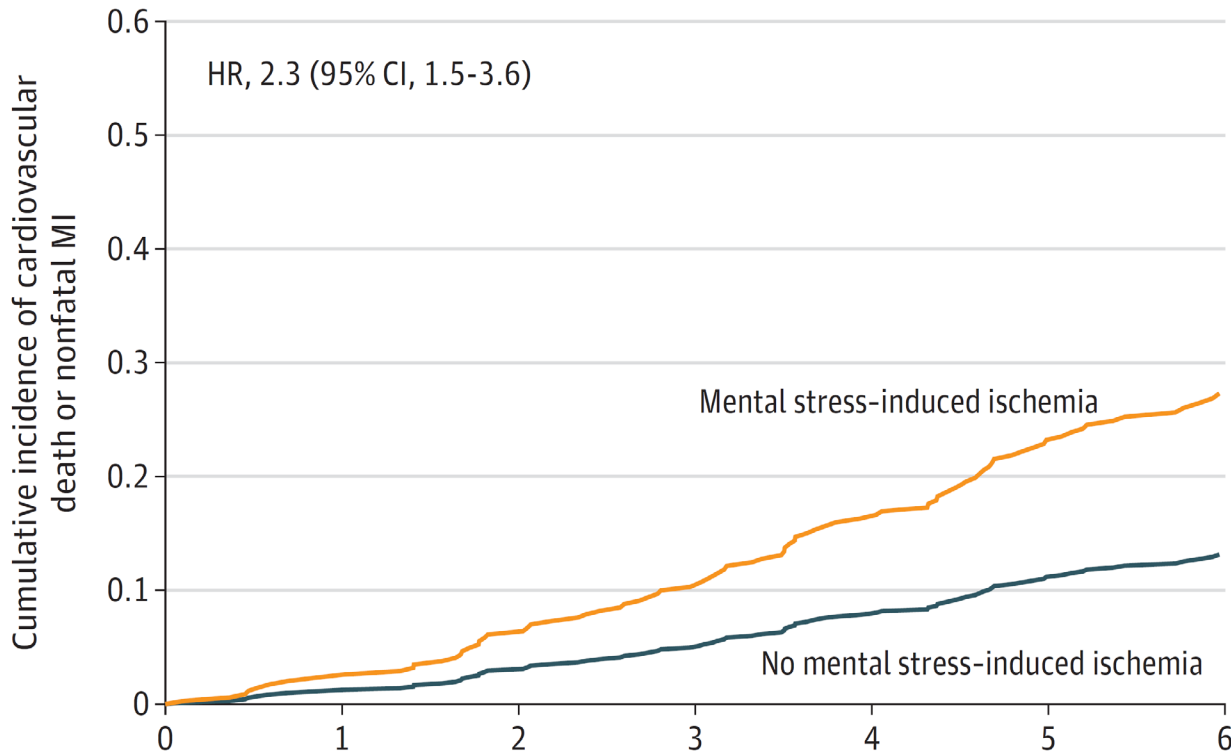
MFR difference between global myocardial blood flow at rest and with vasodilation stress, decrease indicates myocardial dysfunction

Vaccarino... Bremner *Biol Psychiatry* 2021

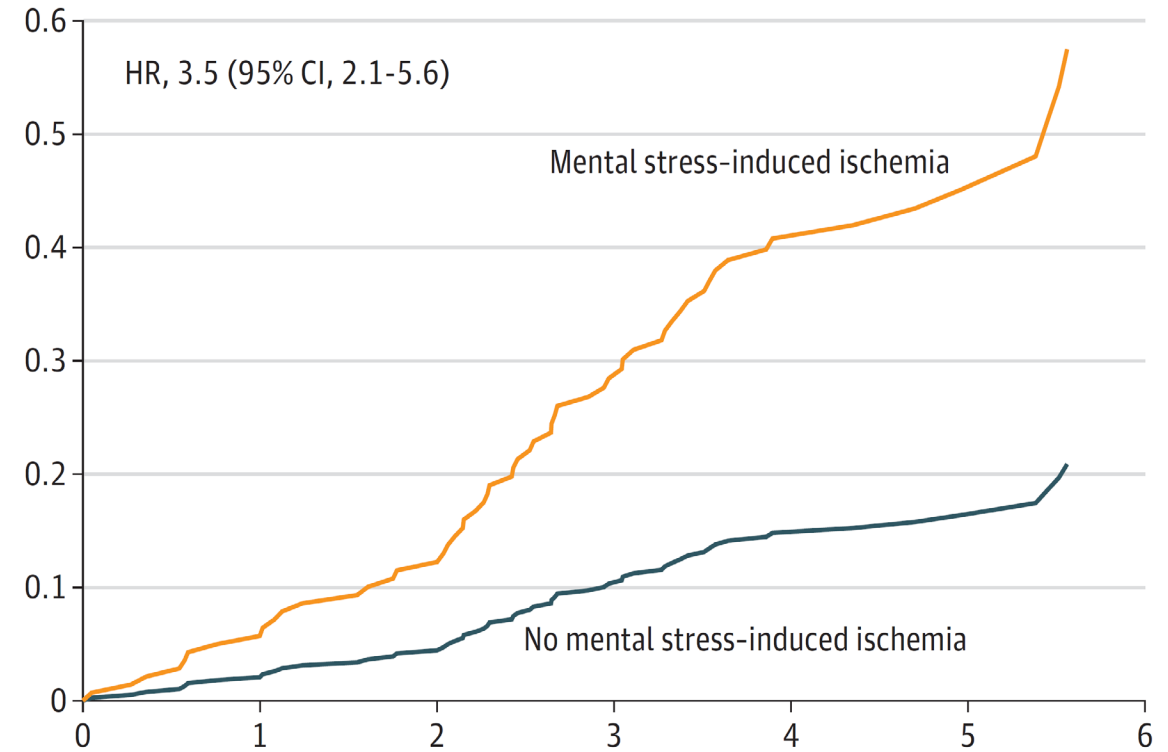


IS MYOCARDIAL ISCHEMIA WITH MENTAL STRESS ASSOCIATED WITH ADVERSE OUTCOMES?

MIPS Study, Stable CHD



MIMS2 Study, Post-MI



In the two cohorts combined: **HR 2.5 (95%CI, 1.8-3.5)**

Associations independent of clinical risk factors and ischemia with a conventional stress test

Increased Mental Stress Induced Myocardial Ischemia in PTSD

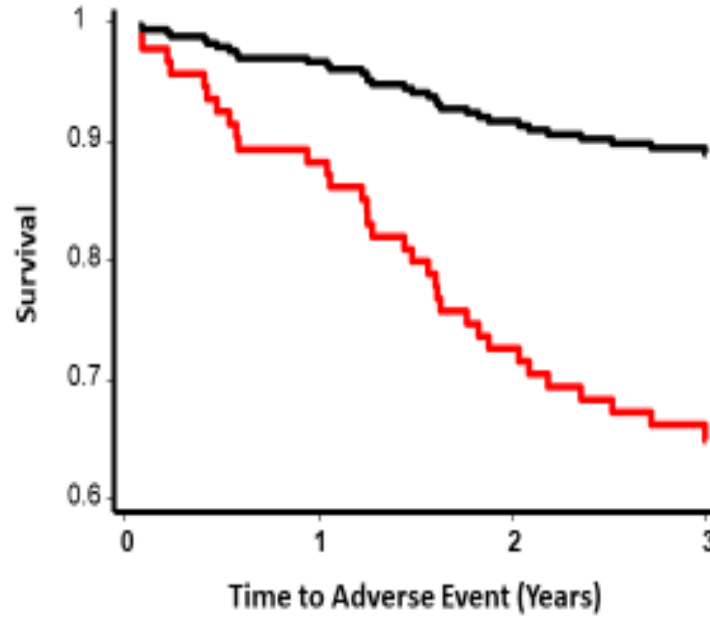
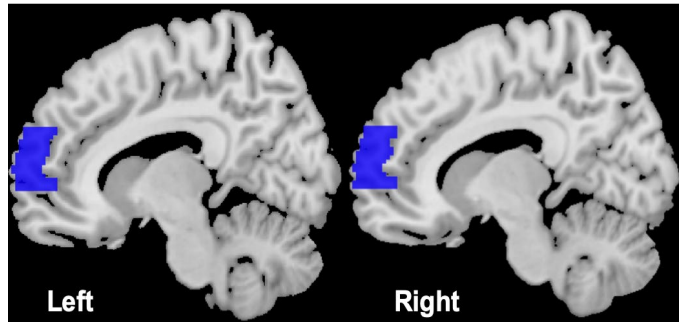
Table 5. Association of Subscales of Posttraumatic Stress Disorder Symptoms With Myocardial Ischemia With Mental Stress or Conventional Stress

| Subscale ^a | Myocardial ischemia with mental stress | | Myocardial ischemia with conventional stress | |
|-----------------------|--|---------|--|---------|
| | 5-Point score increase, OR (95% CI) | P value | 5-Point score increase, OR (95% CI) | P value |
| Reexperiencing trauma | | | | |
| Unadjusted | 1.53 (1.12-2.08) | .007 | 1.12 (0.84-1.51) | .43 |
| Adjusted ^b | 1.87 (1.21-2.91) | .005 | 1.06 (0.77-1.44) | .73 |
| Avoidance and numbing | | | | |
| Unadjusted | 1.27 (1.00-1.62) | .05 | 1.03 (0.82-1.29) | .80 |
| Adjusted ^b | 1.51 (1.07-2.14) | .02 | 1.00 (0.78-1.26) | .94 |
| Arousal | | | | |
| Unadjusted | 1.20 (0.88-1.63) | .24 | 1.14 (0.87-1.50) | .34 |
| Adjusted ^b | 1.42 (0.93-2.16) | .10 | 1.06 (0.79-1.42) | .69 |

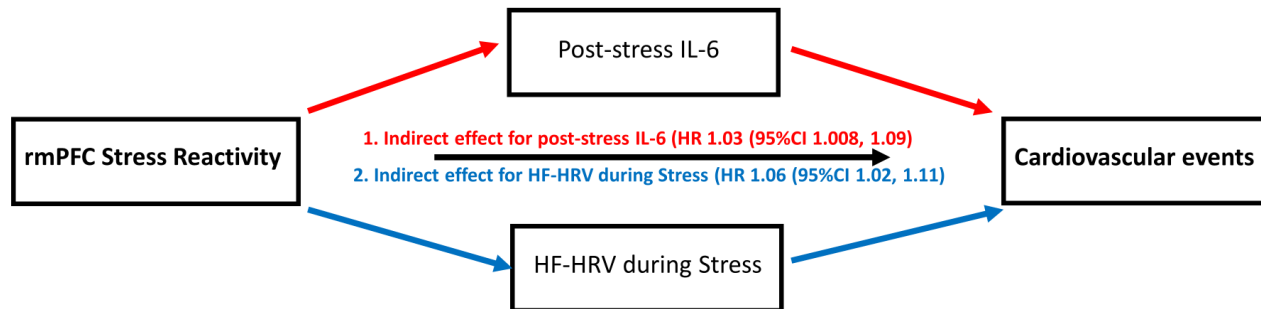
303 Post-MI Patients

Lima... Bremner, Vaccarino *JAMA Network Open* 2020

Higher Activation of Rostromedial Prefrontal Cortex During Mental Stress Predicts Major Cardiovascular Events in CAD



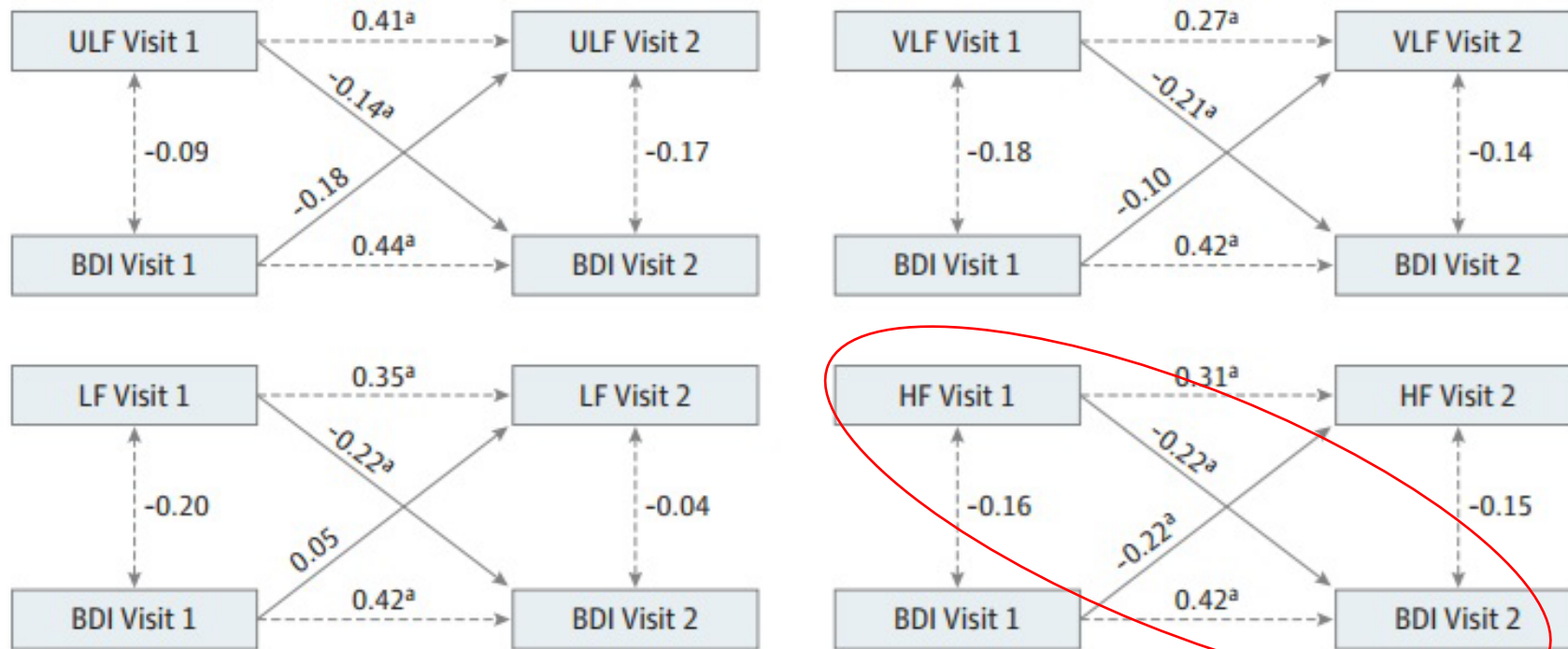
Relationship between Rostromedial Prefrontal Cortex (rmPFC) function and event-free survival. CAD patients with Increased stress-induced rmPFC activation had a decrease in cardiac event-free survival (red line) compared to CAD patients without stress-induced rmPFC activation (black line)



Moazzami... Bremner, Vaccarino, Shah 2020 Circulation

Baseline Low Heart Rate Variability Predicts Future Depression

Figure 2. Illustration of the Cross-Lagged Association Between All Heart Rate Variability (HRV) Domains and Beck Depression Inventory (BDI) Score Using Model 4 Results



Huang... Bremner, Vaccarino
JAMA Psychiatry 2018

Numbers indicate standardized β coefficients from the mixed-effects regression models. HF indicates high frequency; LF, low frequency; ULF, ultra-low frequency; VLF, very low frequency.

^a Significance was $P < .05$.

Baseline depression predicting future low HRV related to antidepressant use.

146 twins from the Vietnam Era Twin Registry at two time points (7 years). BDI=Beck Depression Inventory II

Baseline elevated LF:HF ratio predeployment predicted post deployment PTSD. Minassian et al *JAMA Psychiatry* 2015

IL-6 and PACAP: Relevant Biomarkers in PTSD

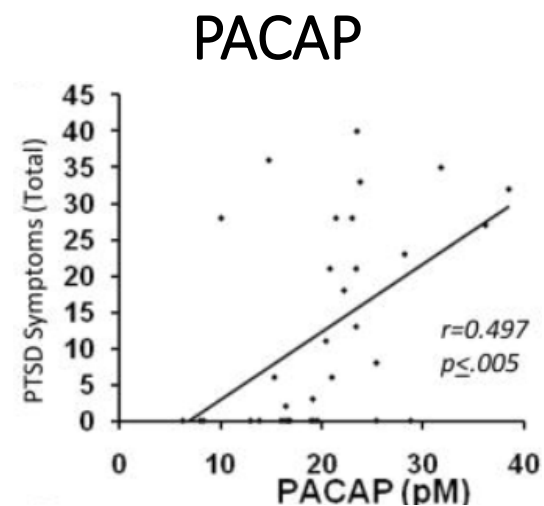
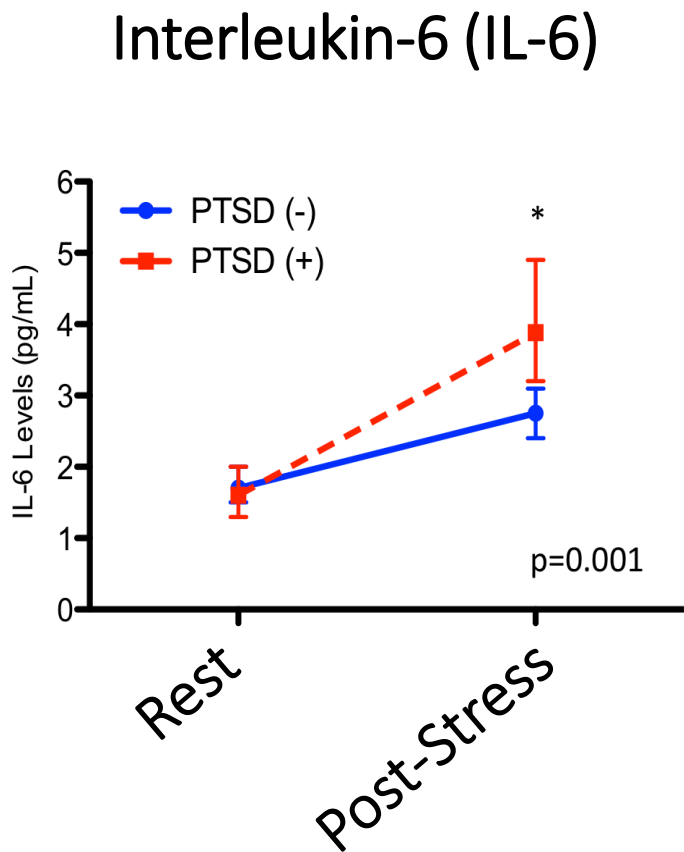


Table 1 | PACAP associations with PTSD symptoms

| | Initial <i>n</i> = 34 | Replication <i>n</i> = 74 | Combined <i>n</i> = 108 |
|---|--------------------------|------------------------------|----------------------------|
| **Correlation of PACAP level with PSS hyperarousal score | 0.006 | 0.015 | 0.001 |
| *High PACAP level with PSS hyperarousal score (Fig. 1c) | 0.001 | 0.01 | 0.0004 |
| *High PACAP level with PSS hyperarousal score (Fig. 1d, adjusted) | 0.01 | 0.001 | 0.00005 |
| *High PACAP level with PSS total score (Fig. 1b) | 0.0003 | 0.15 | 0.008 |
| *High PACAP level with PSS total score (adjusted) | 0.004 | 0.04 | 0.002 |
| *High PACAP level with clinically significant PTSD symptoms (Fig. 1d, adjusted) | 0.0002 | 0.01 | 0.0003 |
| *High PACAP levels with PSS-based PTSD diagnosis ¹ (adjusted) | 0.01 | 0.02 | 0.0008 |

The table shows *P* values of correlations and regression analyses for the initial, replication and combined cohort analyses: 2-tailed for initial and combined; 1-tailed for replication.

'Adjusted' means adjusted for age, substance use and trauma.

** Bivariate correlation.

* Analysis of variance (ANOVA).

Baseline Inflammation (IL-6) Predicts Future Depression

146 twins from the Vietnam Era Twin Registry at two time points (7 years). BDI=Beck Depression Inventory II

Huang... Bremner, Vaccarino *Brain Behav Immun* 2019

Baseline inflammation predicts future PTSD re-experiencing after MI (mainly in Black Women)

Buto... Bremner, Vaccarino *al Brain Behav Immun Reports* 2023

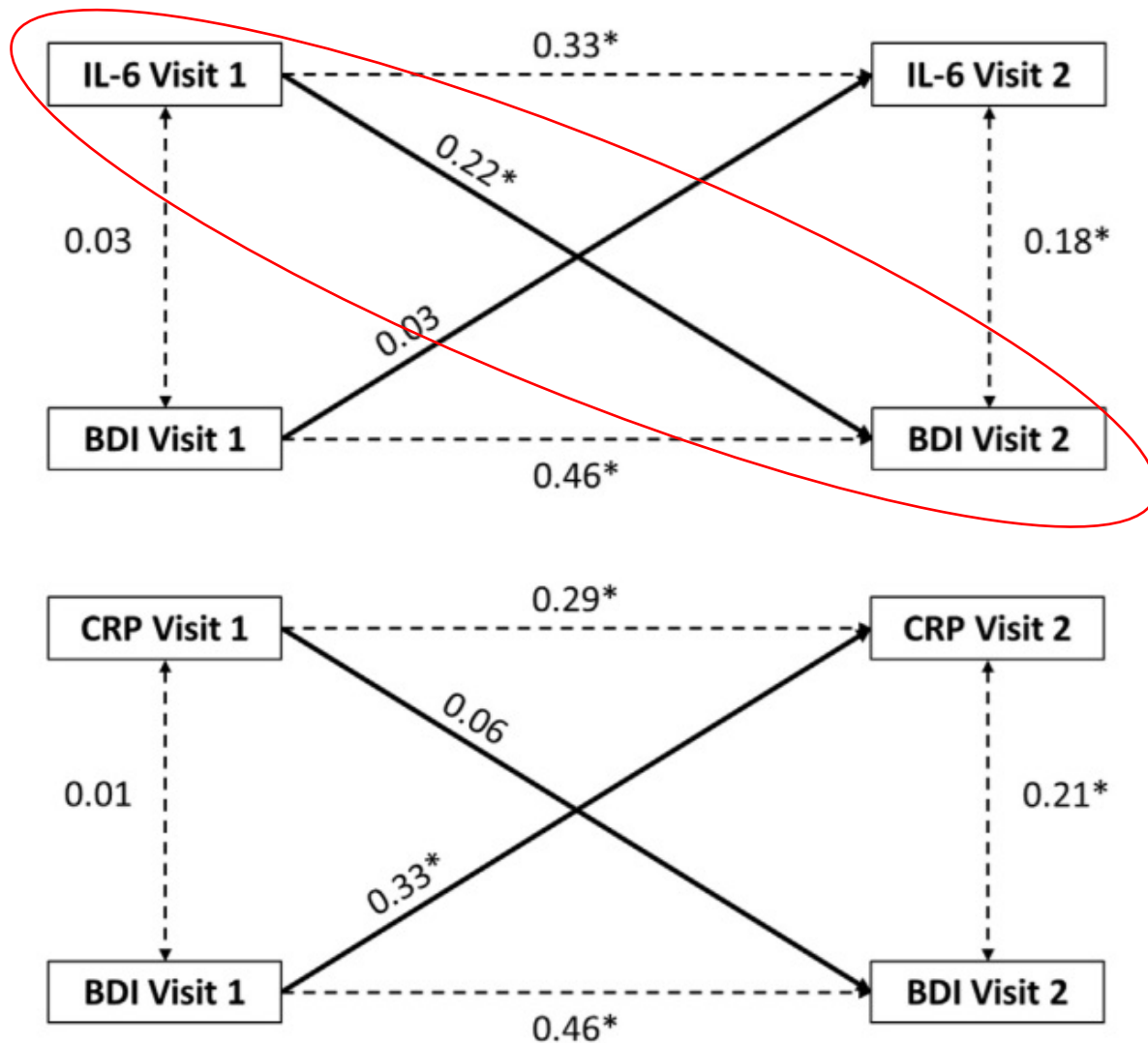
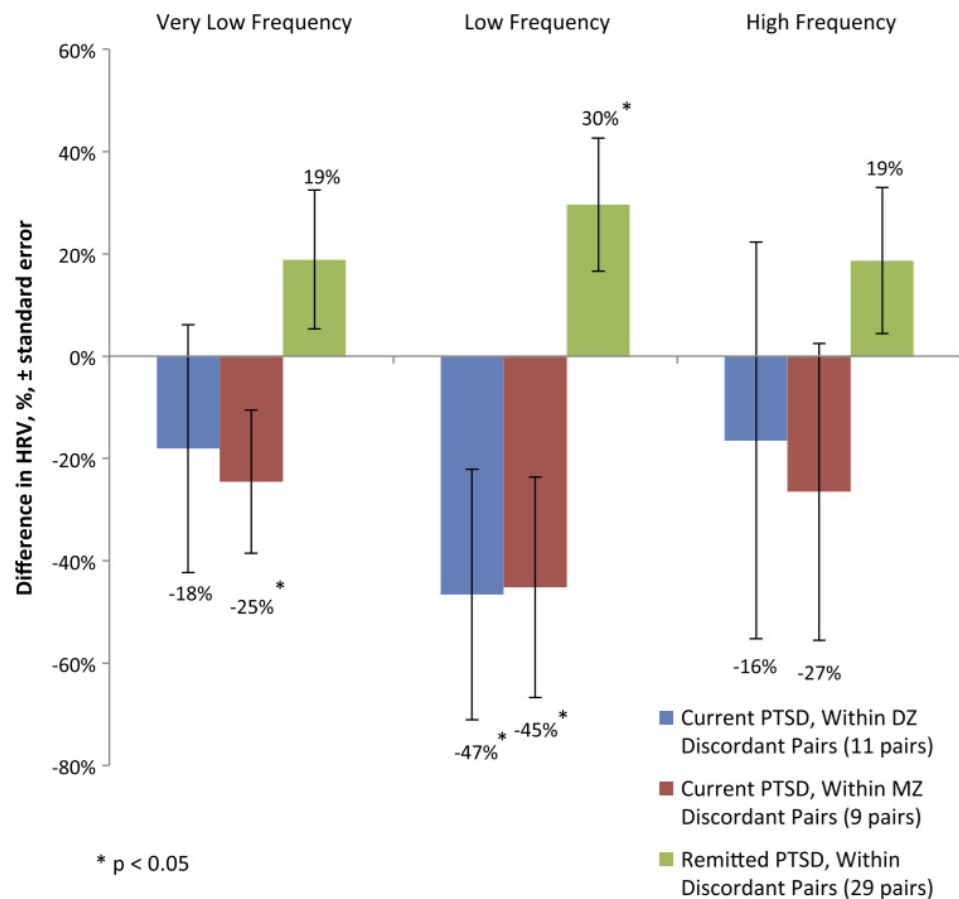
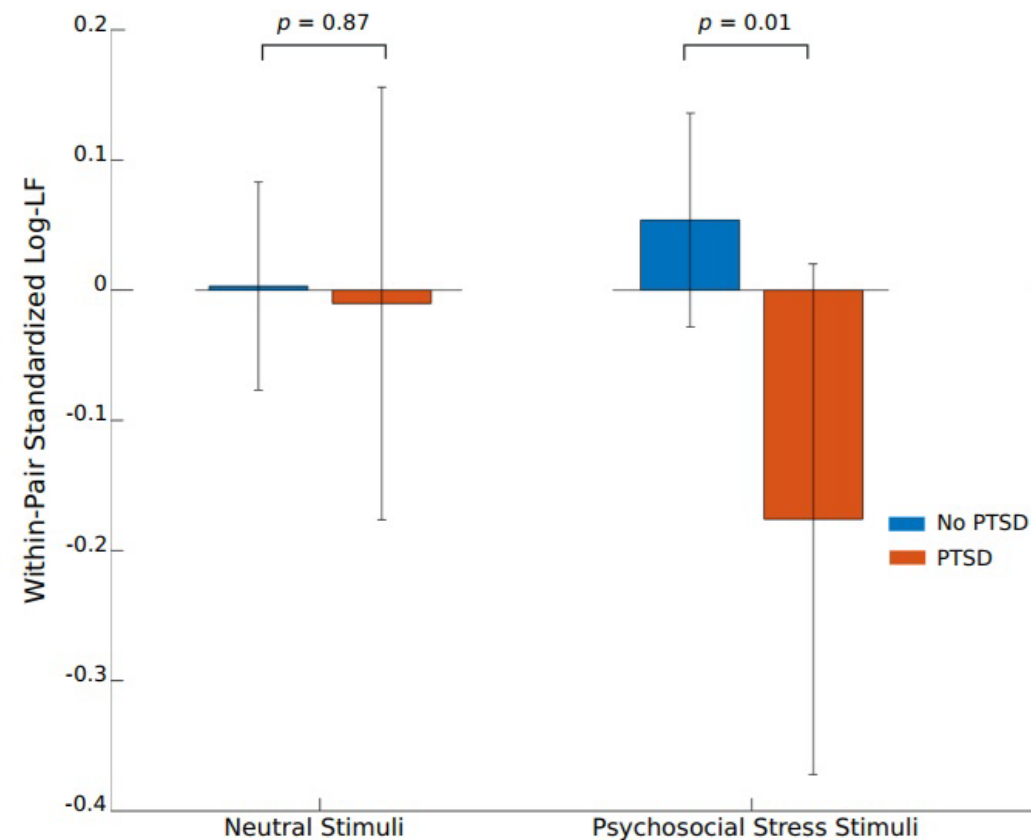


Fig. 1. Illustration of the cross-lagged association between IL-6 (or CRP) and BDI score using Model 4 results (adjusted for smoking, beta-blocker use, education, alcohol use, physical activity, prevalent CAD, BMI, hypertension, diabetes, and antidepressant use). Abbreviations: IL-6: interleukin-6; CRP: C-reactive protein; BDI: Beck Depression Inventory; CAD: coronary artery disease; BMI: body mass index. Numbers indicate standardized beta-coefficients from mixed-effects regression models. *Indicates significant association at $p < 0.05$.

Decreased Heart Rate Variability with Traumatic Reminders, Current but not Past PTSD



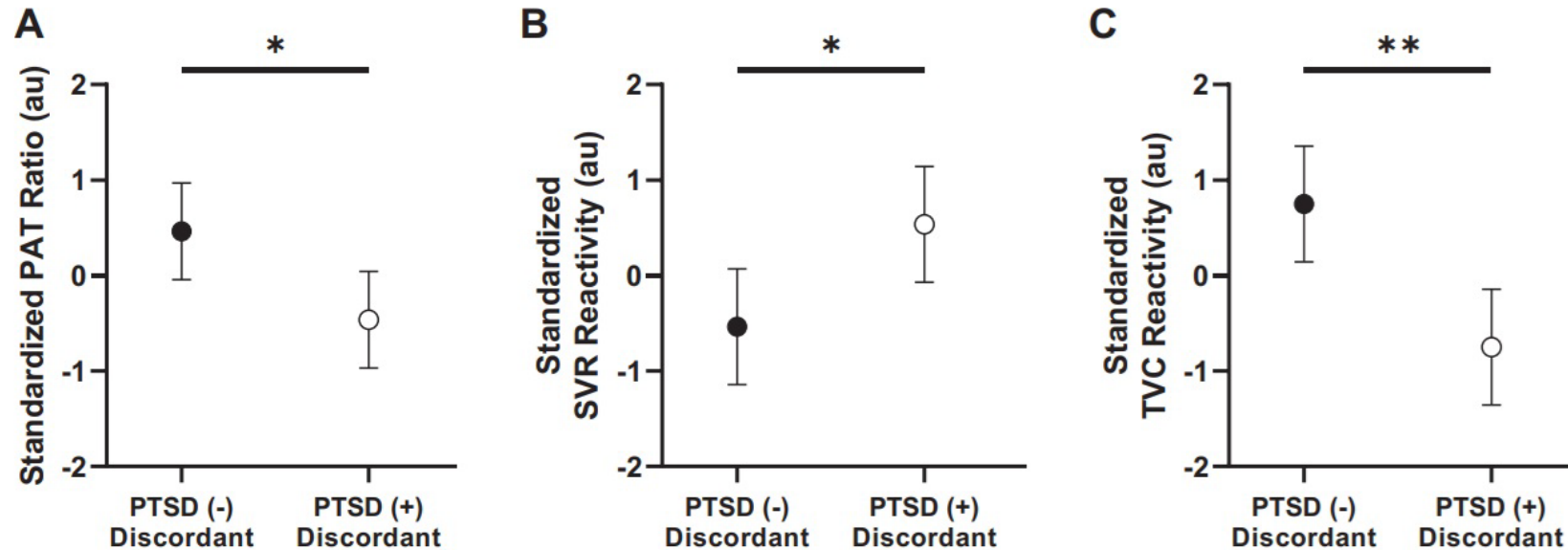
459 twins from Vietnam Era Twin Registry
Shah... Bremner, Vaccarino *Biol Psychiatry*
2013



Heart Rate Variability (HRV) measured during exposure to neutral and personalized trauma scripts. LF=low frequency. 238 twins

Perez Alday... Bremner, Vaccarino, Shah *Psychophysiology* 2023

Increased Peripheral Vasoconstriction with Traumatic Reminders in PTSD



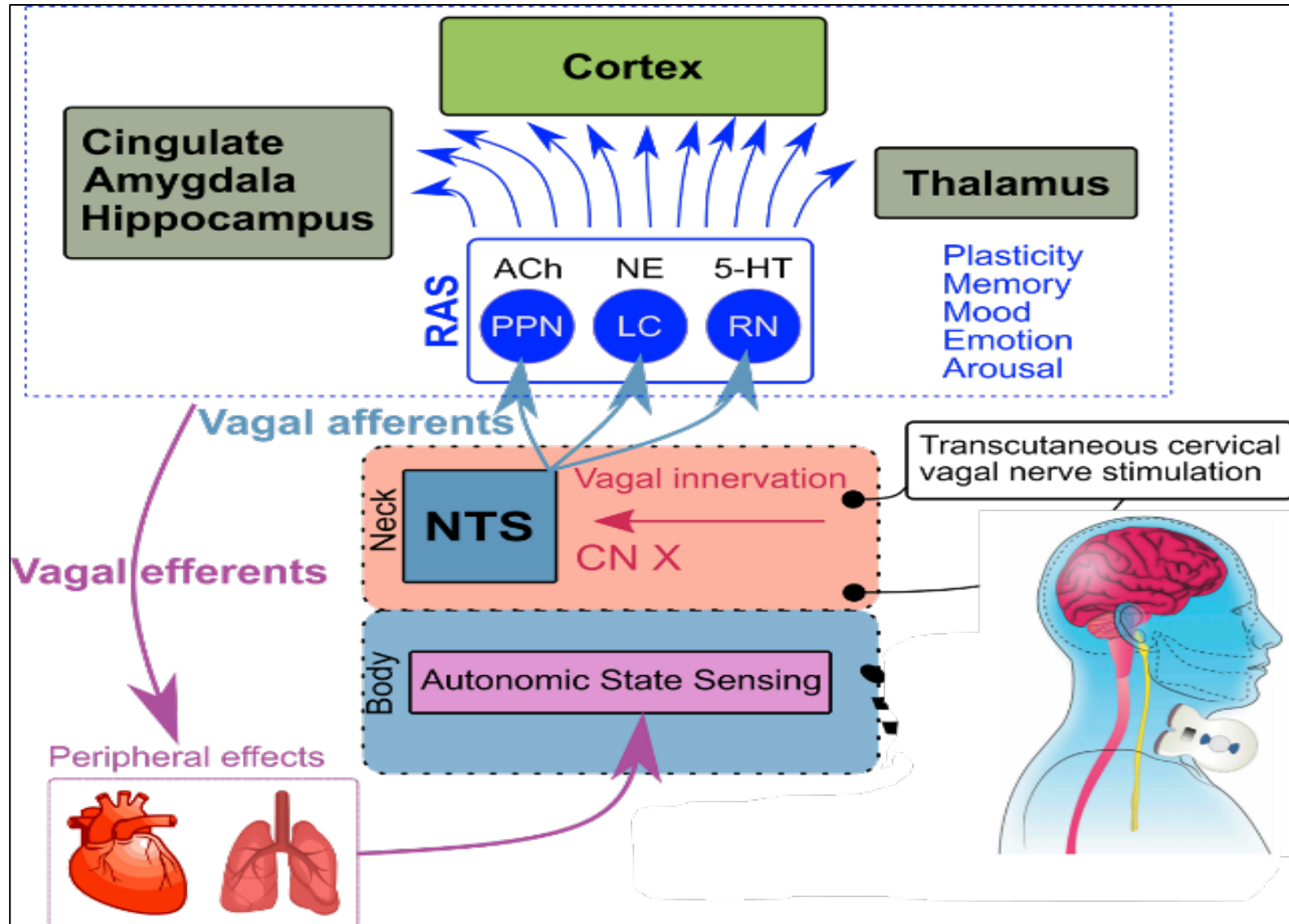
179 Vietnam Era twins including PTSD discordant

Increased peripheral vasoconstriction associated with MSI, poor cardiac outcomes

Figure 2. Standardized peripheral and systemic vasoconstriction responses to trauma script listening in posttraumatic stress disorder (PTSD)-discordant twins. **(A)** Peripheral vasoconstriction indexed by the Peripheral Arterial Tone (PAT) ratio (smaller values indicate greater vasoconstriction during trauma script listening) in 32 PTSD-discordant twins. **(B)** Systemic vasoconstriction indexed by systemic vascular resistance (SVR) reactivity (higher values indicate greater vasoconstriction during trauma script listening) in 22 PTSD-discordant twins. **(C)** Systemic vasoconstriction indexed by total vascular conductance (TVC) reactivity (lower values indicate greater vasoconstriction during trauma script listening) in 22 PTSD-discordant twins. Data are presented as the mean standardized within-twin-pair difference \pm 95% CI, adjusted for cardiovascular disease history (hypertension and coronary heart disease) and risk factors (body mass index, smoking, and physical activity) and antidepressant medication use. * $p < .05$, ** $p < .01$. au, arbitrary unit.

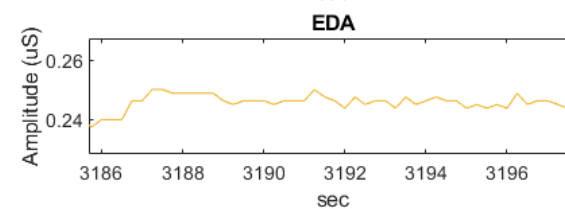
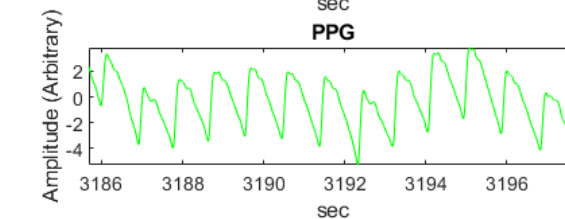
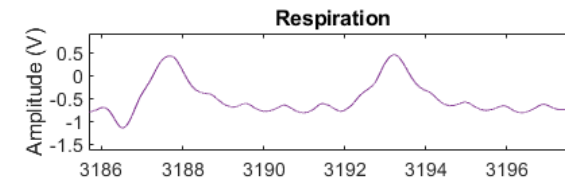
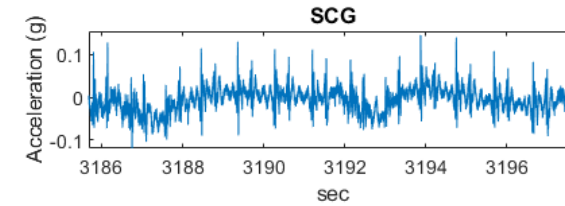
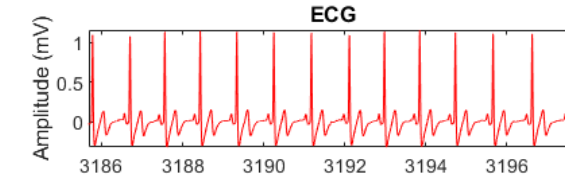
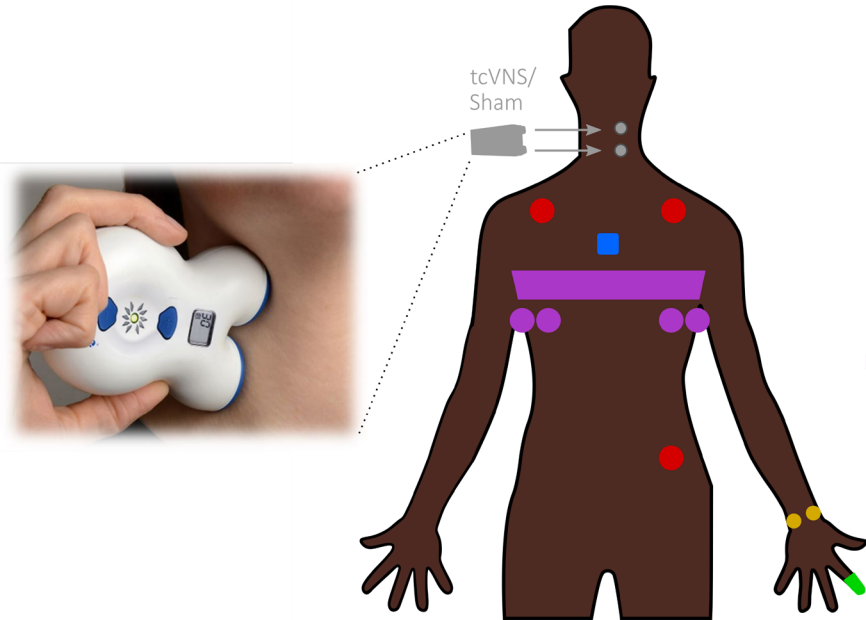
Martin... Bremner, Vaccarino *Biol Psychiatry* 2023

Physiological Correlates of Transcutaneous Vagus Nerve Stimulation (tcVNS)



- *tcVNS activates the Nucleus Tractus Solitarius (NTS) which has projections through norepinephrine (NE), acetylcholine (ACh) and serotonin (5-HT)*
- *These pathways lead to brain areas involved in emotion including the mPFC/anterior cingulate, hippocampus, amygdala and cortex (insula).*
- *Vagal efferents project to peripheral cardiovascular, autonomic and inflammatory pathways.*

Stimulation, Sensing, and Signals

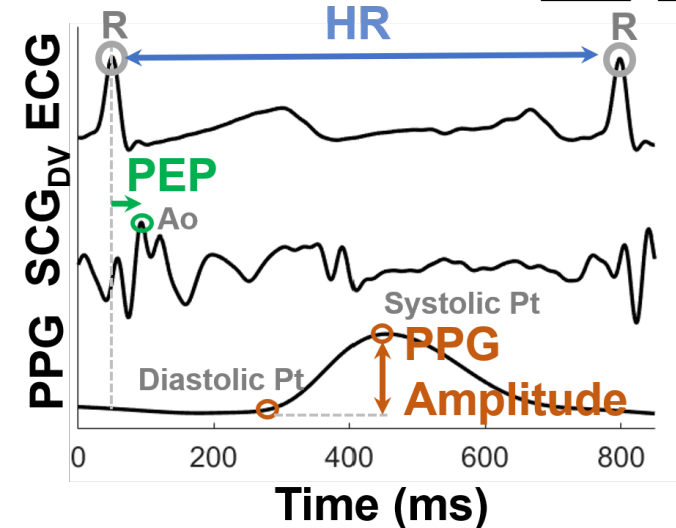


Cardiac

Respiratory

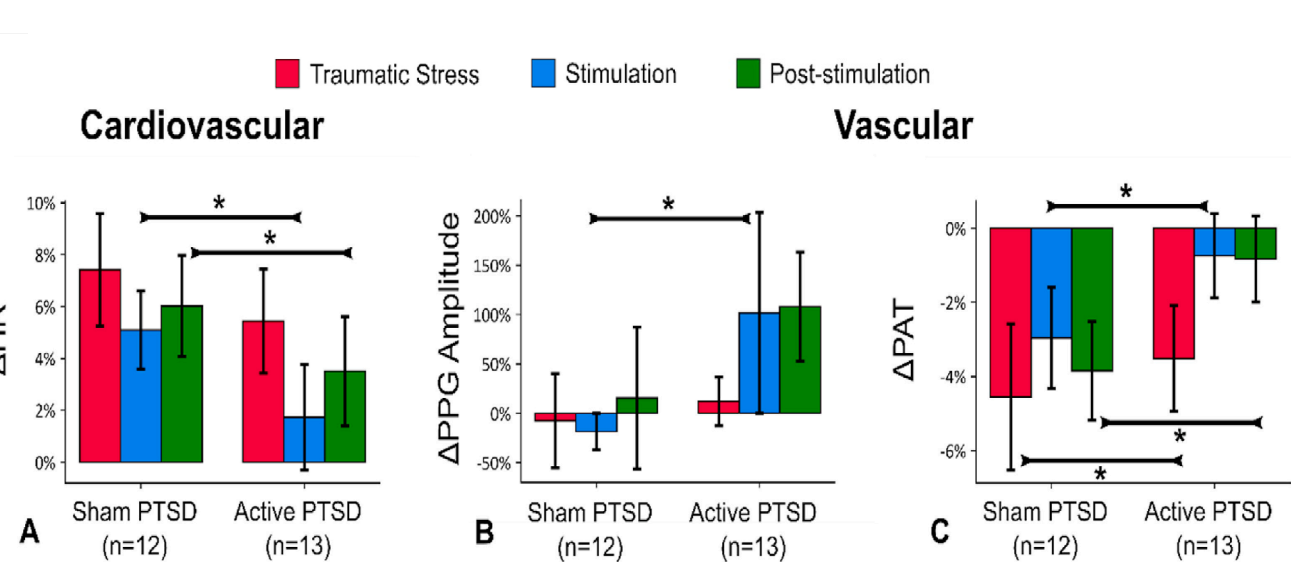
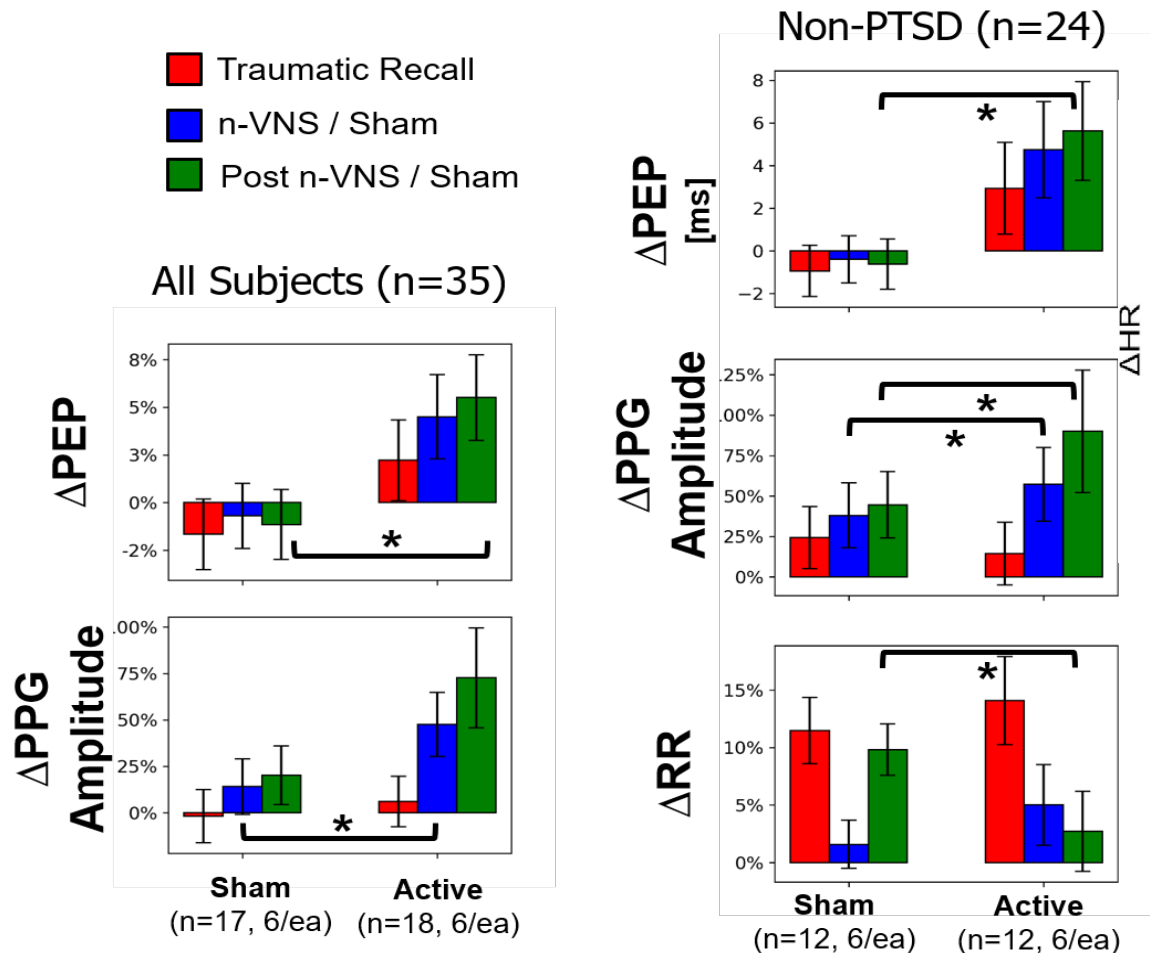
Vascular

Sudomotor



- SCG=seismocardiography;
- PPG=photoplethysmography;
- EDA=electrodermal activity
- HR=heart rate
- PEP=pre-ejection period
- PPG=photoplethysmogram
- SCG=seismocardiogram
- ECG=electrocardiogram
- Ao=aortic valve opening

tcVNS Blocks Sympathetic Response to Stress in PTSD



Decreased HR, RR and PPG and increased PEP (decreased sympathetic function) with nVNS after traumatic scripts stress

HR=heart rate

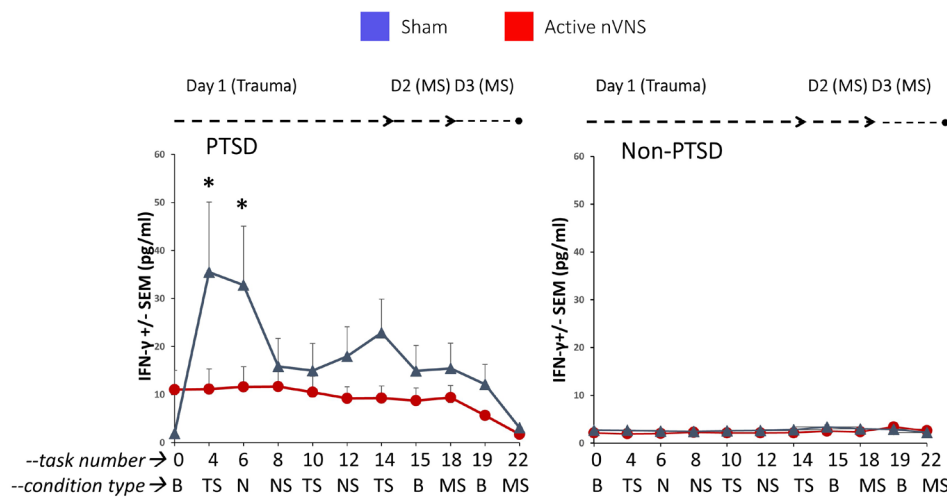
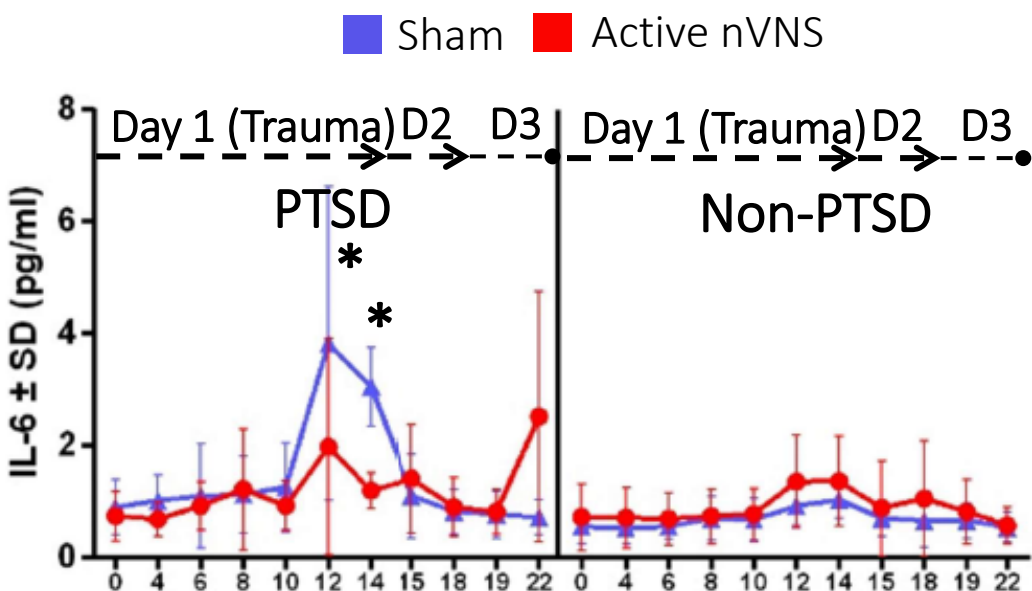
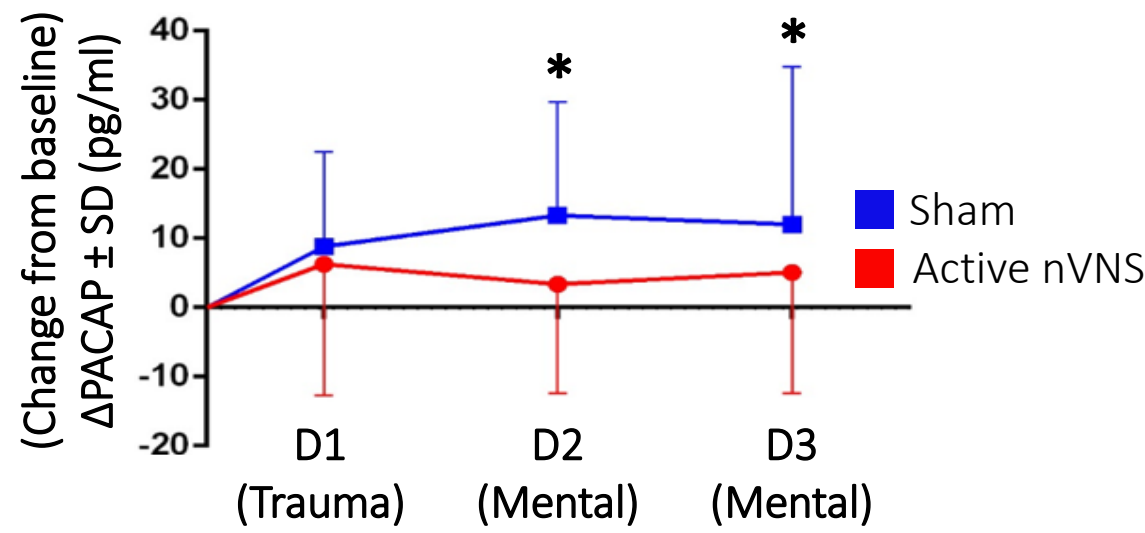
PEP=pre-ejection period

PPG=photoplethysmogram (vasoconstriction)

RR=respiratory rate

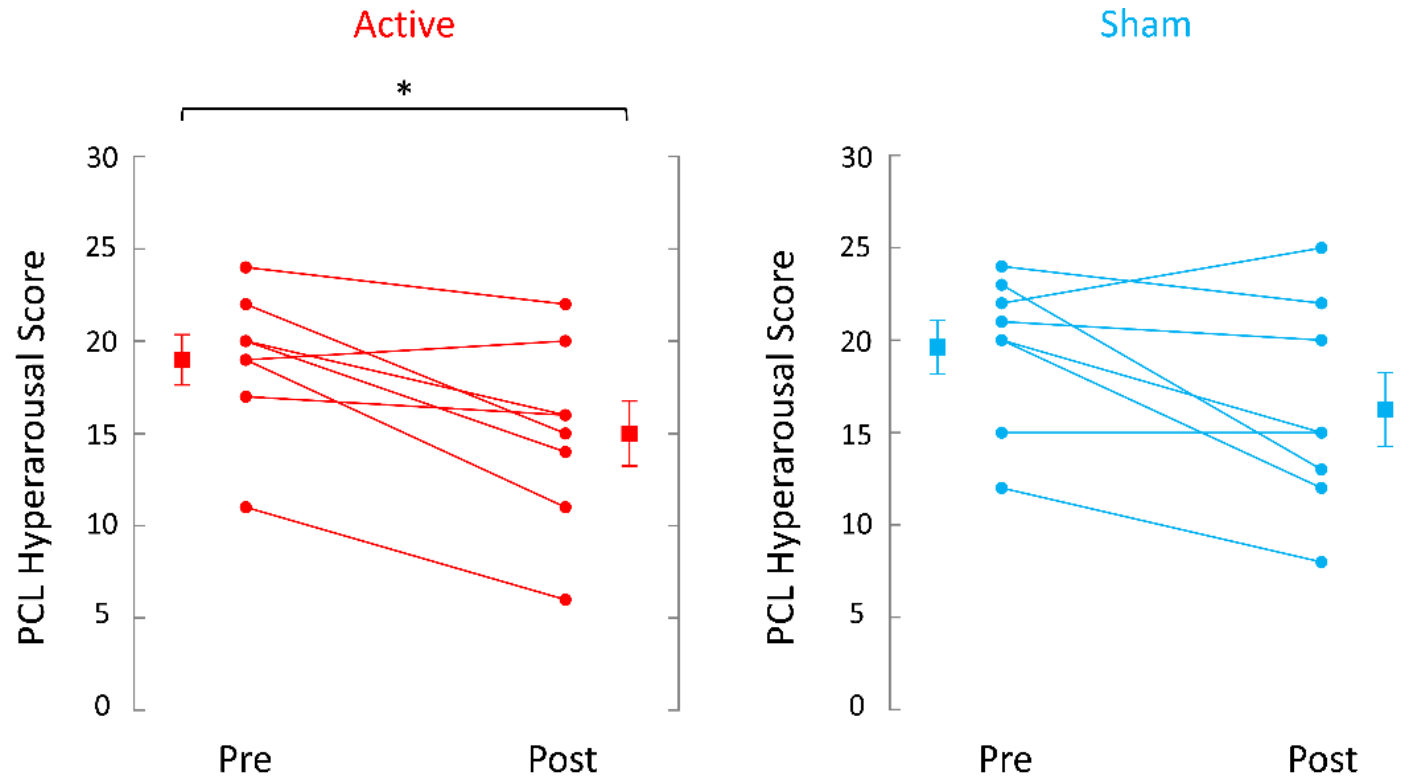
Stress-related elevations blocked by VNS

- IL-6 \propto stress-related inflammation
- PACAP: “Emergency response peptide” \propto stress
- Multiple stress protocol induced a marked increase in IL-6 and PACAP in sham (compared to active)



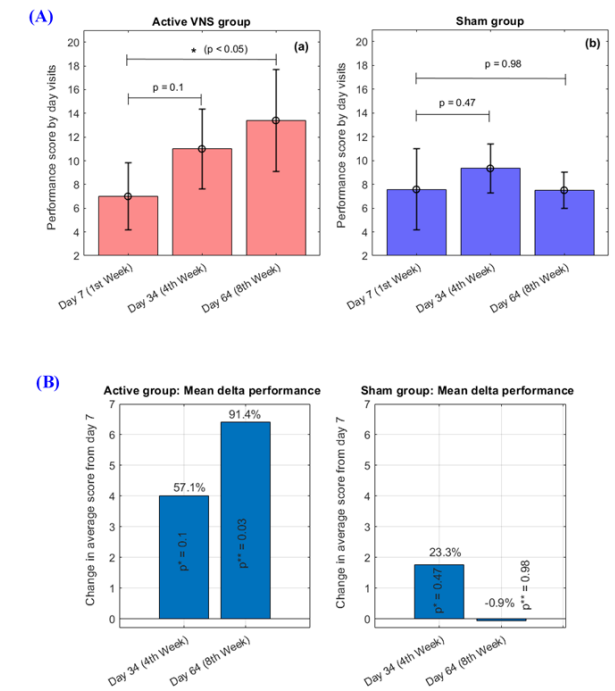
IL-6: Interleukin-6; IFN-gamma: Interferon
 PACAP: Pituitary adenylate cyclase-activating peptide
 *p<0.05 after adjustments based on demographics and background

Effects of Three Months Twice Daily tcVNS on PTSD Symptoms and Memory



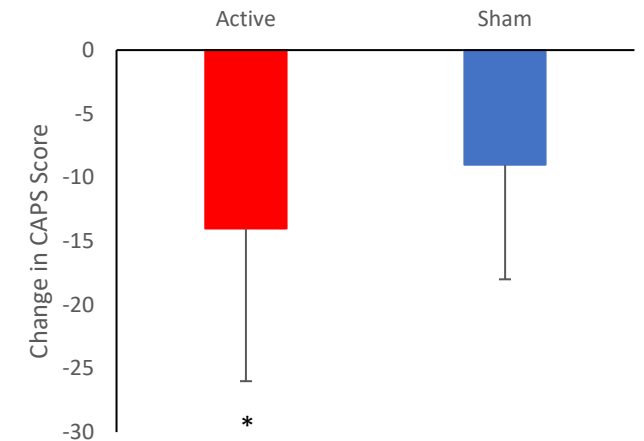
PCL=PTSD Checklist; *p<.05)

Bremner... Inan *J Affect Disord-Rep* 2021



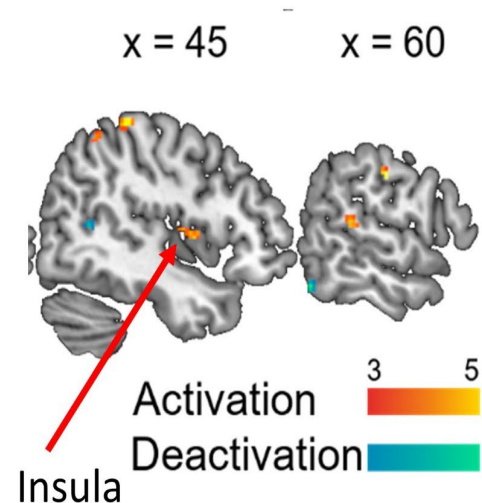
Choudhary... Bremner *J Affect Disord* 2023

35% Greater Decrease in PTSD Symptoms with Three Months of Active tcVNS Versus Sham Stimulation

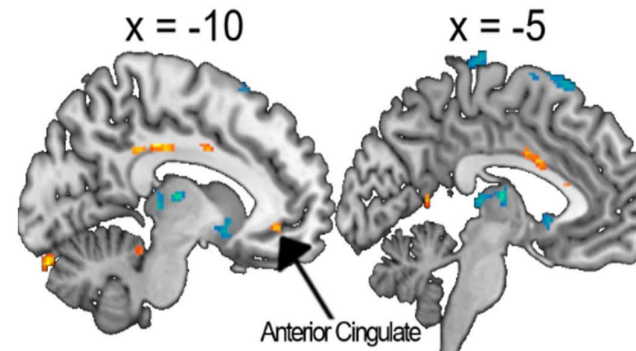


tcVNS Blocks Insula Activation and Enhances Anterior Cingulate Function with Traumatic Scripts in PTSD

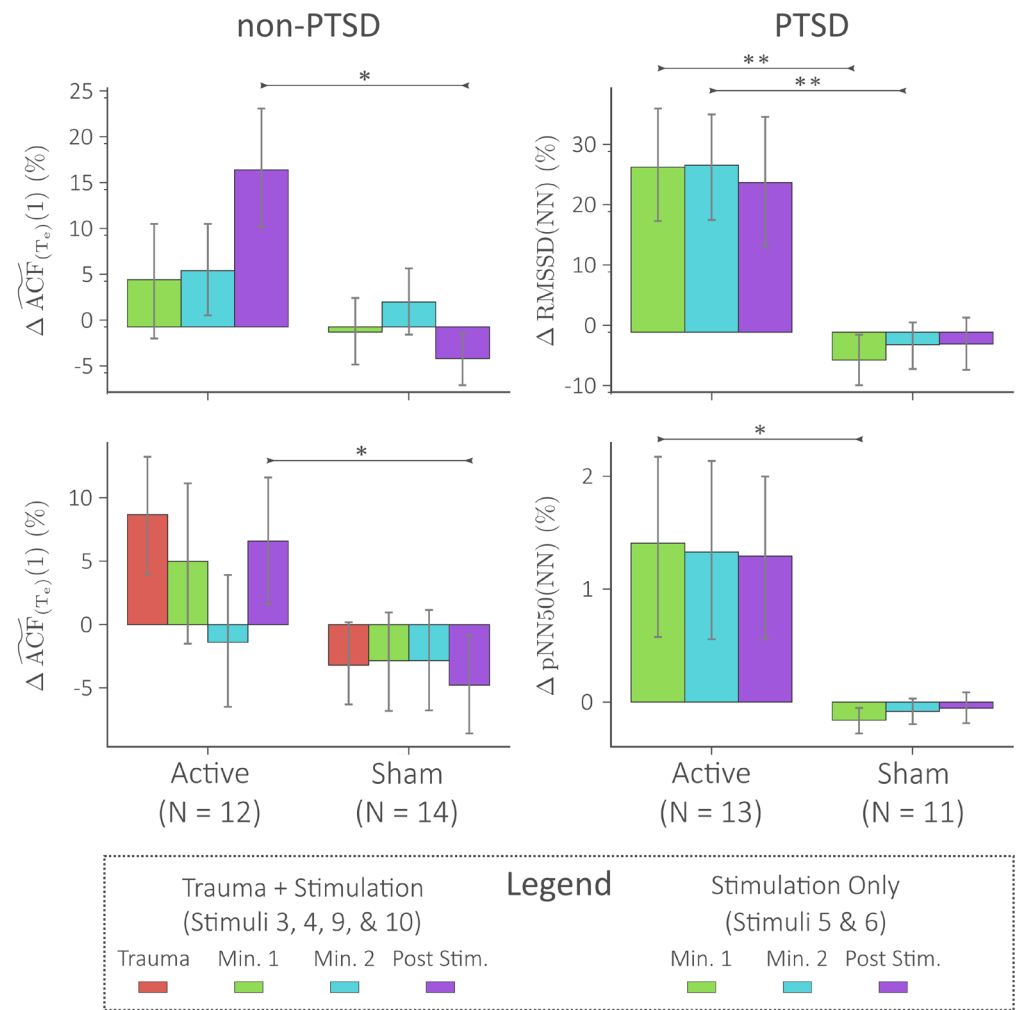
Greater activation
with sham



Greater activation
with active tcVNS

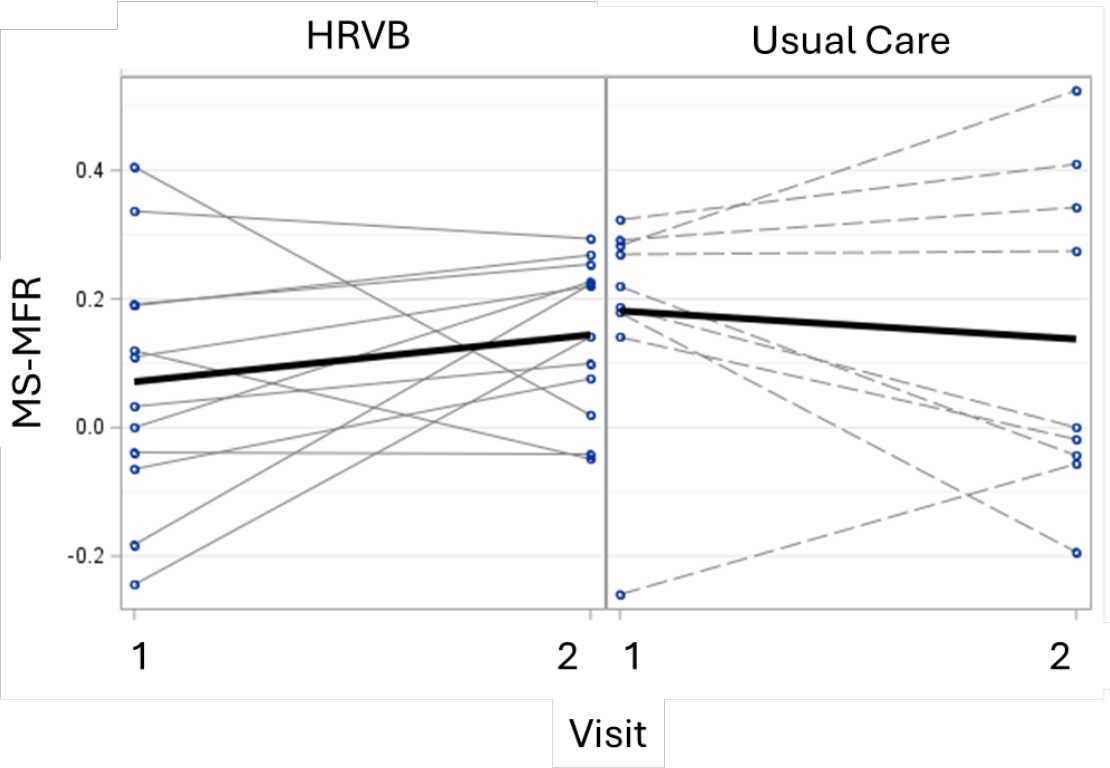


Treatments to Enhance Uniformity of Respiration for PTSD and CHD

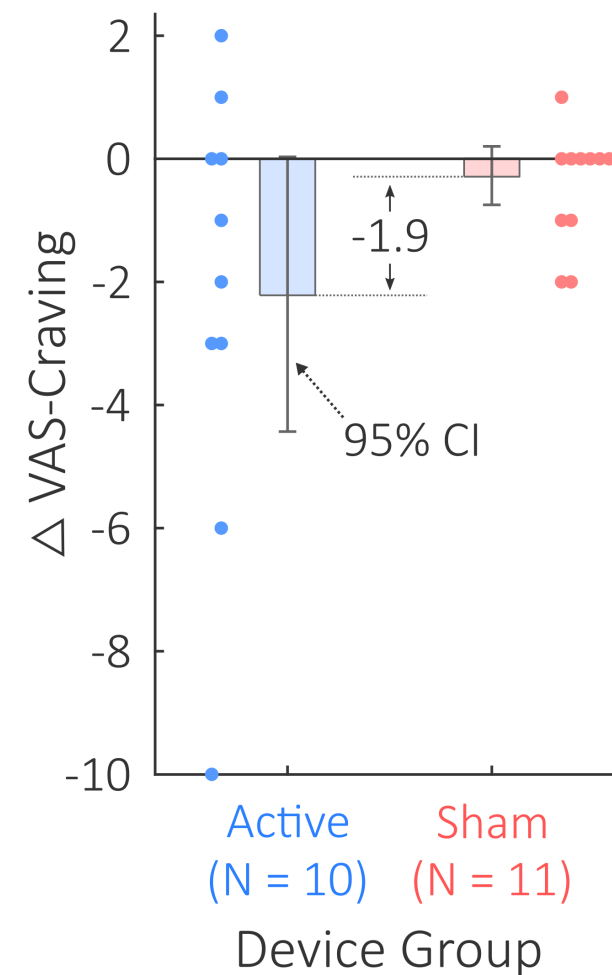
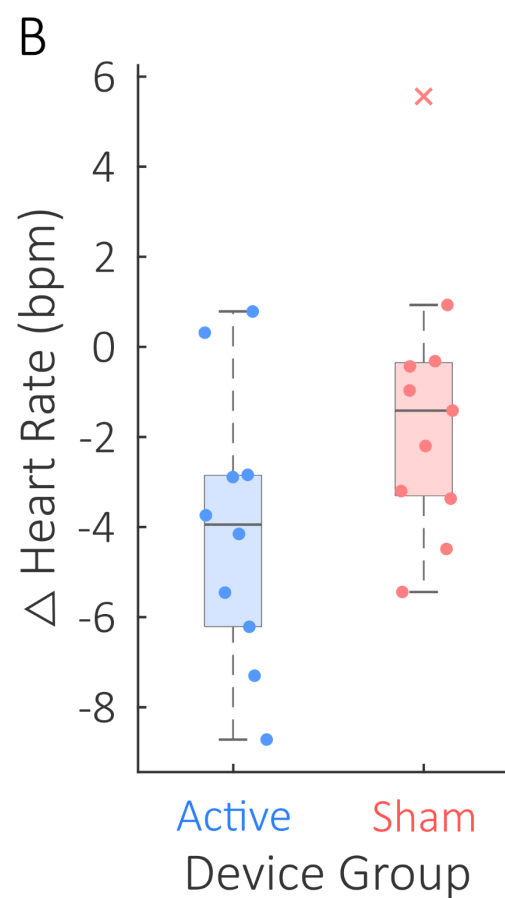
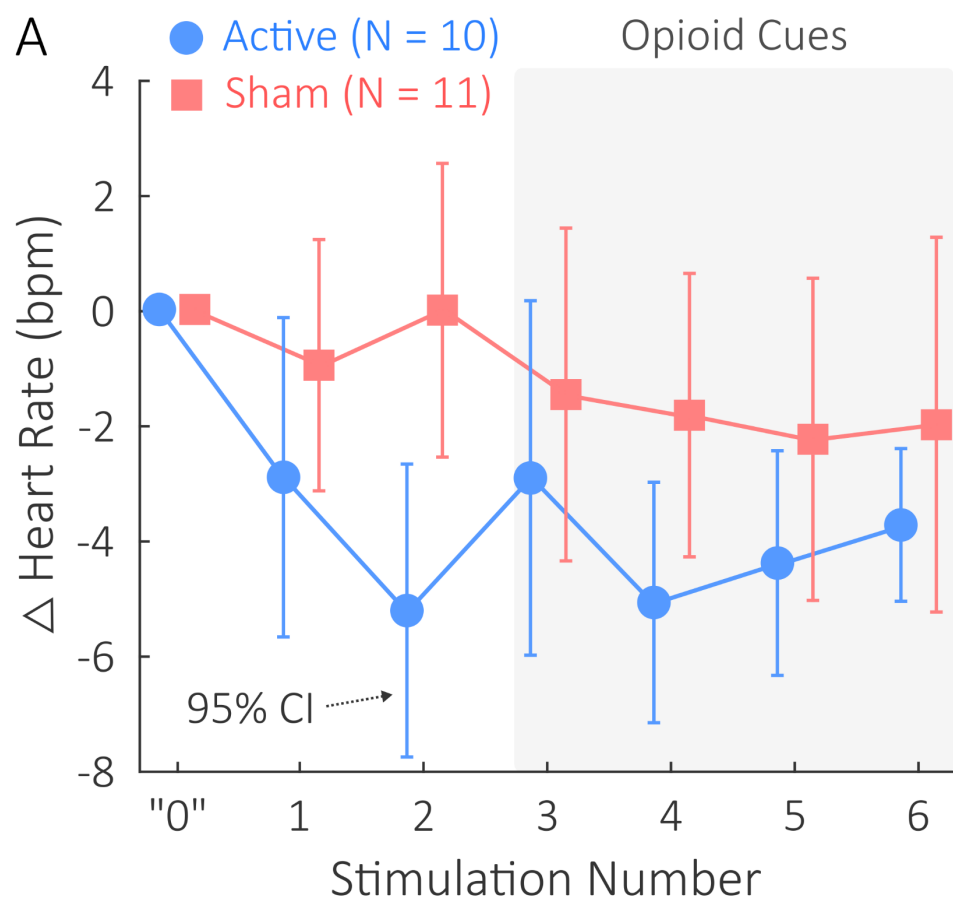


Active= VNS; ACF = autocorrelation function
VNS results in increased uniformity of expiration pattern

Effects of Heart Rate Variability Biofeedback on Myocardial Flow Reserve (MFR) with Mental Stress (MS)



Reduced Heart Rate and Drug Craving with Active VNS



Conclusions

- PTSD associated with increased cardiovascular disease, deficits in cardiac function, and mental stress-induced ischemia (MSI)
- MSI driven by regions of frontal cortex, associated with worse outcome
- Decreased heart rate variability and increased inflammation may be mediator of PTSD, depression, and cardiovascular risk
- VNS associated with reduction in stress, PTSD, opioid craving inflammatory and sympathetic responses to stress
- VNS enhancement in brain areas modulating emotion (anterior cingulate)