

# **Psychoneuroimmunology: Mind, Body, and Behavior**

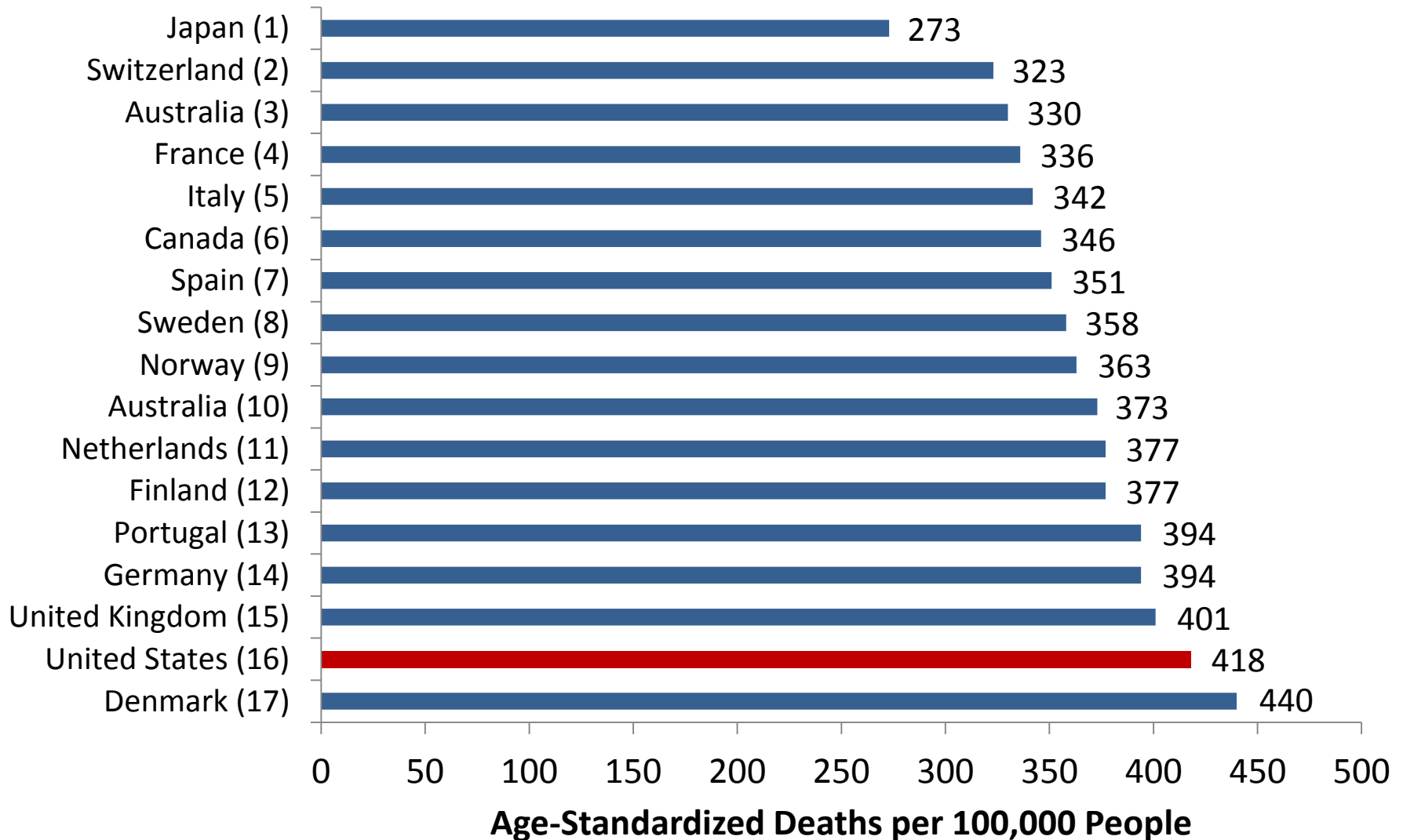
# **Psychoneuroimmunology: Mind, Body, and Behavior**

**George M. Slavich**

Cousins Center for Psychoneuroimmunology  
Department of Psychiatry and Biobehavioral Sciences  
UCLA

Emerging Tools for Innovative Providers  
Pasadena, California  
July 23, 2013

# Disease-Related Mortality in the U.S.



# Life Expectancy in the U.S.

Males			Females		
Rank	Country	LE	Rank	Country	LE

# New



www.newsweek.com

June 14, 1999 : \$3.50

BEHIND THE  
**KOSOVO DEAL**

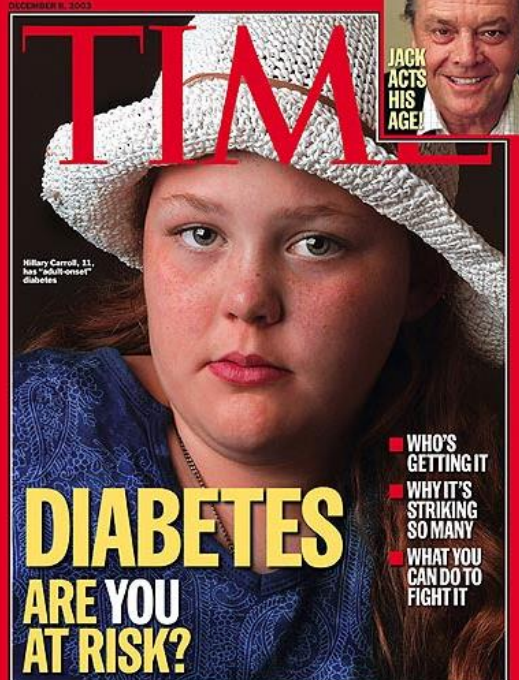
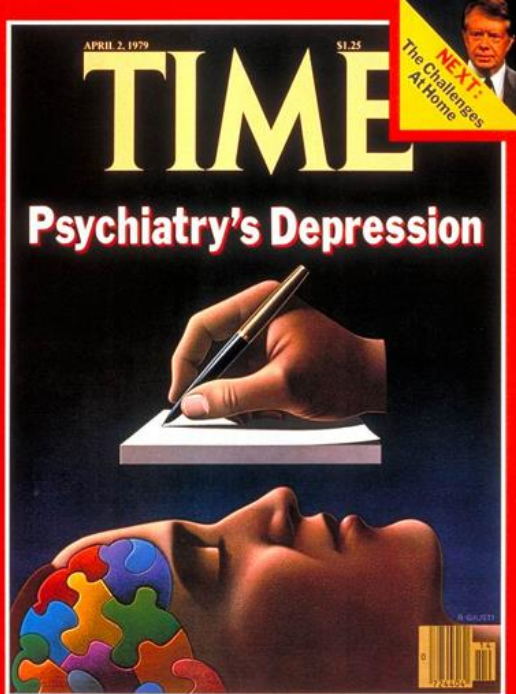
# STRESS

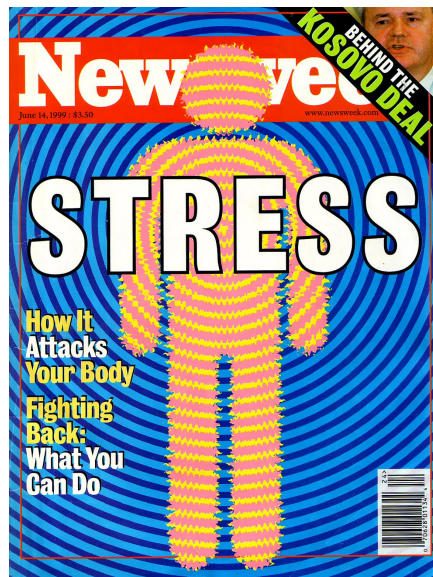
**How It  
Attacks  
Your Body**

**Fighting  
Back:  
What You  
Can Do**

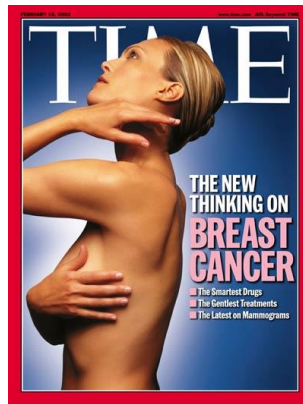
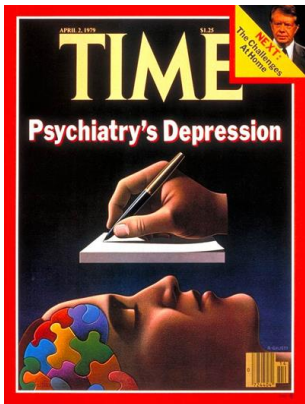








Common Mechanism?





INSIGHTS  
OF THE DECADE

Science

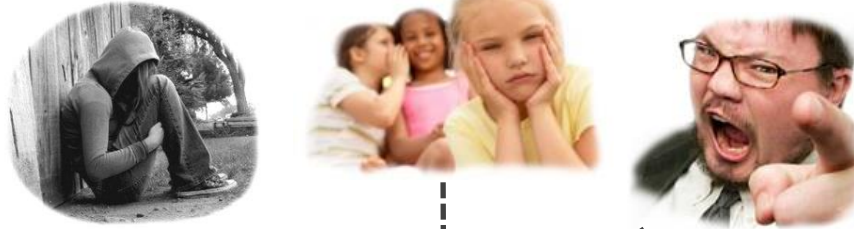
# Inflammation Bares a Dark Side



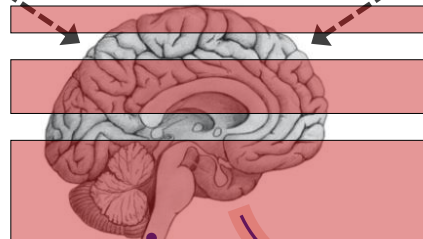
**Burrowing in.** Macrophages were an early clue that chronic disease and inflammation are tightly linked.



**Social Environment**



**Neural Activity**



**Social Stress**



**Neural Sensitivity to Social Threat**

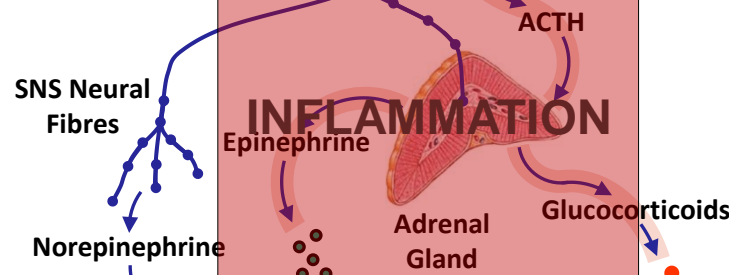
**Molecular Signaling**

**Inflammatory Cytokines**

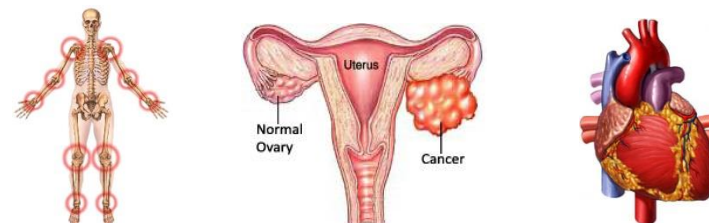
**Disease**



**Physiological Arousal**



**Molecular Signaling/  
Gene Expression**



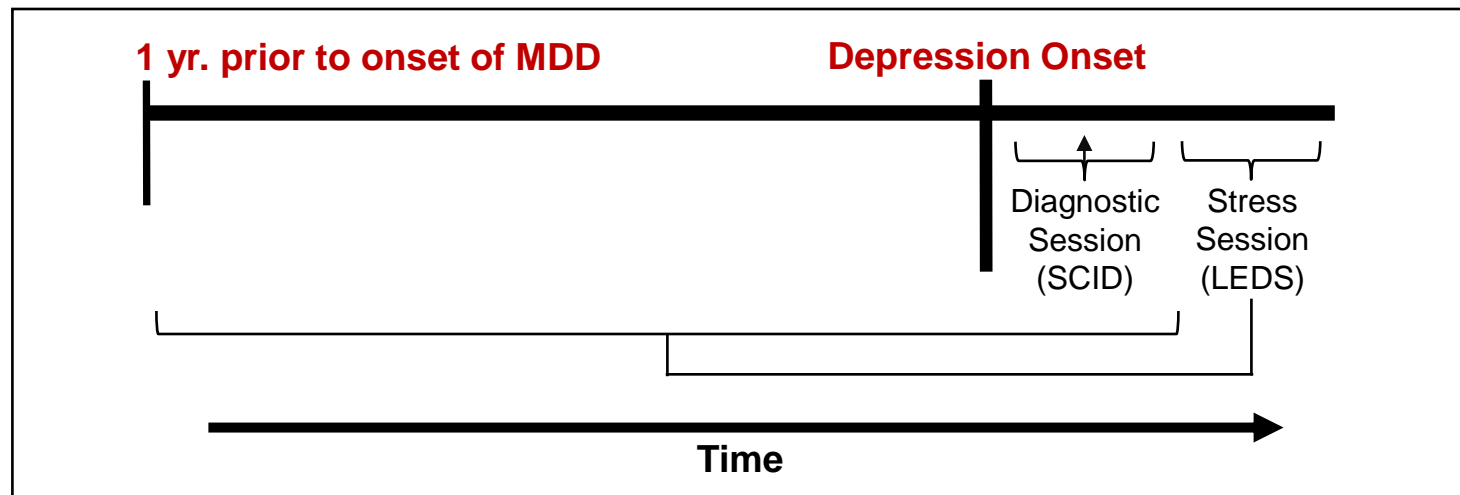
**Disease**

# Life Stress & Onset of Depression

**Q:** How are major life events associated with onset of depression?  
Does this association differ by type of stress?

## Participants

- 100 individuals, diagnosed with MDD (26 men & 74 women,  $M_{age} = 35.1$ )
- Recruited from San Francisco Bay Area & Stanford Psychiatry
- Acute onset of MDD, and no comorbid panic disorder or social phobia, or history of mania, psychotic symptoms, or recent drug or alcohol abuse



# **Life Events and Difficulties Schedule**

(Brown & Harris, 1978)

Most elaborate system for assessing, defining, and rating acute and chronic life stress

## **Semi-Structured Interview**

24-page interview, focusing on 10 life domains  
(health, housing, employment, relationships, etc.)

## **Standardized, Anchored Ratings of Threat**

Panel of independent raters, blind to study variables



# Types of Life Stress and Depression

- Not all types of social stress are “created equal”
- Example: interpersonal loss

Self-Initiated Separation (e.g., Break-up w/ partner)	Other-Initiated Separation (e.g., Dumped)
↑ Controllability	↓ Controllability
↓ Social-evaluative threat	↑ Social-evaluative threat
↓ Loss of social status/regard	↑ Loss of social status/regard

**Targeted Rejection:** Social rejection that is directed at, and meant to affect, a single person, and that involves an active and intentional severing of relational ties with that person

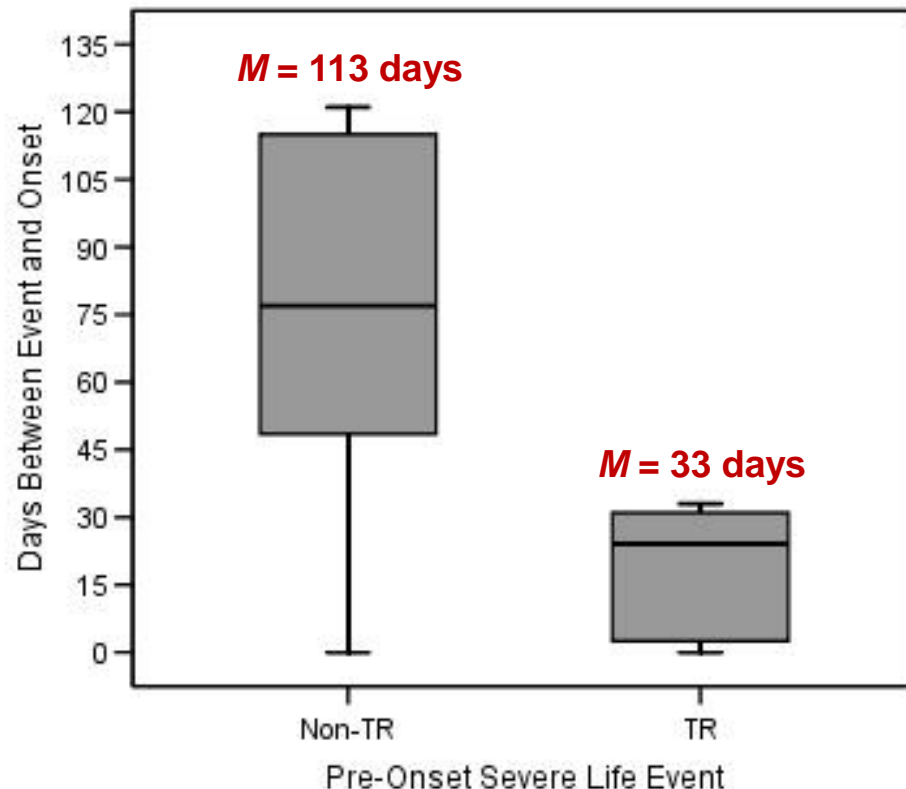


# Targeted Rejection Predicts Hastened Onset of Major Depression

George M. Slavich<sup>1</sup>, Tiffany Thornton<sup>2</sup>, Leandro D. Torres<sup>1</sup>,  
Scott M. Monroe<sup>2</sup>, and Ian H. Gotlib<sup>4</sup>

<sup>1</sup>University of California, San Francisco; <sup>2</sup>University of Oregon;

<sup>3</sup>University of Notre Dame; <sup>4</sup>Stanford University



- All events were rated **severe** according to LEDS
- No difference between TR events in **work** vs. **relationship** domain
- Effects robust when controlling for history of depression and all major demographic variables

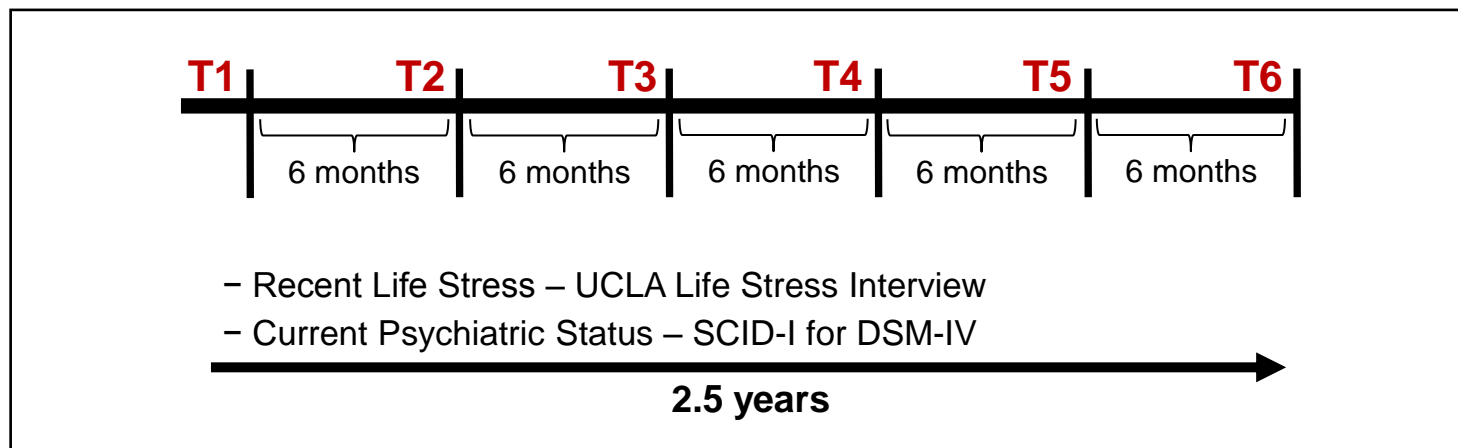
$b = 1.14$ ,  $p = .015$ , odds ratio = 3.13

# Social Stress & Risk for Depression

- Q:** How are major life events associated with onset of depression?  
Does this association differ by type of stress?

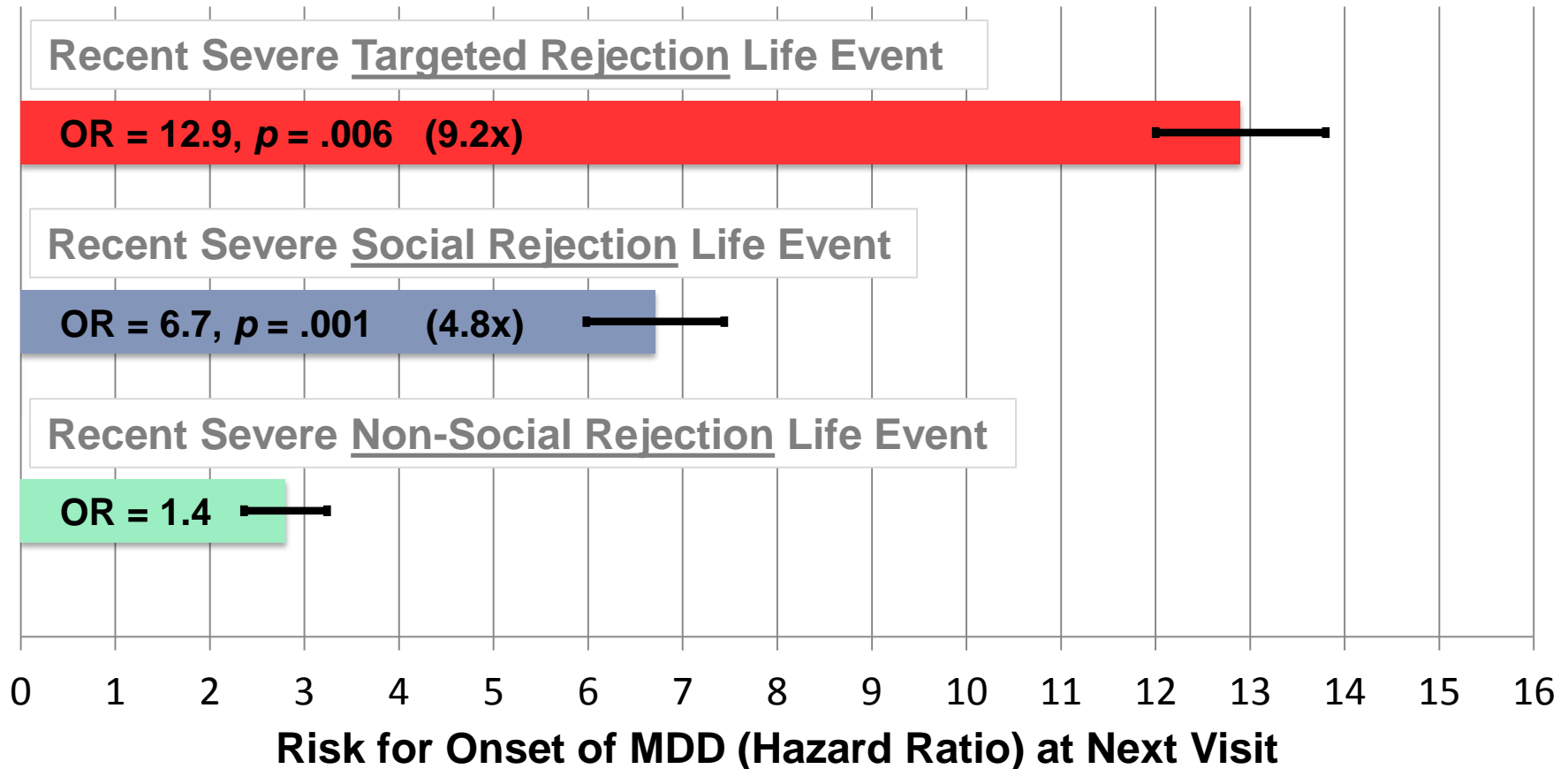
## Participants

- 147 adolescent women, at elevated risk for depression ( $M_{age} = 17.0$ )
- No current or lifetime history of any major psychiatric disorder, but elevated risk for depression
- Assessed every 6 months for 2.5 years





# Graded Effect of Social Stress on Risk for Depression



\* Controlling for within-person changes in waist-to-hip ratio, and between-person differences in age, ethnicity, oral contraceptive use, alcohol consumption, and SES

*Slavich, Murphy, & Miller, in prep*

# Stress, Inflammation, & Disease



## 1) Inflammatory mediators = disease

**Evidence:** higher levels of inflammatory activity in:  
asthma, arthritis, certain cancer, cardiovascular disease, & MDD

## 2) Inflammatory activity regulated by the external social world

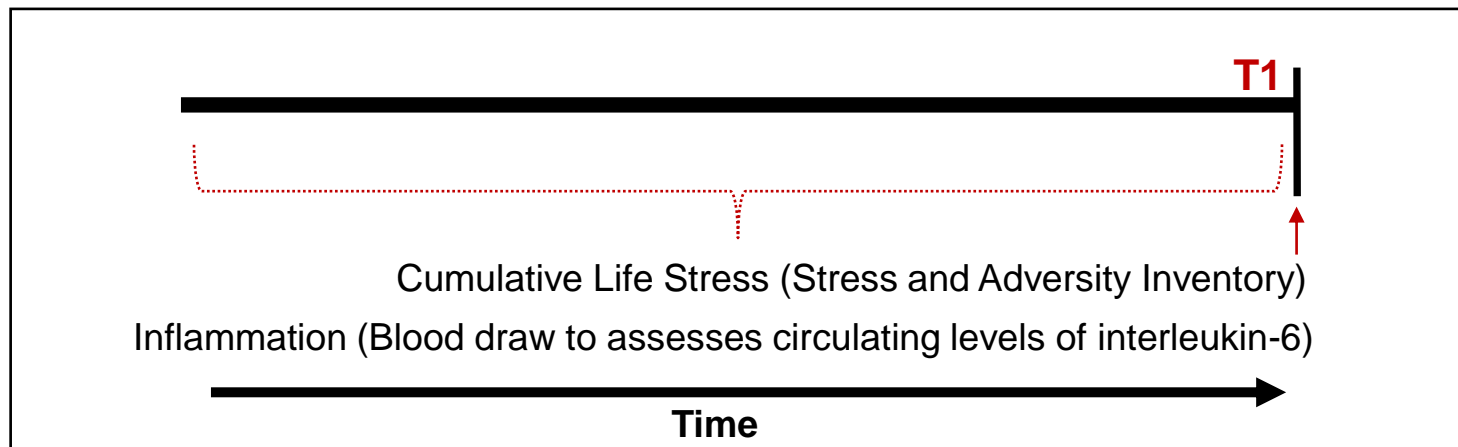
**Evidence:** ??

# Social Stress & Inflammation

**Q:** Is stress associated with increased inflammatory activity?

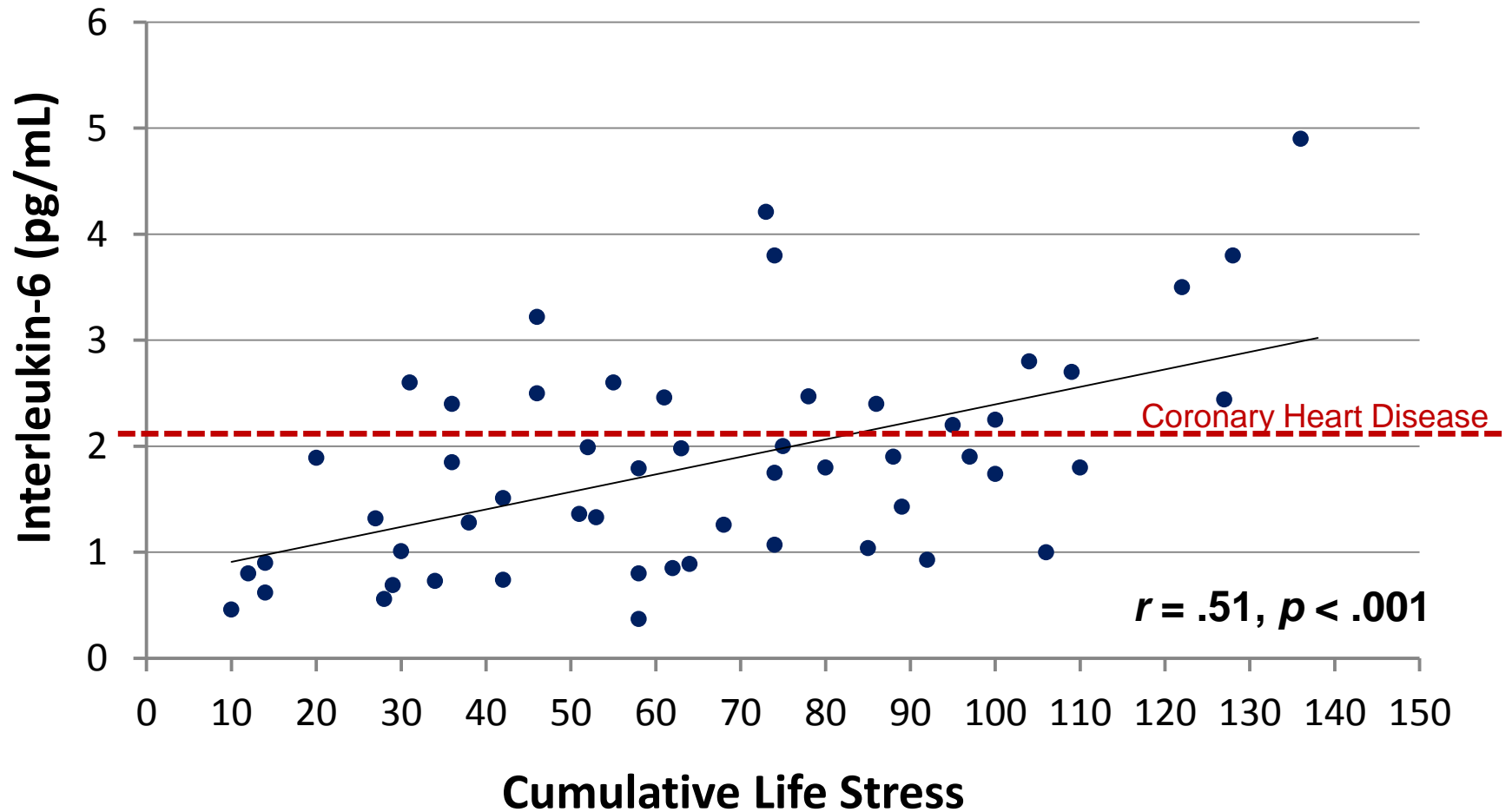
## Participants

- 60 healthy adult women ( $M_{age} = 46.7$ )
- 30 dementia caregivers, 30 non-caregiver control participants
- Cumulative stress & levels of inflammation assessed at study visit



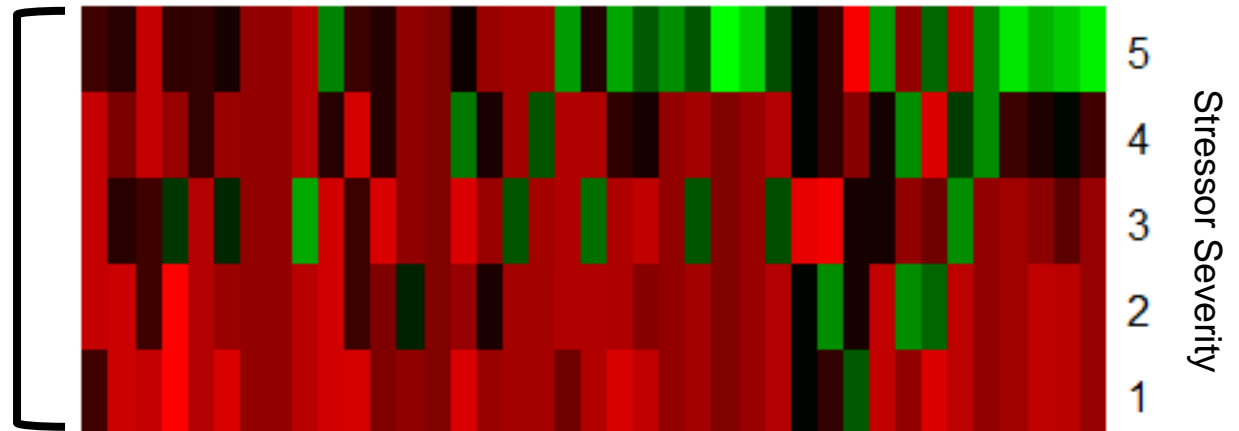


# Cumulative Life Stress & Interleukin-6

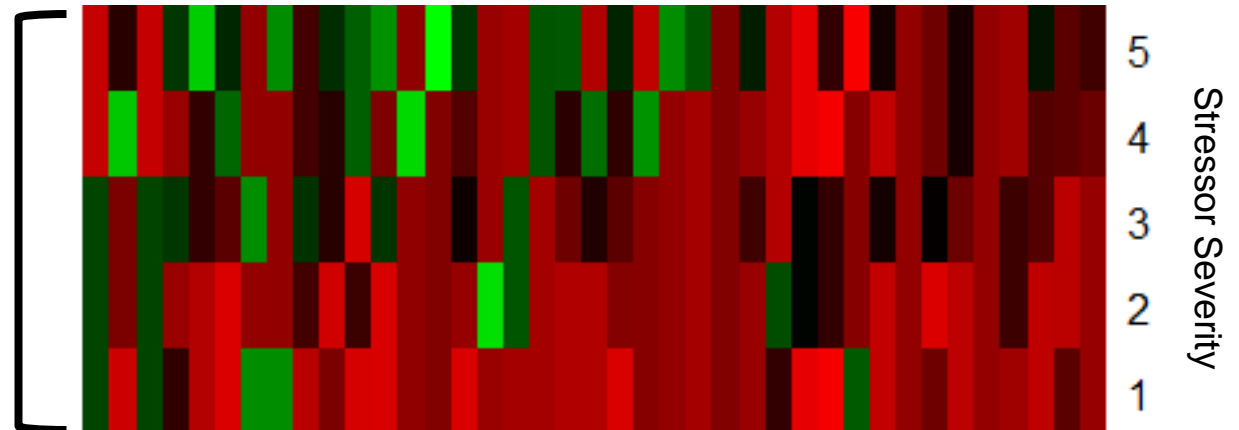


## IL-6 Levels

High Interleukin-6



Low Interleukin-6



d161trs  
d248mils  
e030ehs  
e110hrs  
d181trs  
d052wes  
d057whs  
d176tds  
d243mrs  
e092hrs  
e118hrs  
e218mhs  
d014xds  
d024xds  
d150tds  
d171trs  
d255mrs  
e126ols  
e195mils  
d077hds  
d166oes  
d226ors  
e285ols  
d047wrs  
d155trs  
d238xds  
e268rds  
d062whs  
d072hes  
d082fes  
e101hrs  
e134ors  
e142tds  
e260rds  
e276ols  
d067fes  
d232ohs  
e039whs  
d205mils

Stressor Codes

**Q:** Was there ever a period of time when someone very close to you was being emotionally or physically or sexually abused?



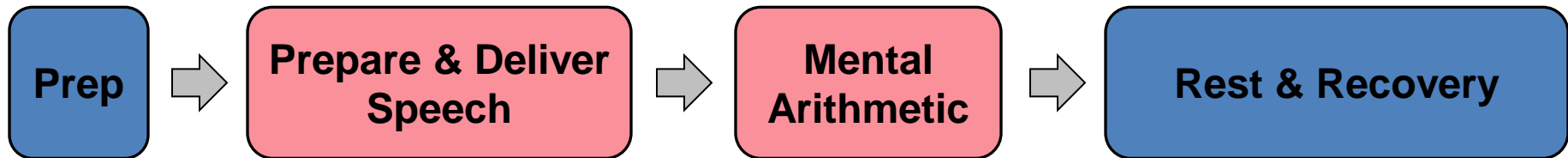
# Laboratory Social Stress Study

**Participants:** 124 healthy young adults (70 females),  
*M* age = 21.25, recruited from the UCLA community

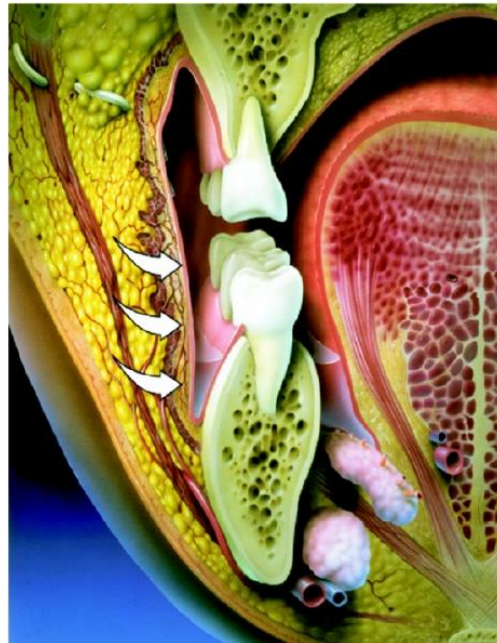
**Social Stressor:** Public speaking & mental arithmetic task



# Laboratory Social Stress Study



Inflammatory  
Markers:  
sTNF-RII & IL-6



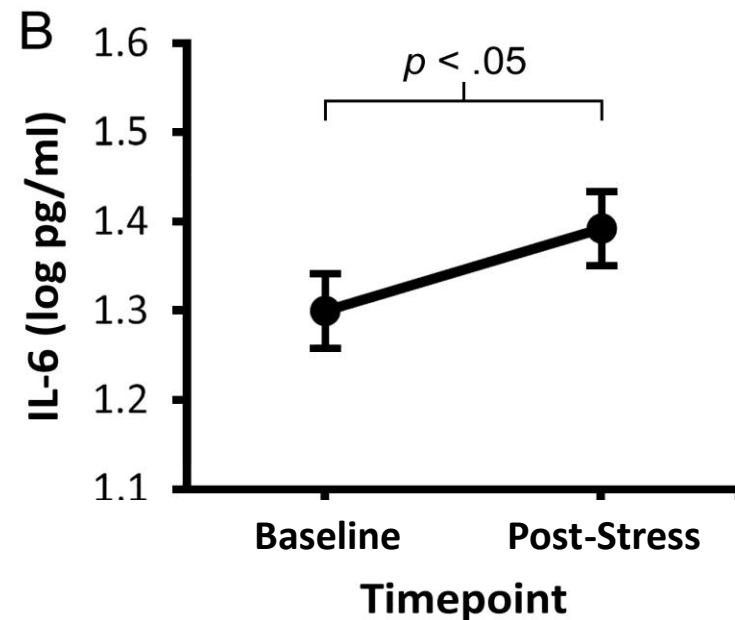
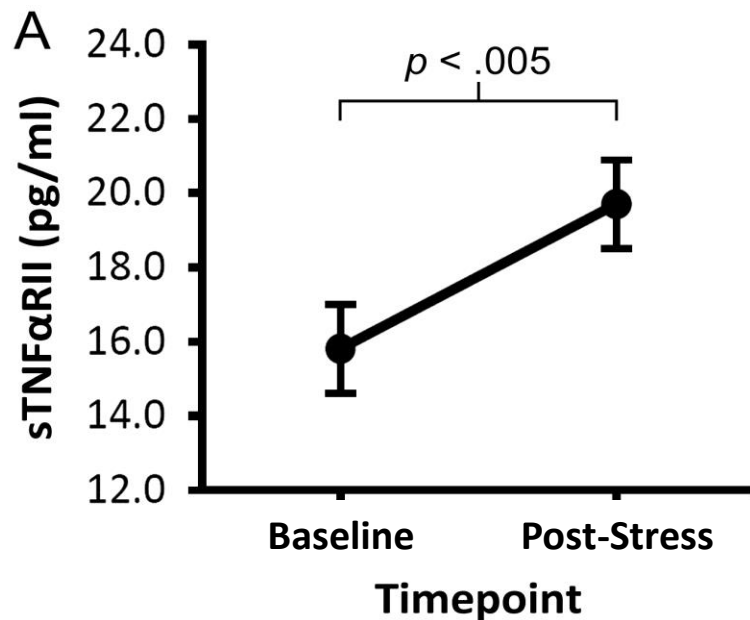
Inflammatory  
Markers:  
sTNF-RII & IL-6



# Neural sensitivity to social rejection is associated with inflammatory responses to social stress

George M. Slavich<sup>a</sup>, Baldwin M. Way<sup>b</sup>, Naomi I. Eisenberger<sup>b</sup>, and Shelley E. Taylor<sup>b,1</sup>

<sup>a</sup>Cousins Center for Psychoneuroimmunology and <sup>b</sup>Department of Psychology, University of California, Los Angeles, CA 90095



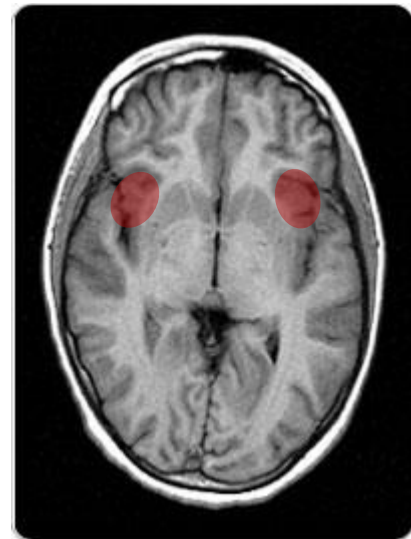


# Pain-Related Neural Systems

## Dorsal Anterior Cingulate Cortex



## Anterior Insula



Engaged during physical & social pain

Involved in the affective or distressing component of pain

Correlates with self-reported feelings of social distress



Bruce



Harold



George



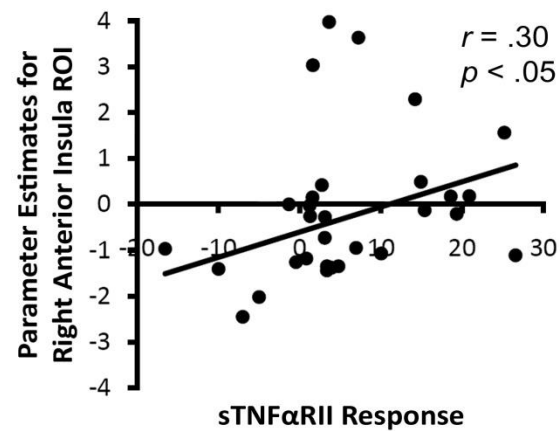
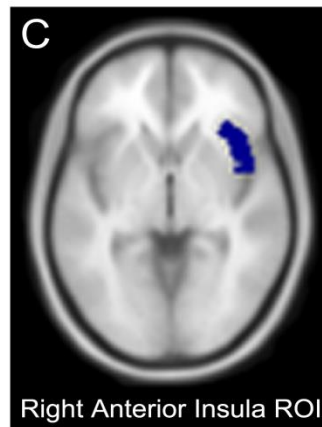
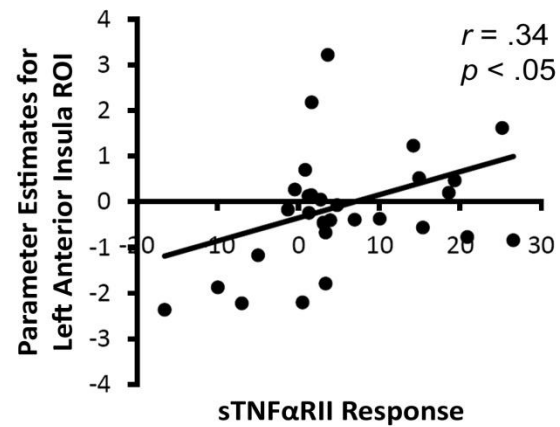
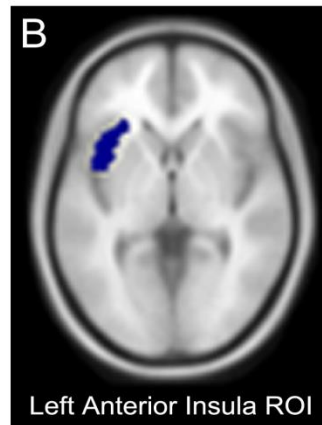
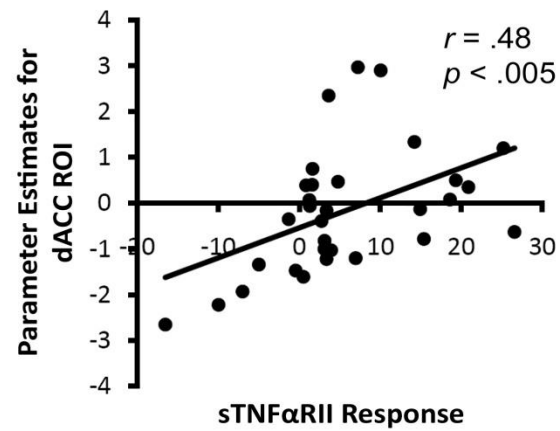
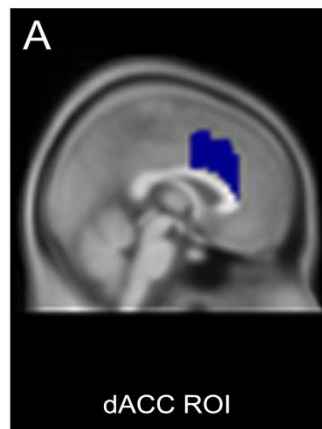
Bruce



Harold



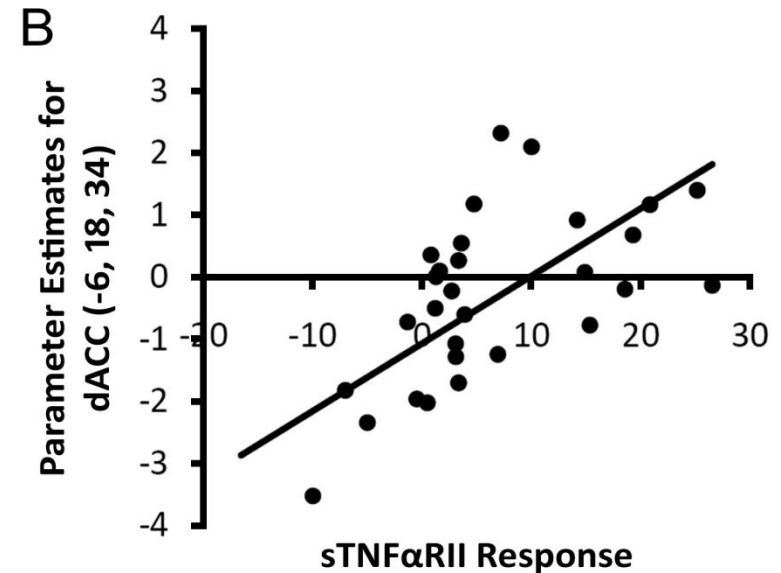
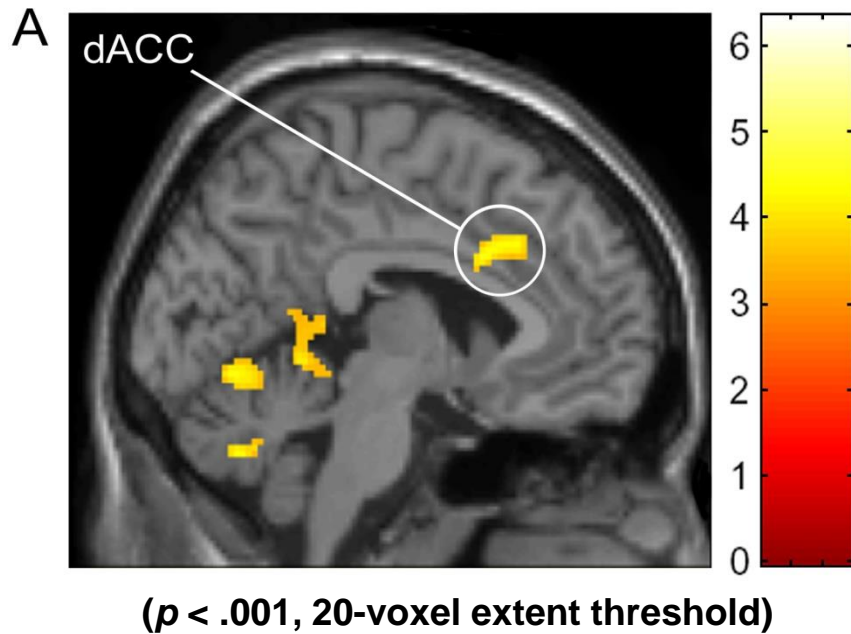
George



# Neural sensitivity to social rejection is associated with inflammatory responses to social stress

George M. Slavich<sup>a</sup>, Baldwin M. Way<sup>b</sup>, Naomi I. Eisenberger<sup>b</sup>, and Shelley E. Taylor<sup>b,1</sup>

<sup>a</sup>Cousins Center for Psychoneuroimmunology and <sup>b</sup>Department of Psychology, University of California, Los Angeles, CA 90095



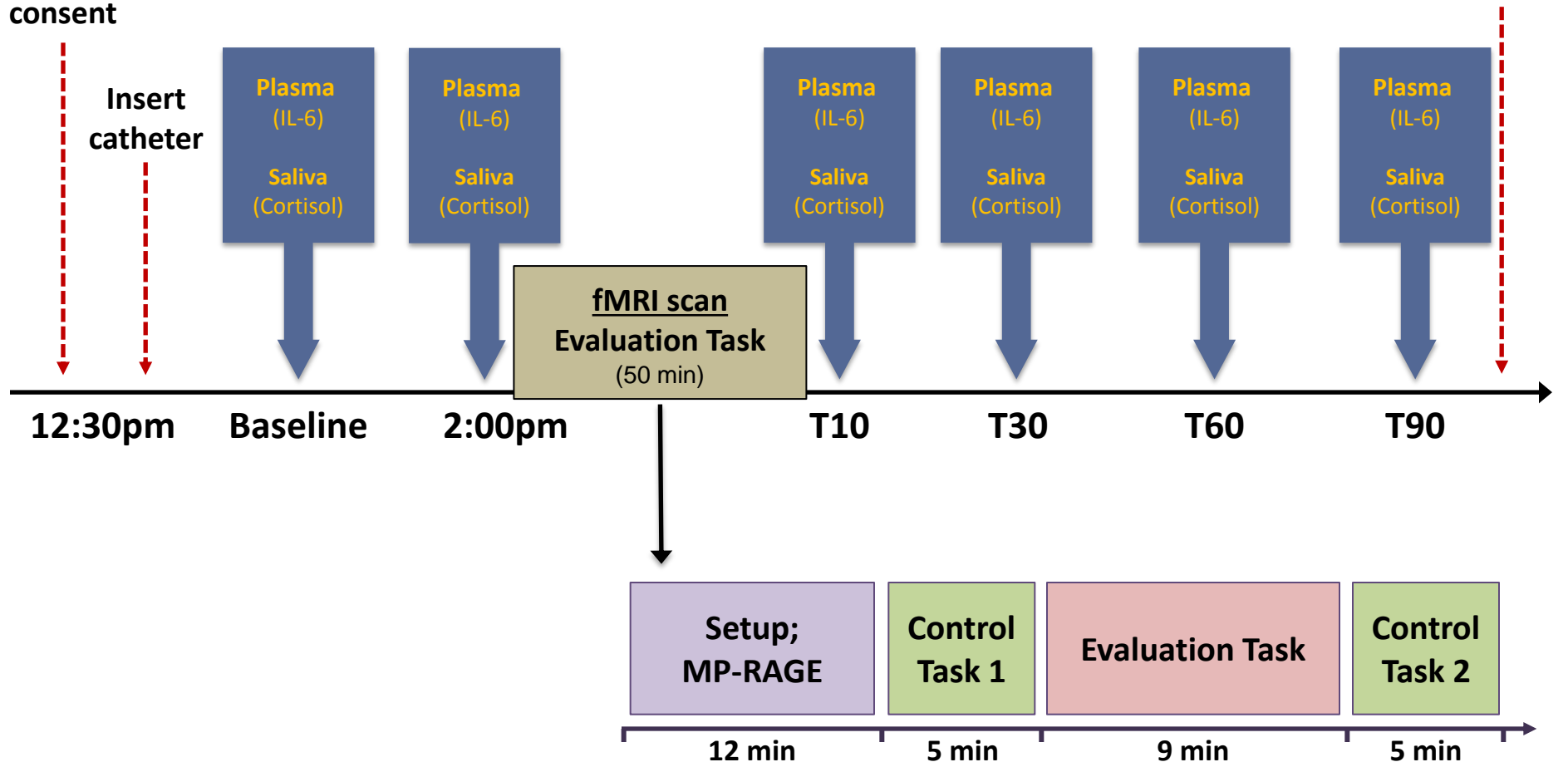


# Social Evaluation & fMRI-Inflammation Study

*"Participating in a study on first impressions..."*

Subject  
arrives;  
Review  
consent

Debrief &  
Dismiss



# Social Evaluation & fMRI-Inflammation Study

**Confederate**  
(in scanner control room)



**Participant**  
(in fMRI scanner)



**ANNOYING**

**EMOTIONAL**

**KIND**

**SENSIBLE**

**ARROGANT**

**FRIENDLY**

**LAZY**

**SERIOUS**

**BORING**

**FUN**

**NERVOUS**

**SHALLOW**

**CARING**

**INSECURE**

**PRACTICAL**

**SINCERE**

**COMPETITIVE**

**INTELLIGENT**

**RESERVED**

**SPONTANEOUS**

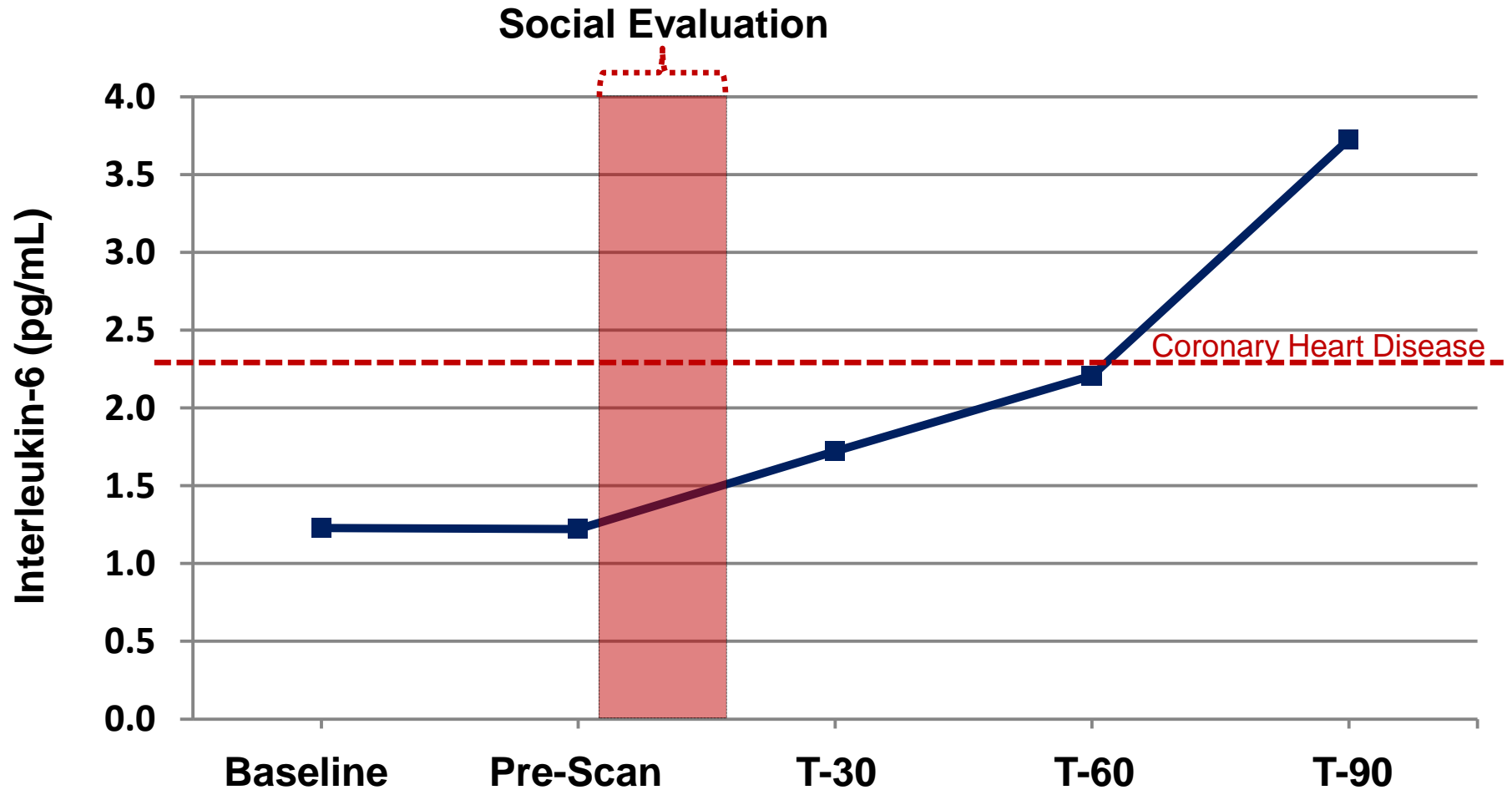
**CONFIDENT**

**INTERESTING**

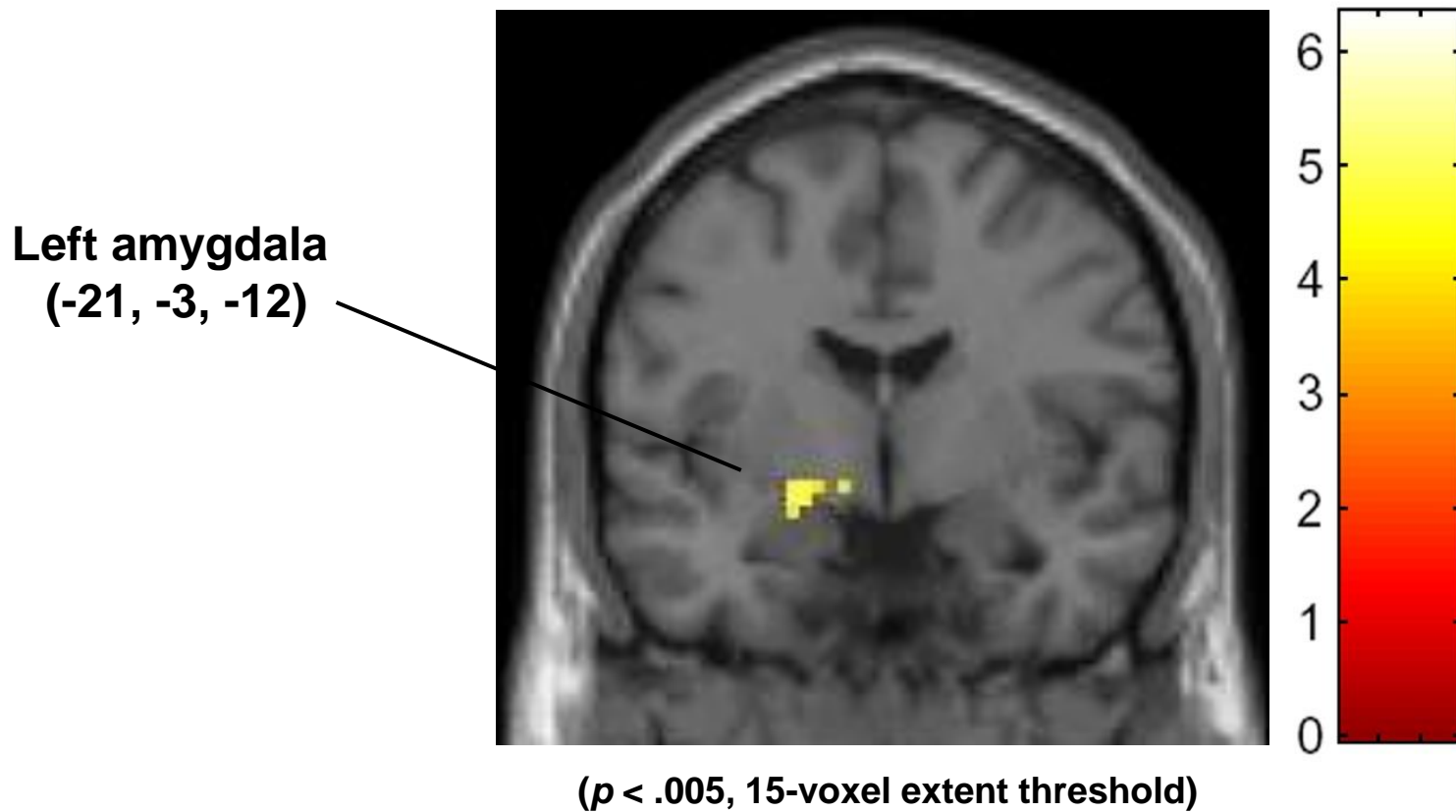
**SELFISH**

**TALKATIVE**

# Social Evaluation & Inflammation

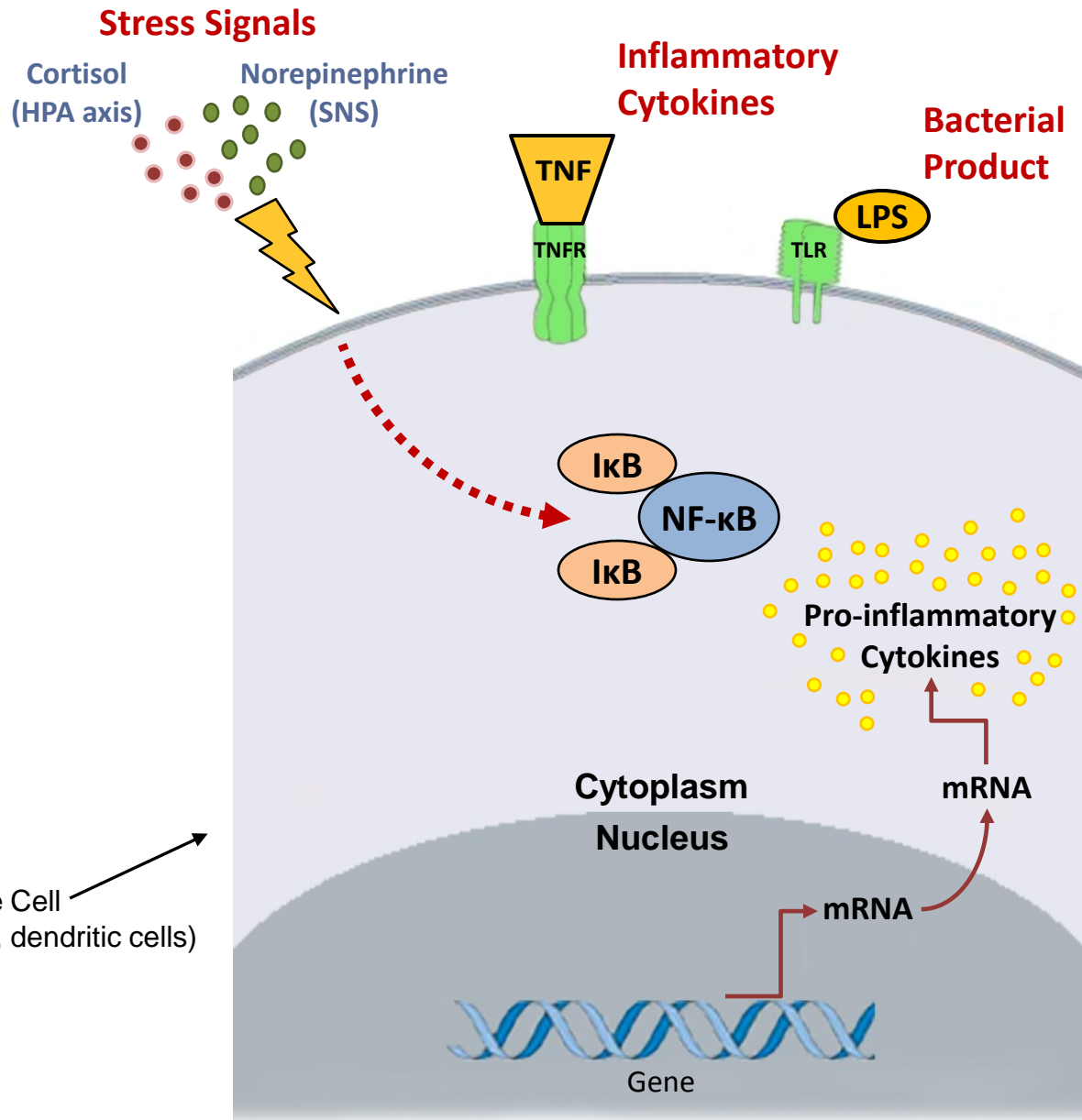


# Neural Correlates of IL-6 Responses









Innate Immune Cell  
(macrophages, dendritic cells)

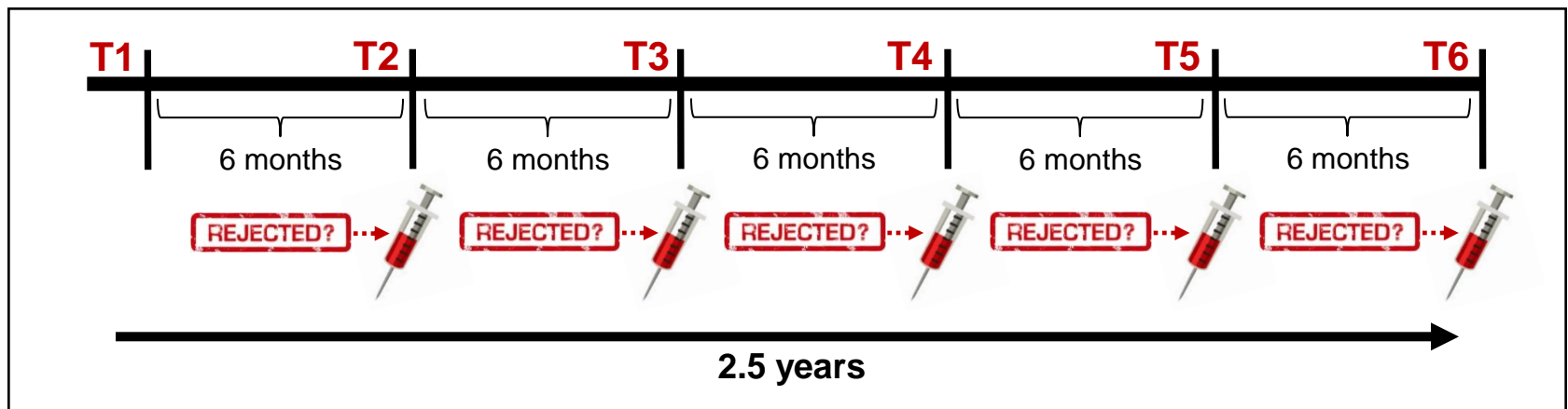
# Targeted Rejection & Gene Expression




Do targeted rejection life events upregulate inflammatory gene expression?

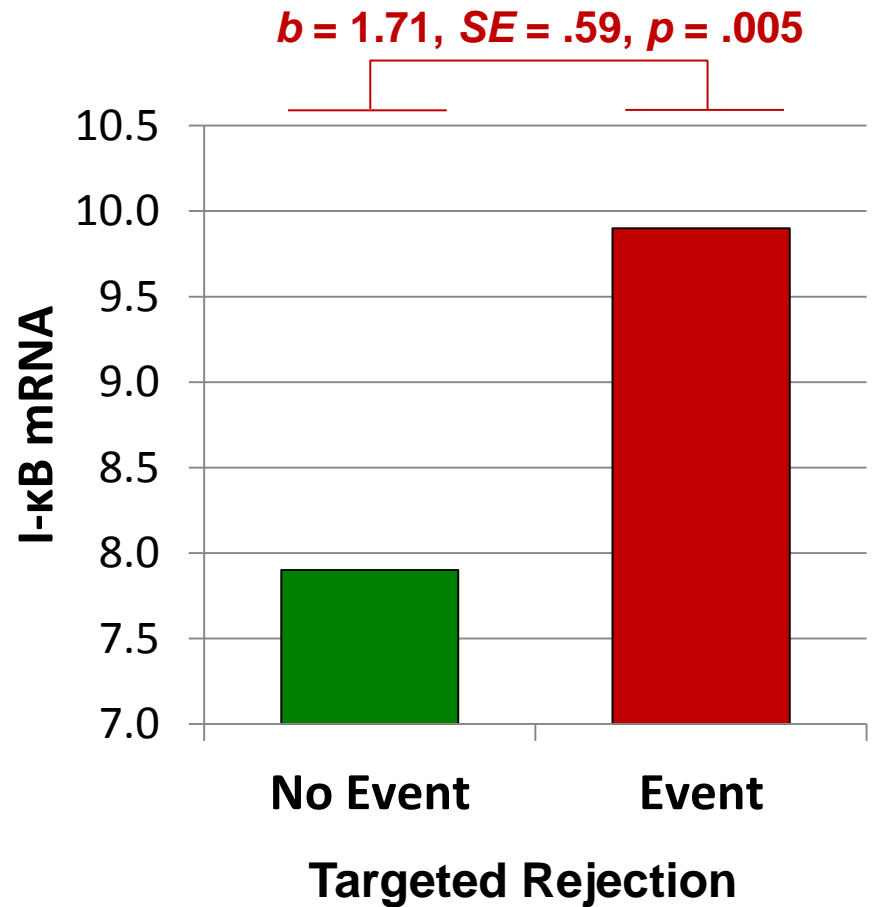
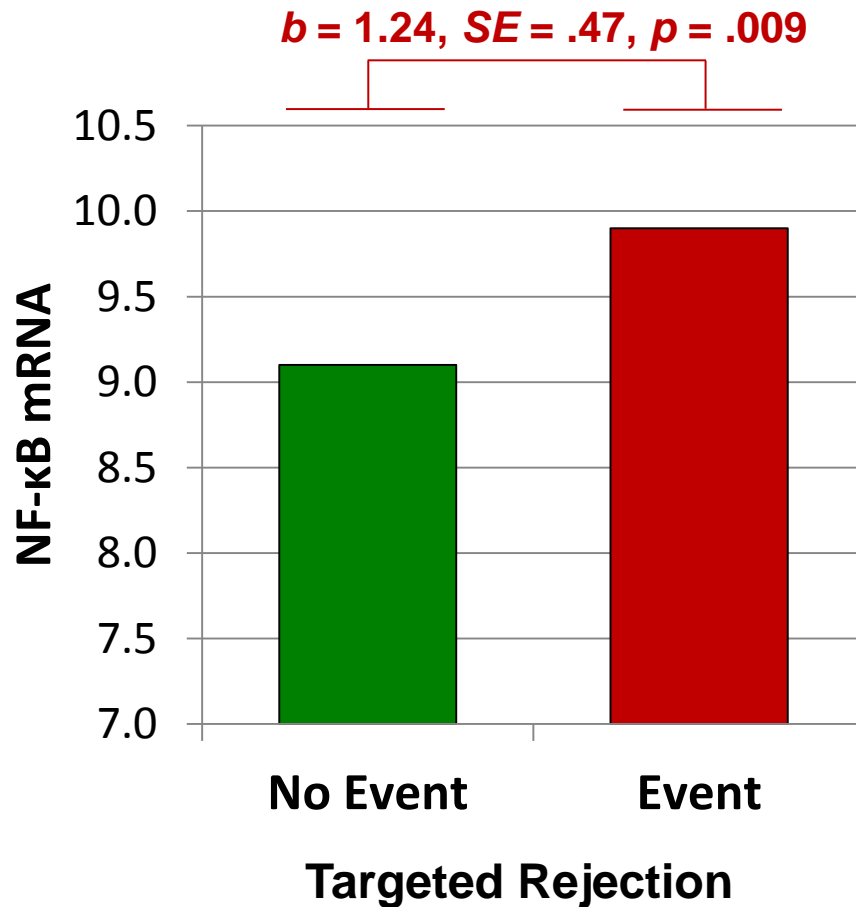
## Participants

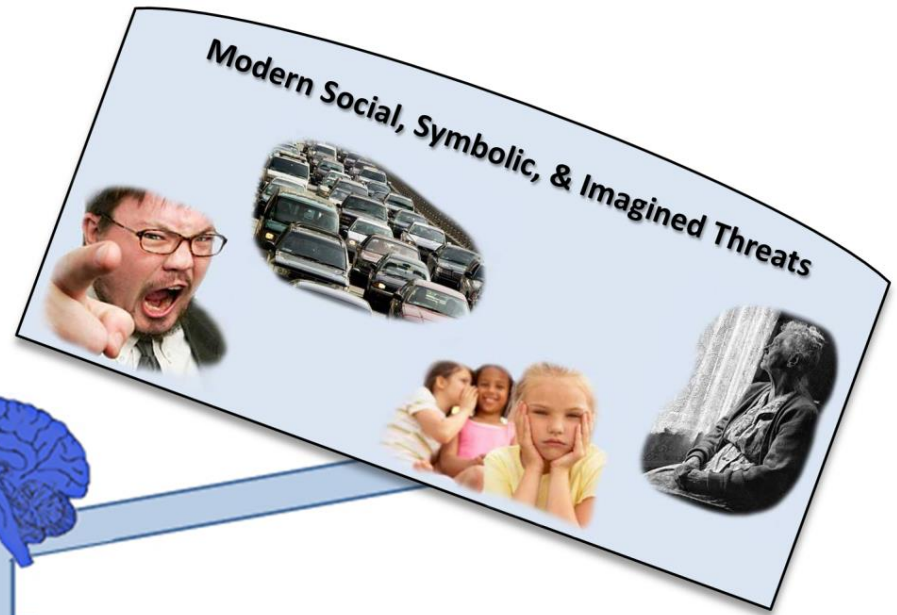
- 147 adolescent women, at elevated risk for depression ( $M_{age} = 17.0$ )
- No current or lifetime history of any major psychiatric disorder, but elevated risk for depression
- Assessed every 6 months for 2.5 years



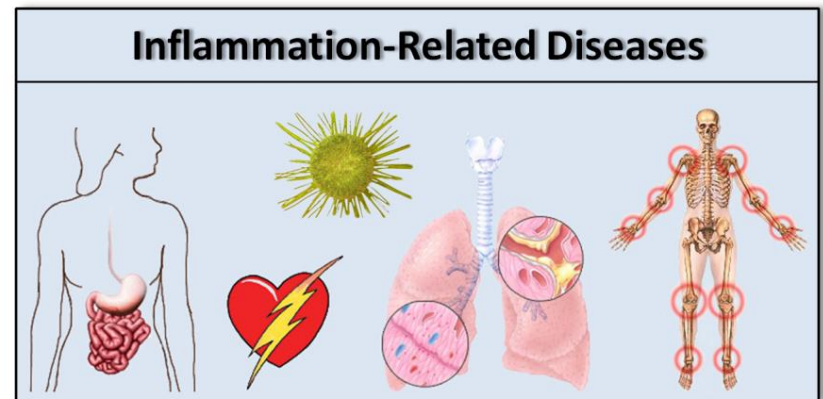
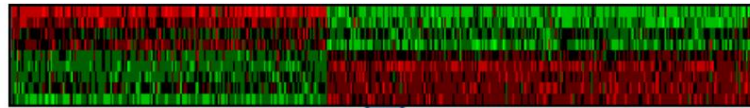
# Targeted Rejection Triggers Differential Pro- and Anti-Inflammatory Gene Expression in Adolescents as a Function of Social Status

Clinical Psychological Science  
XX(X) 1-11  
© The Author(s) 2012  
Reprints and permission:  
sagepub.com/journalsPermissions.nav  
DOI: 10.1177/2167702612455743  
<http://cpx.sagepub.com>  






Leukocyte Conserved Transcriptional Response to Adversity (CTRA)





# Human Social Genomics

- Evidence for new field of “Human Social Genomics”
- Other studies: social isolation upregulates not just a few genes, but >800 genes (**especially tied to experience!**)
- Cannot detect changes in gene expression; therefore, we experience our bodies as being biological stable
- However, 1-2% of our entire molecular makeup must be replaced every day
- As a result, experiences of social threat and rejection on any given day can influence our molecular composition for weeks and months into the future...

# The Emerging Field of Human Social Genomics

**George M. Slavich<sup>1</sup> and Steven W. Cole<sup>1,2</sup>**

<sup>1</sup>Cousins Center for Psychoneuroimmunology and Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, and <sup>2</sup>Department of Medicine, Division of Hematology-Oncology, UCLA Molecular Biology Institute, Jonsson Comprehensive Cancer Center, and UCLA AIDS Institute, University of California, Los Angeles

Clinical Psychological Science

XX(X) 1–18

© The Author(s) 2013

Reprints and permission:

sagepub.com/journalsPermissions.nav

DOI: 10.1177/2167702613478594

http://cpx.sagepub.com



## Abstract

Although we generally experience our bodies as being biologically stable across time and situations, an emerging field of research is demonstrating that external social conditions, especially our subjective perceptions of those conditions, can influence our most basic internal biological processes—namely, the expression of our genes. This research on *human social genomics* has begun to identify the types of genes that are subject to social-environmental regulation, the neural and molecular mechanisms that mediate the effects of social processes on gene expression, and the genetic polymorphisms that moderate individual differences in genomic sensitivity to social context. The molecular models resulting from this research provide new opportunities for understanding how social and genetic factors interact to shape complex behavioral phenotypes and susceptibility to disease. This research also sheds new light on the evolution of the human genome and challenges the fundamental belief that our molecular makeup is relatively stable and impermeable to social-environmental influence.

Download at: [www.uclastresslab.org](http://www.uclastresslab.org)

# Summary of Results

- 1) Experiences involving social threat & rejection strongly impact psychological and physical health
- 2) Naturalistic & laboratory-based social stressors trigger increased levels of pro-inflammatory cytokines
- 3) Rejection engages brain regions involved in physical pain – thus, we have a possible neurobiological explanation for why stress upregulates inflammation
- 4) Social isolation & rejection are associated with genome-wide transcriptional shifts toward a more pro-inflammatory phenotype over time (adaptive value!)
- 5) Experiences of the social environment we have today can impact our molecular milieu, and thus our health, for days and months into the future

FEBRUARY 23, 2004

BUSH'S  
MILITARY RECORDS  
IS DISNEY MOUSETRAPPED?

# TIME

## THE SECRET KILLER

- The surprising link between **INFLAMMATION** and **HEART ATTACKS, CANCER, ALZHEIMER'S** and other diseases
- What you can do to fight it

# STRAIN

Stress and Adversity  
Inventory

**Assesses:** 96 acute life events & Chronic difficulties

**Prompts:** Text & Professionally-recorded voice

**Inputs:** Keyboard or Touch screen

**Time:** ~30 minutes to complete (range = 25-35 min.)

**Outputs:** 445 variables, more than 115 summary scores





## The STRAIN

*Stress and Adversity Inventory*

Thank you for agreeing to complete this interview. I'd like to ask you about a variety of things that you may have experienced during your life. Specifically, I'll be asking you about events that may have happened to you and how you felt about them. I'll also ask you about when these events occurred. To choose an option on the screen, just click on the answer using the mouse. Once you've chosen an option, click the ">> Next" button right below the bottom-right corner of the text box to go to the next question.

When you need to enter information into a response box, first click the box, then use the keyboard to type in your response. Once you've finished typing, click the ">> Next" button to continue.

The interview will take about 35 minutes. We will cover a number of different topics during that time. Please answer each question as accurately as possible. All of your answers will be kept strictly confidential. If you have any questions during the interview, please let the study staff know.

To begin the interview, click the ">> Next" button below.



Okay, we're doing well. School and work occupy a significant part of many peoples' lives. So, I'd like to ask you a few questions about your school and work history.

Have you ever dropped out or failed out of school?

- ☒ Yes
- ☐ No

How many times have you dropped out or failed out of school?

1



2



3



4



5 or more



Survey Powered By [Qualtrics](#)

<< BACK

>> NEXT



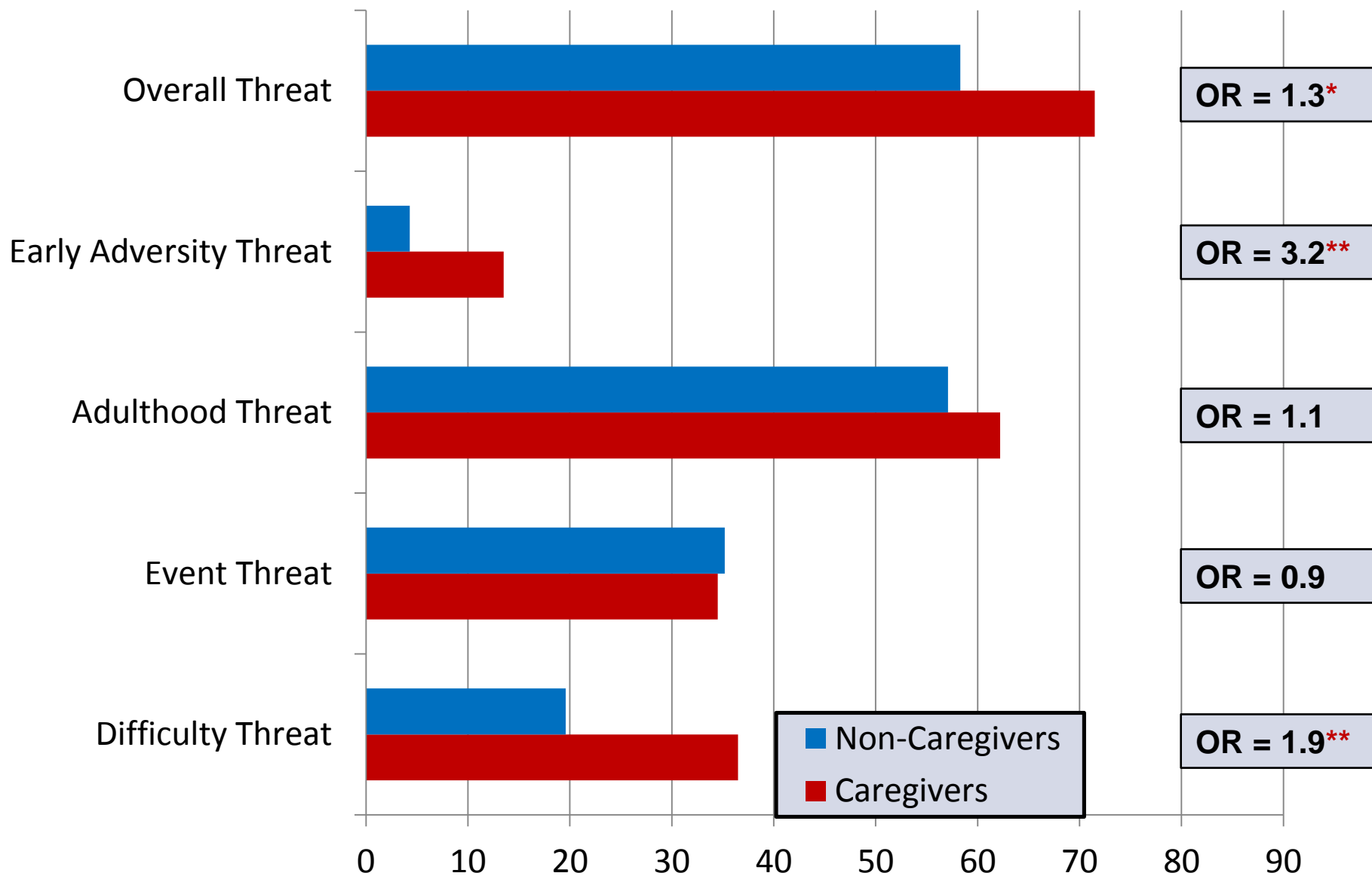
At its worst, how stressful or threatening was this for you?

- ☐ Very slightly or not at all
- ☐ A little
- ☐ Moderately
- ☐ Quite a bit
- ☒ Extremely

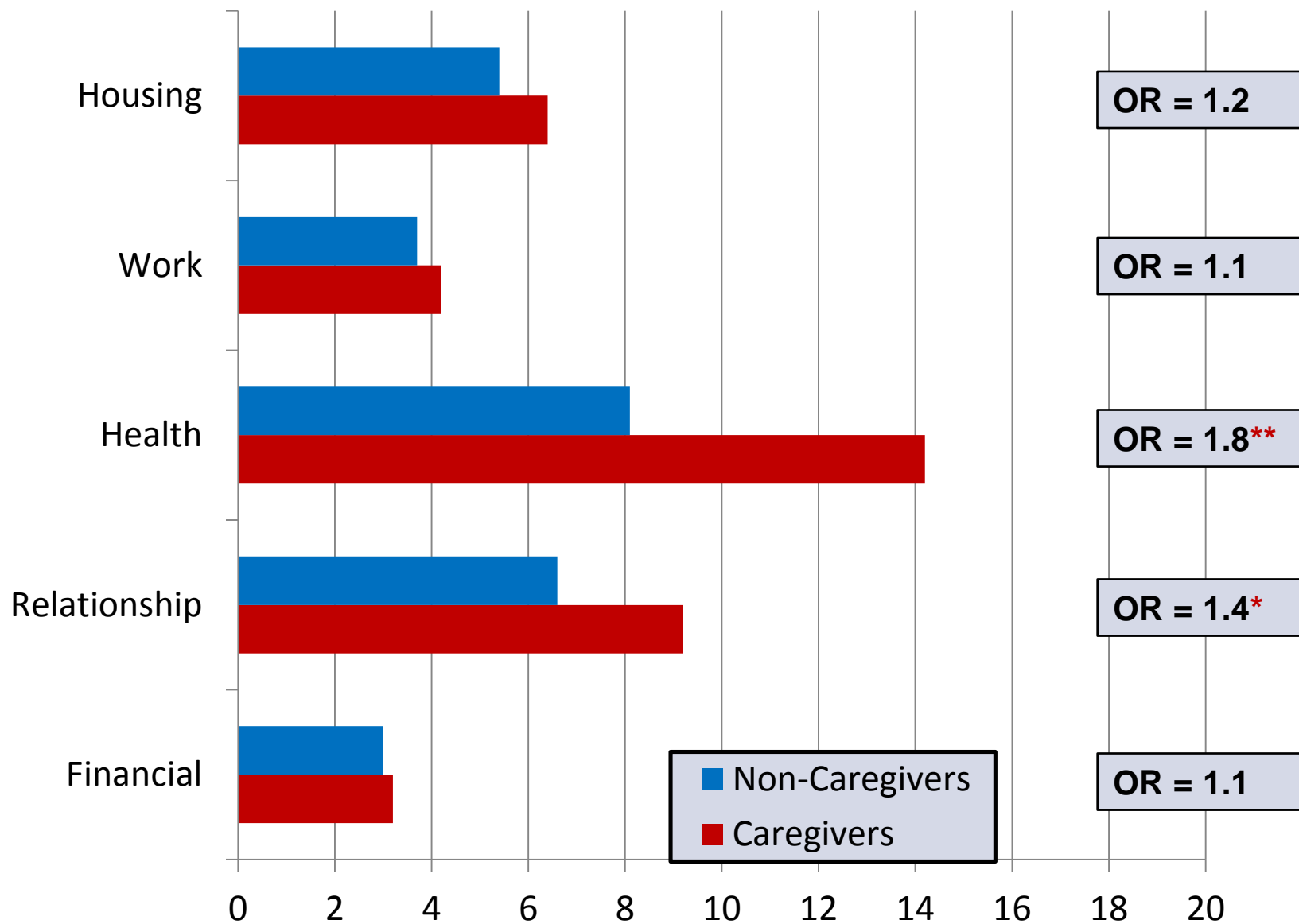


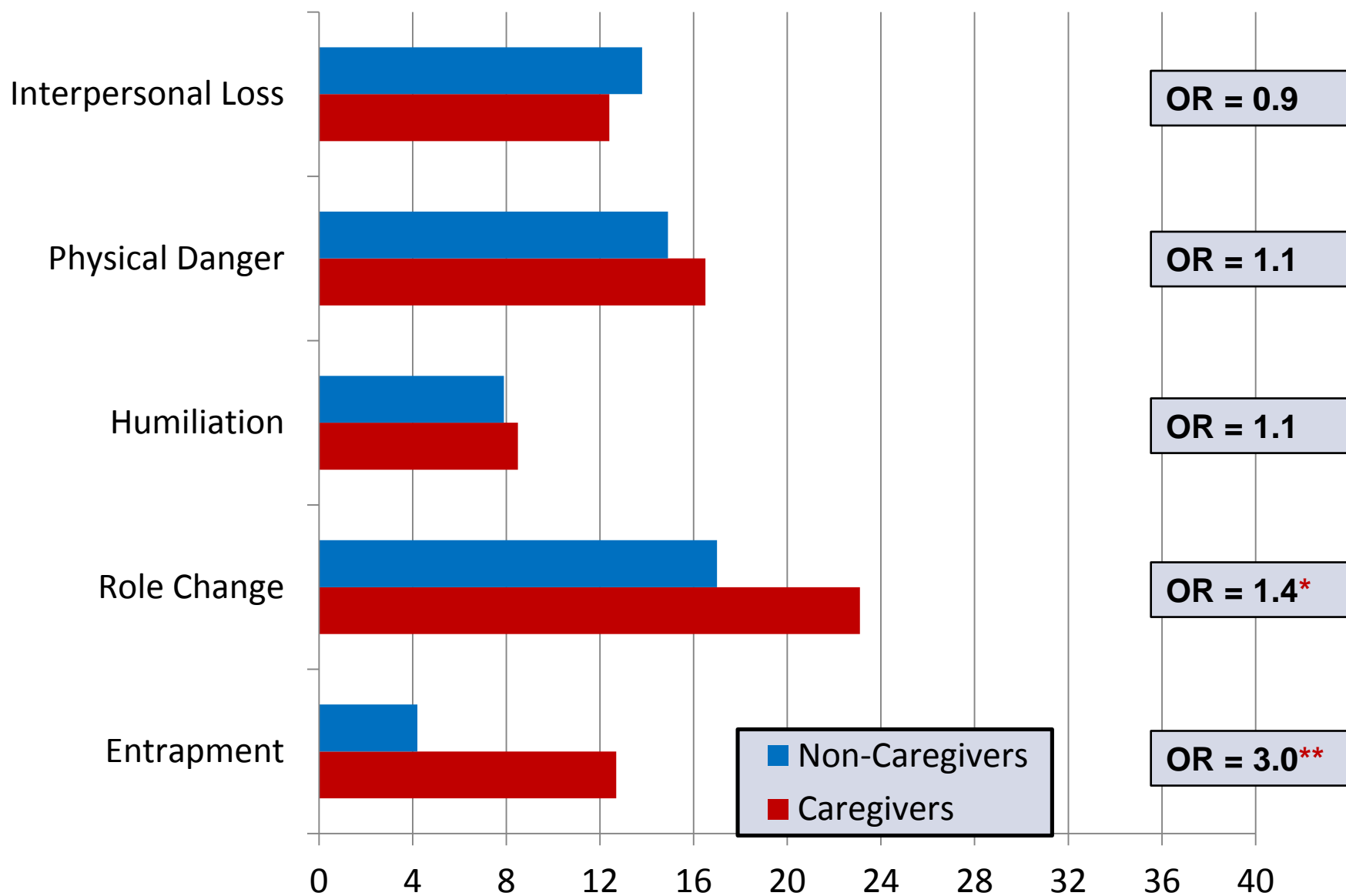
When did this happen?

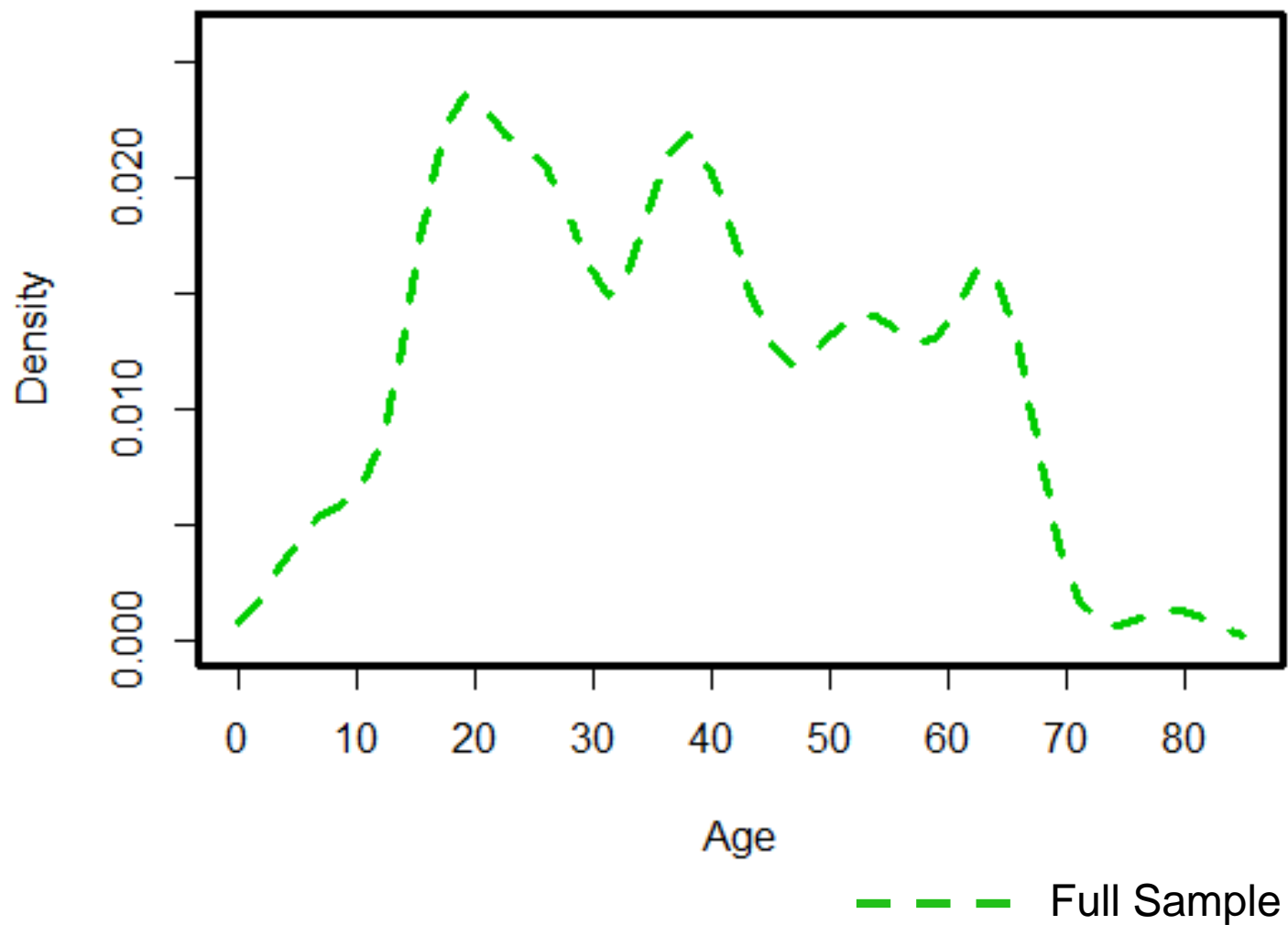
- ☒ 0-3 months ago
- ☐ 3-6 months ago
- ☐ 6-12 months ago
- ☐ 1-2 years ago
- ☐ 2-5 years ago
- ☐ 5 or more years ago



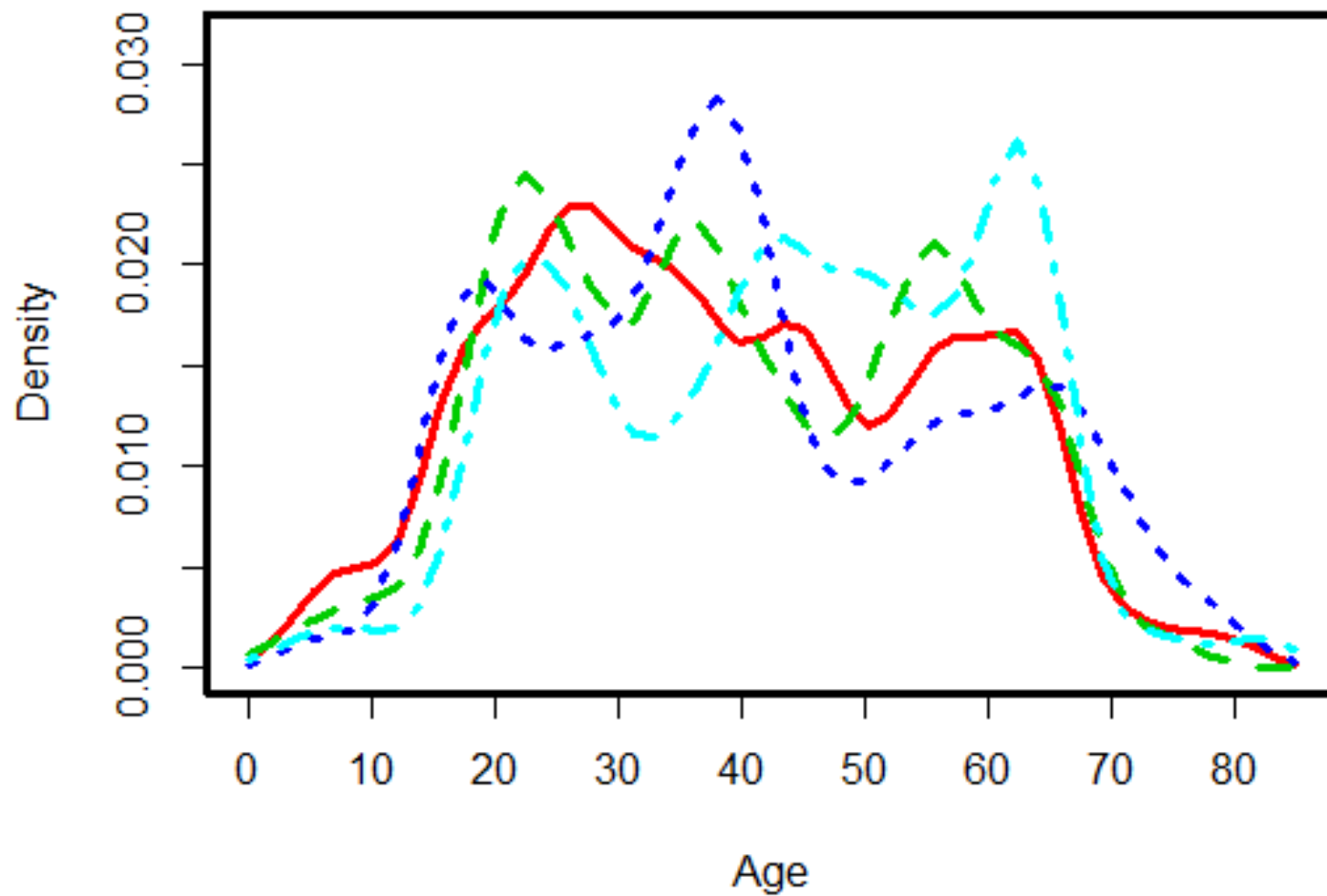




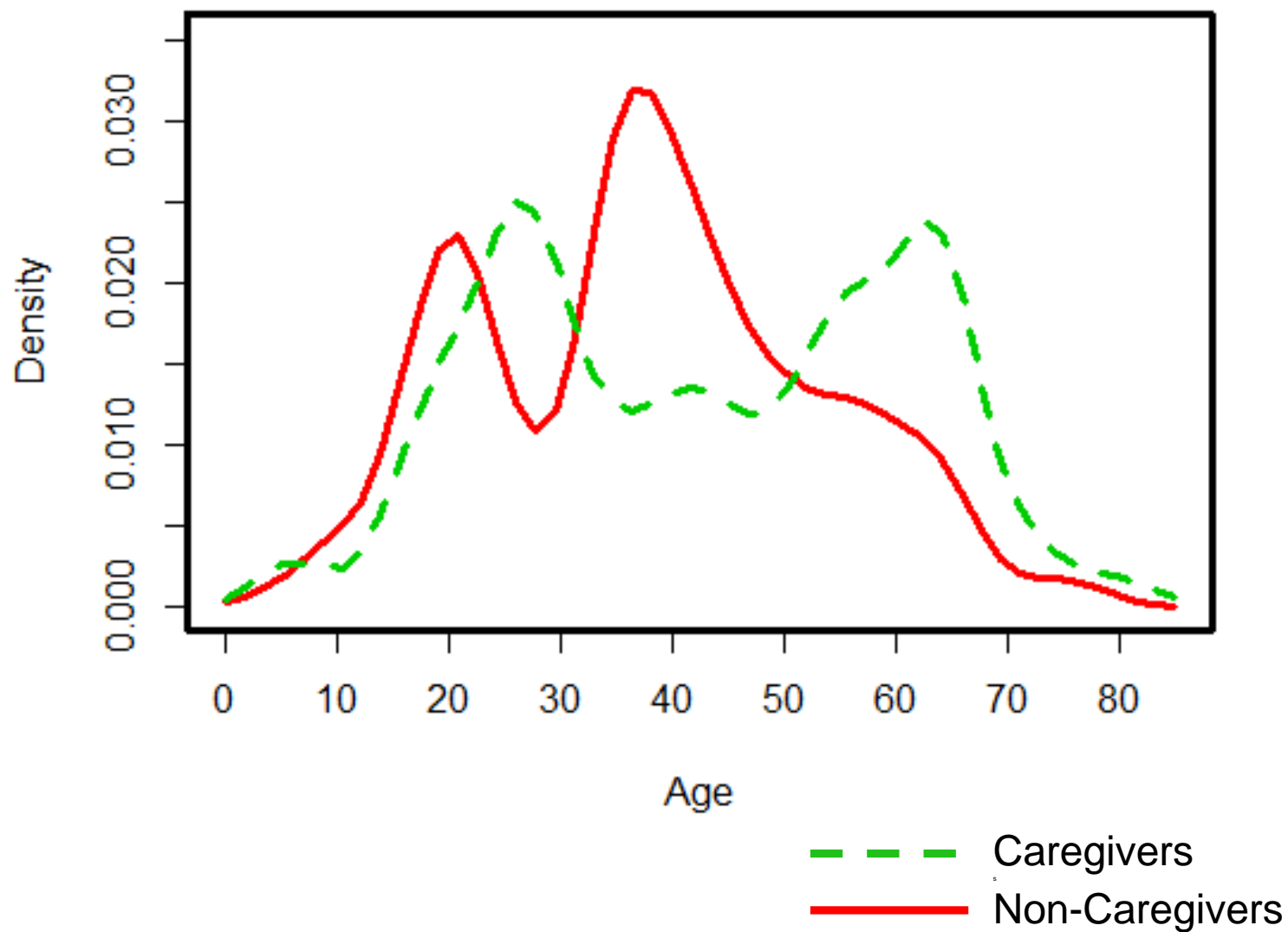




**STRAIN Plot: lifetime stress exposure, one subject**



**STRAIN Plot: lifetime stress exposure, four randomly selected subjects**



<http://EmergingTools.LifeStressTest.com>



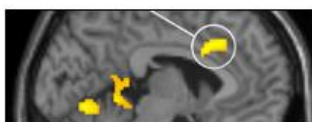
TGGAAGGGTGGCCCCACCGGCCGAGACAGCGAAGCATATGCAGGAAATTCGCGGGATAAGGAA  
 AA**HUMAN SOCIAL GENOMICS**GCTCGGGAGGTGGCCAGGCGGCAGGAAGGCGCCAGCAAT  
 CTGCAGGAACCTTCTTCTGGAAGACCTTCTCCTCCTGCAATAAAACCTCAGCCGAAATTGCAAG  
 TCGA**HOW SOCIAL STRESS**ATTACAGACCTGAAACCTGCGGCTCTGC  
 CCTGGAGGGTGGCCCCACCGGCCGAGACAGCGAGCATATGCAGGAAGCGGAGGAAAAGCAG  
 CTCC**REGULATES**TGACTTTCTCCTCGCTTGGTGGTTTCTAGCA CAGTGCCG  
 AAGCTCGGGAGGTGGCCAGGCGGCAGGAAGGCGCACCCCTTCGGCATGCCGGGACATTGCC  
 CTGC**THE**AGGAACCTTCTTCTGGAAGACCTTCTCCTGeorge Slavich and Steve Cole recently published the first  
 TTTAATTACAGACCTGAAACAAGATGCCATTGTCCcomprehensive review of human social genomics...  
 TTGG**HUMAN GENOME**ACCTCCCTTAGCACAGTGGCCGGGCCCCCTCATAGGAGAGGAGGCGCA  
 GCCGGGACAGAATGCCCAGGAAGGCGCACCCCTTCGGCGCGCCGGGACAGAATAGGTGGCG  
 AGGCGGGCGCACCCCCCAGCAATGCATCGCTGTG  
 CGAGCGAGCATATGCAGGAAGCGGCAGAAGTGCA  
 CCTCGCTTGGTGGTTTGAGTGGACCTCCCTTAGCA CAGTGCCGGGCCCCCTCATAGGAGAGGA

**Human Social Genomics**

[www.uclastresslab.org](http://www.uclastresslab.org)

## Welcome!

The mission of the UCLA Laboratory for Stress Assessment and Research is to support and advance the science of stress and health. We conduct studies that integrate tools and methods from clinical psychology, health psychology, and social neuroscience to examine how and why adverse social conditions, such as social isolation and rejection, affect health. In addition, we develop products that help investigators assess life stress, and provide expert consultation services to a variety of groups including the National Cancer Institute and the National Institute on Aging. By addressing these issues, we aim to explore how stress promotes susceptibility to psychiatric and physical disorders that cause significant public concern, particularly ovarian cancer, breast cancer, and depression.



### Stress+Inflammation

We recently identified the neural pathways involved in inflammatory



### STRAIN is Here!

The STRAIN is an automated system for assessing cumulative



### Come Join the Lab

We are always looking for new undergraduate, graduate, and

## Recent News

- ✦ Slavich & Cole Reveal How Social Experiences Affect Our Genes and Health
- ✦ Immune Response May Link Social Rejection to Later Health Outcomes
- ✦ Slavich & Zimbardo Review Transformational Teaching
- ✦ Slavich wins Raymond D. Fowler Award for Outstanding Contribution to the Professional Development of Graduate Students
- ✦ Slavich wins Theodore H. Blau Early Career Award for Distinguished Professional Contributions to Clinical Psychology

Generously supported by:

# Interventions & Gene Expression

## **Antoni et al., 2012, *Biological Psychiatry***

**RCT:** 10-week CBT stress management intervention for early-stage breast cancer patients

- ↓ pro-inflammatory & metastasis genes & ↑ interferon genes

## **Black et al., 2013, *Psychoneuroendocrinology***

**RCT:** Meditation 12 min/day for 8 weeks in dementia caregivers

- ↓ 68 NF-κB-associated pro-inflammatory genes

## **Creswell et al., 2012, *Brain, Behavior, & Immunity***

**WLCT:** 8-week mindfulness-based stress reduction program in healthy older adults (ages 55-85)

- ↓ 143 NF-κB-associated pro-inflammatory genes