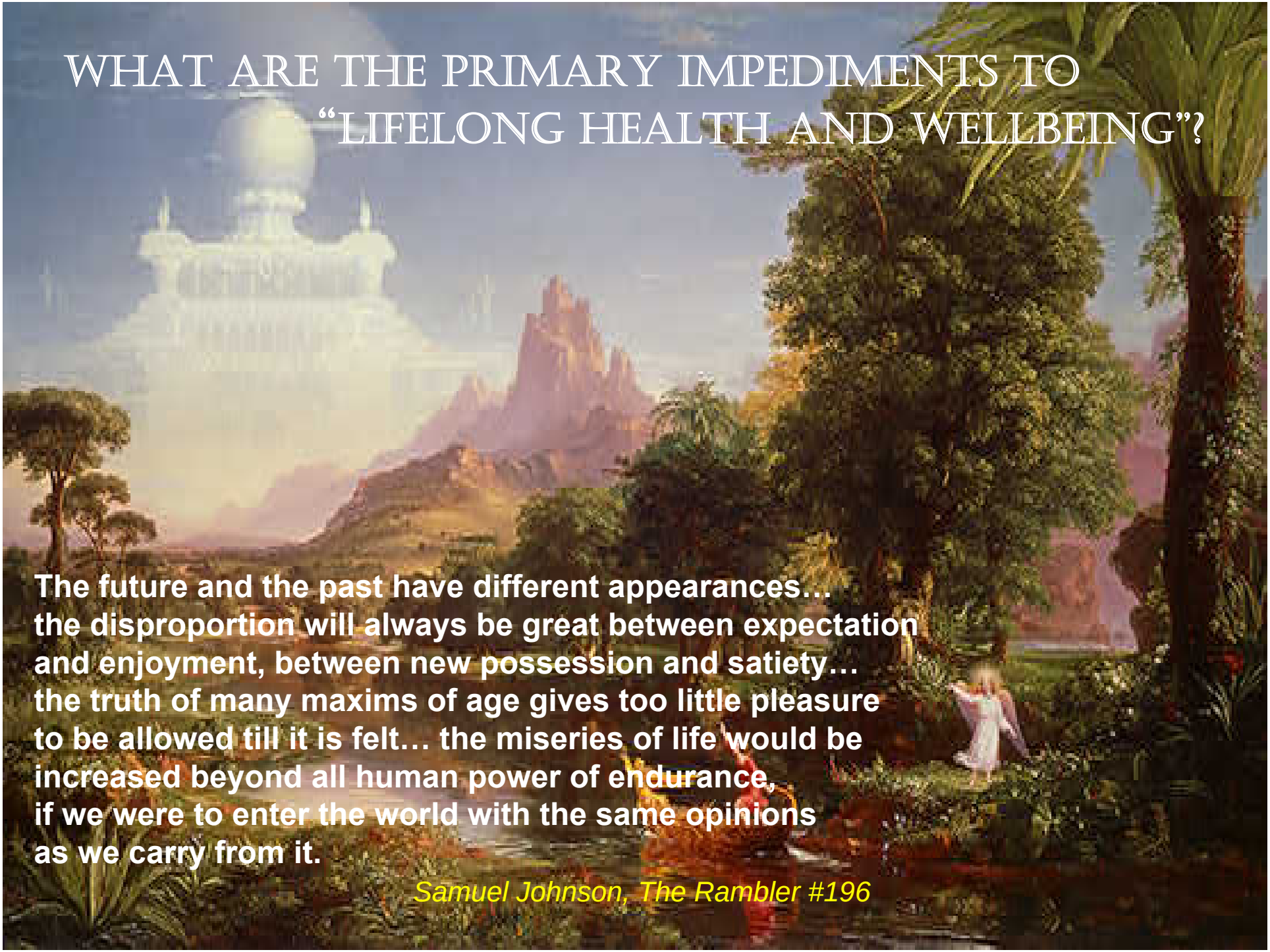
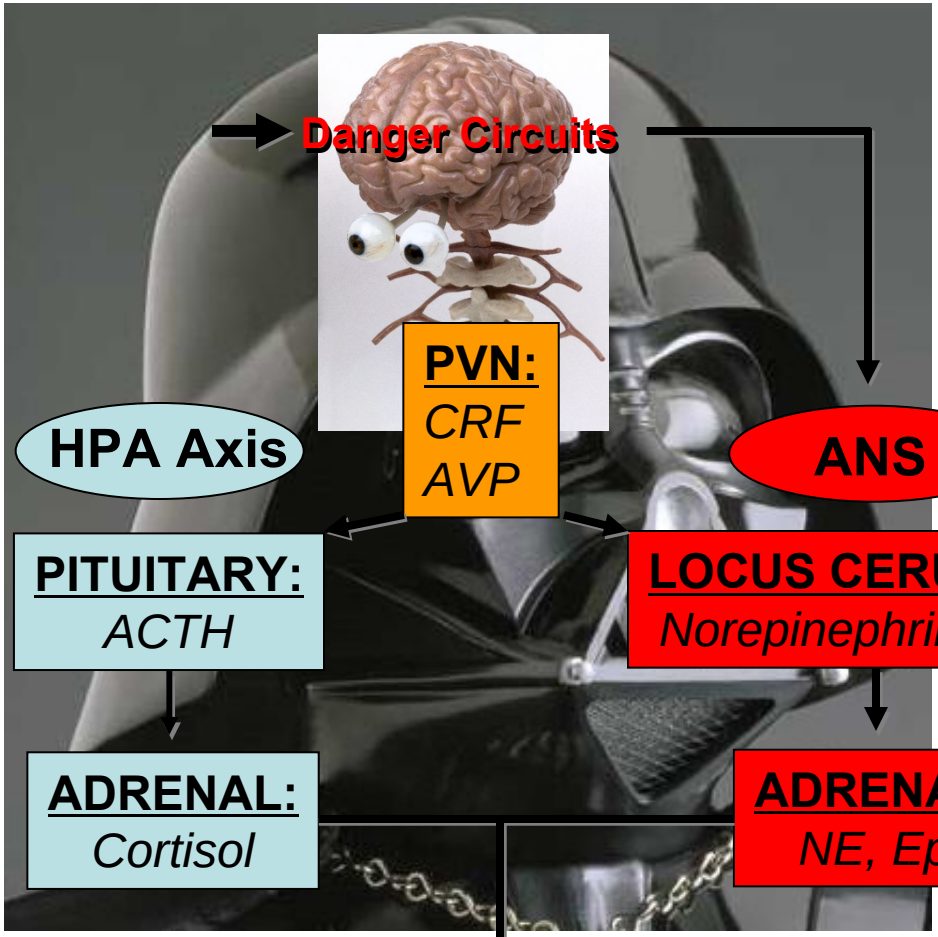
Meditation, Inflammation, and Consternation:

Applying Buddhist Wisdom to Activity in Health-Relevant Danger Pathways

Charles L. Raison, MD
Assistant Professor
Clinical Director
Mind-Body Program
Department of Psychiatry and Behavioral Sciences
Emory University School of Medicine
Atlanta, GA


WHAT ARE THE PRIMARY IMPEDIMENTS TO
"LIFELONG HEALTH AND WELLBEING"?
The future and the past have different appearances…
the disproportion will always be great between expectation
and enjoyment, between new possession and satiety…
the truth of many maxims of age gives too little pleasure
to be allowed till it is felt… the miseries of life would be
increased beyond all human power of endurance,
if we were to enter the world with the same opinions
as we carry from it.
Samuel Johnson, The Rambler #196

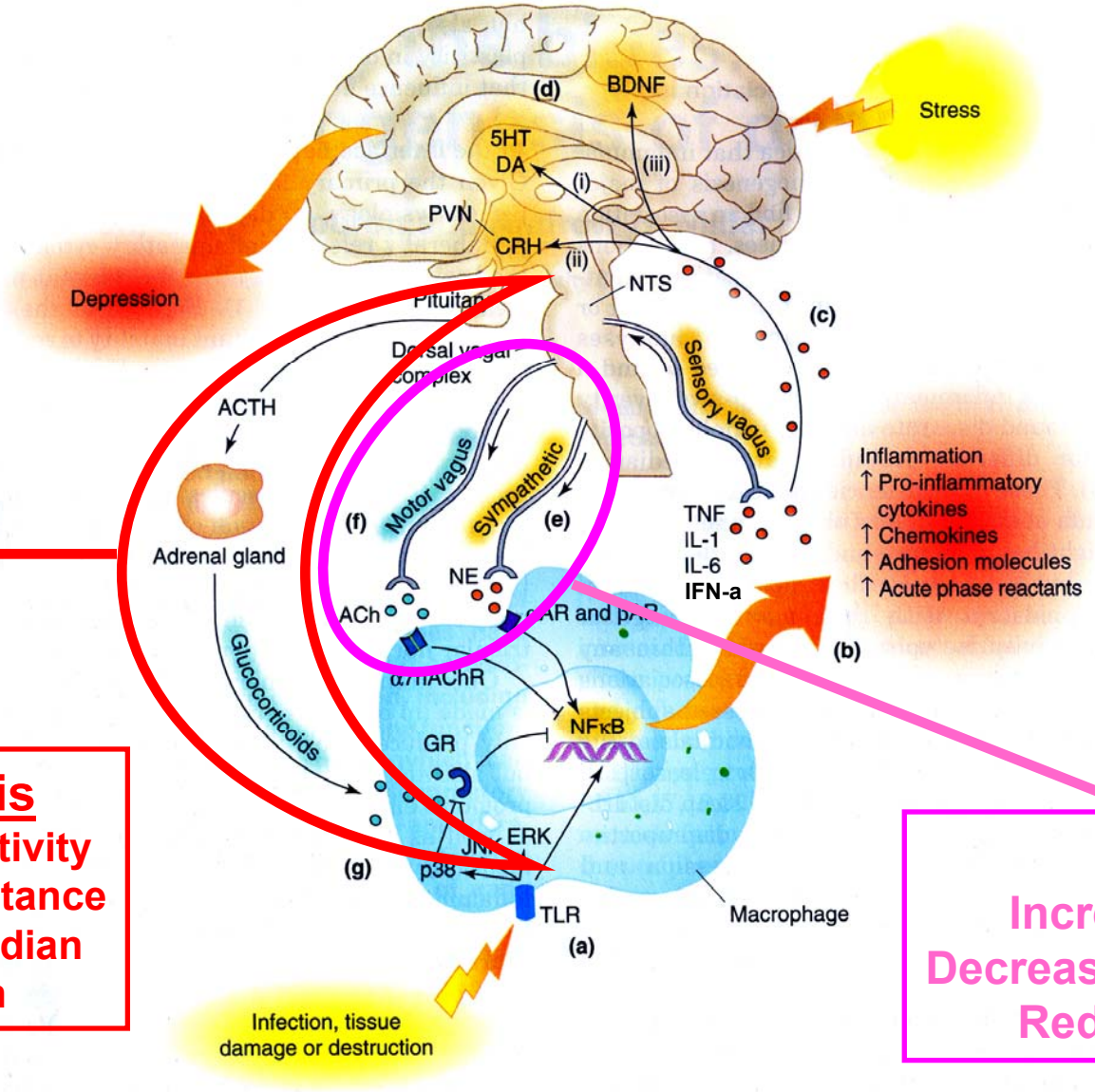

WHAT ARE THE PRIMARY IMPEDIMENTS TO
"LIFELONG HEALTH AND WELLBEING"?
-Psychosocial Stress
-Sickness



FLIGHT RESPONSE:
Production, mobilization, and direction of energy. Shut down of all nonessential bodily, vegetative, functions. Narrowing of attentional focus to perceived danger.

INNATE IMMUNE RESPONSE:
Activation of systemic inflammatory response to prime the immune system for tissue damage from danger situation

Chronic Stress, Depression and the Stress System

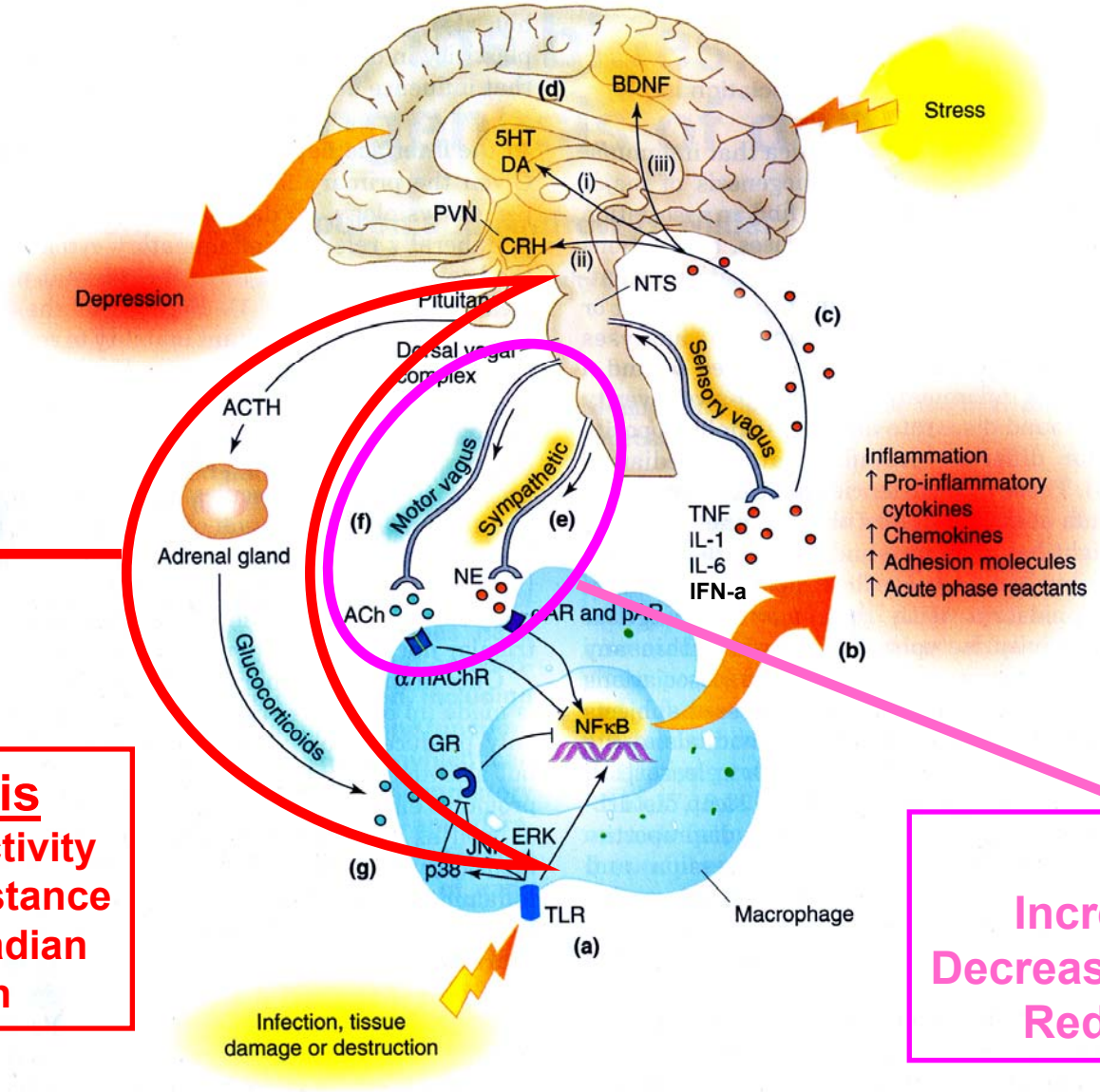


HPA Axis
Increased activity
Develop resistance
Loss of circadian variation

ANS
Increased SNS
Decreased cholinergic
Reduced HRV

Raison et al. *Trend Immun*, 27:24-31, *2006*

Pathways Linking Stress, Inflammation and Depression

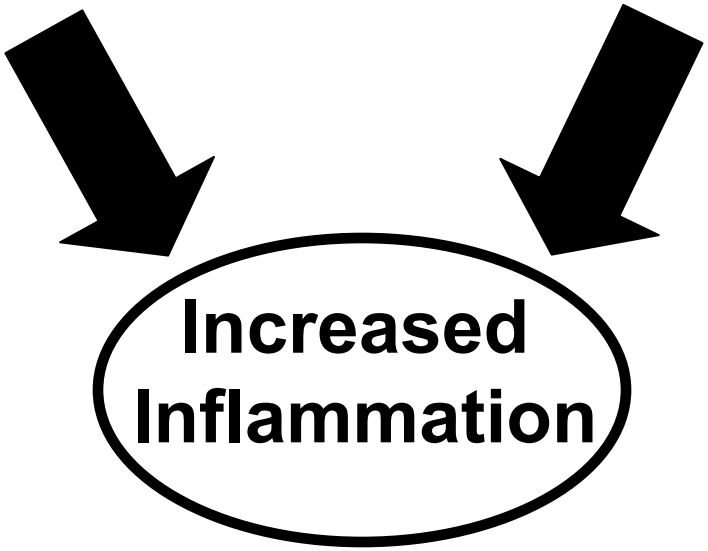


HPA Axis
Increased activity
Develop resistance
Loss of circadian variation

ANS
Increased SNS
Decreased cholinergic
Reduced HRV

Raison et al. *Trend Immun*, 27:24-31, *2006*

Pathways Linking Stress, Inflammation and Depression



HPA Axis
Increased activity
Develop resistance
Loss of circadian variation

ANS
Increased SNS
Decreased cholinergic
Reduced HRV

Raison et al. *Trend Immun*, 27:24-31, *2006*

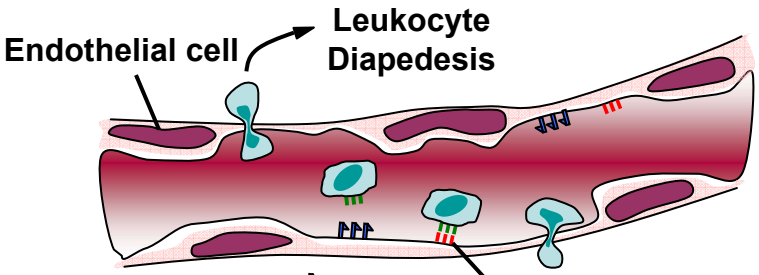

What is Inflammation?

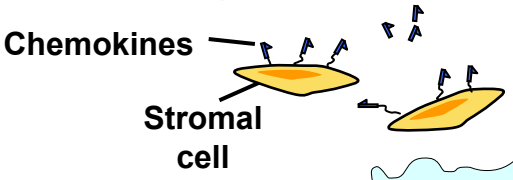
Why does sickness exist?

- **Sickness causes physical and behavioral changes that have promoted overall survival in animals for millions of years. Sickness makes the body inhospitable to microbes and aids in tissue repair.**

Consider fever:

- **Higher body temperature promotes microbial death.**
- **Blocking fever markedly increases mortality after infection in reptiles and mammals.**
- **When infected, reptiles will crawl to hot places to give themselves a fever. If this behavior is blocked, mortality increases**
- **Induction of fever with malaria was the first effective treatment for syphilis.**
- **Blocking fever has been shown to prolong viral infections in humans.**



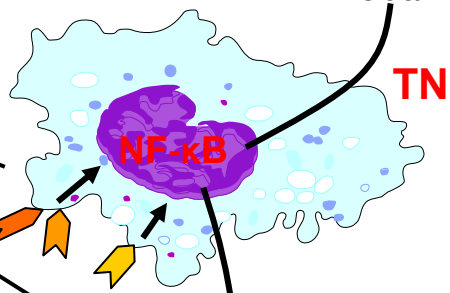


Local

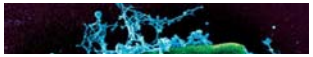
Local Effects

- Increased vascular permeability
- Vasodilation
- Chemokine production
- Expression of adhesion molecules
- Pain

tumor
rubor
calor
dolor



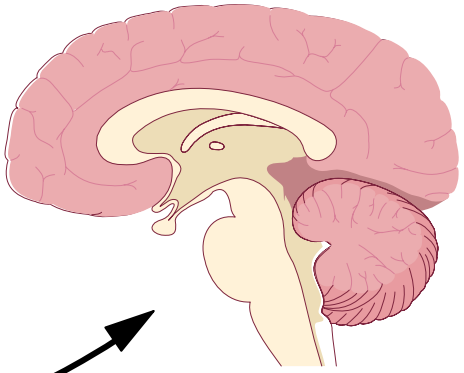
TNF, IL-1, IL-6 IFN-alpha



Toll-like
receptors

TNF
IL-1
IL-6
IFN-alpha

Systemic



ts on Liver

hase Response
ctive protein
amyloid A
globin
1-antichymotrypsin

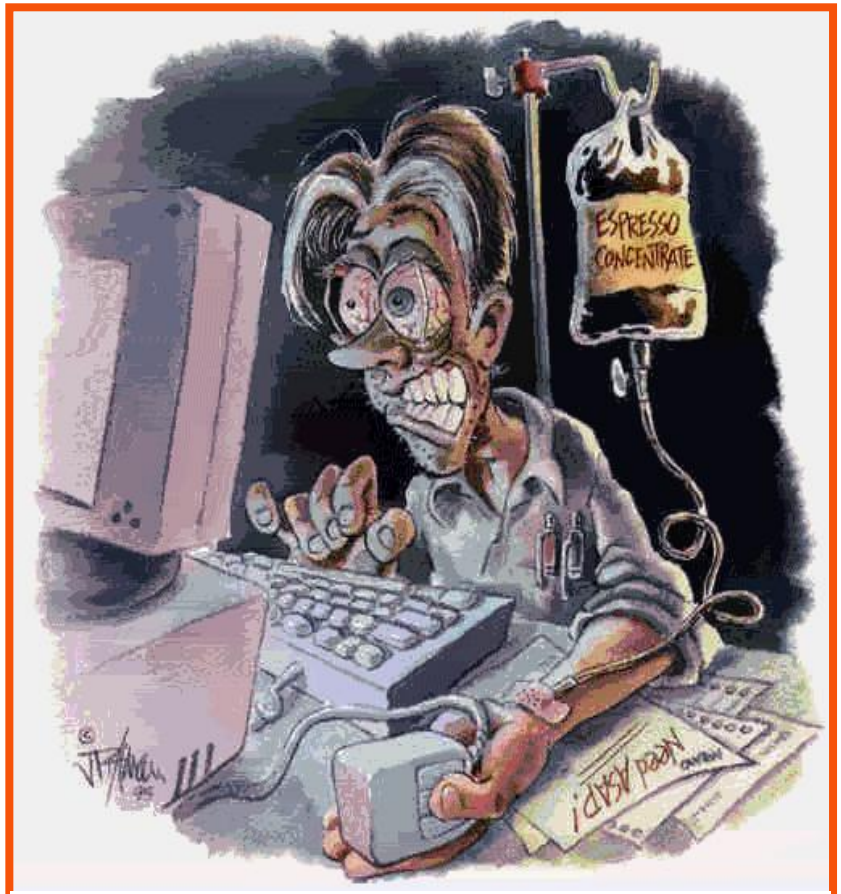
Effects on Brain

- Fever
- Fatigue
- Anorexia
- Anhedonia
- Altered sleep

sickness behavior/ depression

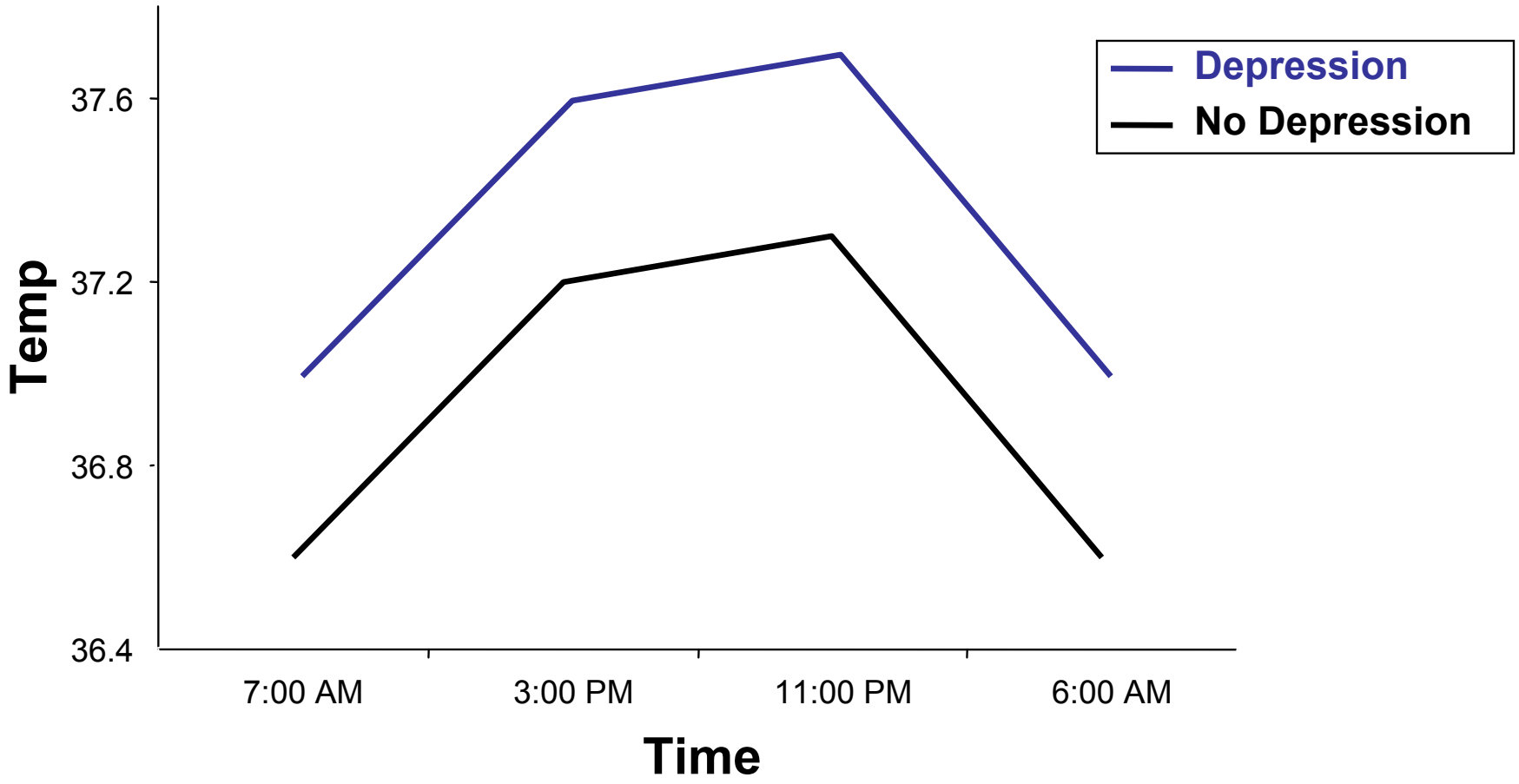
Conservation of energy resources to promote increased metabolic demands of fighting infection and mounting a fever

How Do We Know Stress Activates Inflammation?



Psychosocial Stress Test

Depression is Associated with Elevated Body Temperature in Medically Healthy Patients



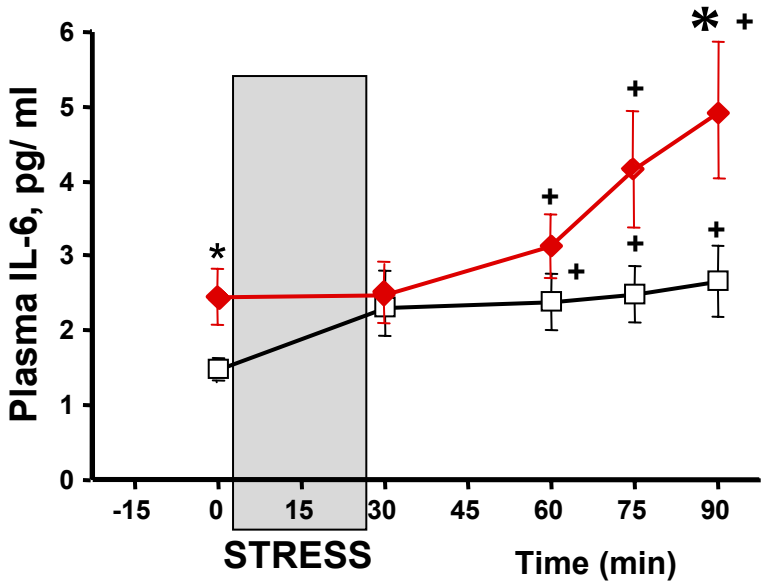
Szuba et al. Biol Psychiatry 1998

How Do We Know Stress Activates Inflammation?

Psychosocial Stress Activates Inflammation: Effect of Depression

Medically Health Men WITHOUT Major Depression (n = 13)

Medically Health Men WITH Major Depression (n = 14)



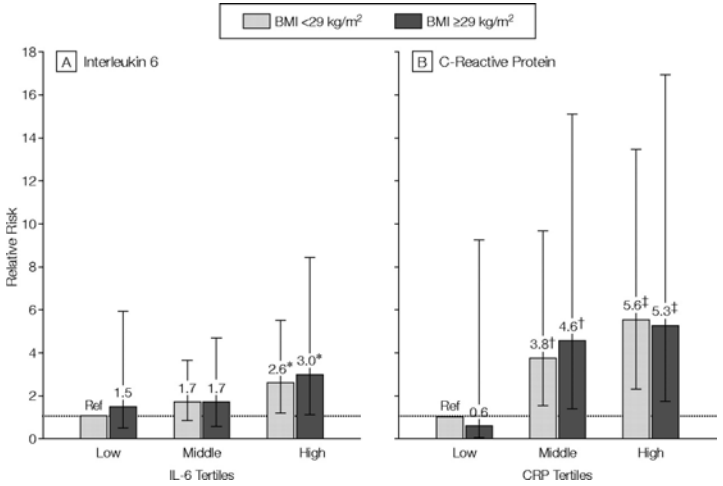
*Between group comparison, p < 0.05

+Within group comparison vs. 0 min time pt, p < 0.05

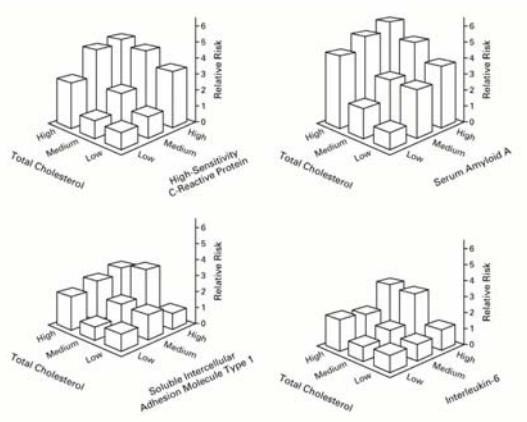
Pace et al., *Am J Psychiatry*, 2006.

Inflammation as a Link Between Stress, Depression and Illness

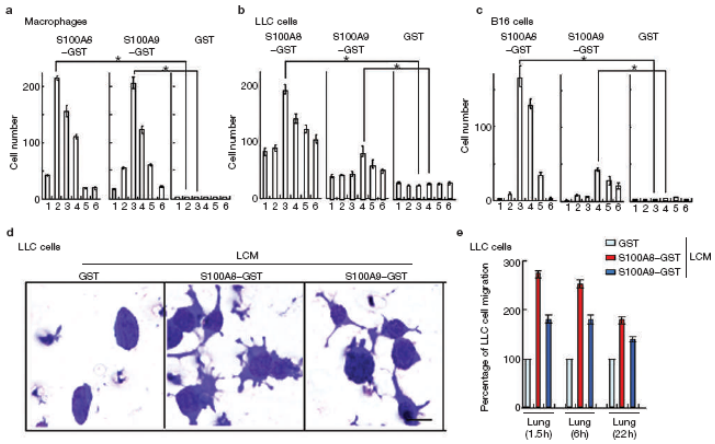
DIABETES



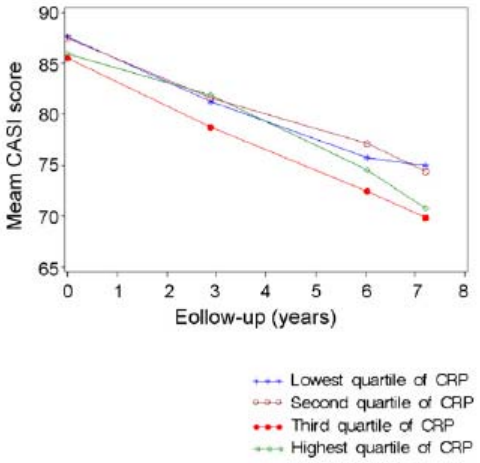
CARDIOVASCULAR



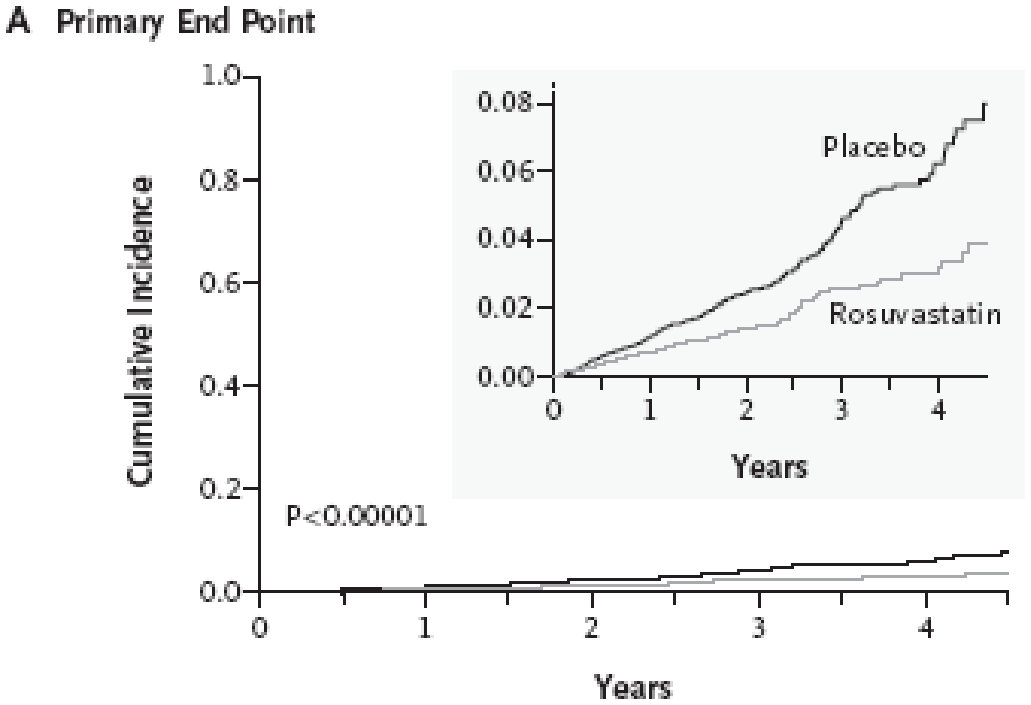
CANCER



DEMENTIA



Lowering Normal hs-CRP Reduces Risk of Future Cardiovascular Events



No. at Risk

Rosuvastatin	8901	8631	8412	6540	3893	1958	1353	983	538	157
Placebo	8901	8621	8353	6508	3872	1963	1333	955	531	174

Subjects: normal cholesterol, triglycerides, BP, hs-CRP > 2 mg/L

Ridker PM et al. NEJM 2008

HYPOTHESIS:
Any strategy that reduces inflammatory responses to psychosocial stress should provide protection against the development of depression and many other stress-related medical conditions.

But what strategy?

Positive Social Connectivity Associated with Reduced Inflammation

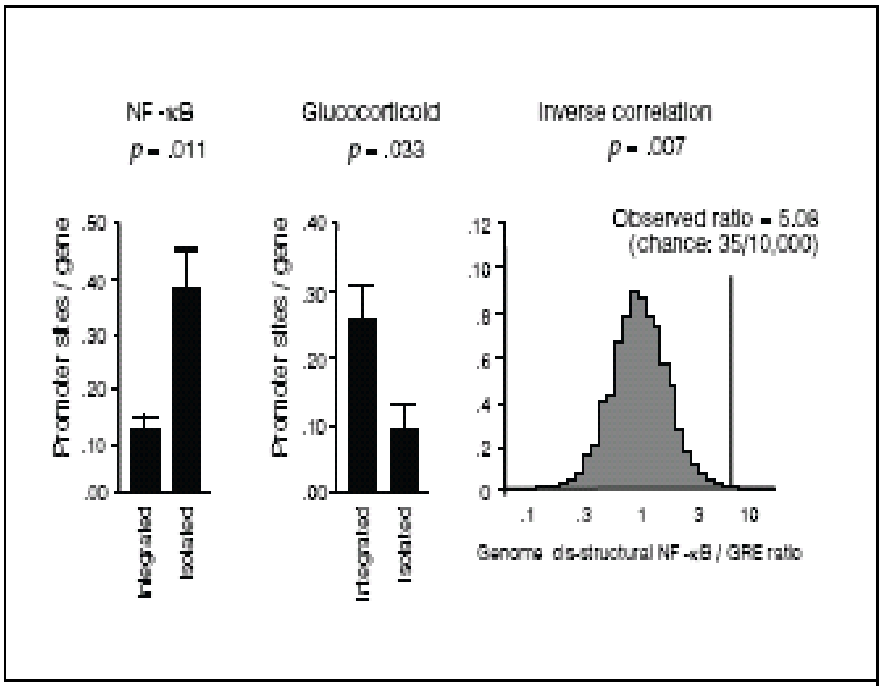


Figure 2
Transcriptional activity of GR and NF-κB signaling pathways. TELiS bioinformatics analysis assessed transactivational activity based on the relative prevalence of GR and NF-κB response elements in the promoters of all 209 transcripts over-expressed in high- versus low-lonely individuals (data represent mean ± standard error prevalence of response elements within promoters from each group). Contributions of in-vitro regulatory influences to the observed inverse skew of NF-κB and GR response elements within differentially expressing promoters was tested by comparison to a null distribution of genome-wide DNA cis-structural associations generated by 10,000 random samples of 209 transcripts assayed by Affymetrix U133A arrays.

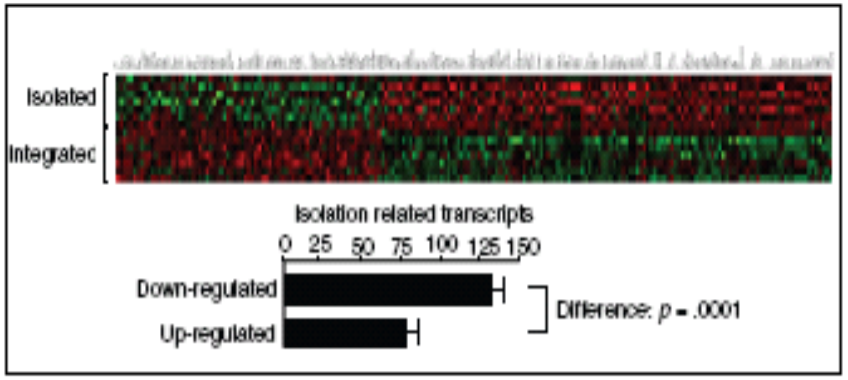


Figure 1
Differential gene expression in high- versus low-lonely individuals. Genome-wide transcriptional profiles were assessed in peripheral blood leukocyte RNA samples collected from individuals in the top and bottom 15% of the distribution of subjective social isolation. Analysis by Affymetrix U133A high-density oligonucleotide arrays identified 209 transcripts showing >20% difference in mean expression levels across groups (green = over-expression in high-lonely, red = under-expression). High subjective social isolation is associated with a statistically significant net reduction in the number of expressed genes (131 down-regulated versus 78 up-regulated, p value by exact binomial test).

		Social Network Index				
		1 (low)	2	3	4 (high)	*p*
Men	Model 1	4·15 (0·36)	4·10 (0·25)	3·68 (0·27)	3·43 (0·33)	**0·0001**
IL-6 (pg/ml)	Model 2	3·91 (0·36)	3·99 (0·25)	3·61 (0·29)	3·43 (0·33)	**0·002**
	Model 3	3·85 (0·38)	3·97 (0·27)	3·59 (0·28)	3·52 (0·35)	**0·03**
Women	Model 1	3·98 (0·27)	3·51 (0·20)	3·45 (0·18)	3·47 (0·22)	**0·03**
IL-6 (pg/ml)	Model 2	3·67 (0·27)	3·36 (0·20)	3·42 (0·18)	3·46 (0·22)	0·46
	Model 3	3·64 (0·28)	3·33 (0·21)	3·43 (0·19)	3·38 (0·23)	0·39
Men	Model 1	3·82 (0·57)	3·72 (0·41)	3·39 (0·44)	3·37 (0·54)	0·08
CRP (mg/l)	Model 2	3·23 (0·57)	3·45 (0·40)	3·10 (0·44)	3·13 (0·53)	0·31
	Model 3	3·18 (0·62)	3·41 (0·43)	3·09 (0·46)	3·34 (0·57)	0·96
Women	Model 1	4·85 (0·39)	4·69 (0·29)	4·74 (0·26)	4·79 (0·32)	0·99
CRP (mg/l)	Model 2	3·92 (0·37)	3·88 (0·27)	4·12 (0·24)	4·16 (0·30)	0·27
	Model 3	3·90 (0·38)	3·86 (0·28)	4·15 (0·26)	4·21 (0·31)	0·20

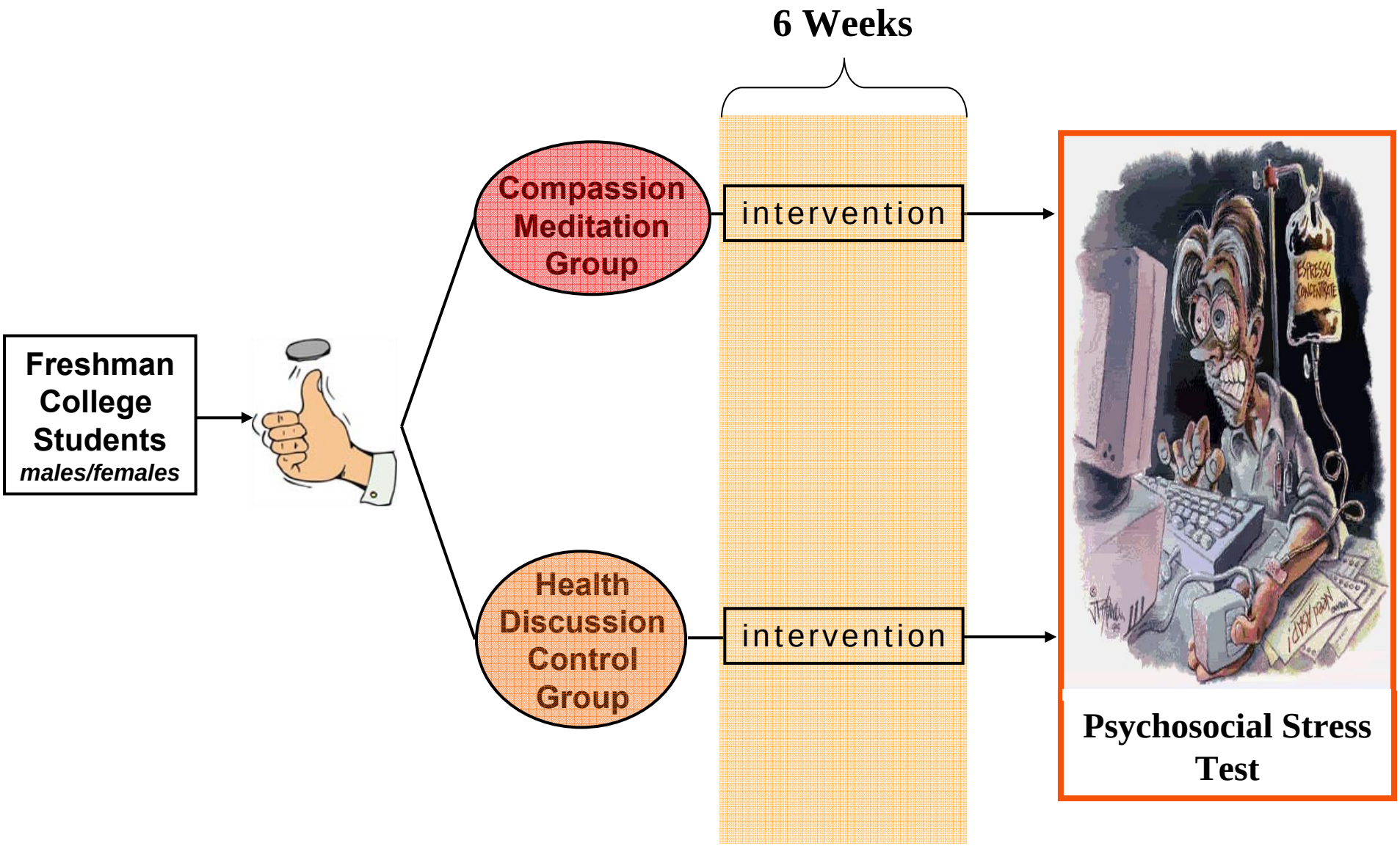
Social Networks Index =1 means no/very few social networks; =4 means many social networks.
Model 1 adjusted for age.
Model 2 adjusted for age, smoking, systolic blood pressure, total:HDL cholesterol ratio, body mass index, lipid-lowering medication, antihypertensive medication, diabetes, and prevalent cardiovascular disease.
Model 3 adjusted for all factors in Model 2 + depression and education.

Loucks EB et al. J Biosoc Sci 2006

Why Study Compassion Meditation in Particular?

Compassion Meditation Protocol Developed by LTN, PhD

Week 1	**Developing Attention and Stability of Mind** Introduction of basic meditation techniques for focusing attention for increasingly longer periods of time. *These techniques are included in the practice of all subsequent compassion meditation components.*
Week 2	**Developing Compassion for Oneself through Mindfulness of Sensations,** Feelings and Emotions_Introduction of techniques to develop awareness of how thoughts and actions contribute to subjective experiences of happiness or suffering, and techniques to increase identification of habitual, conditioned reactions.
Week 3	**Cultivating Equanimity and Appreciation** Introducing practices designed to challenge unexamined thoughts and feelings determining categories of friend, enemy and stranger; introducing the perspective that all persons are all alike in wanting to be happy, and appreciating others for the ways they benefit us.
Week 4	**Developing Affection and Empathy** Techniques will be presented for developing undifferentiated affection for others, based on the many ways that others benefit us each day. The meditators will be introduced to the concept of empathy for others: identifying with their happiness and suffering alike.
Week 5	**Wishing and Aspirational Compassion** Using the concepts of appreciation and empathy as a starting point, the meditator will be guided toward the first stages of compassion: the wish that all beings might be happy and free of suffering, and the aspiration to help them achieve that.
Week 6	**Active Compassion for Others** The meditation training culminates in the generation of active compassion: practices introduced to develop a determination to work actively to alleviate the suffering of others. When this training is successful, this state of mind becomes ingrained and spontaneous.


6 Weeks
Freshman College Students
males/females
Compassion Meditation Group
Health Discussion Control Group
intervention
intervention
Psychosocial Stress Test

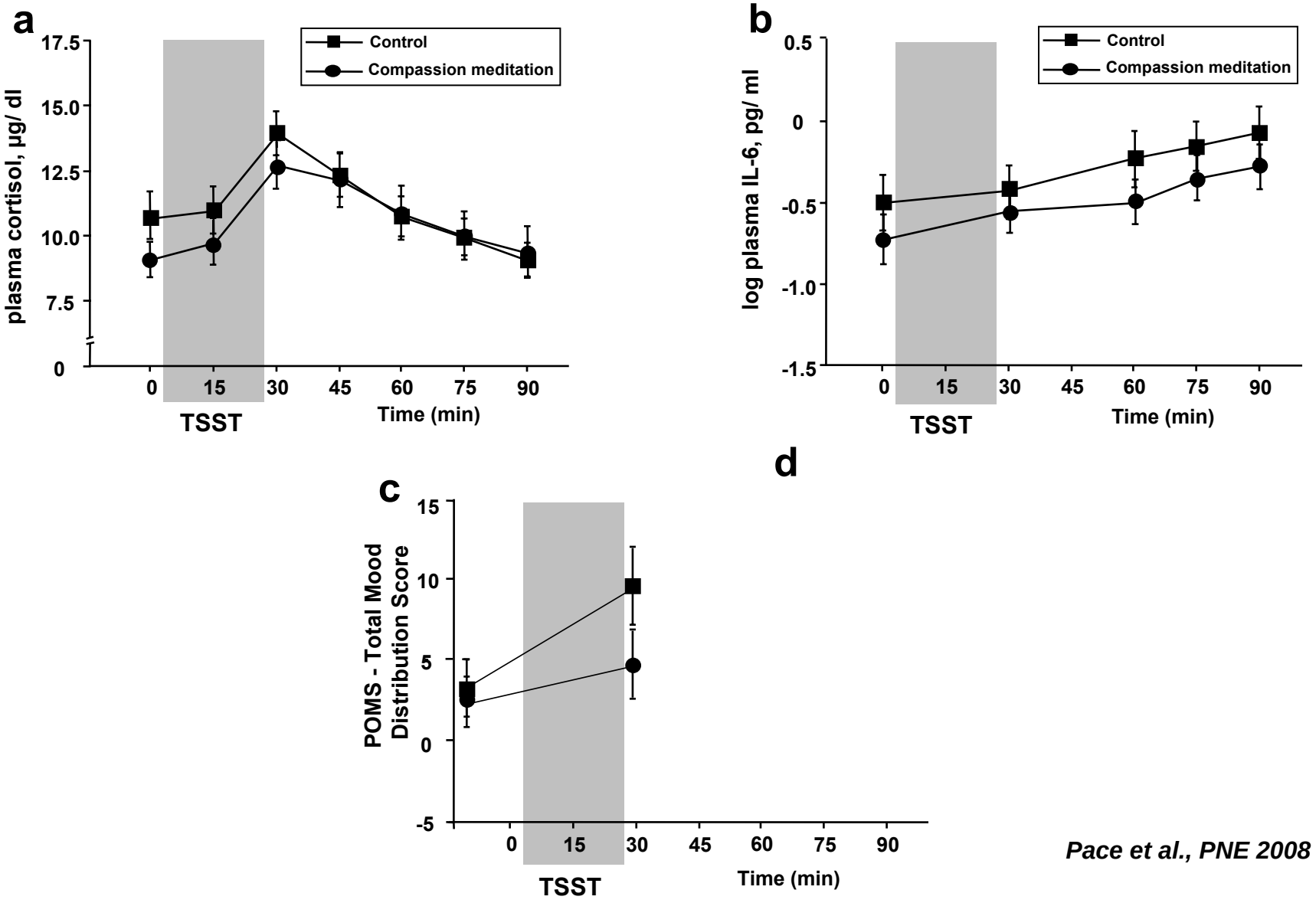
Effect of Compassion Meditation on Inflammatory, Neuroendocrine and Behavioral Responses to Psychosocial Stress

STUDY HYPOTHESES:

1. **Randomization to six weeks of training in compassion meditation will reduce interleukin (IL)-6, cortisol and behavioral distress responses to a standardized laboratory psychosocial stressor (Trier Social Stress Test [TSST]) in medically-healthy young adults when compared to randomization to a health discussion control group.**

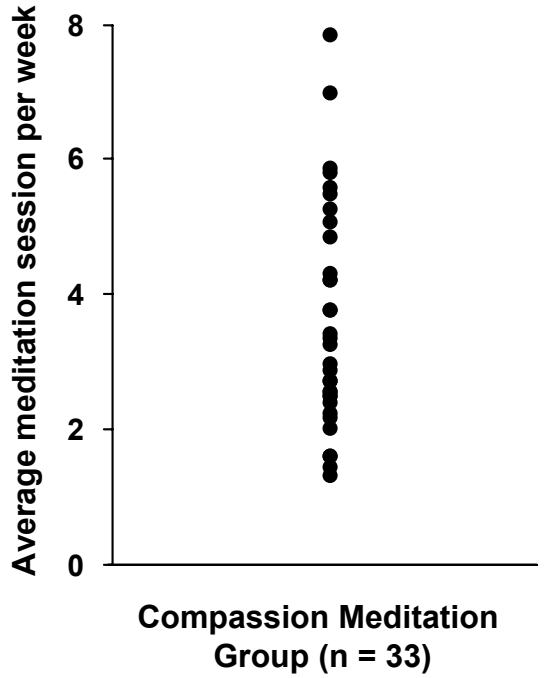
2. **In participants randomized to compassion meditation training, amount of meditation practice during the study will be associated with inflammatory, neuroendocrine and behavioral responses to the TSST.**

Effect of Compassion Meditation on Inflammatory, Neuroendocrine and Behavioral Responses to Psychosocial Stress

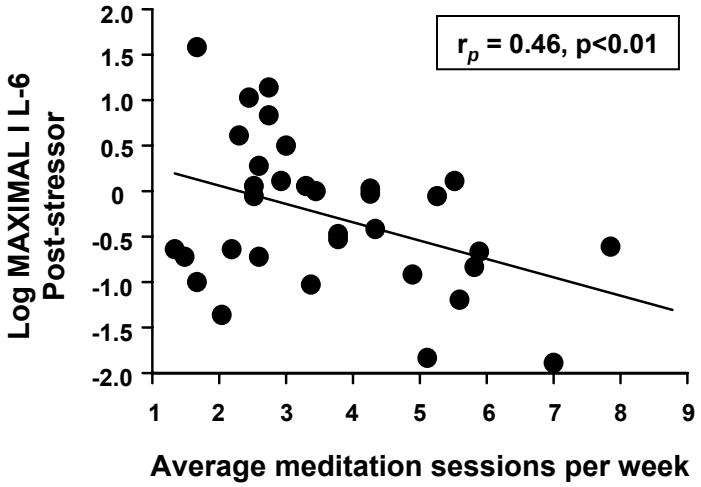


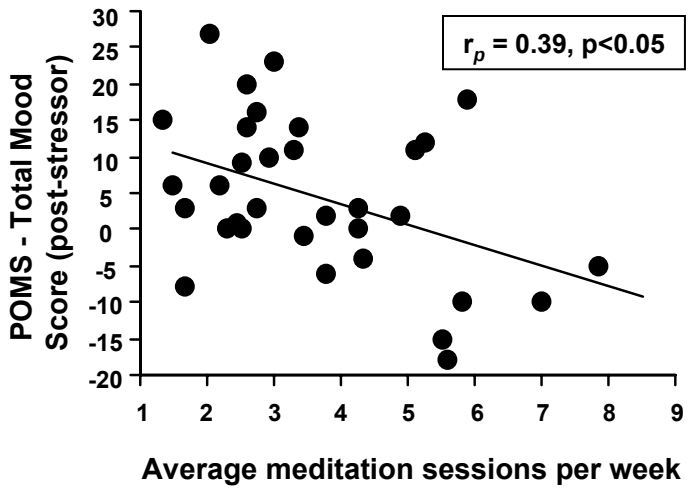
Pace et al., PNE 2008

Distribution of Meditation Practice Exposure in Compassion Group



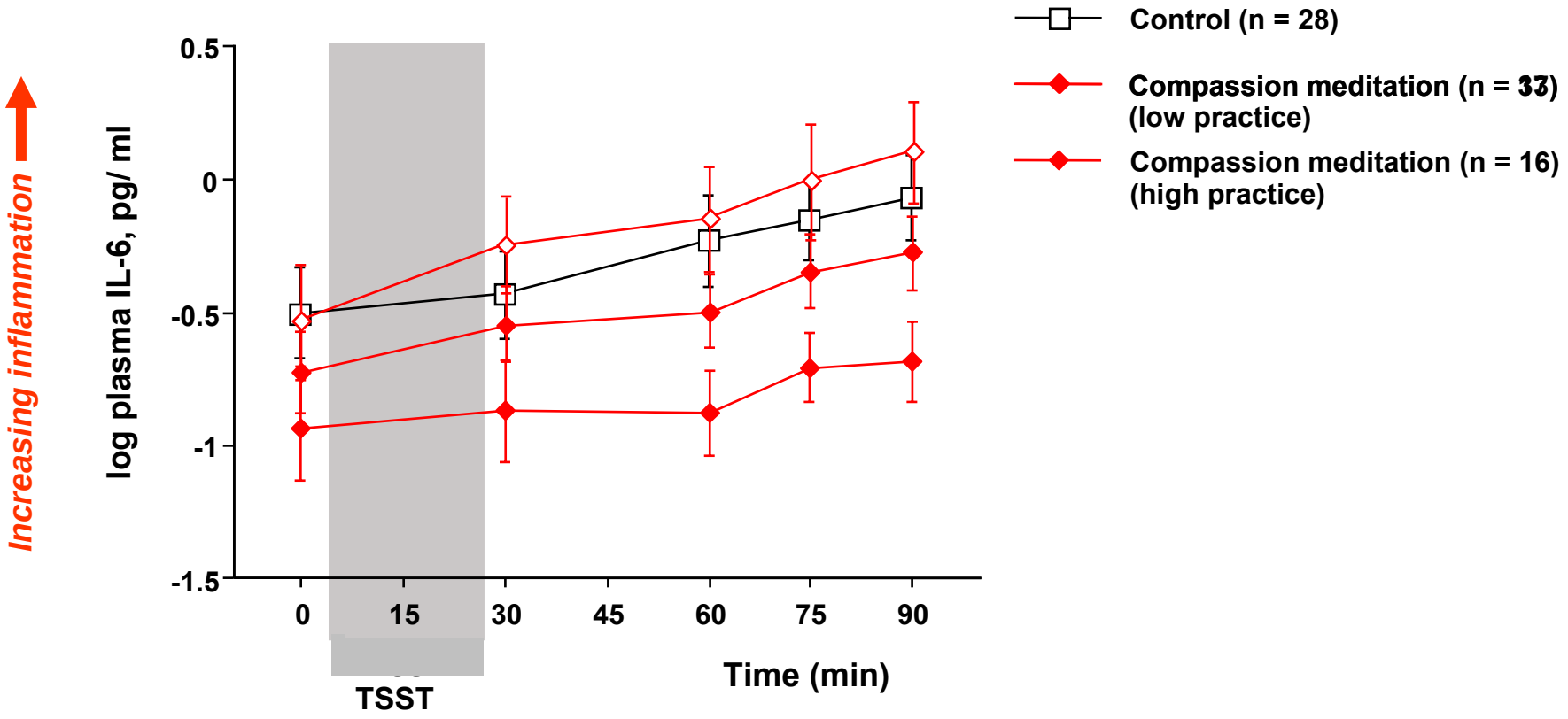
Evidence for a "Dose-Response" Relationship Between Amount of Meditation Practice and IL-6 and POMS Responses to the TSST



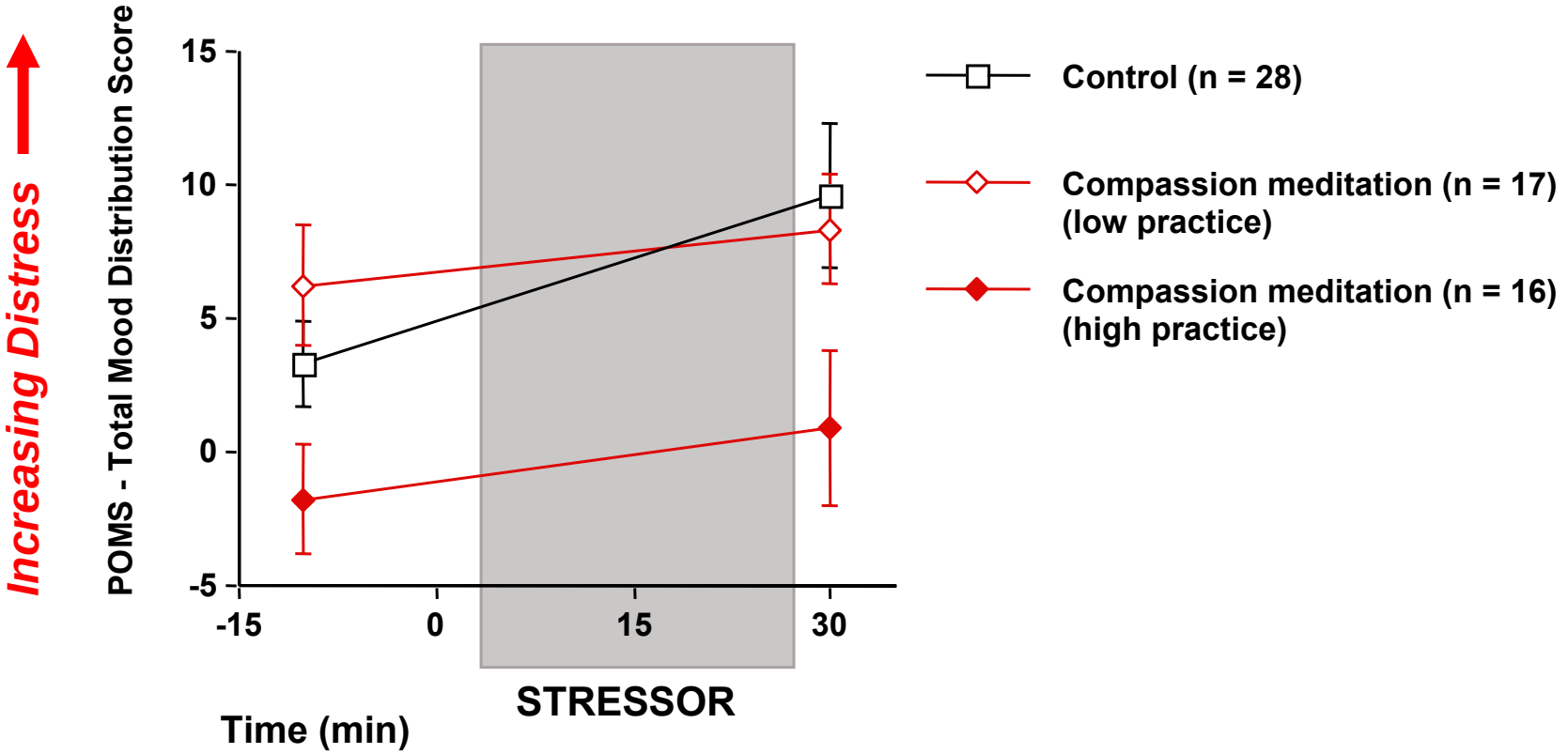


Pace et al., PNE 2008

Effect of Meditation Practice on IL-6 Responses to the TSST when Compared to Control Subjects



Effect of Meditation Practice on Distress Responses to the TSST when Compared to Control Subjects



Relationship of Meditation "Dosage" and Outcomes: Review of Recent Publications

PRACTICE EFFECT

EEG in advanced practitioners prior to and during open compassion Meditation but unbalanced groups (Lutz et al., 2004)

No main effect of group, but practice associated with feeling rested in CA patients (Shapiro et al., 2003)

No main effect of group but practice associated with reduced distress increased well-being in RA patients (Pradhan et al., 2007)

Improvement in stress, symptoms and well-being in healthy controls taught MBSR but no control condition (Carmody et al., 2007)

NO PRACTICE EFFECT

Improved antibody responses and greater left EEG in MBSR vs. wait list (Davidson et al., 2003)

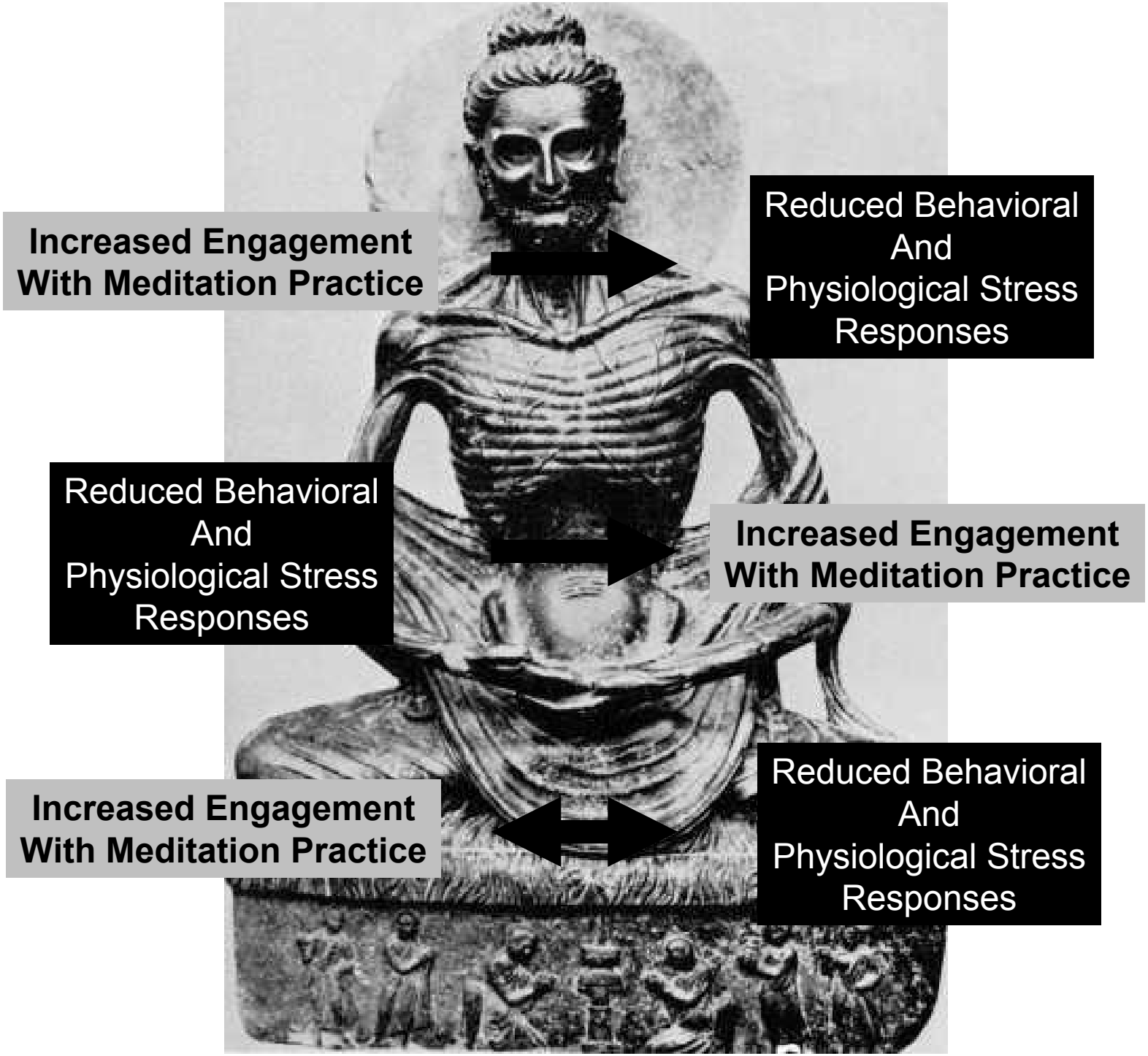
QOL, mood, stress and immune parameters with MBSR but no control condition (Carlson et al., 2003)

Reduced stress, cortisol and cytokines with long-term MBSR but no control condition (Carlson et al., 2003 and 2007)

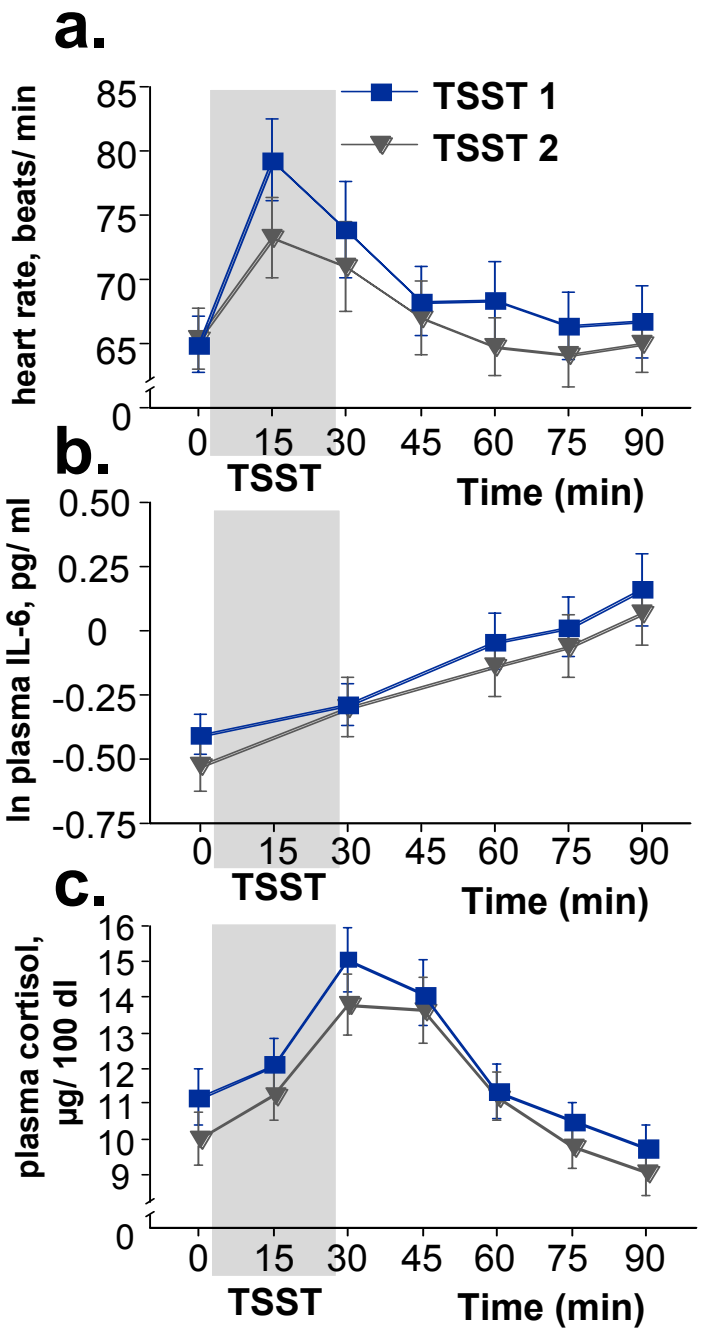
Improved stress, negative affect, anxiety, well-being, mindfulness MBSR but no control condition (Shapiro et al., 2007)

High mean practice

Low mean practice


Increased Engagement With Meditation Practice
Reduced Behavioral And Physiological Stress Responses
Reduced Behavioral And Physiological Stress Responses
Increased Engagement With Meditation Practice
Increased Engagement With Meditation Practice
Reduced Behavioral And Physiological Stress Responses

Repeatability of TSST in 30 Medically-Healthy Adults

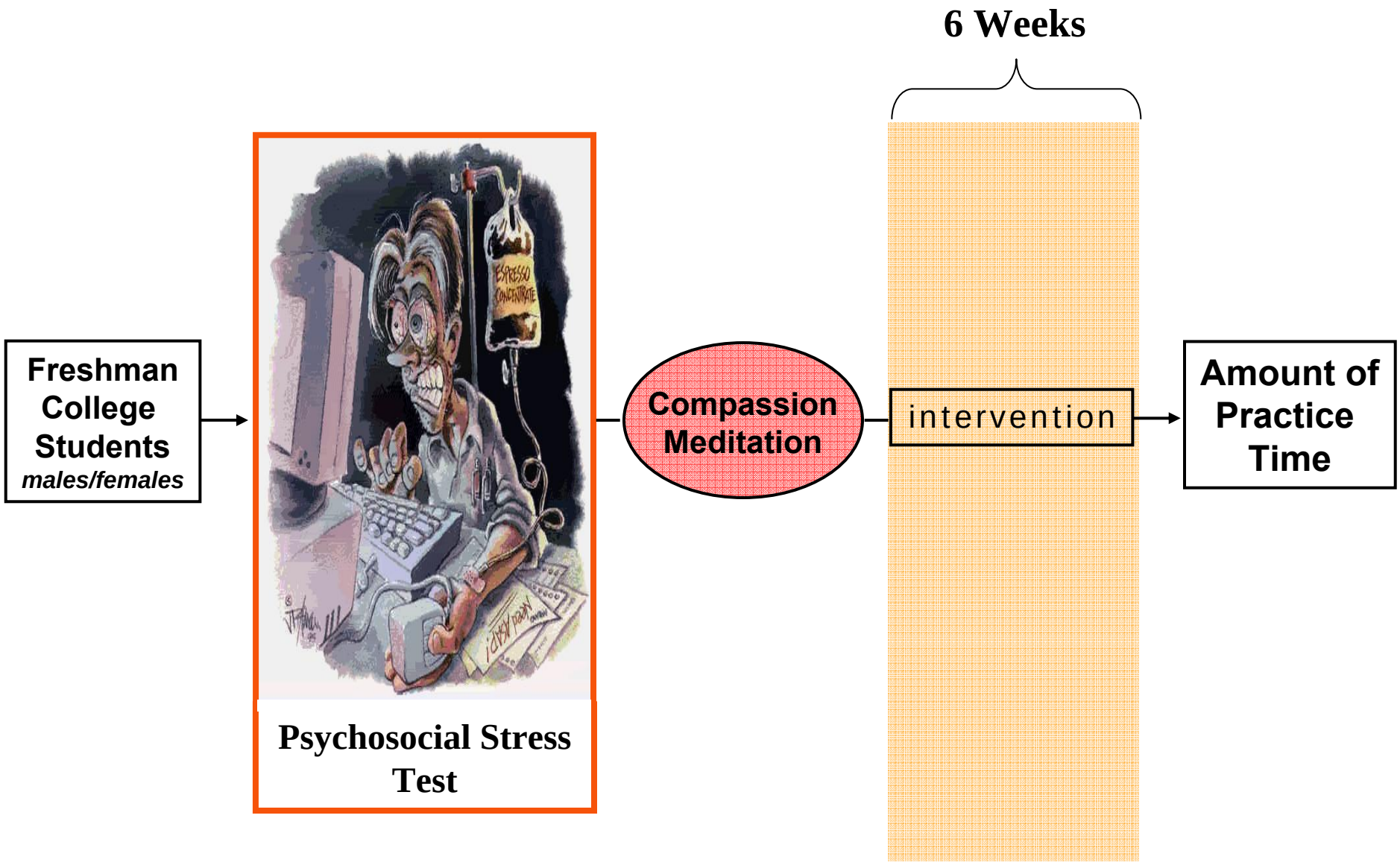


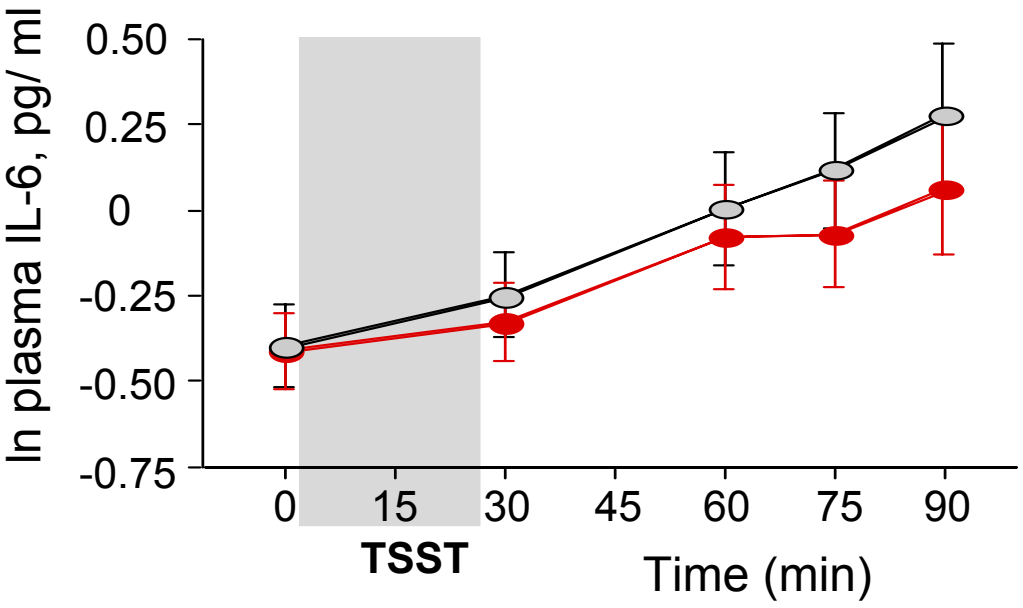
Do Physiologic and Behavioral Responses to Psychosocial Stress Predict Subsequent Compassion Meditation Practice Time

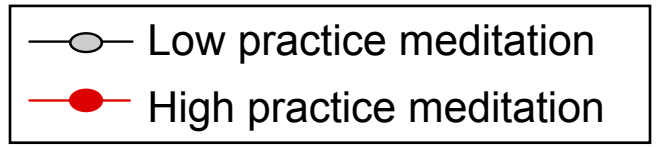
STUDY HYPOTHESES:

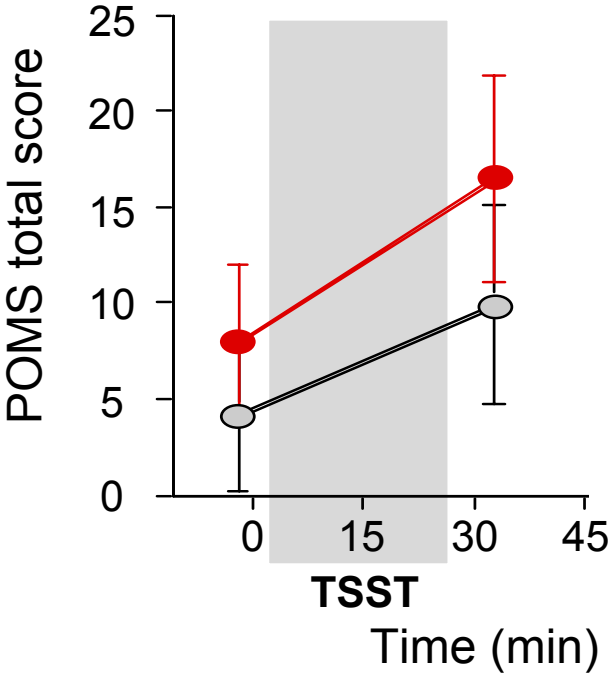
1. **Behavioral distress and physiological (cortisol, IL-6) responses to a TSST will not predict subsequent engagement with a compassion meditation training program, as measured by amount of weekly meditation practice time.**

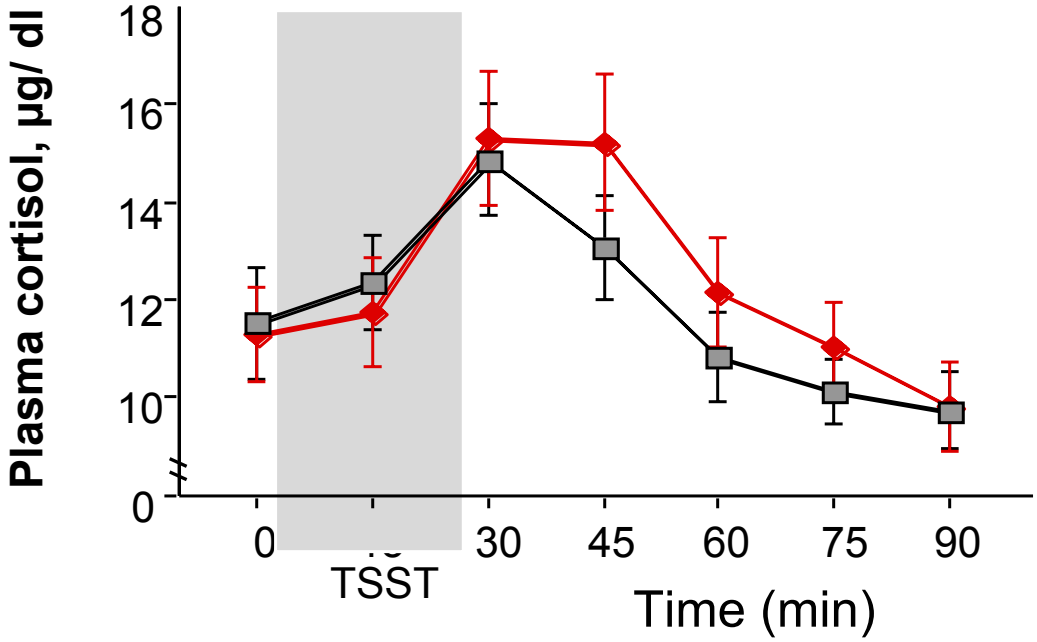
2. **High practice time meditators who received a TSST after training will show lower IL-6 and distress responses to the TSST than will high practice time meditators who received a TSST prior to meditation training. No differences in TSST responses will be seen in low practice time meditators who received a TSST either prior to or upon completion of training.**


6 Weeks
Freshman College Students
males/females
ESPRESSO CONCENTRATE
Psychosocial Stress Test
Compassion Meditation
intervention
Amount of Practice Time

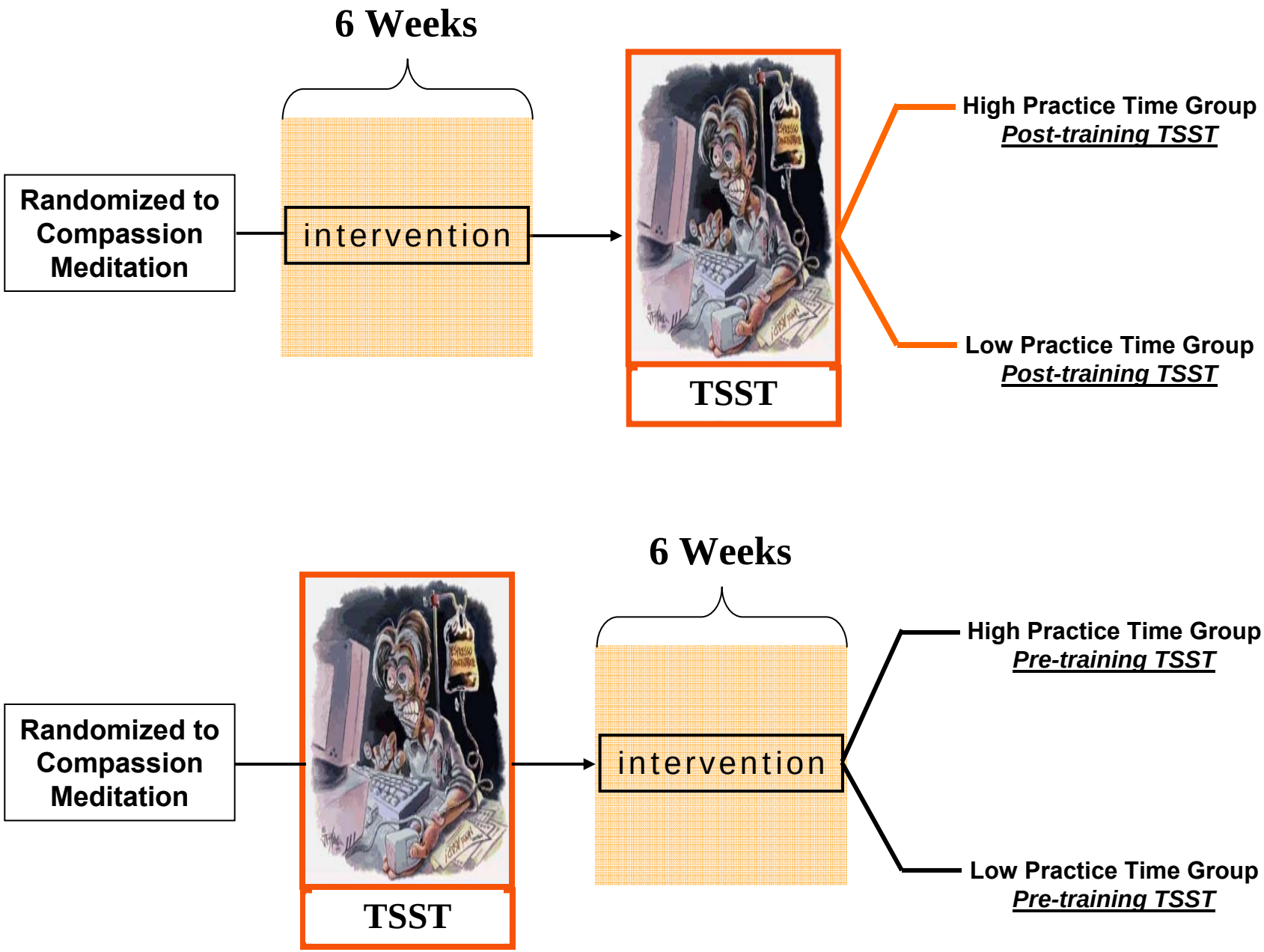




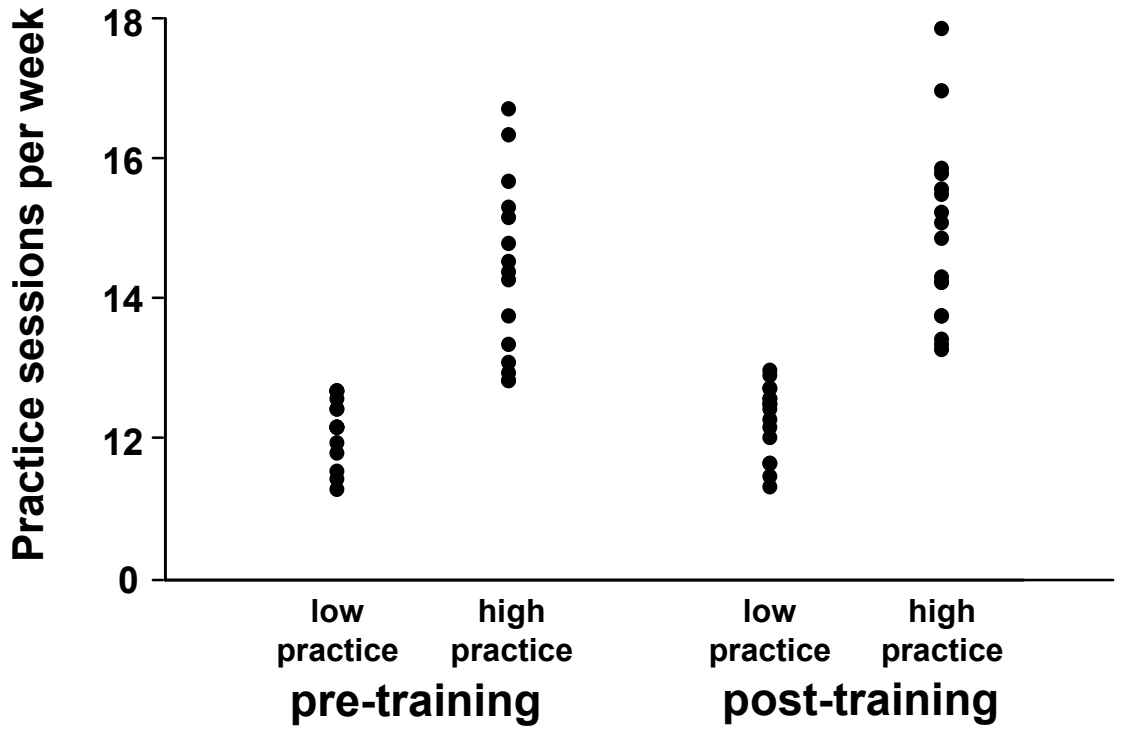




Pace et al., in preparation

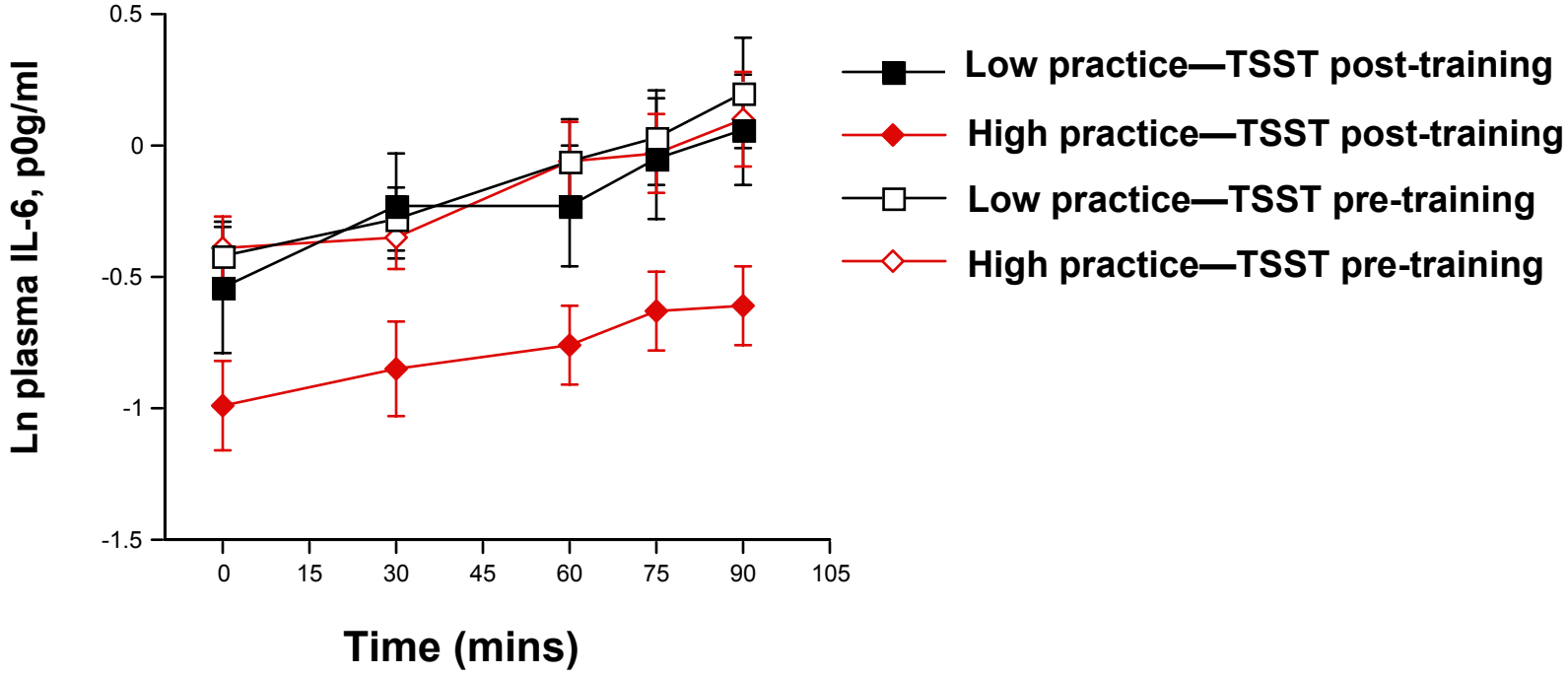

6 Weeks
Randomized to Compassion Meditation
intervention
TSST
High Practice Time Group
Post-training TSST
Low Practice Time Group
Post-training TSST
6 Weeks
Randomized to Compassion Meditation
TSST
intervention
High Practice Time Group
Pre-training TSST
Low Practice Time Group
Pre-training TSST

Degree of Engagement in Pre- and Post Training TSST Practice Groups



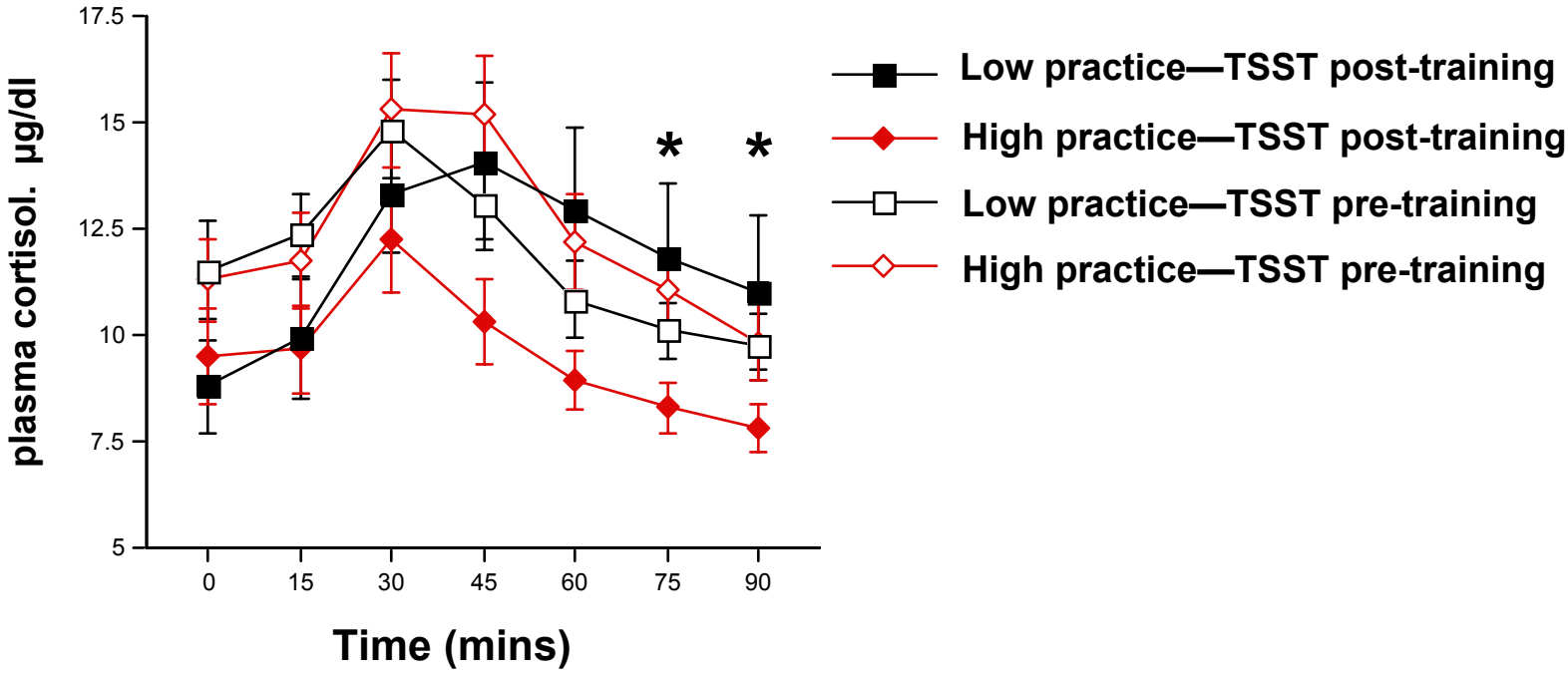
Pace et al., in preparation

High Practice Time Meditators Who Undergo TSST After Training Have Reduced IL-6 Responses to the Stressor



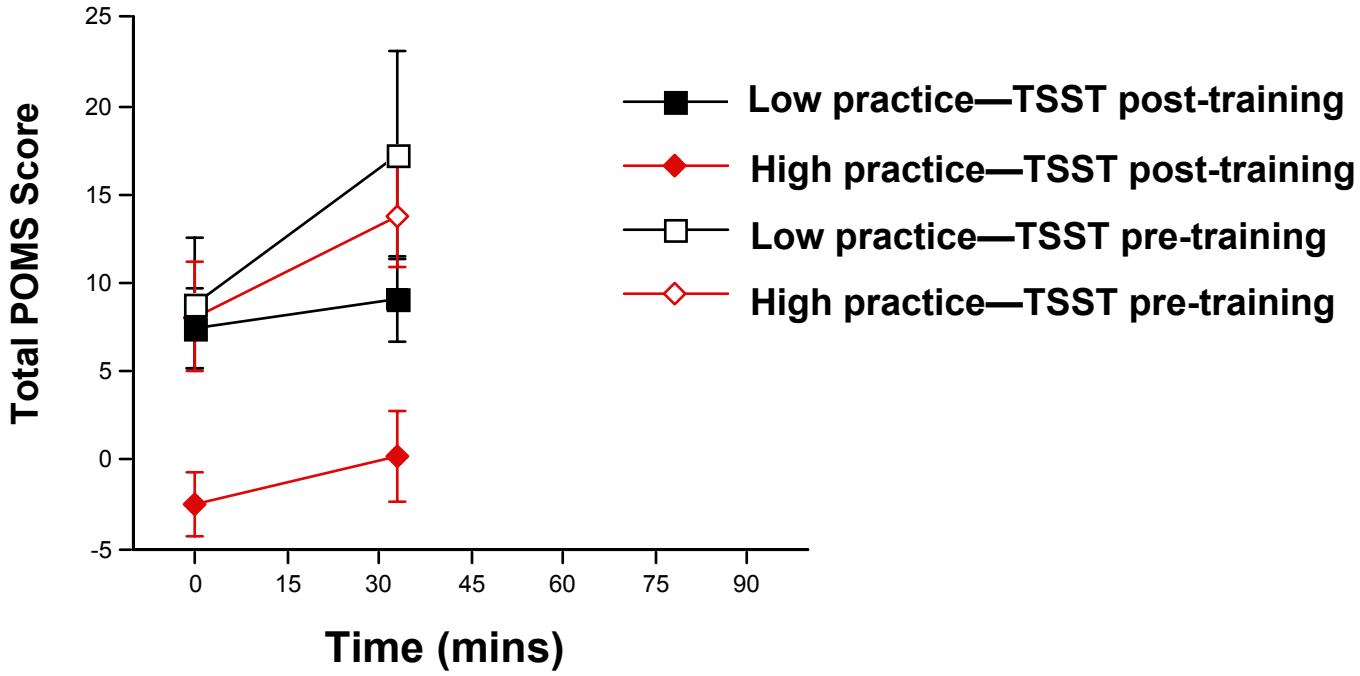
Pace et al., in preparation

High Practice Time Meditators Who Undergo TSST After Training Show Faster Cortisol Recovery from the Stressor



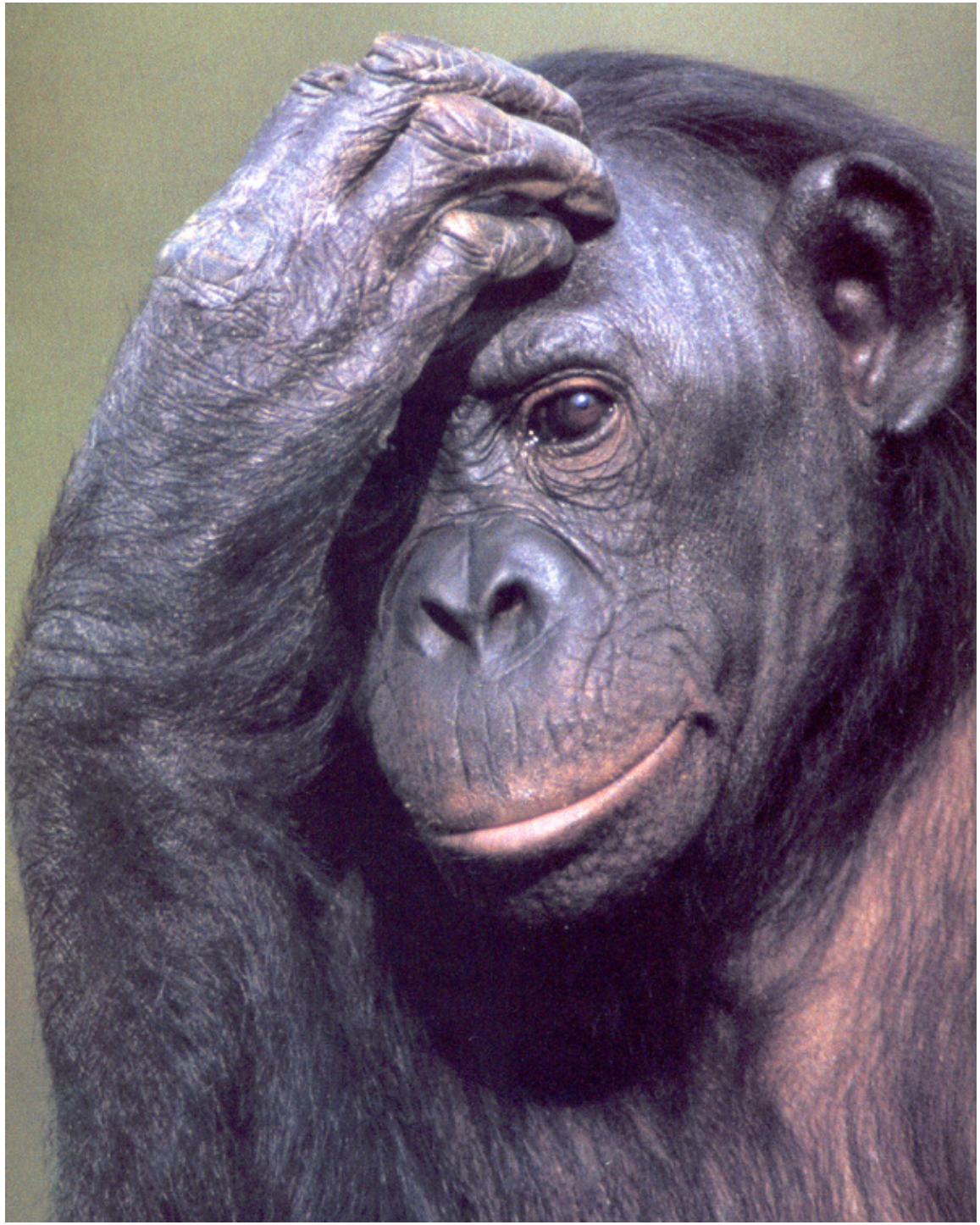
Pace et al., in preparation

High Practice Time Meditators Who Undergo TSST After Training Have Reduced POMS Distress Responses to the Stressor



Pace et al., in preparation

What Next?



THE CALM STUDY

PREDICTIVE HEALTH INSTITUTE

SCREENING

Males/females age 25-65
Medically healthy
No current MDD
No history of Schiz/BPDI
No curent. substance abuse
No current psych treatment
No prohibited medications
No current/past meditation

Eligible Subjects: (N=385)

random.

Stratify By: Depressive Symptoms

Pre-Assess

Post-Assess

Follow-up Assessments
Every 6 months (4 total)

INTERVENTION

FOLLOW-UP

Compassion (n=120)

Mindful Attention (n=120)

Control Group (n=145)

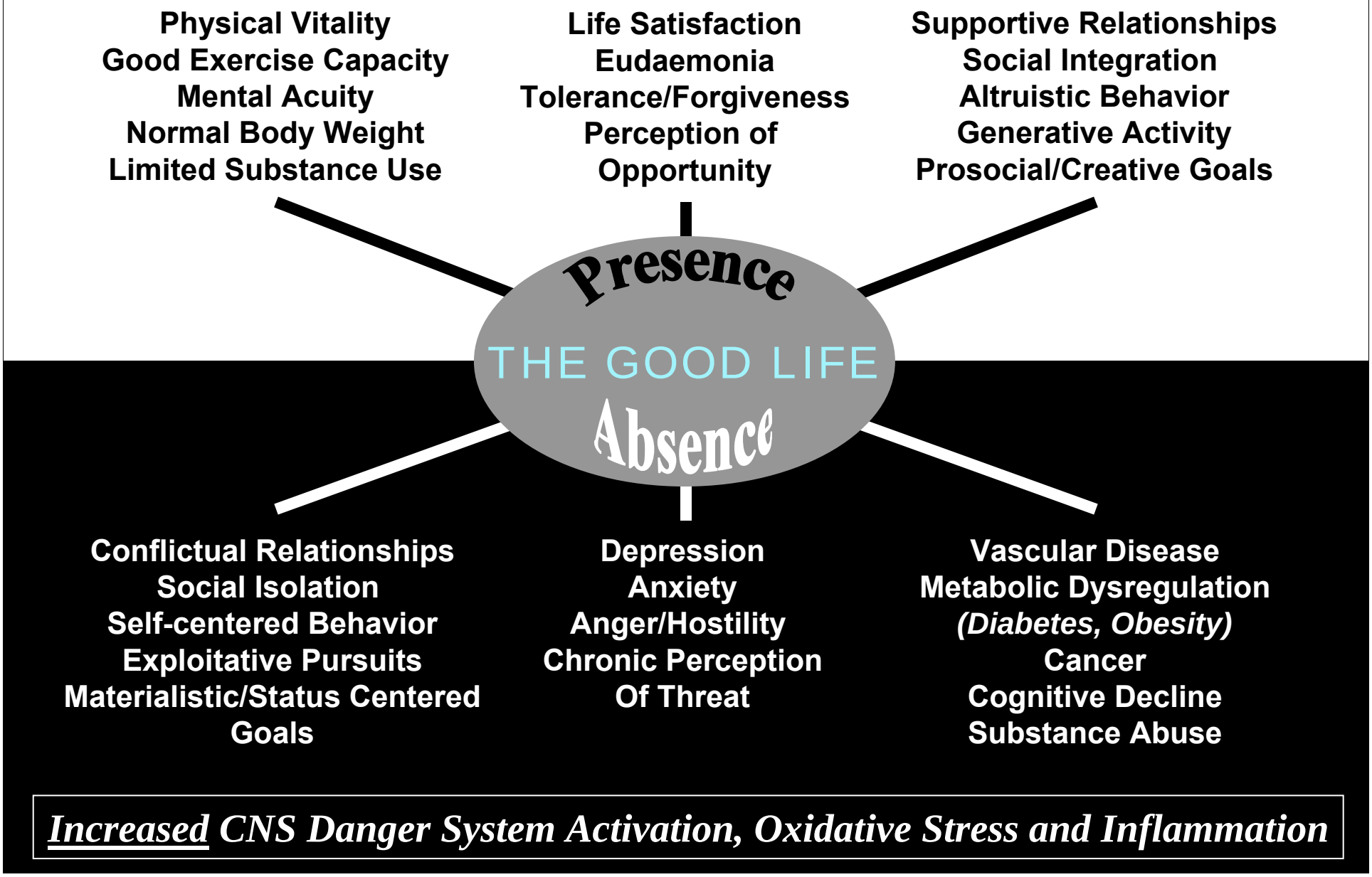
8 Weeks

2 Years

Cyberball Social exclusion fMRI
Trier Social Stress Test (TSST)
Behavioral/physical health assess.
RIT attentional assess.
Vascular fx/oxidative assess.
at rest and after stress

Behavioral/physical health assess.
(Vascular fx/oxidative assess.
at rest and after stress
RIT attentional assess.
final assessment only)

***Reduced* CNS Danger System Activation, Oxidative Stress and Inflammation**



***Increased* CNS Danger System Activation, Oxidative Stress and Inflammation**


Put More Simply...