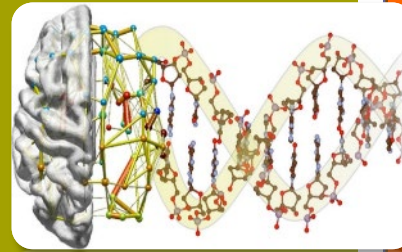


***Not So* Lost in Translation:**

Examples of Bench to Bedside To Community Health Research

ADVISORY COUNCIL ON WOMEN'S HEALTH RESEARCH

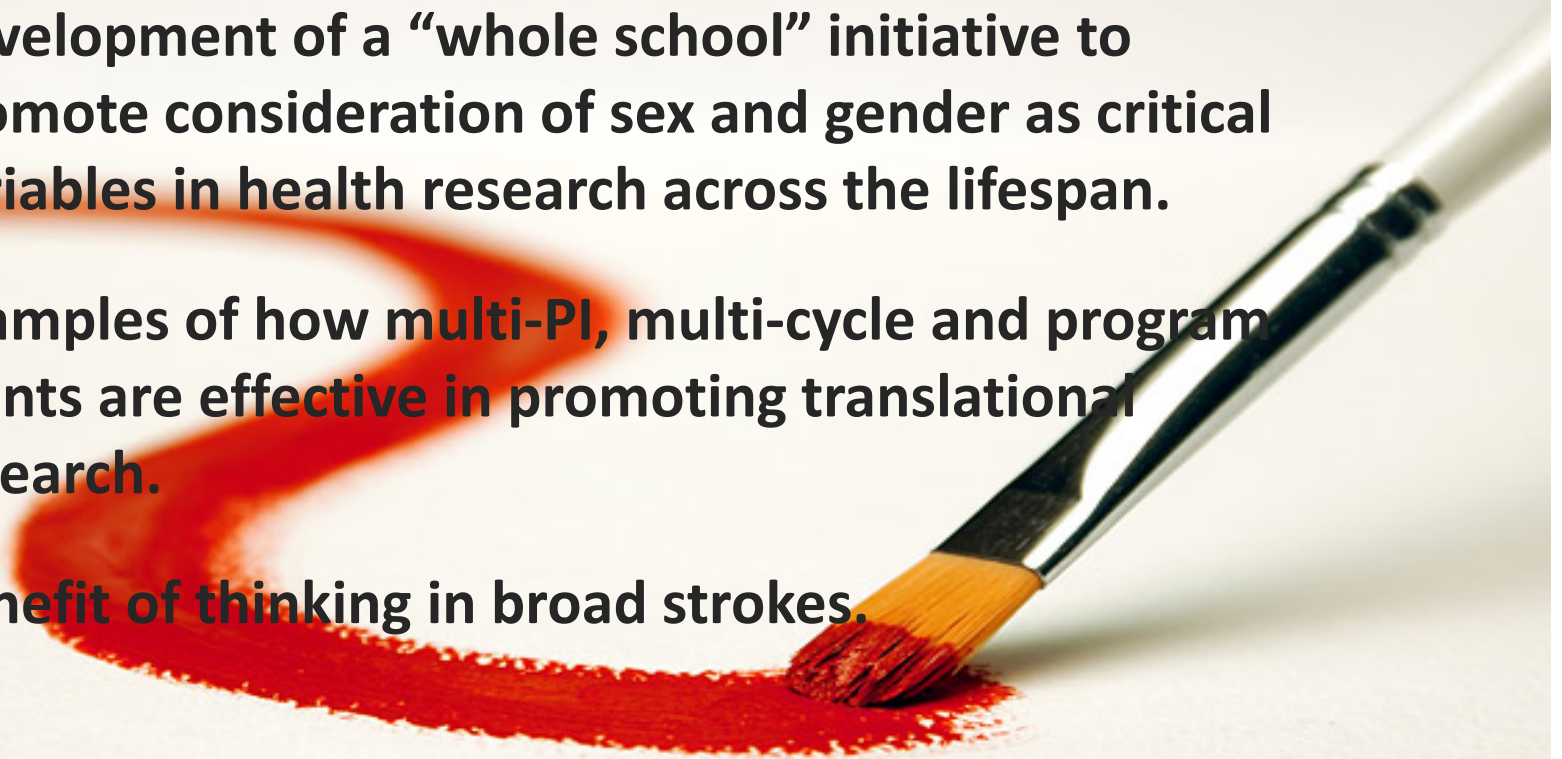
April 4, 2017



Penn
PROMOTES
Research on Sex and Gender in Health

Overview

- **Our mission statement.**
- **Development of a “whole school” initiative to promote consideration of sex and gender as critical variables in health research across the lifespan.**
- **Examples of how multi-PI, multi-cycle and program grants are effective in promoting translational research.**
- **Benefit of thinking in broad strokes.**

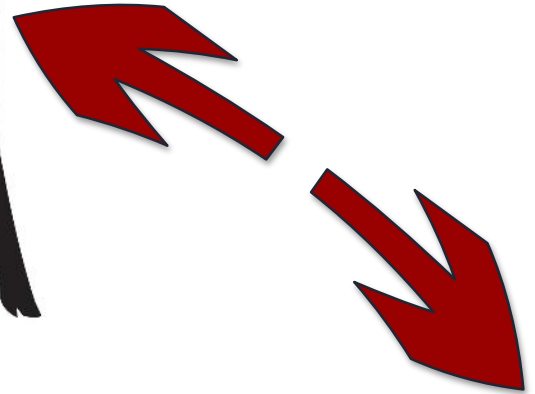
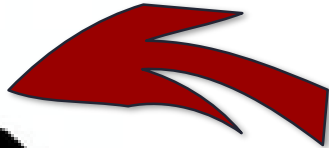
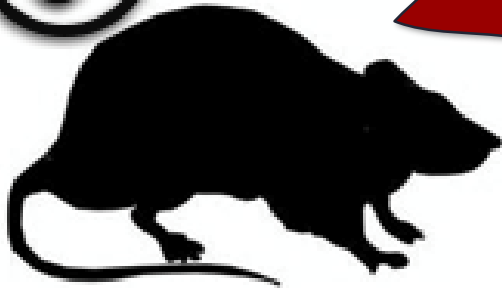
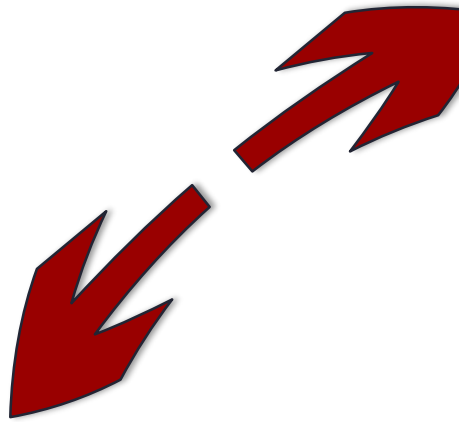
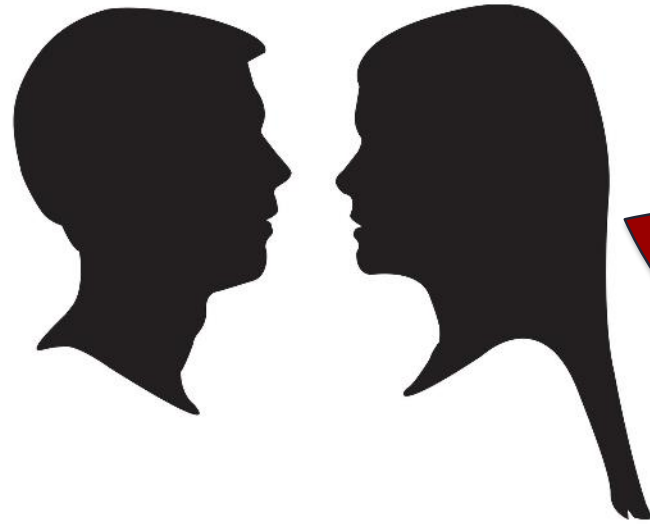


Our *All-HEALTH* Mission Statement

To advance **HEALTH**
FOR ALL by considering
the role of sex and
gender in **ALL HEALTH**
related research.



“It’s not a great mission statement,
but we’ll revise it if things get better.”















Overview

- Our mission statement.
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- Examples of how multi-PI, multi-cycle and program grants are effective in promoting translational research.
- **Benefit of thinking in broad strokes.**



Timeline

PCWBW
Established
Sept 2009

2011

2012

2015-2017 &
Beyond

Sortor, PsyD

L. Sortor, PsyD
N. Epperson, MD
S. Mathews, MD

Specialized Center of Research

L. Sortor, PsyD
N. Epperson, MD
2 Research Staff

L. Sortor,
N. Epperson
D. Kim, MD
S. Mathews, MS
4 Research Staff
4 Students

Ellen
Freeman

4 Students

ent
ciD
D.

Doctoral Student
M. Sammel, SciD
T. Bale, Ph.D.
Post-Docs
Instructors

K24
2 R01s

K24
2 R01s
Pharma
R21

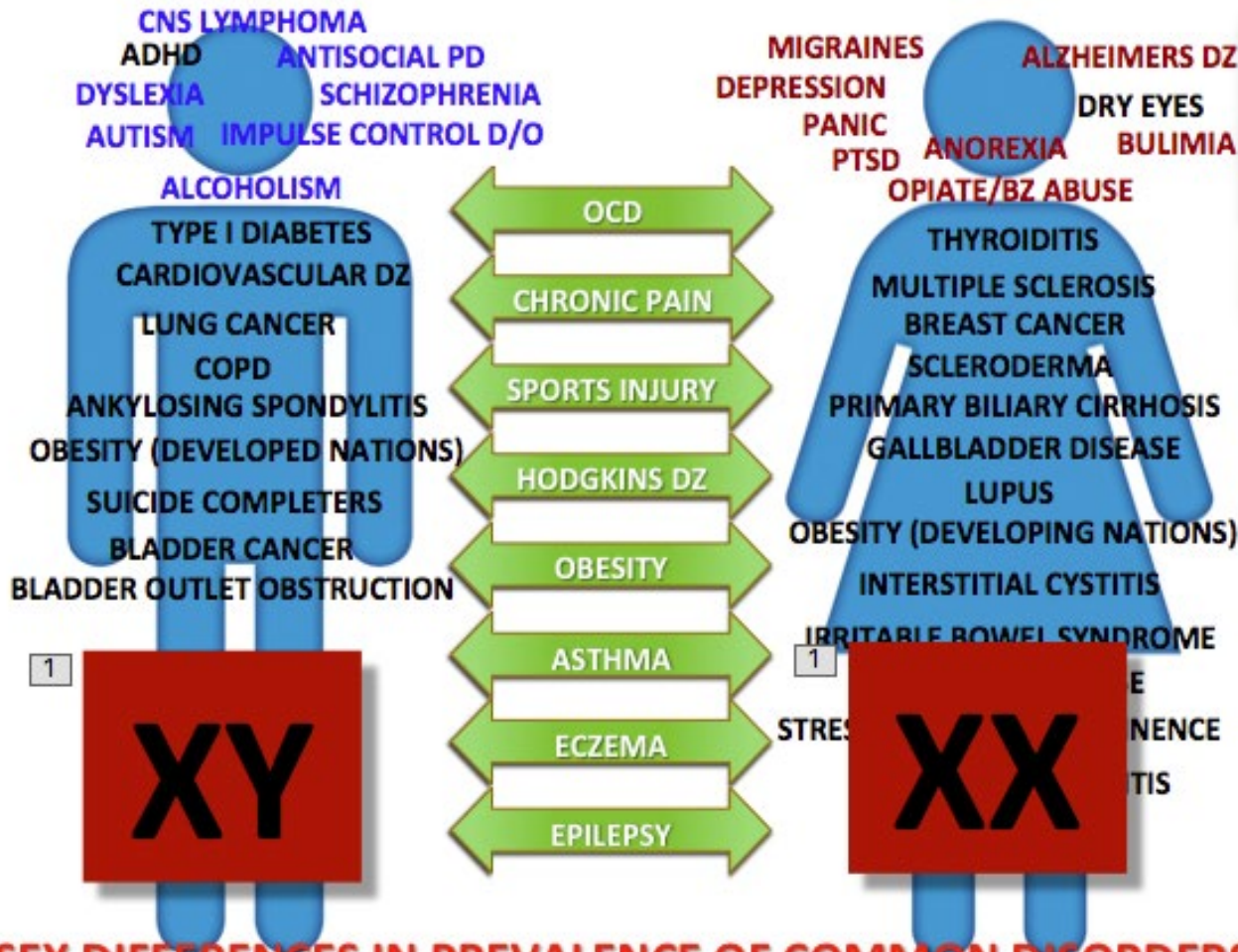
Mary Sammel
Pharma
R21
P50 (SCOR)

Tracy Bale

3
3
Ph
P50
BIRCWH

BIRCWH
K12

Penn PROMOTES Research on Sex and Gender in Health



SEX DIFFERENCES IN PREVALENCE OF COMMON DISORDERS



Home

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Faculty and Staff

BIRCWH ▾

PCWBW ▾

Bale Lab ▾

News ▾

Resources

Penn PROMOTES 2017
Retreat

Supporting Penn PROMOTES

Penn PROMOTES

Research on Sex and Gender in Health

Penn PROMOTES Research on Sex and Gender in Health was established in 2012 as the result of a National Institute of Mental Health and Office of Research on Women's Health grant to study mood disorders across the female lifespan. **Jointly awarded to Dr. C. Neill Epperson and Dr. Tracy Bale**, this grant hopes to improve our understanding of how diseases, and affective disorders in specific, affect men and women differently. Together, Drs. Epperson and Bale hope to shed light on the gender differences in common mental health disorders such as depression, anxiety and somatic complaints.

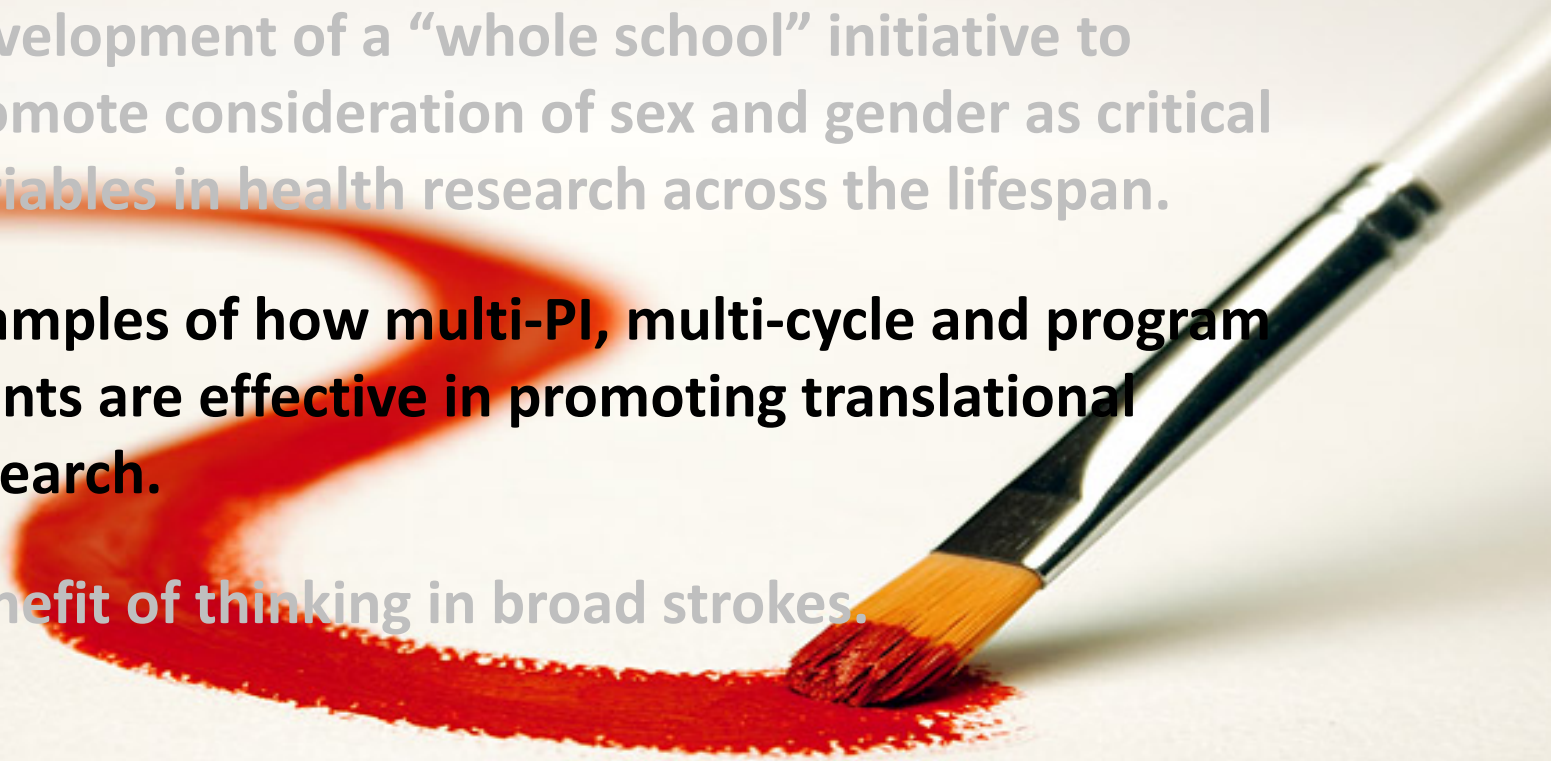
Penn PROMOTES takes an interdisciplinary approach to answering these questions about sex and gender in health, incorporating perspectives from the School of Medicine, School of Veterinary Medicine, School of Arts and Sciences and beyond. Over the past 4 years, Penn PROMOTES has evolved to include 3 programs of research all aiming to unearth many questions and answers about how gender plays a role in health today. Primarily, Penn PROMOTES serves as a virtual Center, incorporating the research of the Penn Center for Women's Behavioral Wellness, the Bale Lab, and the Penn BIRCWH.

Penn PROMOTES Impact

- Assessed status of consideration of SABV and gender in clinical research being conducted at Penn (manuscript under review, *Biology of Sex Differences*).
- Trained Investigational Review Board (IRB) members regarding protocol compliance with NIH guidelines.
- Change in language of template to require discussion of SABV in all IRB submissions.
- Request for proposals for pilot funding received 22 applications from four schools across the university.
 - Nursing, School of Medicine, Wharton, and Annenberg Center for Communication

Overview

- Our mission statement.
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- **Examples of how multi-PI, multi-cycle and program grants are effective in promoting translational research.**
- Benefit of thinking in broad strokes.



SPECIALIZED CENTER OF RESEARCH



Impact of peri-pubertal stress/adversity on sex bias for affective disorders

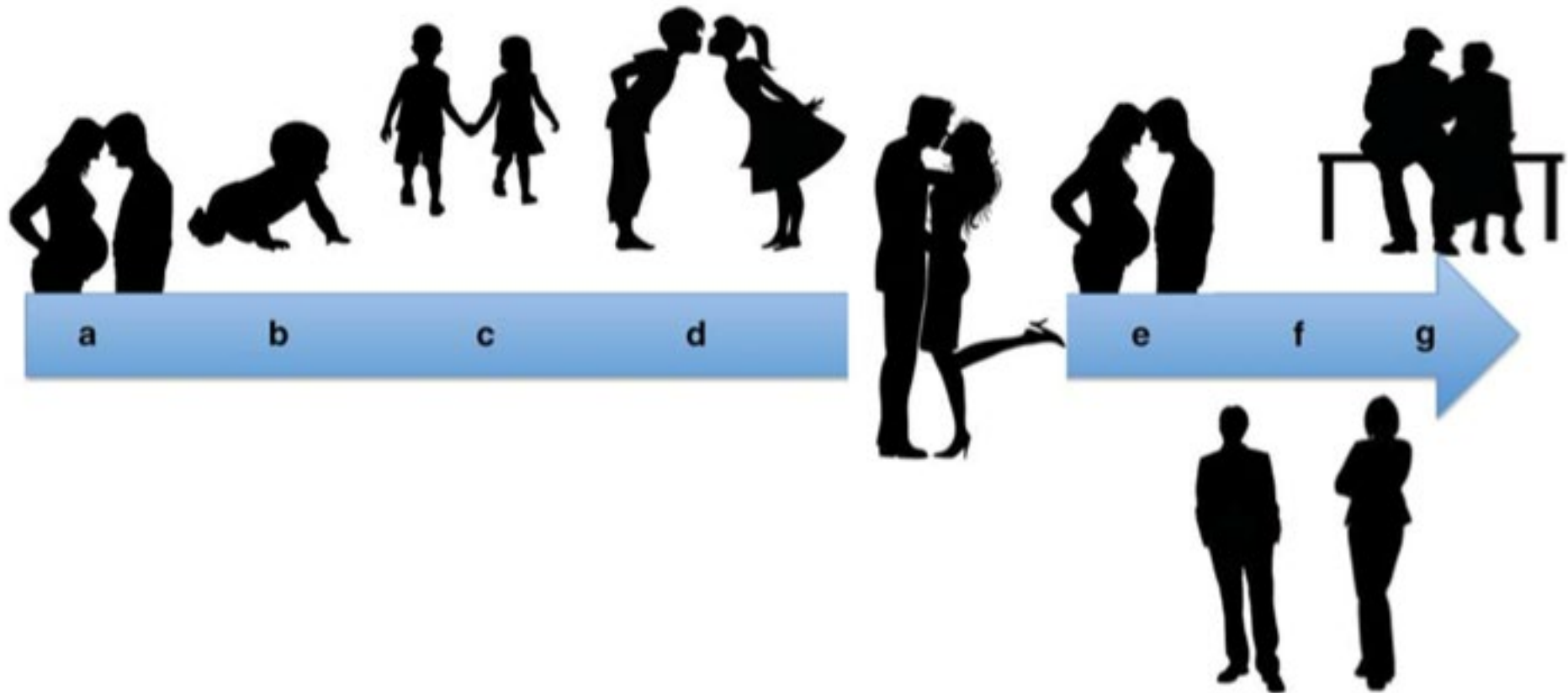


ORWH

NIMH
National Institute
of Mental Health



Critical Windows Across Development



Developing Translational Models



Tracy Bale



Katie Morrison



**Chronic Variable
Stress**

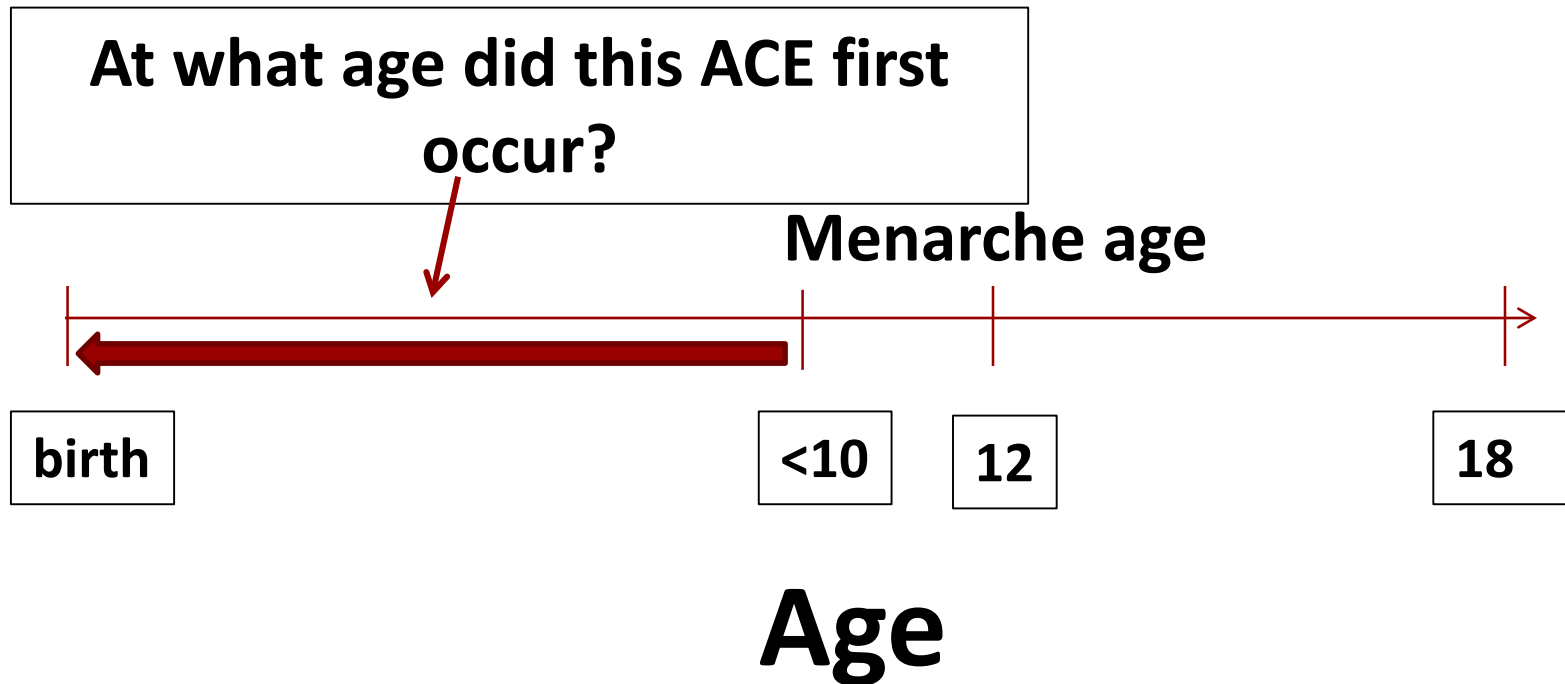


**Adverse Childhood
Experiences**

HOW ARE WE QUANTIFYING EARLY LIFE ADVERSITY?

- ✓ **Adverse Childhood Events (ACE)-Questionnaire developed and used in the collaborative study between the CDC and Kaiser-Permanente in San Diego area.**
 - ✓ 3 Questions about abuse (physical, emotional and sexual)
 - ✓ 2 Questions regarding neglect (physical and emotional)
 - ✓ 1 Question regarding separation or divorce
 - ✓ 4 Questions regarding household dysfunction (domestic violence, substance abuse, parental mental illness, imprisonment)
- ✓ **“Stressed” group are those with ≥ 2 ACEs (High ACE Group)**

Prepubertal Time Window



- ✓ Kappa for ACE report (range .63-.91 for individual items and .81 overall).

SCOR Pregnancy Projects

- Maternal psychophysiology during and after pregnancy
 - Electromyography of the eye blink (acoustic startle)
 - Response to pleasant, unpleasant, neutral stimuli
 - Salivary cortisol (acoustic startle & social stress test)
 - Autonomic response (acoustic startle & social stress test)
 - Maternal depression/negative affect

- Maternal-Infant Stressor—
 - Mother-Infant separation (salivary cortisol)
 - Infant restraint and noise stress (salivary cortisol)

Maternal ACE Effect on Pregnancy and Fetal-Infant Outcomes

- 1500 pregnant women complete the ACE questionnaire.
 - Prevalence of adverse birth outcomes.
- 150 mothers undergo longitudinal assessment of psychophysiology and stress regulation during and after pregnancy.
- 3-D ultrasound to measure fetal adrenal development.
- **Maternal and infant stress regulation at 6 months of age.**



Does maternal ACE history impact fetal-infant stress responsiveness



Grace Ewing



Jessica Podcasy

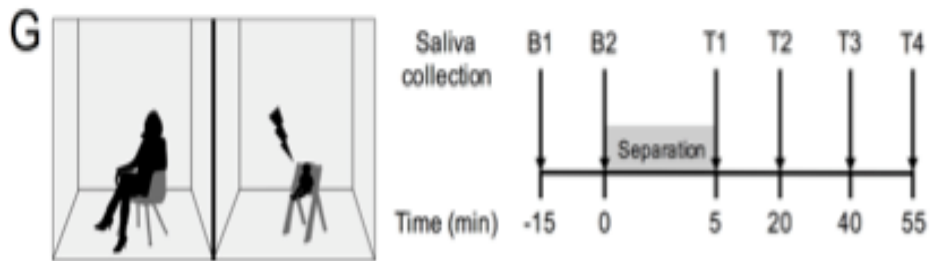


Stephanie Critini

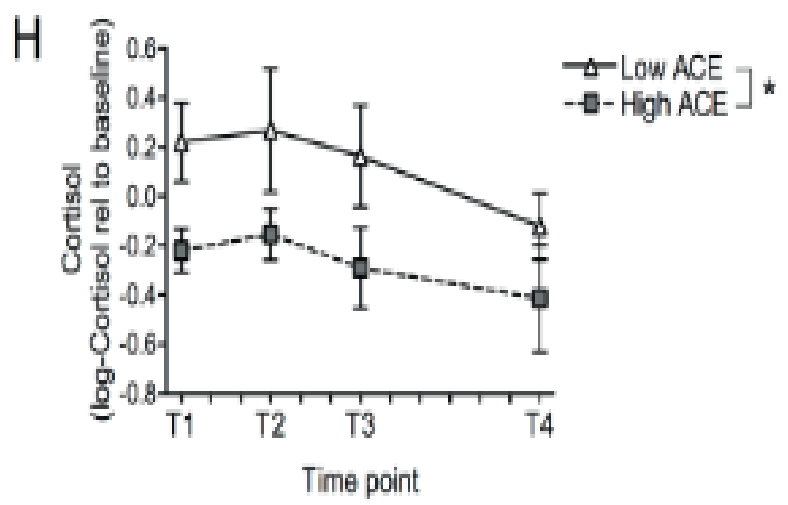
- Infants of mothers in High and Low ACE Groups undergo a laboratory stressor at 6 months of age.
- Restraint Stress (3 minutes)
- Loud noise bursts



ACE Effects During Maternal-Infant Separation



- 25 mother-infant pairs.
- Moms (mean age 27 yrs) followed through pregnancy,
- Not depressed,
- 12 in high 'preadolescent' adversity group.



Translational Model

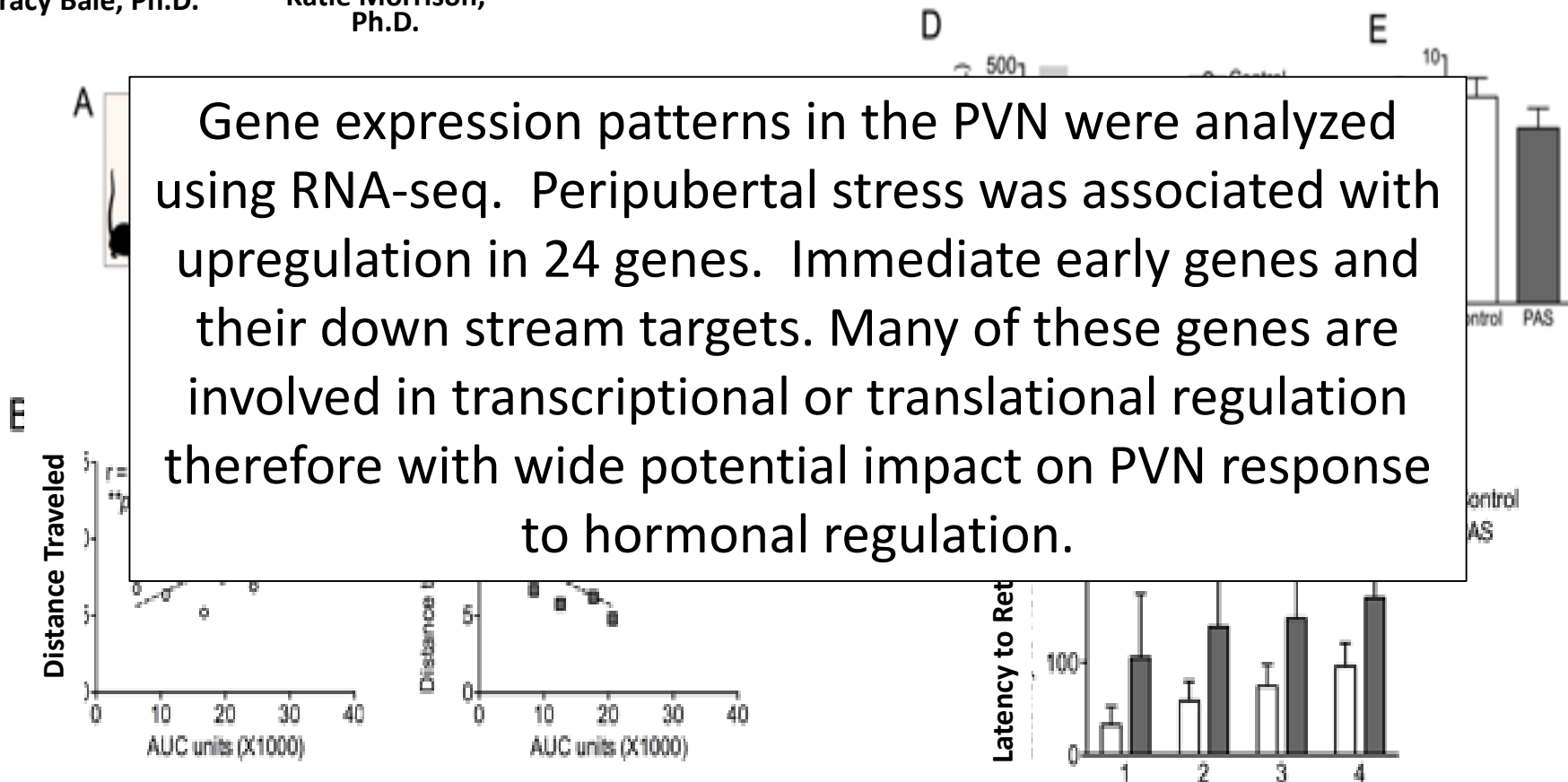


Tracy Bale, Ph.D.



Katie Morrison, Ph.D.

Gene expression patterns in the PVN were analyzed using RNA-seq. Peripubertal stress was associated with upregulation in 24 genes. Immediate early genes and their downstream targets. Many of these genes are involved in transcriptional or translational regulation therefore with wide potential impact on PVN response to hormonal regulation.



What About Fathers?

➤ National Longitudinal Study of Adolescent to Adult Health (Add Health Study)

- Fathers (N=1865) followed longitudinally from middle or high school to age 24-32 years.
- Assessed history of ACEs.
- 2-fold increased risk for “reported” learning problems and ADHD among offspring (N=3130) of fathers who reported childhood abuse/maltreatment.
- Limitations to be addressed in Dr. Wade’s K23 Study.



Roy Wade, Jr,
MD, PhD
BIRCIWH
SCHOLAR

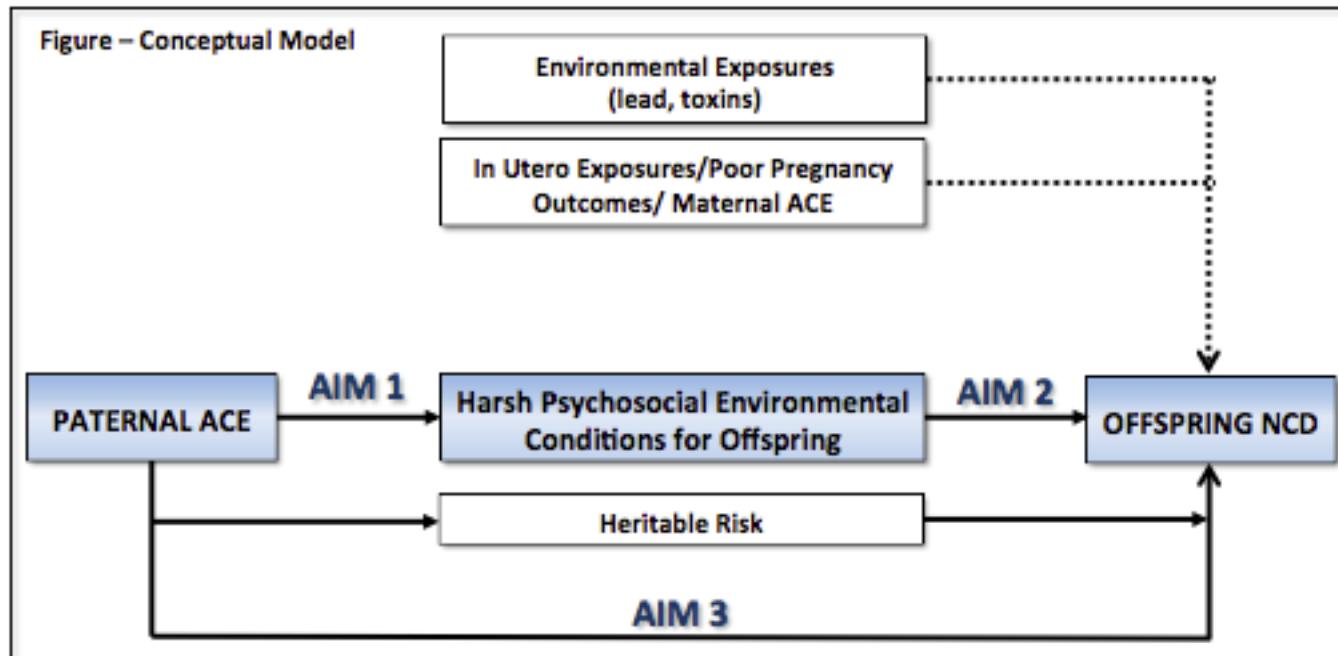
What About Fathers?



Roy Wade, Jr,
MD, PhD

➔ CHOP Pediatric Cohort (N=20,000)

➔ Paternal ACE effects on offspring risk for cognitive and behavioral disorders.



SCOR Aging Projects



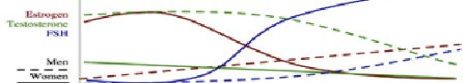
- Risk for first episode MDD is 2-fold during the peri-versus pre-menopause. Risk for relapse of MDD is 5-fold.
- Cognitive difficulties are common complaint in some, but not all menopausal women.

Early adversity contributes to increased risk.

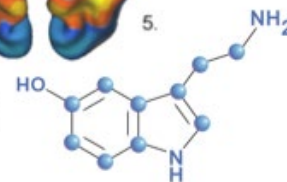
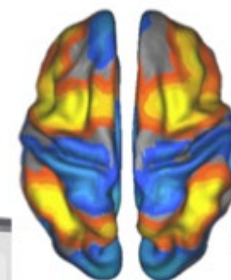
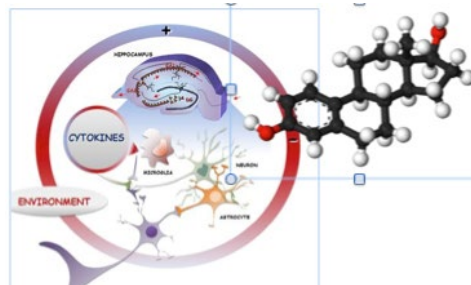
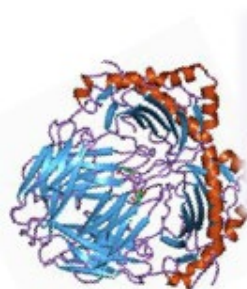
SCOR Aging Projects



14 years of comprehensive evaluation



Stage (For Women Only)	Menopausal Transition			Postmenopausal	
	Early	Late	Early	Late	
Age	early-mid 40's	late 40's	early 50's	mid-late 50's	
Estrogen	↓	↓	↓	↓	
Progesterone	↓	↓	↓	↓	
LH	↑	↑	↑	↑	
FSH	↑	↑	↑	↑	



Serotonin

Penn Ovarian Aging Cohort: Natural Menopause

- Prospective community cohort study of 436 women
- 50% Caucasian, 50% African American; Philadelphia County
- Enrolled as premenopausal women and followed for 14 years
- Followed across menopause stages:
 - Premenopause: Regular cycles, no change,
 - Late Premenopause: ≥ 7 days change in cycle length
 - Early Transition: One skipped cycle
 - Late transition: amenorrhea for 3-11 months
 - Postmenopause: amenorrhea for 12 months



Mary Sammel



Ellen Freeman, Ph.D.



Ellen Freeman, Ph.D.

From: Longitudinal Pattern of Depressive Symptoms Around Natural Menopause

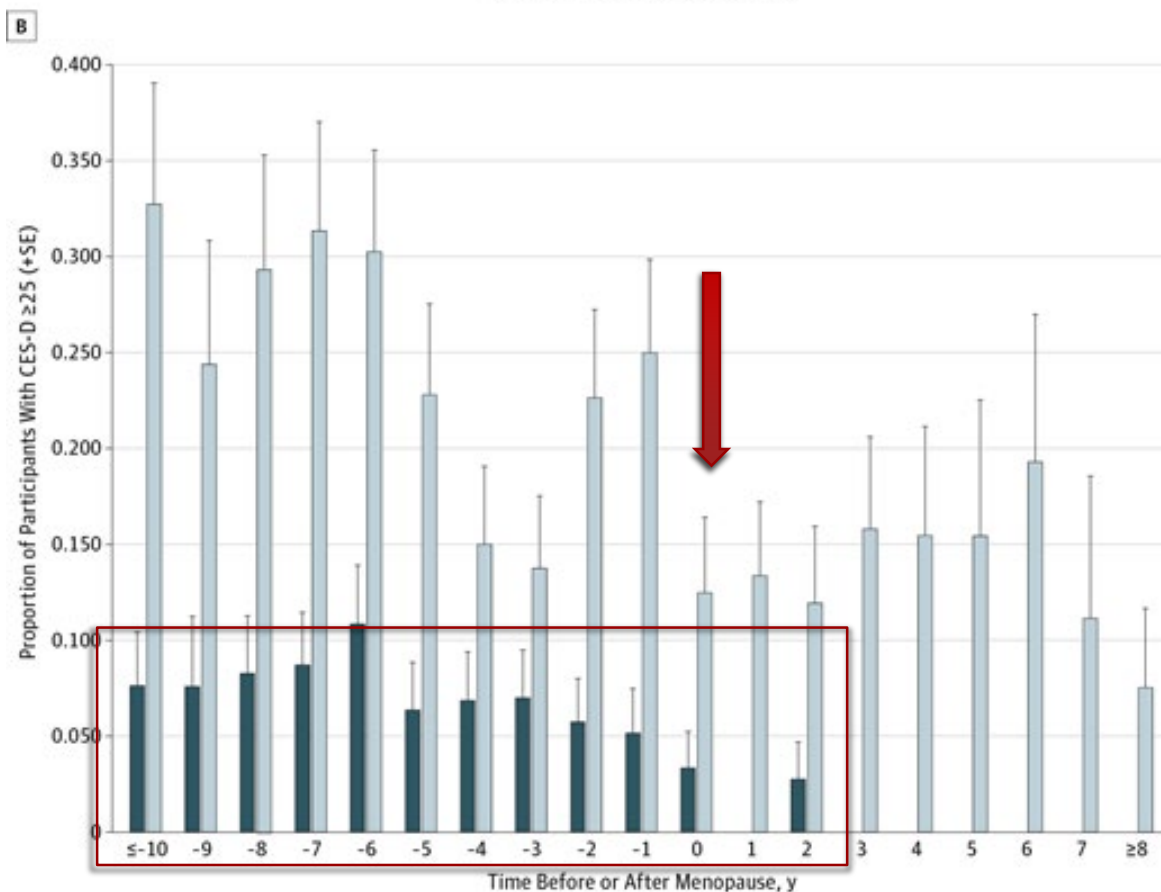
JAMA Psychiatry. 2014;71(1):36-43. doi:10.1001/jamapsychiatry.2013.2819

NIH | National Institute on Aging

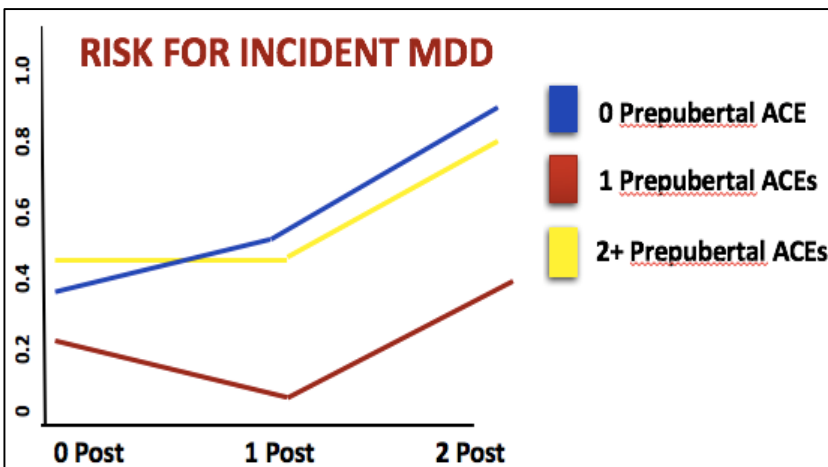
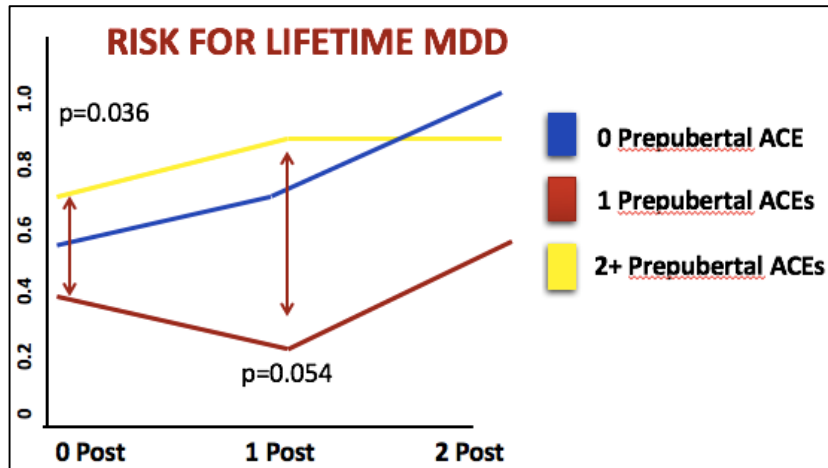
Recurrent Depression

Menopause Onset Depression

Do ACEs Contribute to Peri-Menopause Onset Depression



Impact of ACE History on Depression Risk



- ➔ Those with 2+ pre-pubertal ACEs have the greatest risk for lifetime MDD.
- ➔ One pre-pubertal ACE appears protective.
- ➔ Pattern is similar for incident menopause MDD, but smaller sample.

How Trauma In One's Teens Can Affect Mental Health In Mid-Life



Alice G. Walton, CONTRIBUTOR

I cover health, medicine, psychology and neuroscience. [FULL BIO](#) ✓

Opinions expressed by Forbes Contributors are their own.

The links between childhood stressors and adult behaviors, moods and anxiety are becoming clearer and clearer with each passing study. The things we go through as kids often stay with us over the years—especially if we don't get treated along the way. A new [study](#) in *Journal of Clinical Psychiatry* finds that the stresses and traumas that a woman goes through in her teen years are linked to a greater risk of depression in peri-menopause, even if she didn't experience depression before that. It's not totally clear where the link lies, but it's very likely at the level of the molecules—the stress and reproductive hormones and the markers of inflammation.



Shutterstock

Forbes

<https://www.forbes.com/sites/alicegwalton/2017/03/29/how-trauma-in-ones-teens-can-affect-mental-health-in-mid-life/#6f067256287d>

The new study from the University of Pennsylvania followed 243 women from the time they were premenopausal (aged 35 to 47) for the next 16 years. They were tested regularly for mood and cognitive problems, and their hormones measured from time to time; the women also reported when they went through menopause. Toward the end of the study period, the women filled out questionnaires about the kinds of stresses and traumas they'd been through in their childhoods and teenage years.



Advertisement

[5 Herbs That Beat Anxiety](#)

Doctors Reveal 1 Weird Compound to Calm Anxiety That May Surprise You. Go to [nutreance.com](#)

[5 Foods Hurting The Liver - And How You Can Avoid Them](#)

[5 Prostate Cancer Signs](#)

[1 Worst Carb After Age 50](#)

Trauma as a Teen May Boost Depression Risk Around Menopause

Likelihood was more than twice as high, study reports



Cognition Across Natural Menopause

ORIGINAL ARTICLE

Endocrine Research

Menopause Effects on Verbal Memory: Findings From a Longitudinal Community Cohort

C. Neill Epperson, Mary D. Sammel, and Ellen W. Freeman

Departments of Psychiatry (C.N.E., E.W.F.), Obstetrics and Gynecology (C.N.E., E.W.F.), Penn Center for Women's Behavioral Wellness (C.N.E.), Penn Center for the Study of Sex and Gender in Behavioral Health (C.N.E., M.D.S., E.W.F.), and Department of Biostatistics and Epidemiology and Center for Clinical Epidemiology and Biostatistics (M.D.S.), Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania 19104



Ellen Freeman, Ph.D.



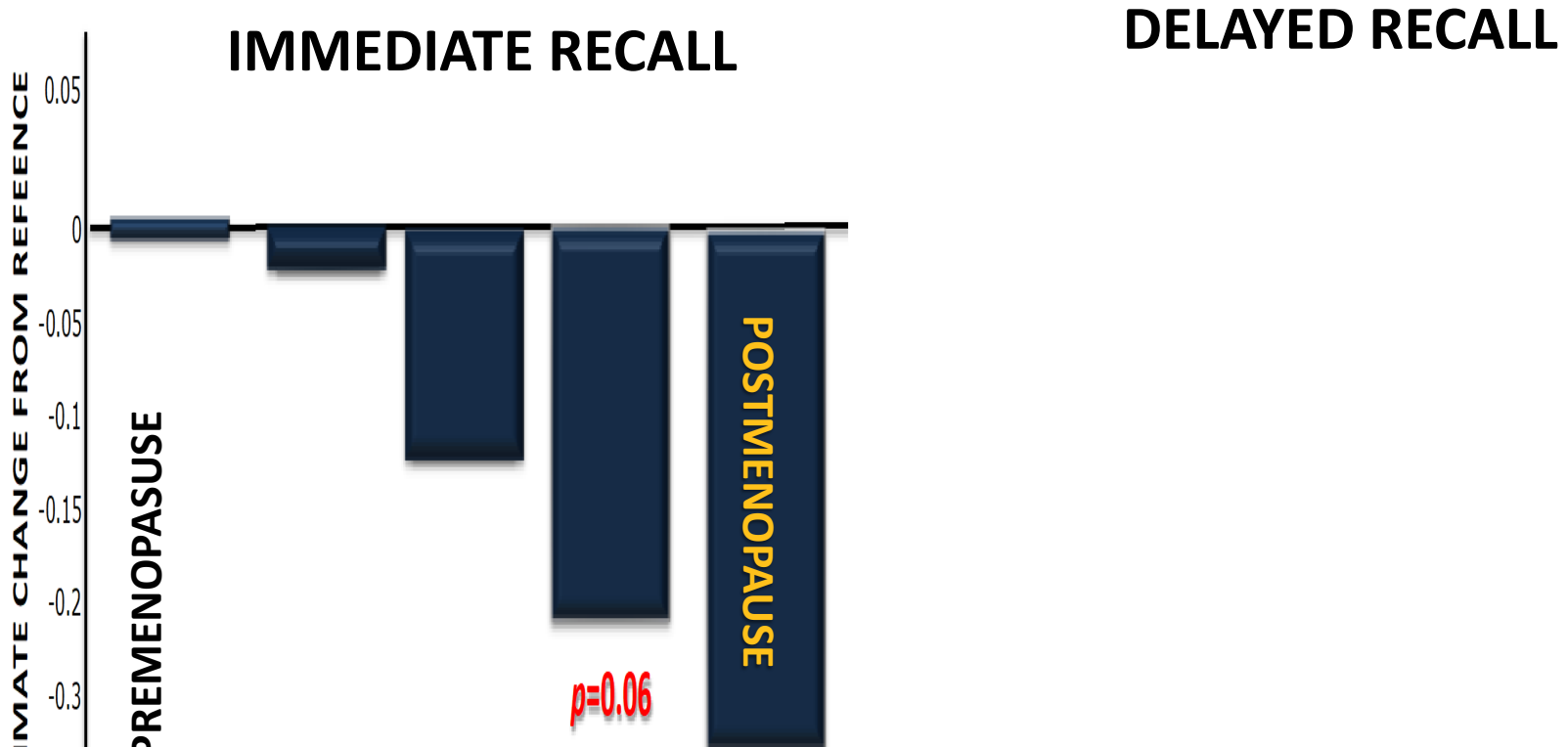
Mary Sammel, Ph.D.



ORWH

NIH | National Institute
on Aging ■ ♦ ✦ ✧

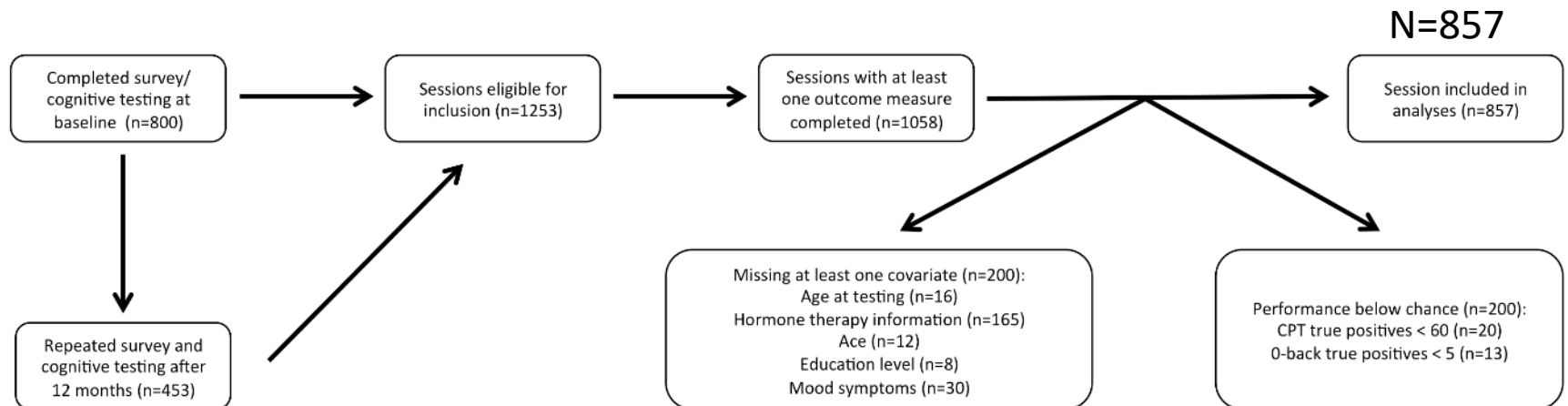
VERBAL MEMORY PERFORMANCE DECLINES ACROSS THE MENOPAUSE TRANSITION

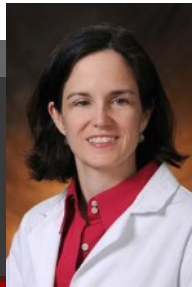


Early adversity contributes to increased risk.

What About ACE Effects on Cognition at Menopause?

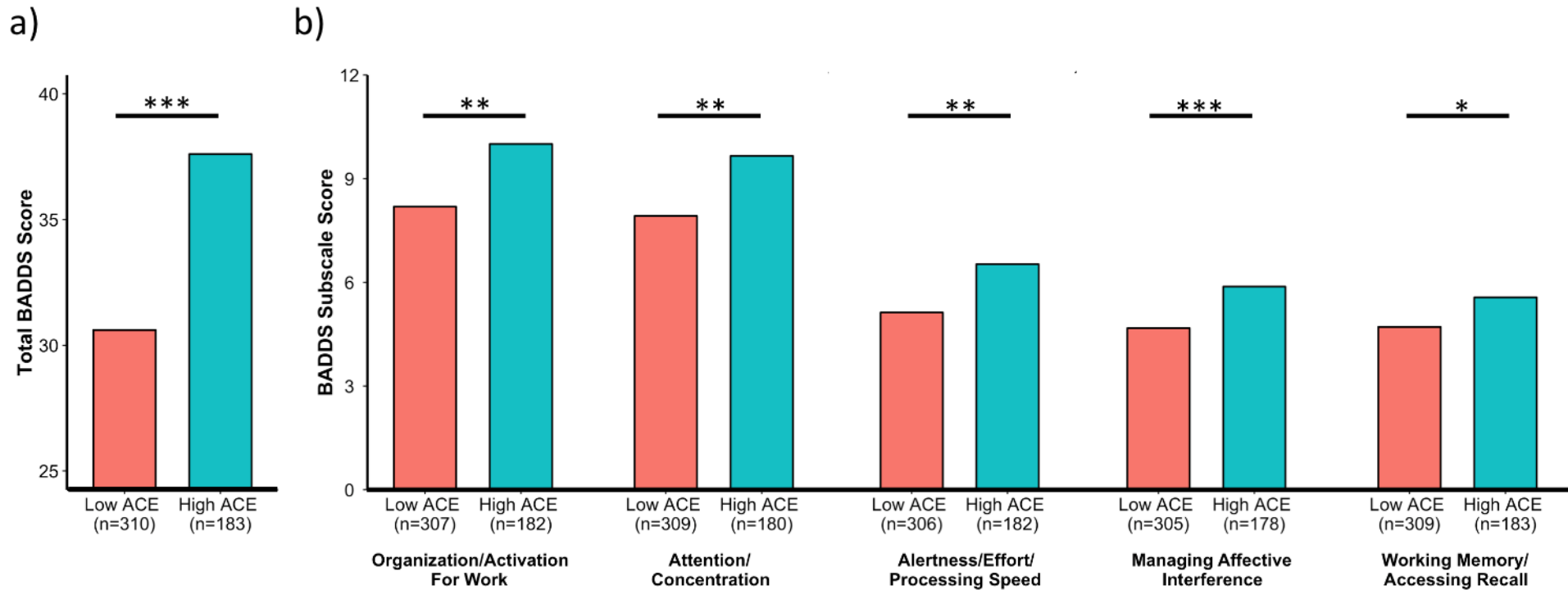
- Women post-risk reduction salpingo-oophorectomy (RRSO) due to cancer history or genetic risk (n=800 at time one and 453 at time 2).
- Data collected using on-line recruitment, primarily through a support group; **Facing our Risk of Cancer Empowered (FORCE)**.
- Completed assessments and cognitive battery on-line.





ACE effect on subjective EF measures

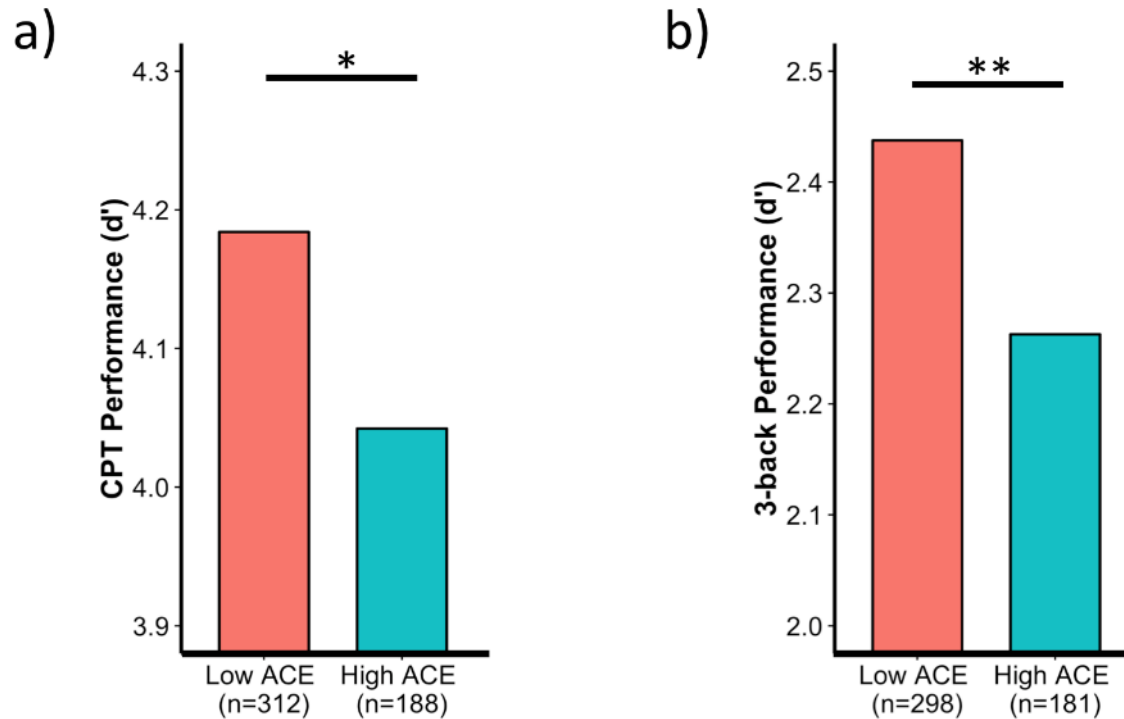
Sheila Shanmugan



*p<0.05, **p<0.01, ***p<0.001

ACE effect on objective EF measures

Figure 3



* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$



Getting Under the Skin

- Ovarian hormonal changes occurring during the menopause transition could unmask vulnerability to depression and cognitive complaints.
- Estradiol dampens synthesis of a number of pro-inflammatory cytokines.

NUMBER	Pre-Menopause	Peri-Menopause	Post-Menopause
Subjects	100	106	30
Replicates	214	274	82
Ave # of Replicates (Range)	2.1 (1-4)	2.6 (1-6)	2.7 (1-12)

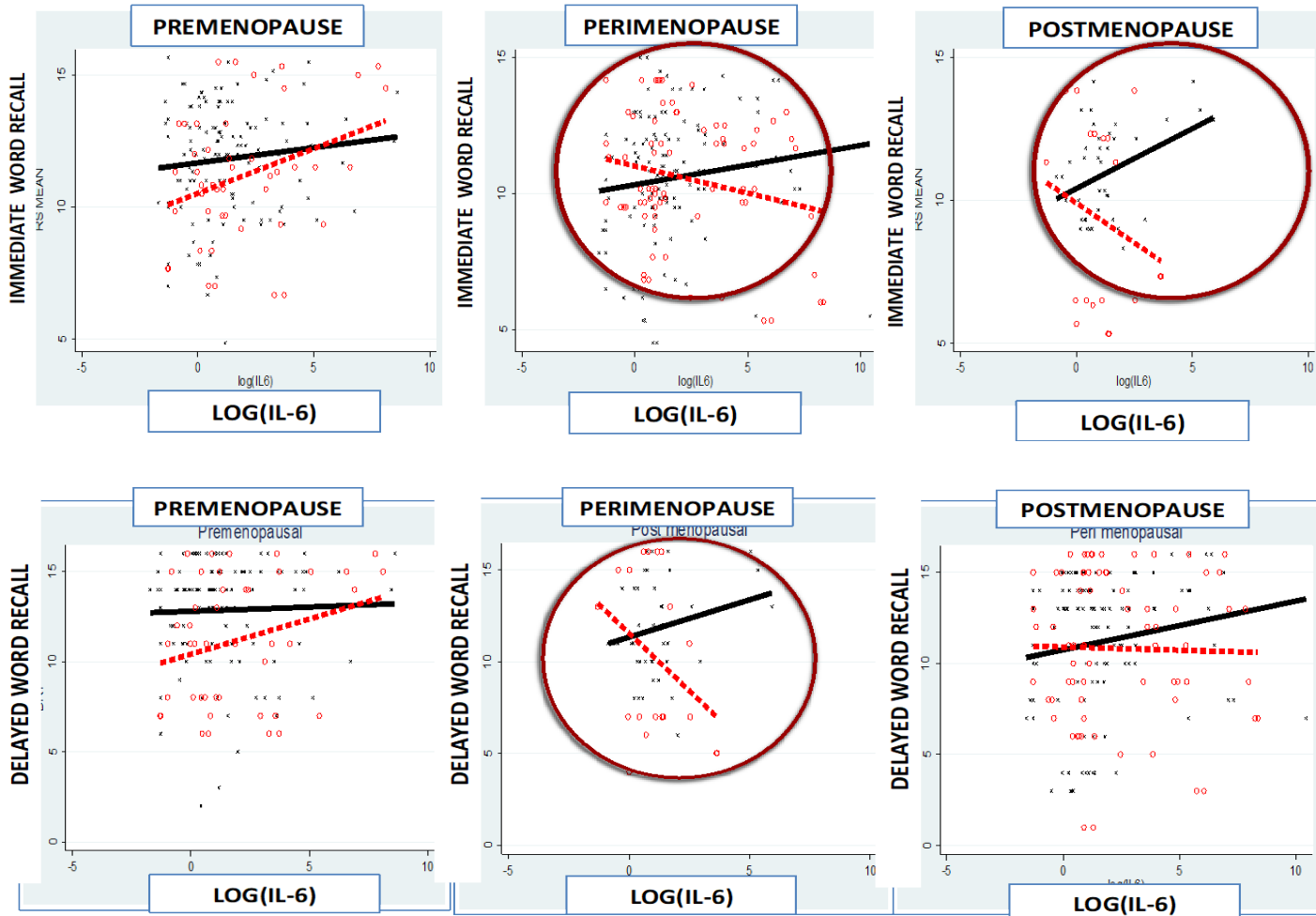
Prepubertal ACE x Cytokine x Menopause Stage: Impact on Cognitive Measures

	DIGIT SYMBOL	SYMBOL COPY	DELAYED RECALL	IMMEDIATE RECALL
hsCRP	0.482	0.401	0.742	0.023
IL-1 β	0.327	0.874	0.382	0.027
IL-6	0.020	0.037	0.016	0.173
TNF- α	0.118	0.715	0.029	0.025

Included in the model:

Age, race, BMI, Smoking status, depression severity

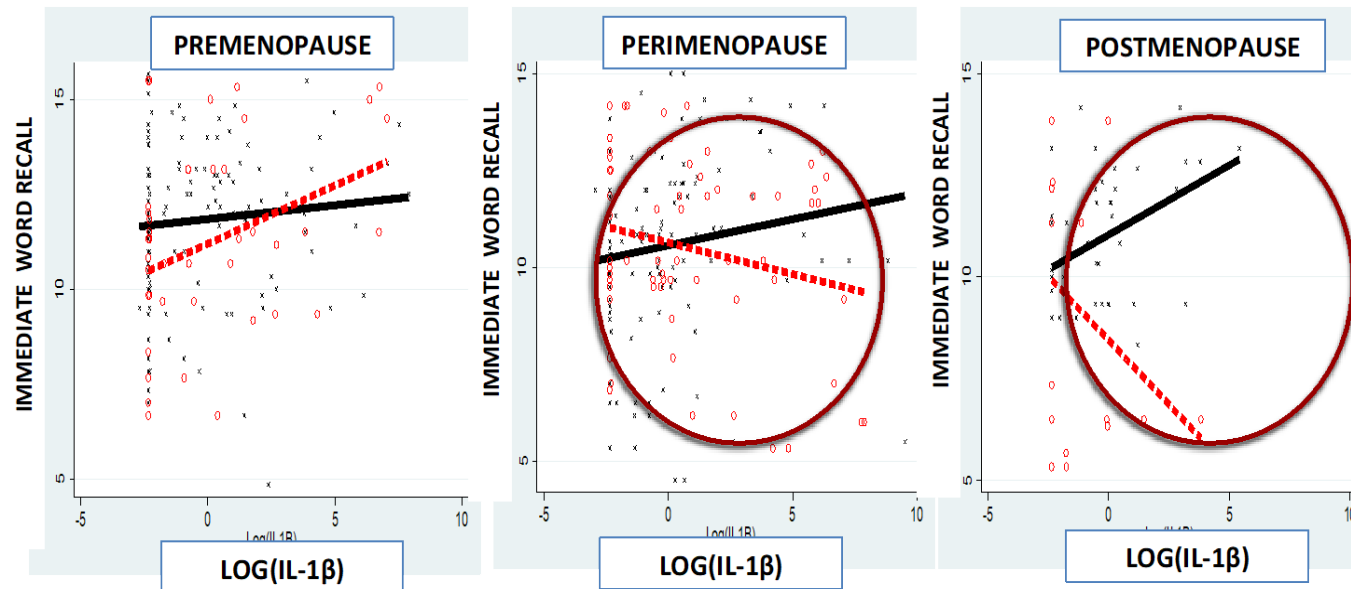
Prepubertal ACE & IL-6 Across the Transition: Immediate and Delayed Word Recall



Interaction
 $p=0.17$

Interaction
 $p=0.016$

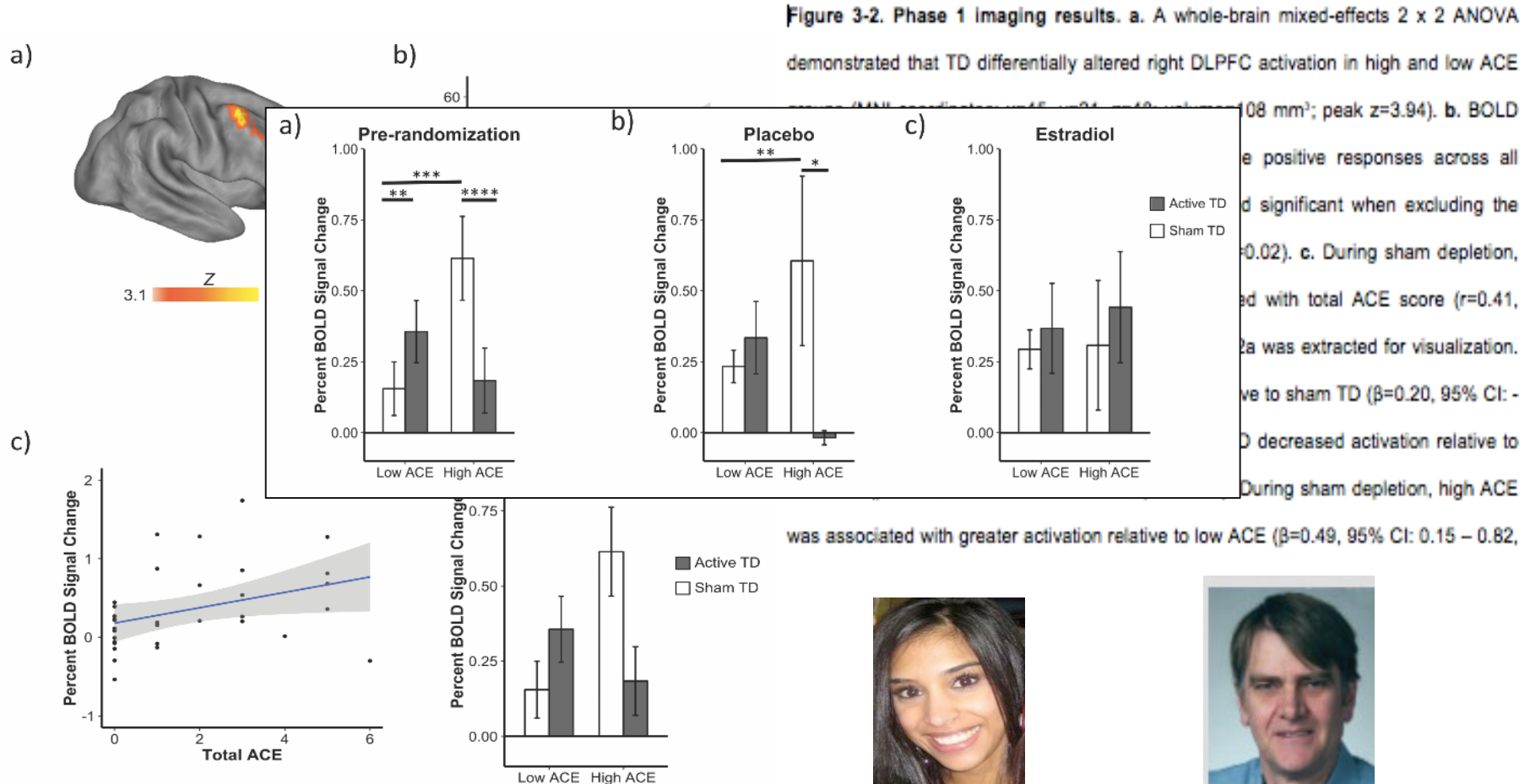
Prepubertal ACE & IL-1 β Across the Transition: Immediate Word Recall



Interaction
 $p=0.027$

ACE history may contribute to increased risk for verbal memory declines at menopause through effects on cytokine production.

ACEs are associated with enduring effects on brain function, response to neurotransmitter and hormone manipulations



Sheila Shanmugan

James Loughead

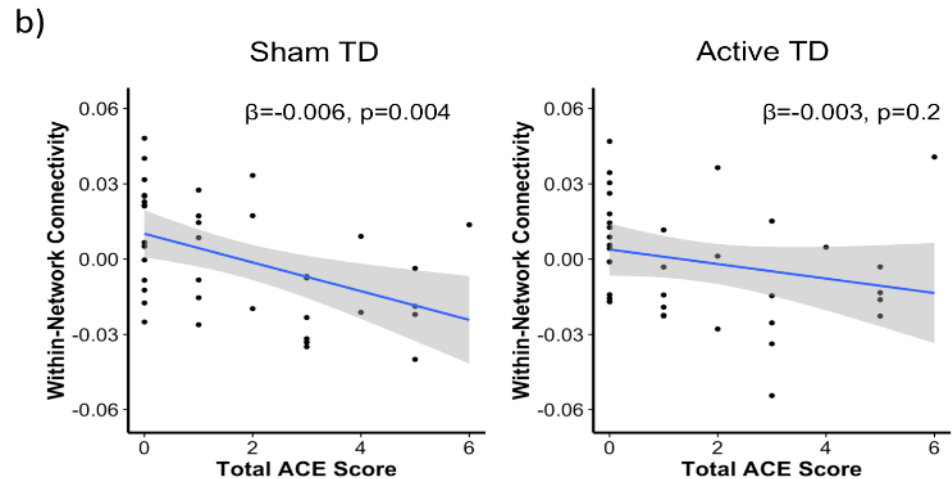
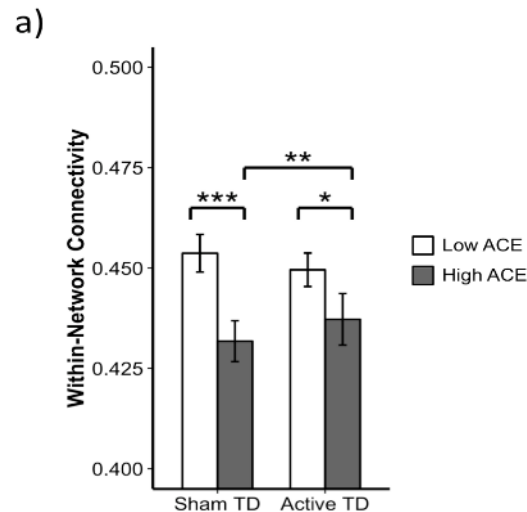
ACEs are associated with enduring effects on brain function, response to neurotransmitter and hormone manipulations



- Sensory/somatomotor hand
- Sensory/somatomotor Mouth
- Cingulo-opercular task control
- Auditory
- Default mode
- Memory retrieval
- Visual
- Fronto-parietal task control
- Saliency
- Subcortical
- Ventral attention
- Dorsal attention
- Cerebellar
- Uncertain

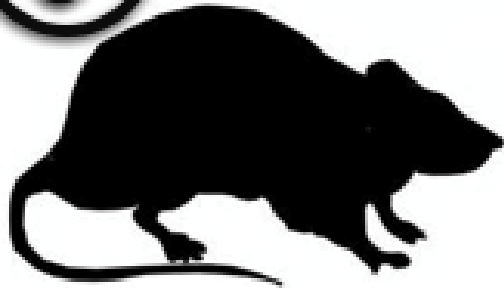
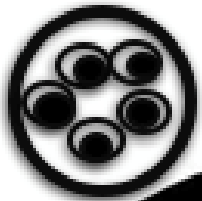
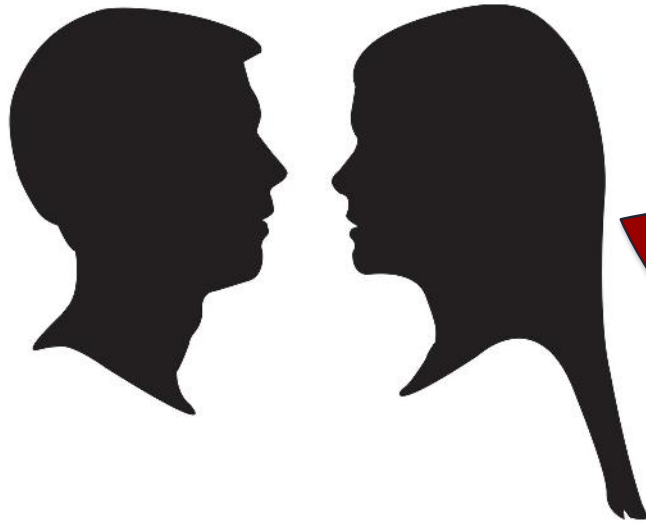


Sheila Shanmugan James Loughhead



Overview

- Our mission statement.
- Development of a “whole school” initiative to promote consideration of sex and gender as critical variables in health research across the lifespan.
- Examples of how **multi-PI**, multi-cycle and program grants are effective in promoting **translational** research.
- **Benefit of thinking in broad strokes.**
 - **Can CVS model mimic human adversity?**
 - **Childhood adversity can be measured in large populations or clinical settings. How useful for determining risk?**
 - **Is childhood adversity, broadly speaking, critical for reproductive related affective and cognitive disorders as well as sex bias?**



??



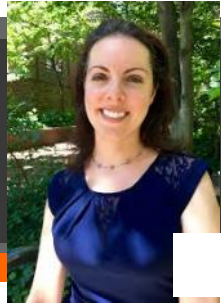


Summary

- ➔ Animal models of stress can be developed to mimic human stressors.
- ➔ Ecologically relevant stressors are necessary to determine mechanisms.
- ➔ Close collaborative relationships, such as those fostered by P50s or multi-cycle R01s are critical to success of ***bench to bedside to community research***.



Grace Ewing



Jeanette Bradley



Claudia Iannelli

To A Great Team: NKS!



Gianna Melendez

De Mott



James Loughead



Ellen Freeman



Ruben Gur



Tom Brown



Joanna Marks



Emily Lipner



Susan Domcheck



Lindsay Sortor



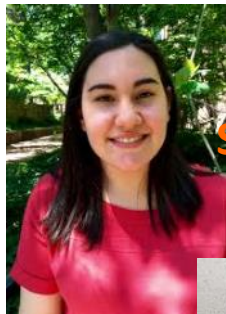
Tracy Siegel



Mark Elliot



Kosha Ruparel



Stephanie Criniti



Kathryn Czarkowski



Mary Sammel



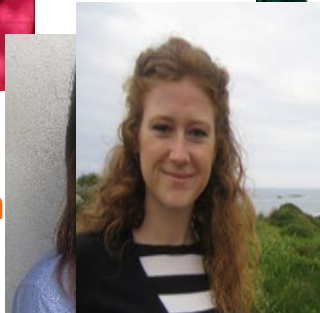
Sheila Shanmugaravi



Ravi PNR

Brendan McGeehan

Carrie Malanga



Katie Morrison



Kim



Sarah Mathe

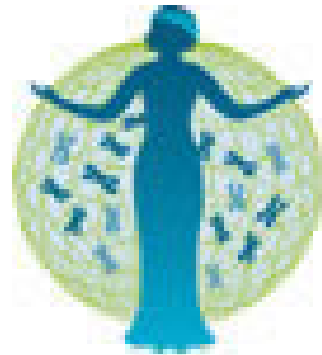


Ravi Reddy



Tracy Bale

And our Funding Sources!



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NATIONAL INSTITUTE
ON DRUG ABUSE



NIMH
National Institute
of Mental Health

Shire

SAGE
THERAPEUTICS