David Eddie, Ph.D.

# *Written in the body: What biomarkers reflecting brain-body communication can tell us about addiction recovery*

***November 8, 2018***

MASSACHUSETTS GENERAL HOSPITAL
Center for Addiction Medicine

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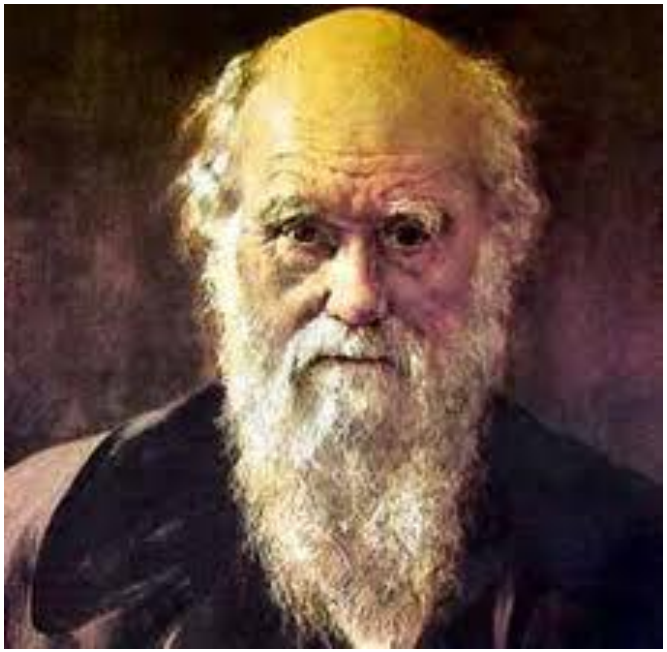
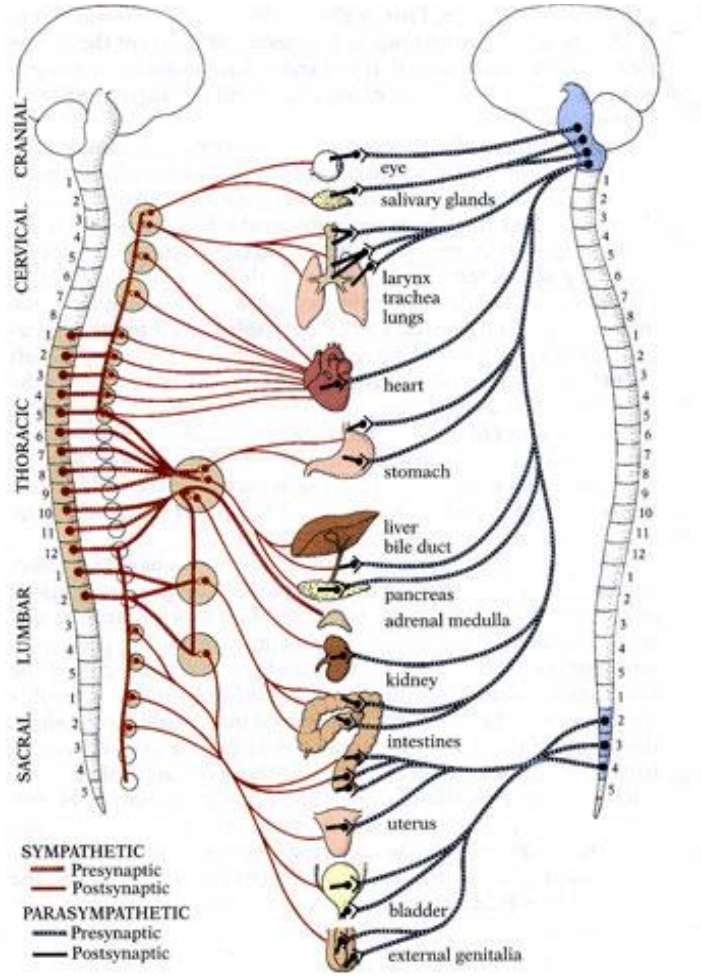
The importance of two-way communication between the brain and the heart during emotion has been known for over 100 years. Darwin, commenting on the work of the French physiologist Claude Bernard wrote:

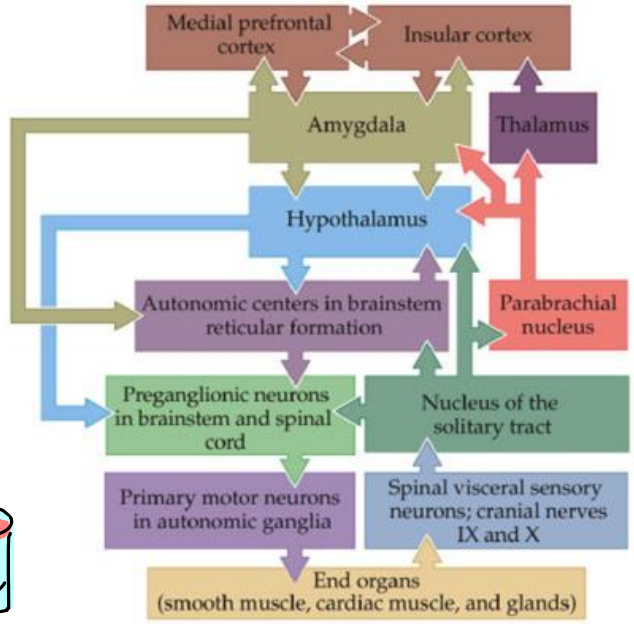
"…and this deserves special notice, that when the heart is affected it reacts on the brain; and the state of the brain again reacts through the pneumo-gastric nerve (vagus) on the heart; so that under any excitement there will be much mutual action and reaction between these, the two most important organs of the body." (Darwin, 1872).

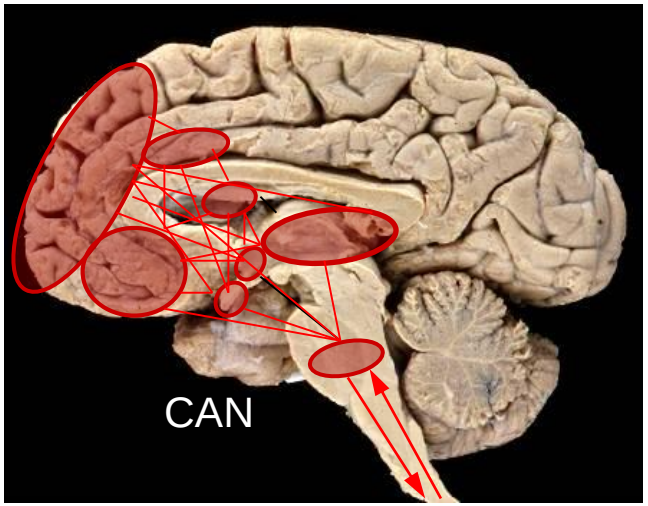


**Sympathetic** **Parasympathetic**

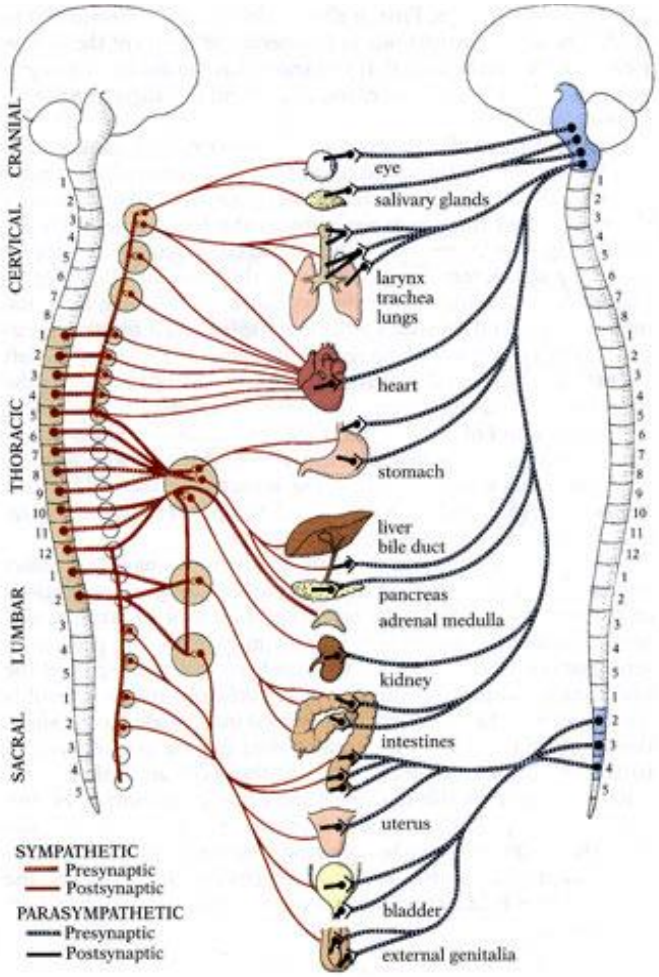


# Central Autonomic Network (CAN)

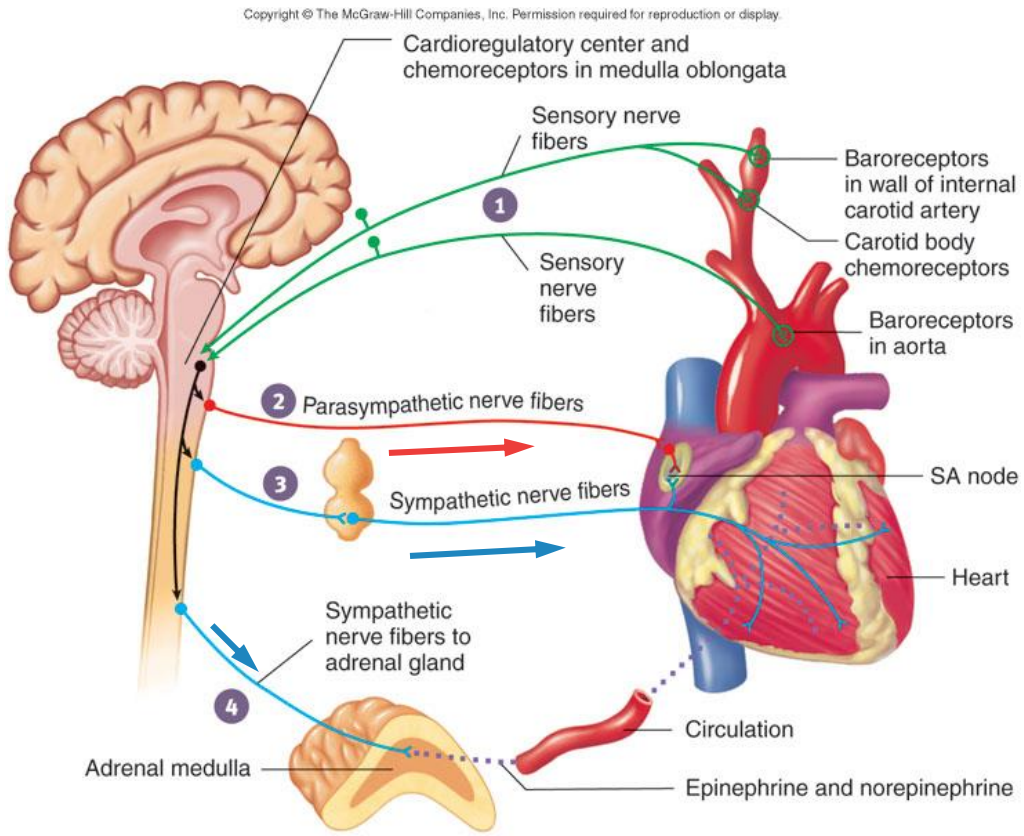



**Sympathetic** **Parasympathetic**

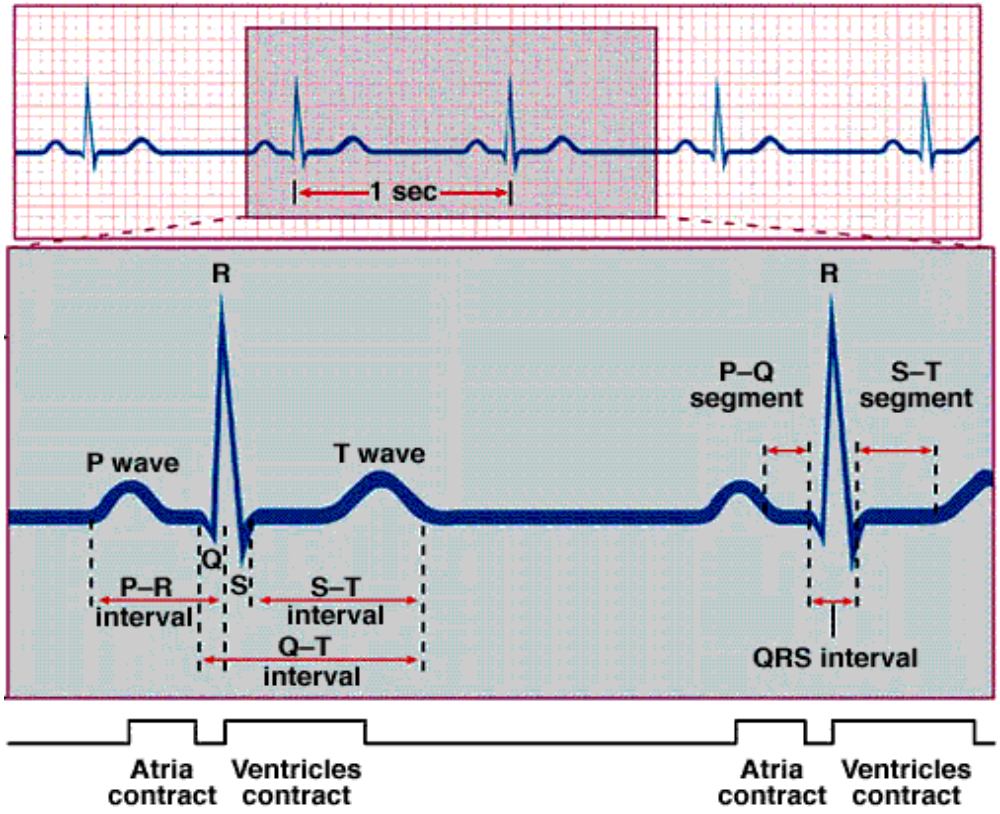


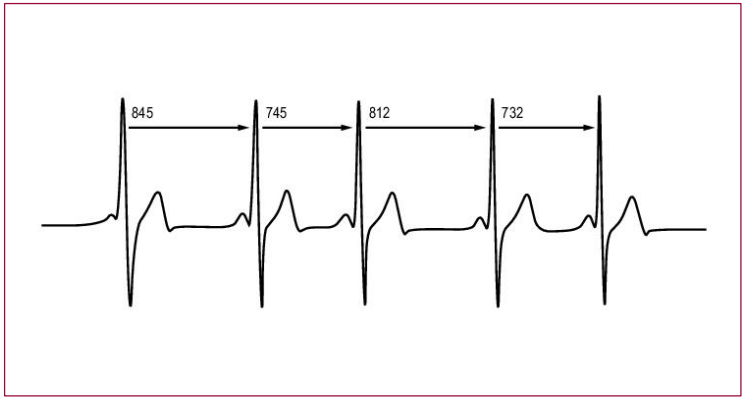
# Measuring CAN Activation




*Because the CAN affects regulatory actions via the cardiovascular system, indices of neurocardiac processes provide reliable measures of dynamic emotion regulation processes.*

# Measuring CAN Activation

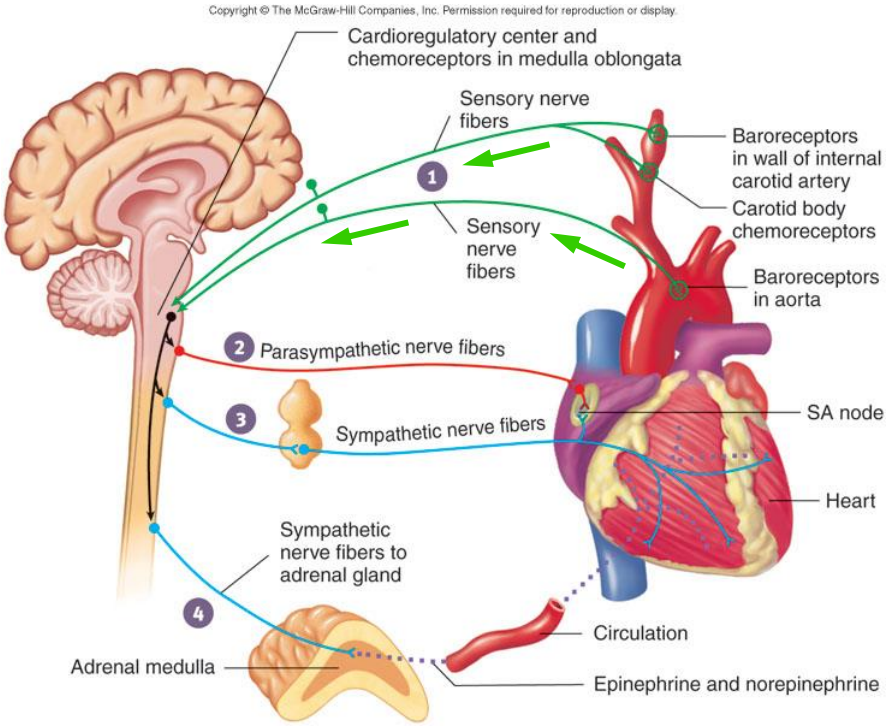


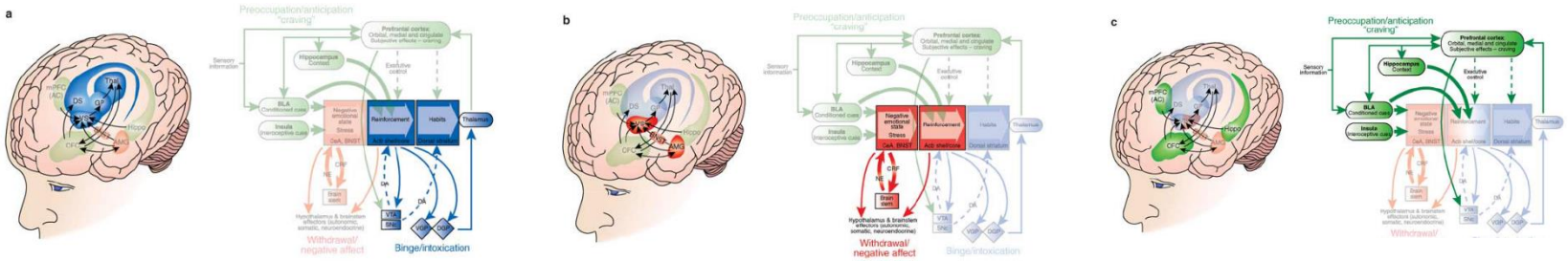

*Heart rate variability (HRV) reflects fine-grained, moment-to-moment changes initiated by the CAN in response to environmental and interoceptive stimuli.*

# Baroreflex Sensitivity (BRS)

- Bodily mechanism that, together with the CAN, generates HRV. Determines how well the body can respond to neural commands.
- Hypothesize that BRS is a mechanism that is protective by increasing HRV and stress resilience, and reducing HR, cue reactivity and craving (⬇ sympathetic activity)

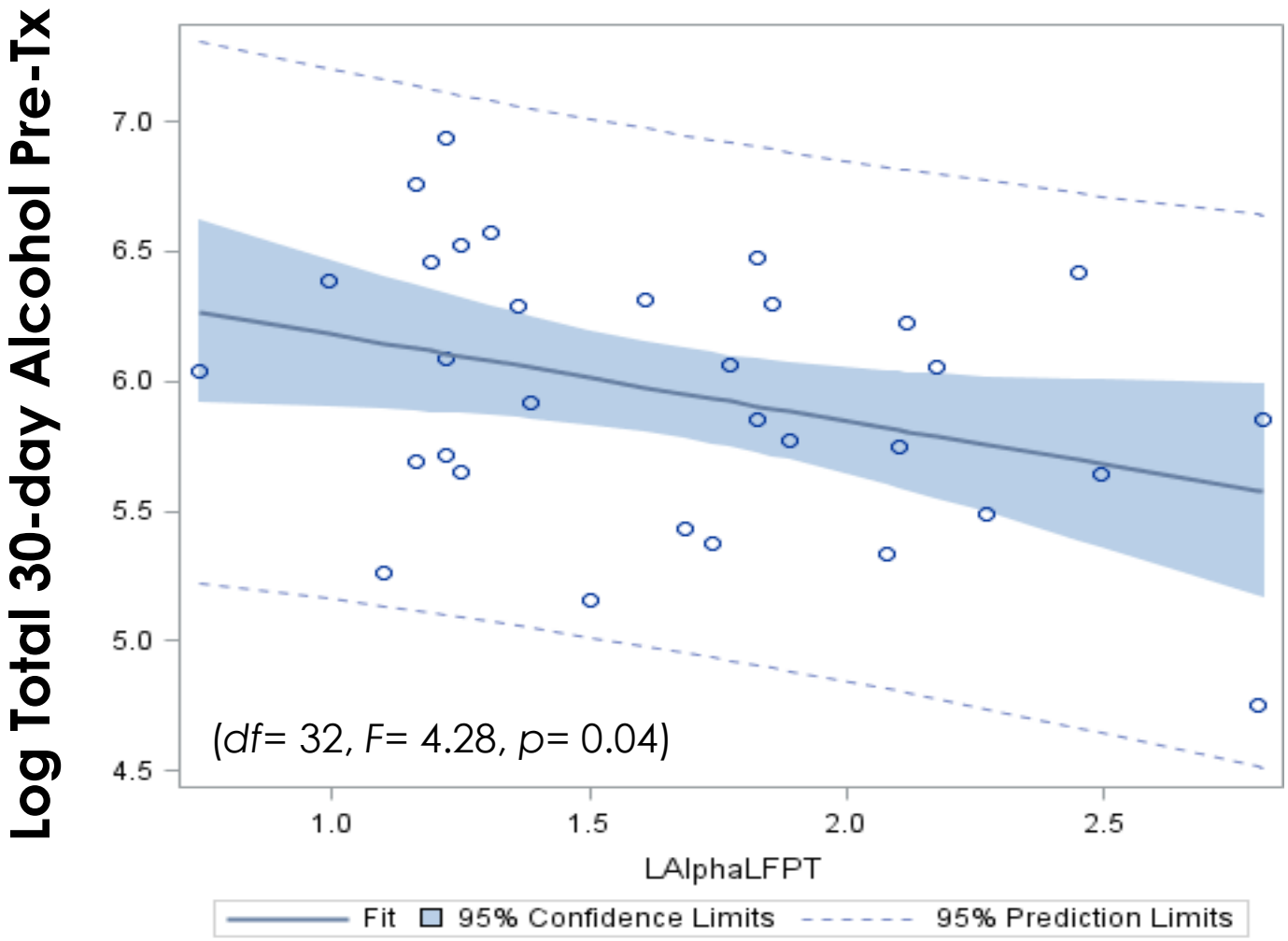


# Alcohol impairs feedback between the brain



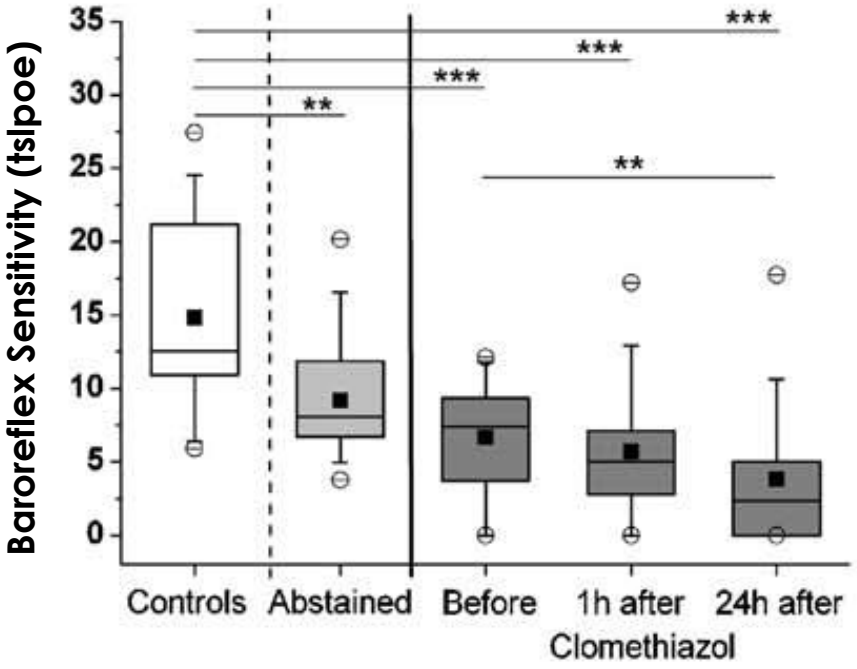

# and body

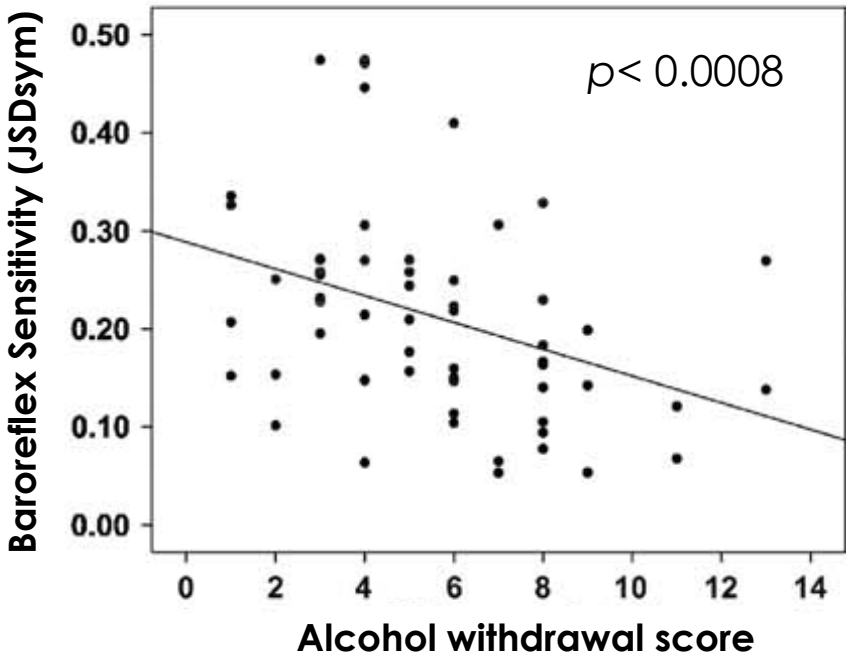
- Increases sympathetic arousal, as measured by heart rate and muscle sympathetic activity (Buckman, Eddie et al., 2015; Eddie et al., 2013; van de Borne, Mark, Montano, Mion, & Somers, 1997)
- Decreases parasympathetic vagus nerve activity, as measured by heart rate variability (Buckman, Eddie et al., 2015; Eddie et al., 2013; Levanon, Goss, & Chen, 2002; Reed, Porges, & Newlin, 1999)
- Negatively influences blood vessels (Bau et al., 2007)
- Dampens baroreflex sensitivity (Buckman, Eddie et al., 2015; Romanowicz et al., 2011; Bar et al., 2006)




**Log Baroreflex Sensitivity**

*Bates et al., Unpublished*




*Notes*, **$p < 0.001$, ***$p < 0.0001$; tslope= baroreflex sensitivity to tachycardic events; JSDsym= joint symbolic dynamics sympathetic

Bar, K. J., Boettger, M. K., Boettger, S., Groteluschen, M., Neubauer, R., Jochum, T., . . . Voss, A. (2006). Reduced baroreflex sensitivity in acute alcohol withdrawal syndrome and in abstained alcoholics. *Drug and alcohol dependence*

# Acamprosate (Campral) may reduce alcohol use/craving by restoring autonomic balance

*Alcohol & Alcoholism* Vol. 33, No. 6, pp. 602–605. 1998

**RAPID COMMUNICATION**

IMPROVED
ABST
M. W. A
Departments

*Alcohol & Alcoholism* Vol. 34, No. 2, pp. 197–222, 1999

A THREE-PATHWAY PSYCHOBIOLOGICAL MODEL

ROEL
Amsterda

PERSPECTIVES

Drug A
and All
*George F. Koob,*

**Acamprosate in alcohol dependence: how does it work?**

JOHN
*Division*

ORIGINAL INVESTIGATION

**The effects of acamprosate on alcohol-cue reactivity and alcohol priming controlled trial**

Anders Hammarberg · Nitya Jayar
Olof Beck · Johan Franck · Malcol

European Neuropsychopharmacology (2007) 17, 558–566

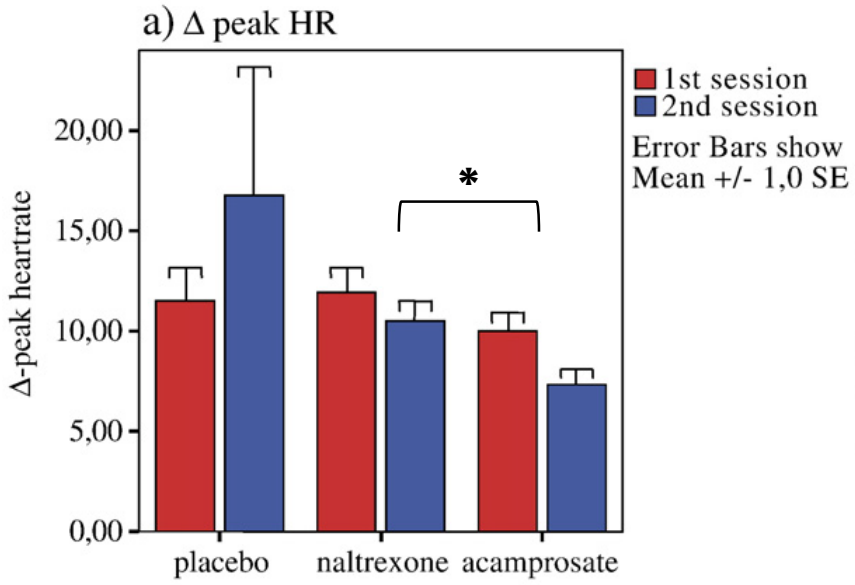
ELSEVIER

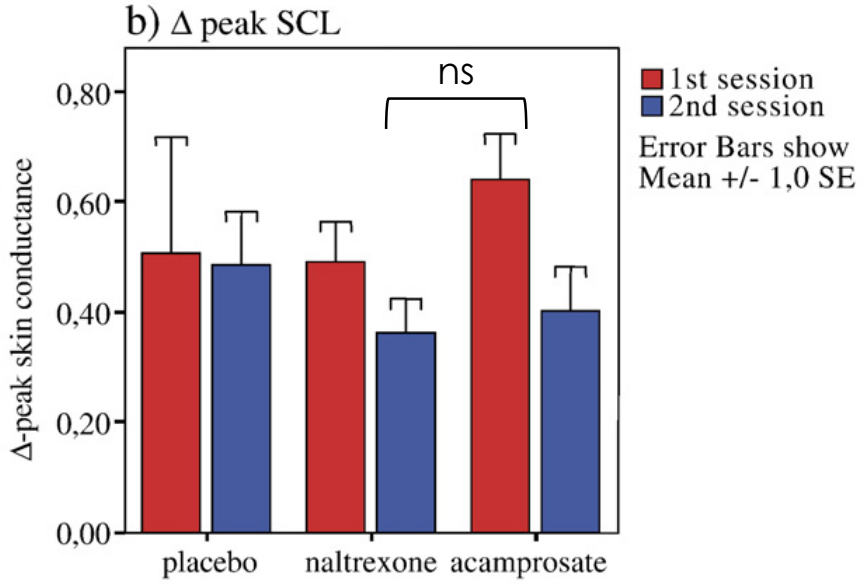
www.elsevier.com/locate/euroneuro

**The effect of naltrexone and acamprosate on cue-induced craving, autonomic nervous system and neuroendocrine reactions to alcohol-related cues in alcoholics**☆

Wendy Ooteman [a,b,*], Maarten W.J. Koeter [a,b], Roel Verheul [c,d], Gerard M. Schippers [a,b], Wim van den Brink [a,b]

# *Acamprosate (Campral) may reduce alcohol use/craving by restoring autonomic balance*




- Physiological reactivity to craving induction before and after three weeks of medication in adults with alcohol use disorder.
- Left bar represents cue-exposure session 1, right bar cue-exposure session 2.
- HR = heart rate, SCL = skin conductance level

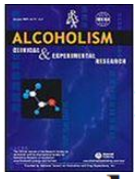
Ooteman, W., Koeter, M. W. J., Verheul, R., Schippers, G. M., & van den Brink, W. (2007). The effect of naltrexone and acamprosate on cue-induced craving, autonomic nervous system and neuroendocrine reactions to alcohol-related cues in alcoholics. *European Neuropsychopharmacology*

# *Prazosin also reduces alcohol use/craving*

## Noradrenergic targets for the treatment of alcohol use disorder

Carolina L. Haass-Koffler [1,2,3] · Robert M. Swift [1,4] · Lorenzo Leggio [2,3]


Alcoholism: Clinical and Experimental Research




## Prazosin Effects on Stress- and Cue-Induced Craving and

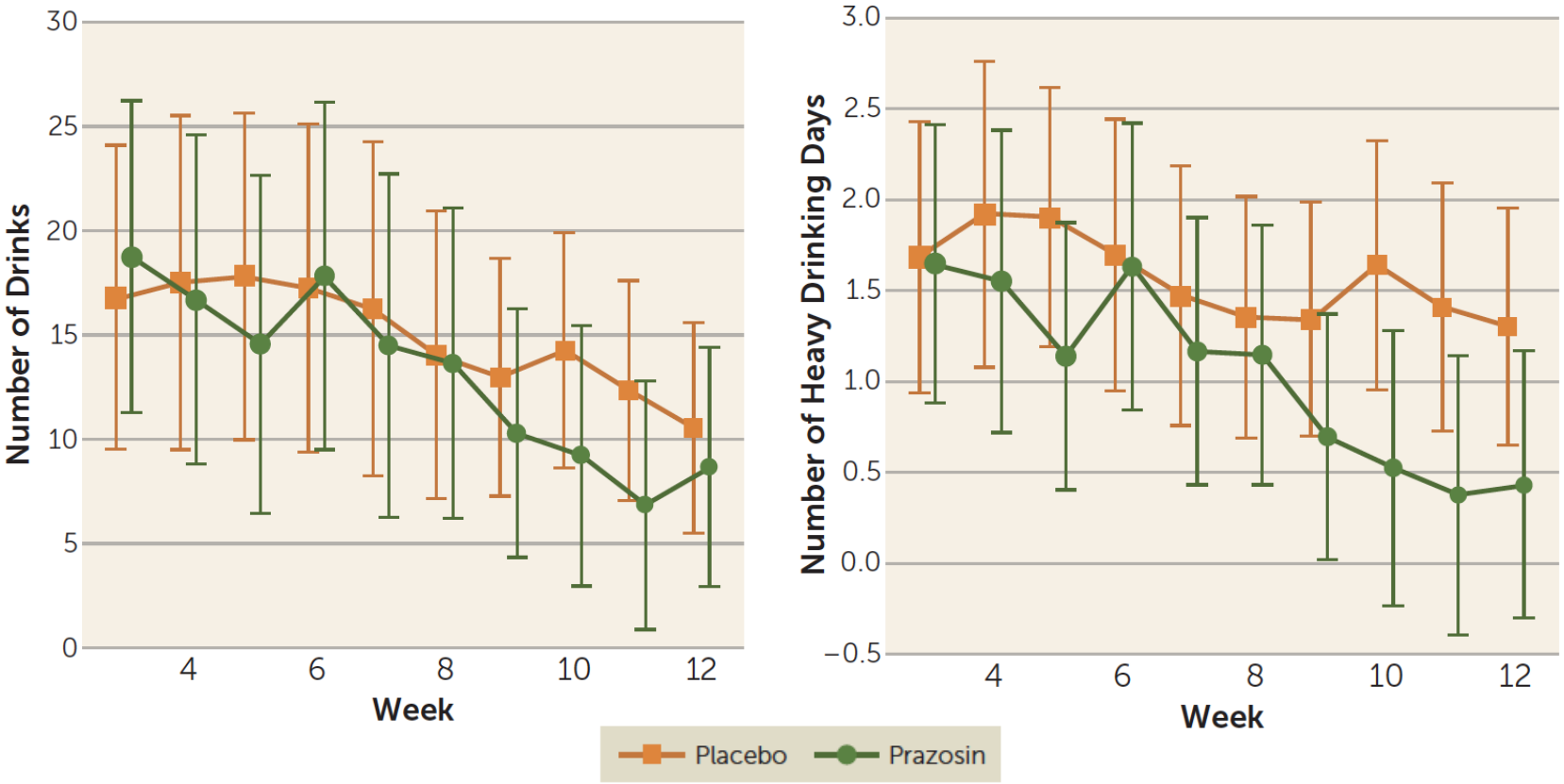

## Double-Blind Randomized Clinical Trial of Prazosin for

Editor's Choice


## A Randomized, Placebo-controlled, Clinical Trial of Prazosin for the Treatment of Alcohol Use Disorder

*Claire E. Wilcox, MD, J. Scott Tonigan, PhD, Michael P. Bogenschutz, MD, Joshua Clifford, BA, Rose Bigelow, MS, and Tracy Simpson, PhD*

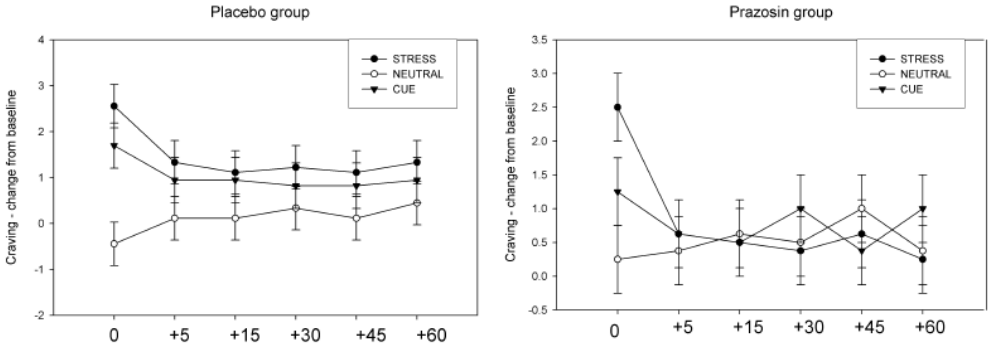
# *Prazosin also reduces alcohol use/craving*




- Significant group x time interaction. Prazosin associated with greater reductions in number drinks and heavy drinking days.

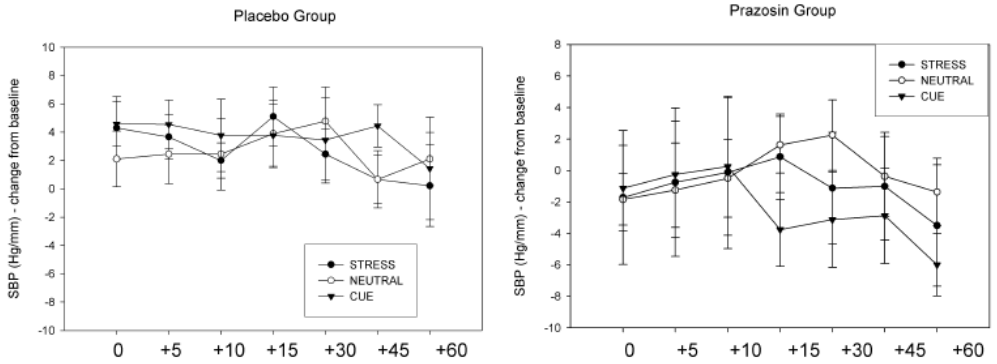
Simpson, T. L., Saxon, A. J., Stappenbeck, C., Malte, C. A., Lyons, R., Tell, D., . . . Raskind, M. (2018). Double-blind randomized clinical trial of prazosin for alcohol use disorder. *American Journal of Psychiatry*

## Alcohol Craving



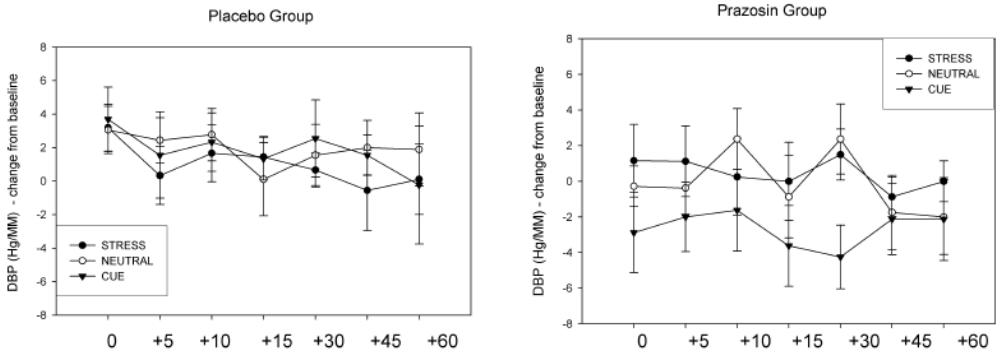

Prazosin reduced alcohol craving during cue exposure (main effect, *p*= 0.0001)

## Systolic Blood Pressure




Trend observed for prazosin reducing SBP (main effect, *p*= 0.06)

## Diastolic Blood Pressure




Prazosin reduced DBP during cue exposure (main effect, *p*= .01), and resulted in decreased DBP reactivity to alcohol, vs. neutral cues (*p* = 0.0003)

Fox, H. C., Anderson, G. M., Tuit, K., Hansen, J., Kimmerling, A., Siedlarz, K. M., . . . Sinha, R. (2012). Prazosin effects on stress-and cue-induced craving and stress response in alcohol-dependent individuals: Preliminary findings. *Alcoholism: Clinical and Experimental Research*


ORIGINAL RESEARCH

Editor's Choice

# A Randomized, Placebo-controlled, Clinical Trial of Prazosin for the Treatment of Alcohol Use Disorder

*Claire E. Wilcox, MD, J. Scott Tonigan, PhD, Michael P. Bogenschutz, MD, Joshua Clifford, BA, Rose Bigelow, MS, and Tracy Simpson, PhD*

**Objectives:** The noradrenergic system plays an important role in the pathophysiology of alcohol use disorder (AUD). Medications in this class may reduce drinking. Our aims were to investigate this in a unique sample of individuals with AUD.

**Methods:** Thirty-six individuals with AUD were randomized to treatment with prazosin, an alpha-1 noradrenergic antagonist, or placebo, for 6 weeks (target daily dose 16 mg). Hierarchical linear modeling was used to examine the effect of treatment group on rate of change in primary (drinks per week [DPW]) and several secondary outcome measures.

indicate that it might have some efficacy in individuals who can tolerate it. Further work exploring the clinical utility of DBP as a treatment matching variable, and defining optimal values using sensitivity and specificity analyses, is warranted.

**Key Words:** adherence, adrenergic, alcohol use disorder, blood pressure, prazosin

(*J Addict Med* 2018;12: 339–345)

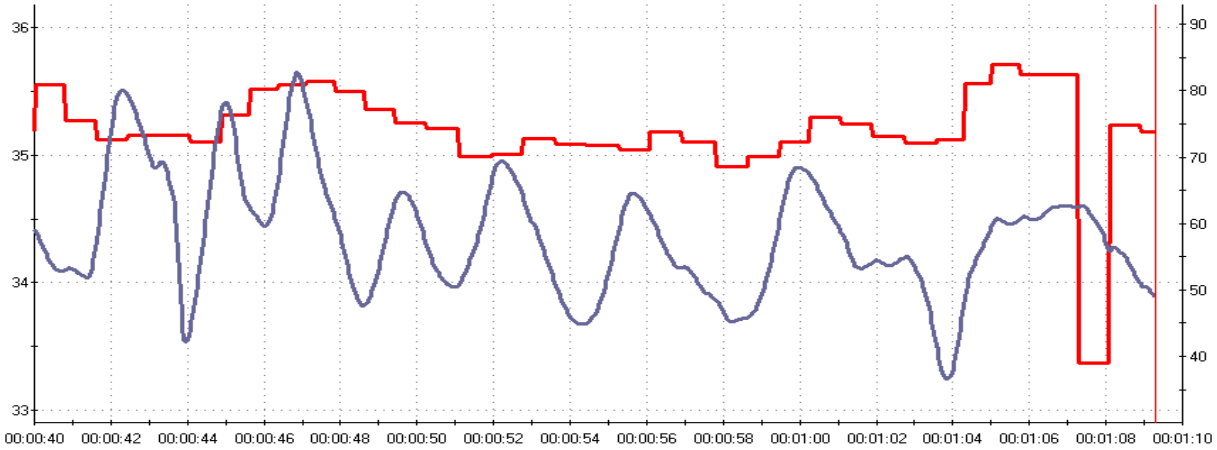
The norepinephrine system plays an important role in AUD development and maintenance (Koob, 2008;

*"Prazosin was associated with greater rates of reduction in drinking compared with placebo in individuals with high, but not low diastolic blood pressure."*

Wilcox, C. E., Tonigan, J. S., Bogenschutz, M. P., Clifford, J., Bigelow, R., & Simpson, T. (2018). A randomized, placebo-controlled, clinical trial of prazosin for the treatment of alcohol use disorder. *Journal of Addiction Medicine*

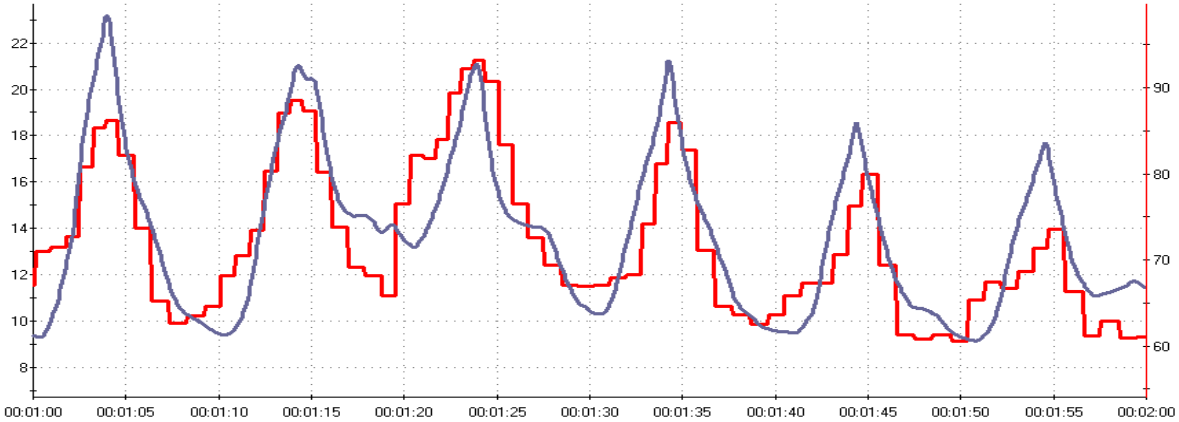
# Before and After

Blue = Respiration



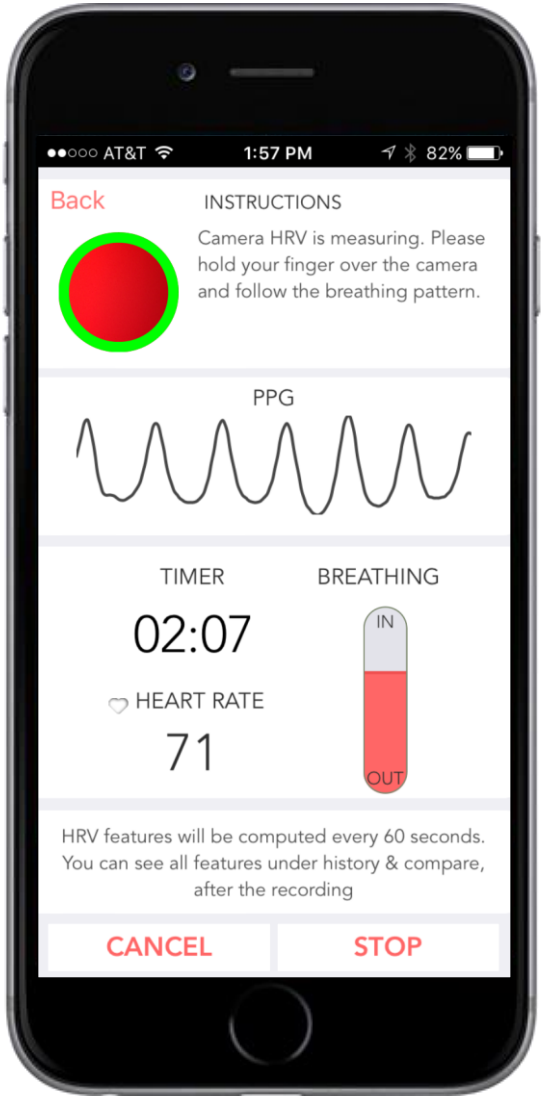

Red = Heart Rate

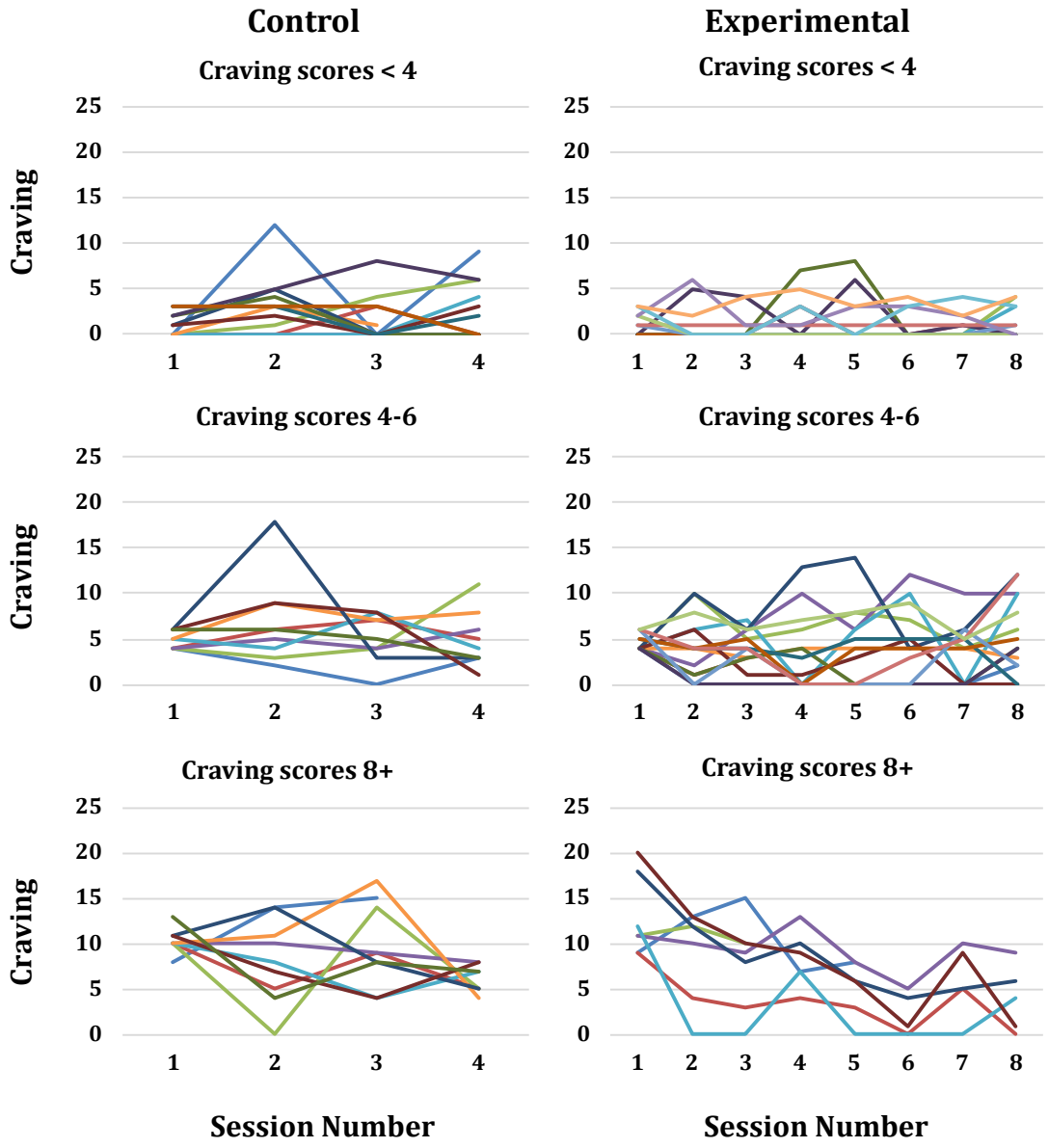
Regular Breathing
(Chaos)




Paced Breathing
(Resonance)

# *Heart Rate Variability Biofeedback Apps*




Control
β= –0.08 (0.17)

Experimental
β= –0.22 (0.07)*

Eddie, D., Conway, F. N., Alayan, N., Buckman, J. F., & Bates, M. E. (2018). Assessing heart rate variability biofeedback as an adjunct to college recovery housing programs. *Journal of Substance Abuse Treatment*

## Take Home Points

- Brain/body communication plays an important role in addiction and addiction recovery.
- Need to be considering the brain/body relationship in the addictions treatment space (not just the brain).
- Treatments exist that can buffer relapse risk by restoring autonomic balance.

# Acknowledgments

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