IS IT ME OR IS IT HOT IN HERE? MENOPAUSE, MOOD & COGNITION

NAS Workshop on Women's Health
March 7, 2018

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Perelman School of Medicine
University of Pennsylvania

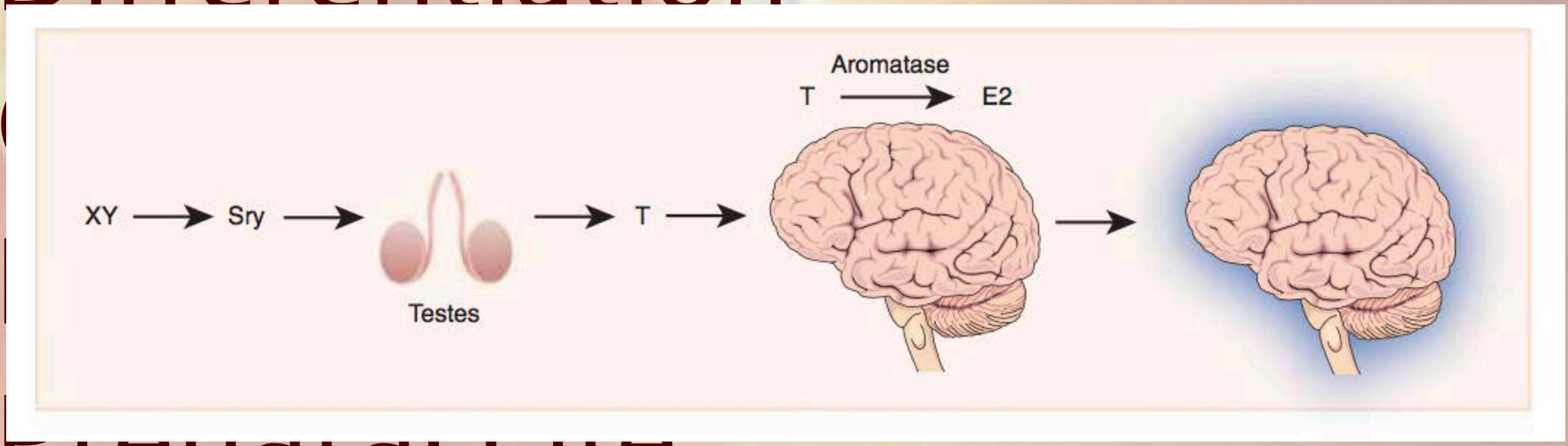
Penn PROMOTES
Research on Sex and Gender in Health

Sex Differences: Lifespan Approach

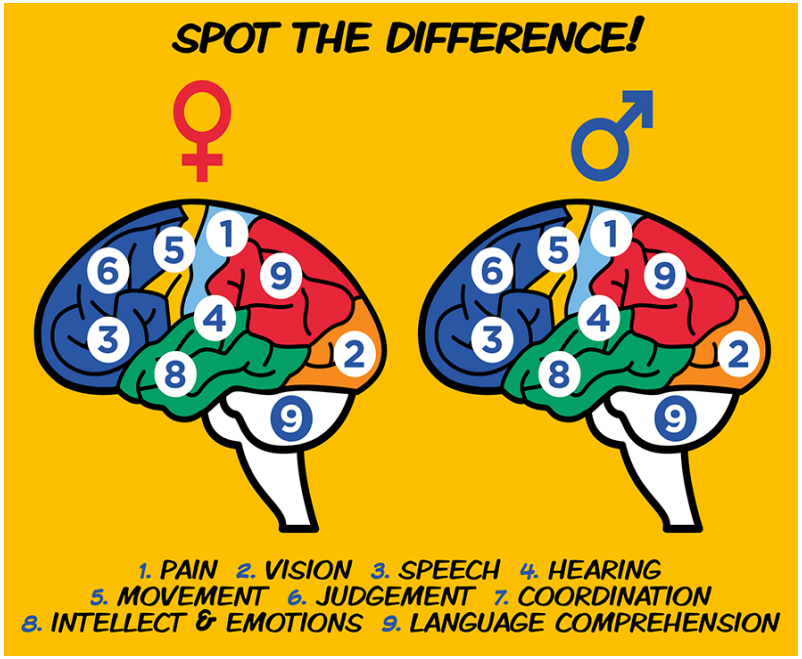
Sexual Differentiation Of the Brain Begins in Prenatal Life

Bale & Epperson, NPP (2017) 42:386-396

Sexual Differentiation



Bale & Epperson, NPP (2017) 42:386-396



Second and Third Trimesters

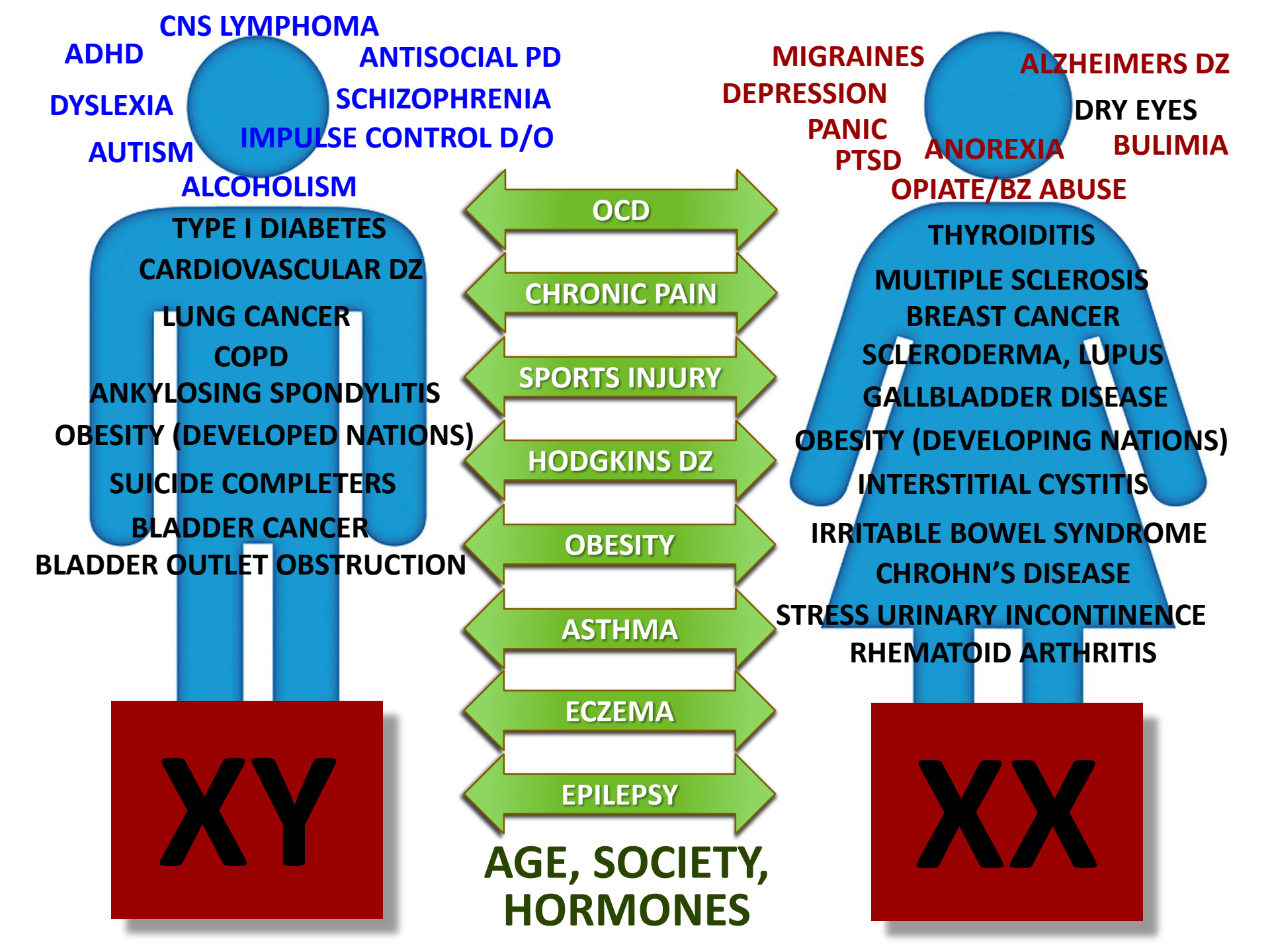
First Trimester

MALE ⟷ **FEMALE**

ORGANIZATIONAL EFFECTS OF SEX STEROIDS

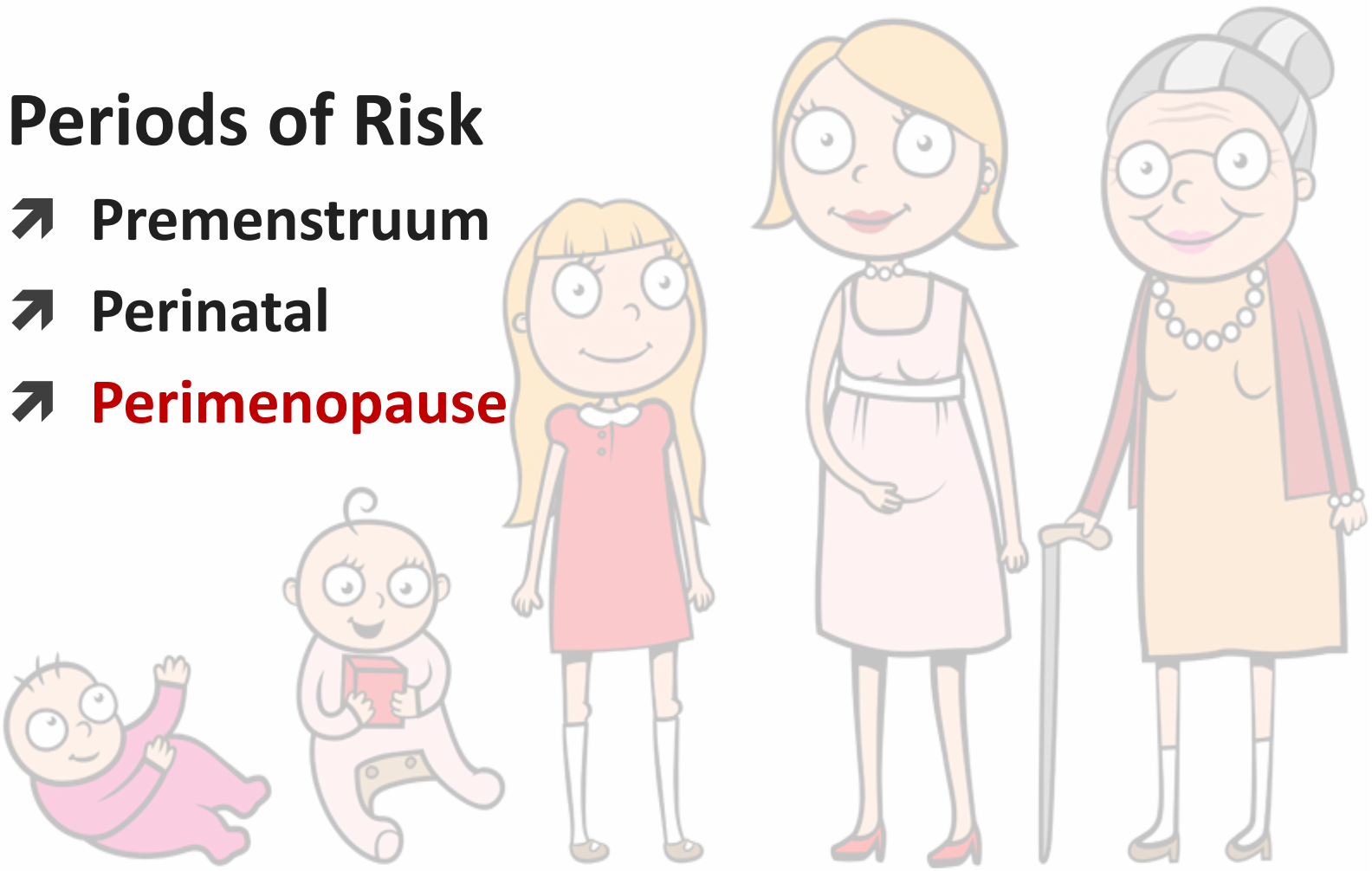
Gonadal Steroids Across the Lifespan: Activational Effects of Sex Steroids

HOW DOES THIS IMPACT HEALTH?


CNS LYMPHOMA
ADHD
ANTISOCIAL PD
DYSLEXIA
SCHIZOPHRENIA
IMPULSE CONTROL D/O
AUTISM
ALCOHOLISM
TYPE I DIABETES
CARDIOVASCULAR DZ
LUNG CANCER
COPD
ANKYLOSING SPONDYLITIS
OBESITY (DEVELOPED NATIONS)
SUICIDE COMPLETERS
BLADDER CANCER
BLADDER OUTLET OBSTRUCTION
XY
MIGRAINES
ALZHEIMERS DZ
DEPRESSION
DRY EYES
PANIC
ANOREXIA
BULIMIA
PTSD
OPIATE/BZ ABUSE
THYROIDITIS
MULTIPLE SCLEROSIS
BREAST CANCER
SCLERODERMA, LUPUS
GALLBLADDER DISEASE
OBESITY (DEVELOPING NATIONS)
INTERSTITIAL CYSTITIS
IRRITABLE BOWEL SYNDROME
CHROHN'S DISEASE
STRESS URINARY INCONTINENCE
RHEMATOID ARTHRITIS
XX
OCD
CHRONIC PAIN
SPORTS INJURY
HODGKINS DZ
OBESITY
ASTHMA
ECZEMA
EPILEPSY
AGE, SOCIETY, HORMONES

Hormones & the Female Lifespan in 10 minutes

- **Periods of Risk**
  - **Premenstruum**
  - **Perinatal**
  - **Perimenopause**

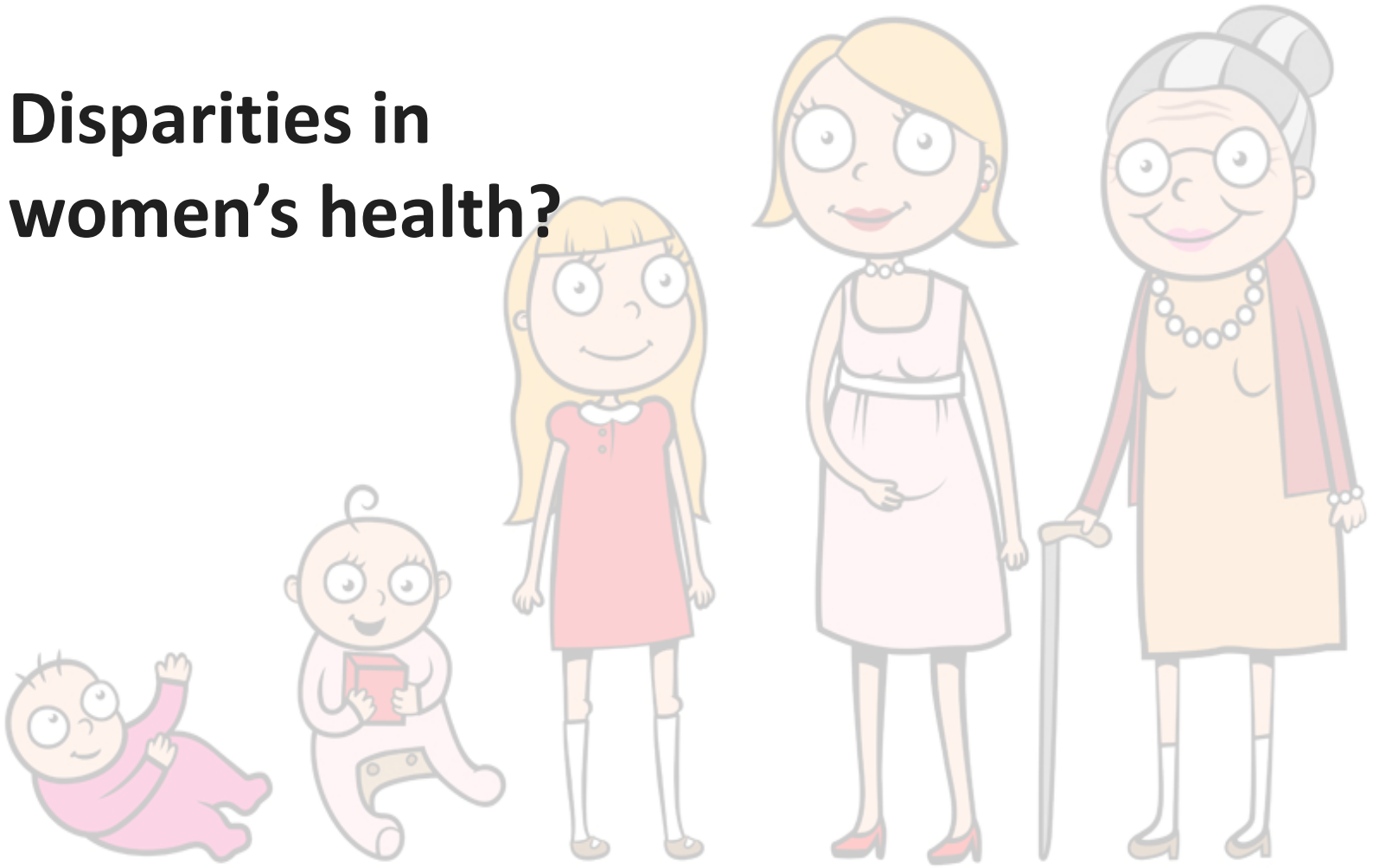


Hormones & the Female Lifespan in 10 minutes

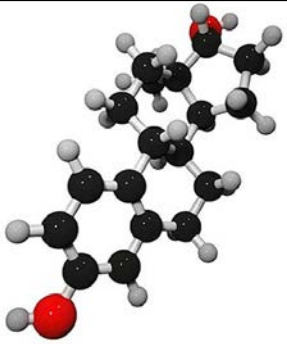
- **What do hormones contribute?**
  - **Ovarian hormones**
  - **Stress hormones**

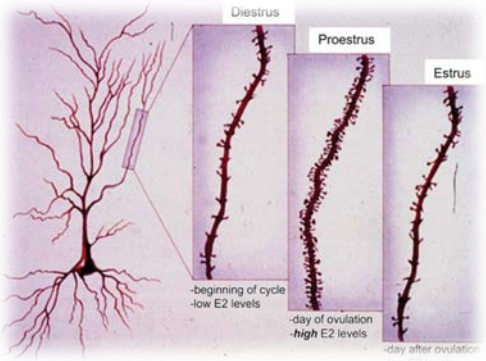
Hormones & the Female Lifespan in 10 minutes

- **Disparities in women's health?**



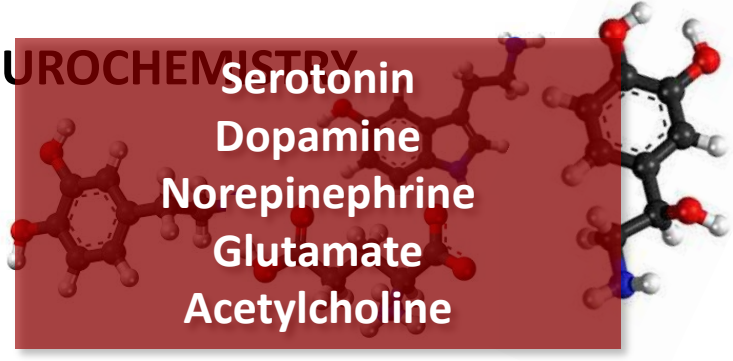
ESTRADIOL





NEUROCHEMISTRY

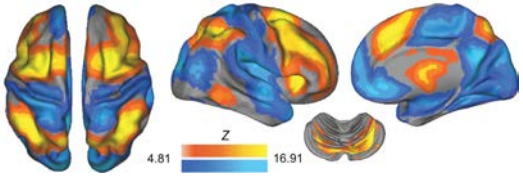
Serotonin
Dopamine
Norepinephrine
Glutamate
Acetylcholine



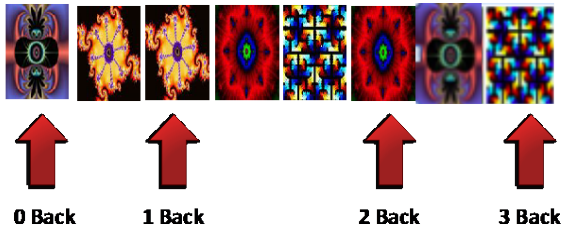
STRUCTURE

FUNCTION

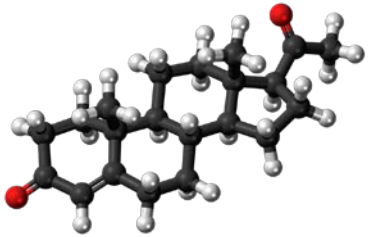
Figure S2



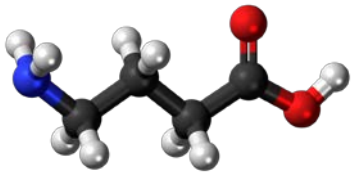
BEHAVIOR



PROGESTERONE



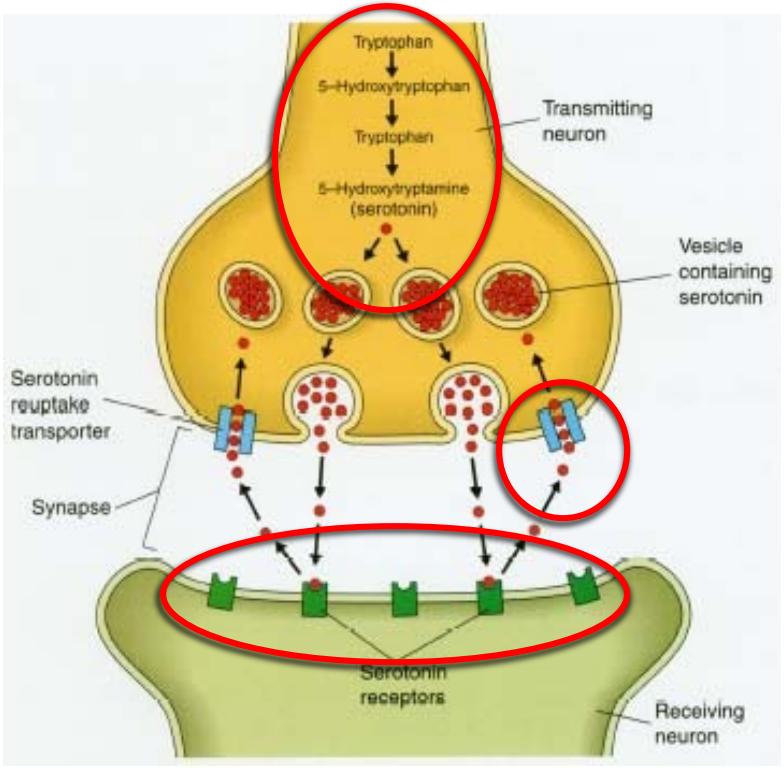
NEUROCHEMISTRY



INFLAMMATION

HORMONE EFFECTS: 101

Estradiol Effects: Serotonin



↑ Tryptophan hydroxylase mRNA (1)

↓ Clearance of 5-HT

↓ MAO Activity (2)

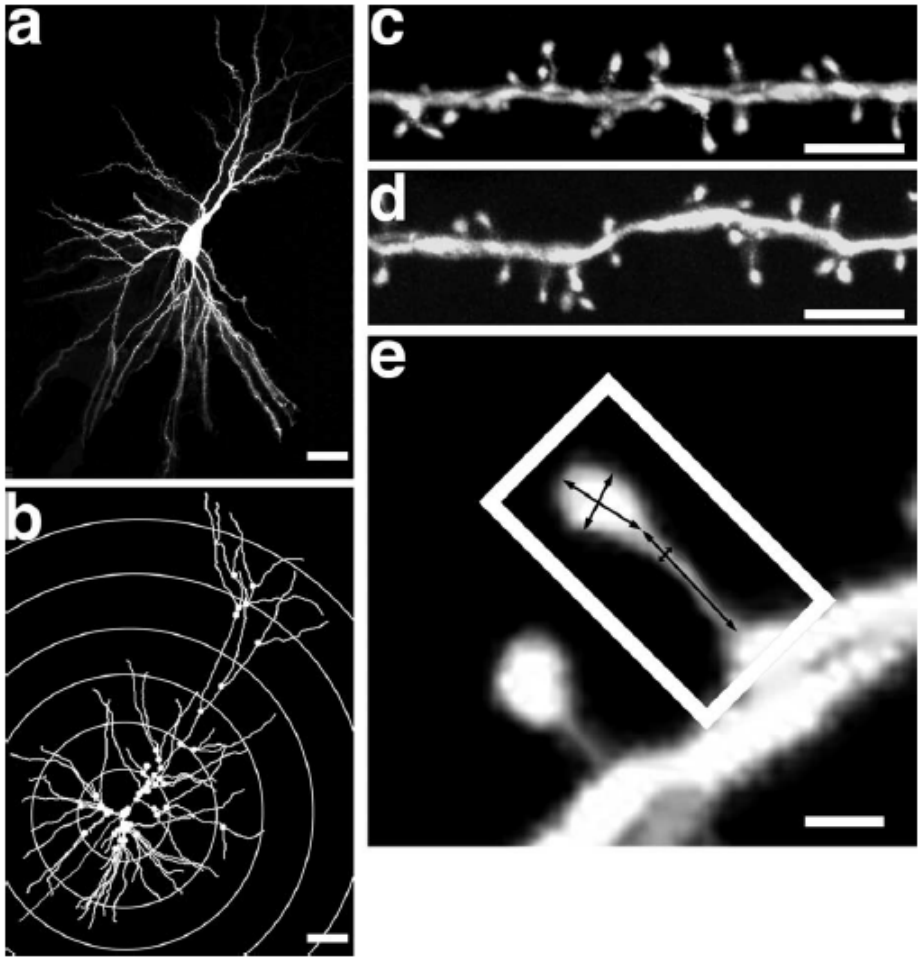
↑ Post-synaptic 5HT-2A receptor density.[3]

↓ potency of estradiol on TPH2 gene expression.[4]

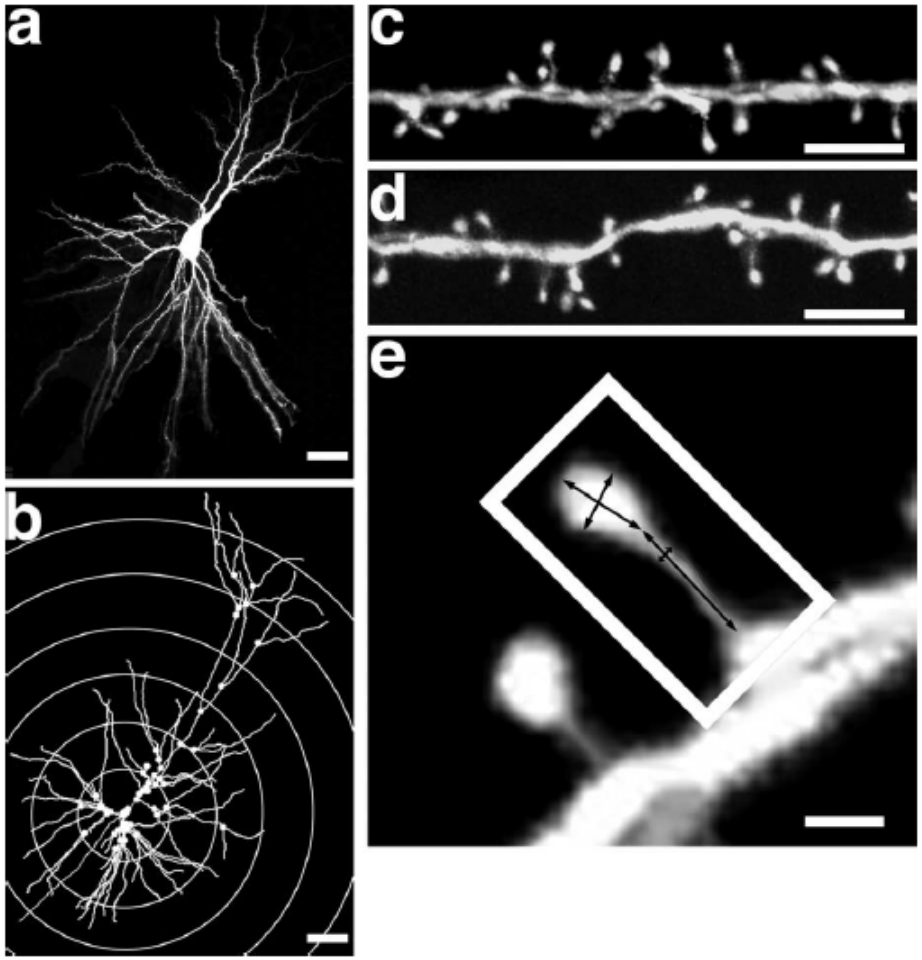
↓ 5HT1A receptor binding.[5]

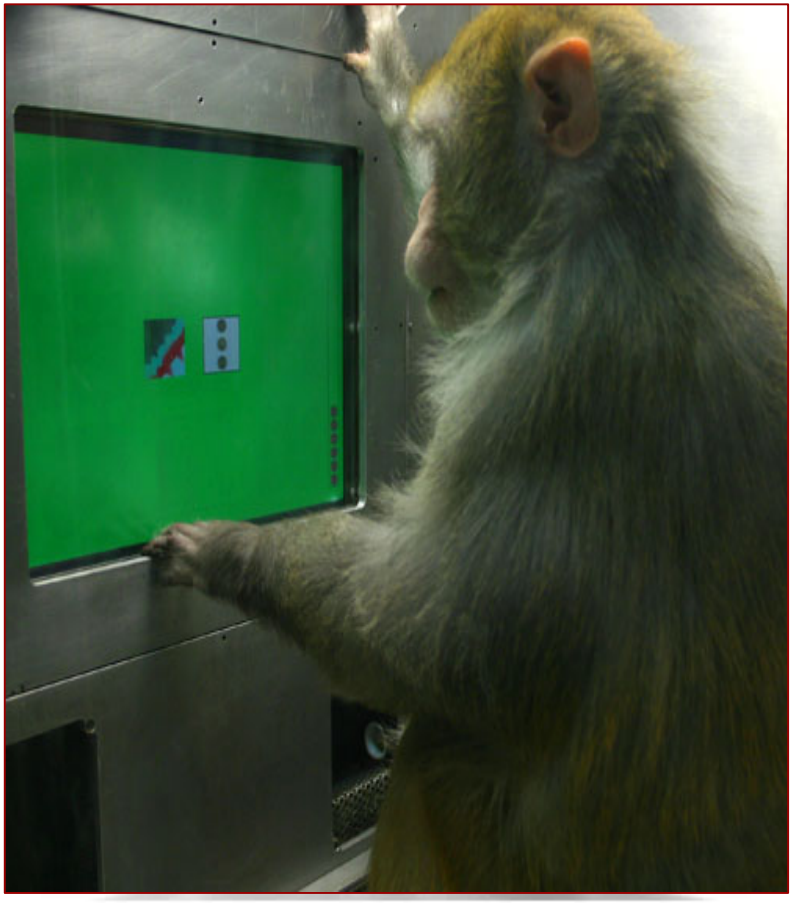
1) Sanchez RL et al., (2005) Mol Brain Res 135”194-203.
2) Benmansour S et al., (2009) Neuropsychopharm 34:555-64
3) Kugaya A et al., (2003) AJP 160:1522-24
4) Shively & Bethea, J Pharmacogenomics, 2003
5) Murrough et al., (2011) AGP 68:892-90

Age, Stress, Estrogen: Impact on Neuronal Plasticity and Learning & Memory

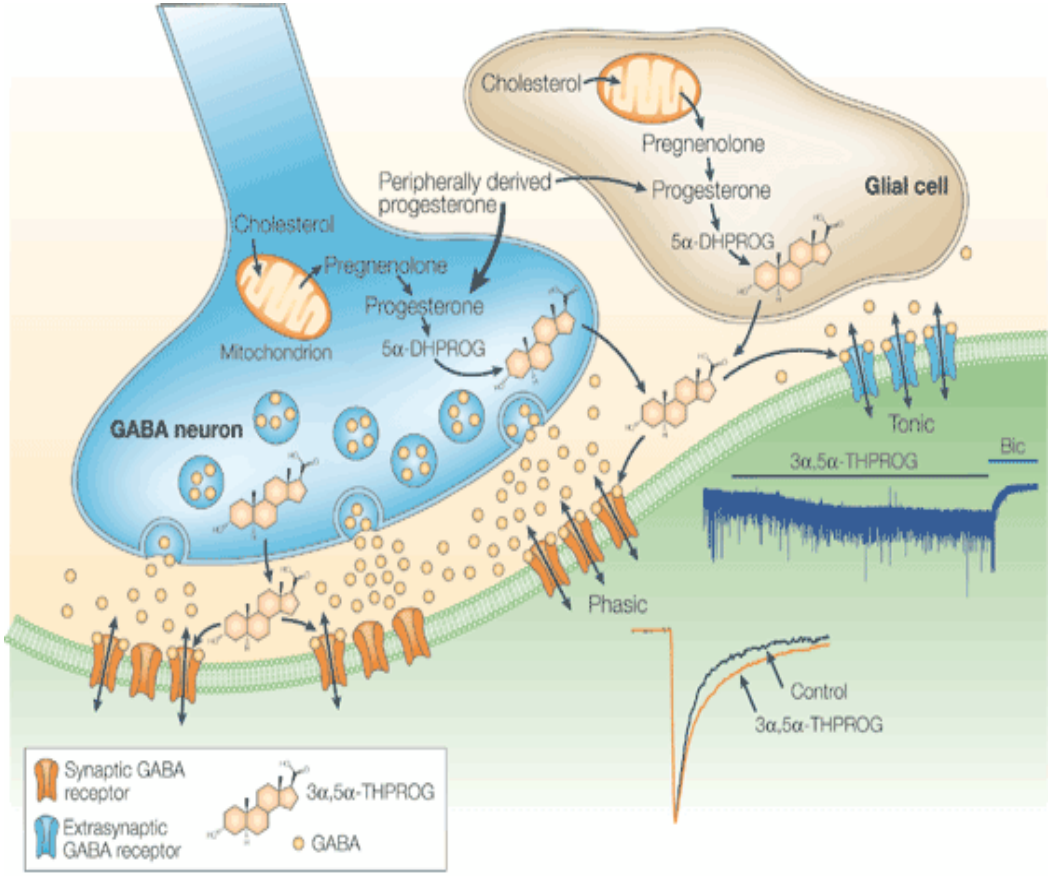


Age, Stress, Estrogen: Impact on Neuronal Plasticity and Learning & Memory





Progesterone, ALLO & the GABA-A Receptor



- Potent GABA-A receptor agonist.
  - Alcohol
  - Benzodiazepines
  - Barbiturates
- Increased synthesis when under acute stress.

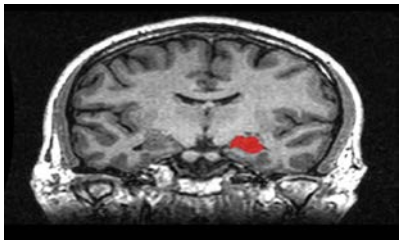
Belelli et al., (2005) Nat Rev Neurosci 6:565-75
Pinna et al., (2009) Curr Opin Pharm, 9:24-30

THE FLEXIBLE FEMALE BRAIN

Timing of Stress: Regional Impact

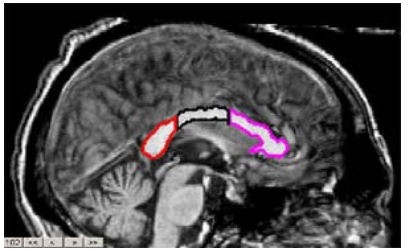
3-5 years old

hippocampus



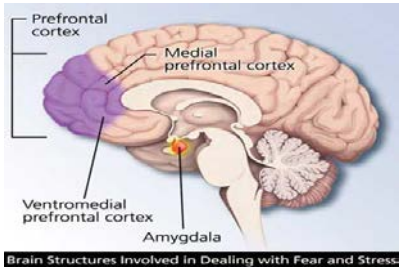
9-10 years old

mid-corpus callosum



14-16 years old

Prefrontal Cortex



Teicher & Samson, AJP 2013 170:10, 1114-1132

Timing of Stress: Regional Impact

ars old

ears old

1 ears old

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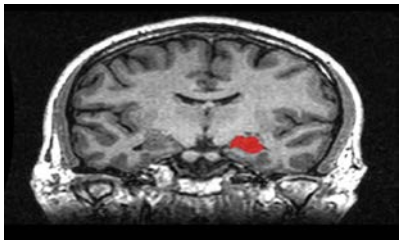
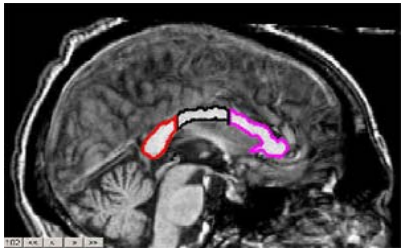
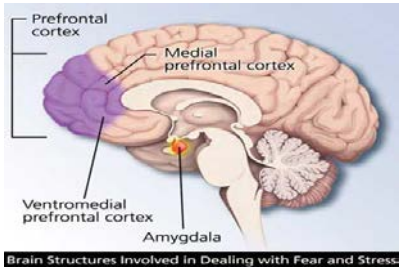






Teicher & Samson, AJP 2013 170:10, 1114-1132


THE
MENOPAUSE
TRANSITION:

ON AVERAGE, GIRLS BORN TODAY WILL LIVE A 3RD OF THEIR LIFE IN THE POSTMENOPAUSE

Cognition Across Natural Menopause

Ellen Freeman, Ph.D.

Mary Sammel, Ph.D.

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

NIMH National Institute of Mental Health

ORWH

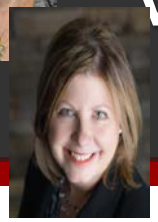
NIH National Institute on Aging

Penn Ovarian Aging Study

- 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: ≥7days change in cycle length
  - Early Transition: One skipped cycle
  - Late transition: amenorrhea for 3-11 months
  - Postmenopause: amenorrhea for 12 months

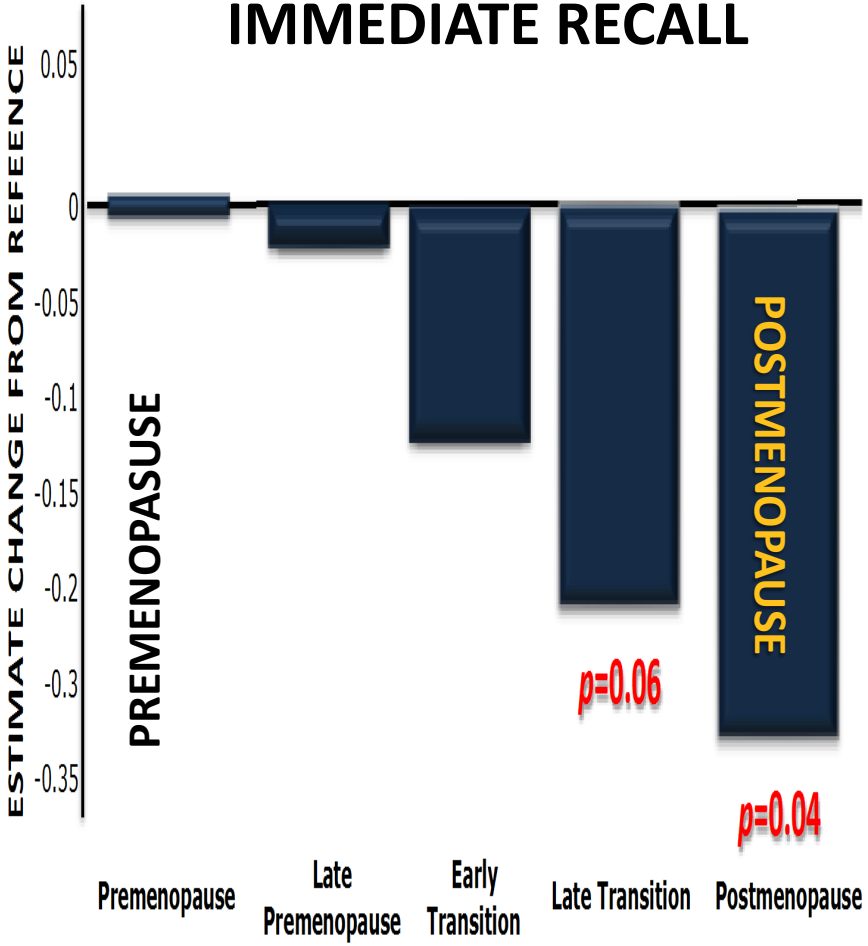
Ellen Freeman, Ph.D.

NIH National Institute on Aging

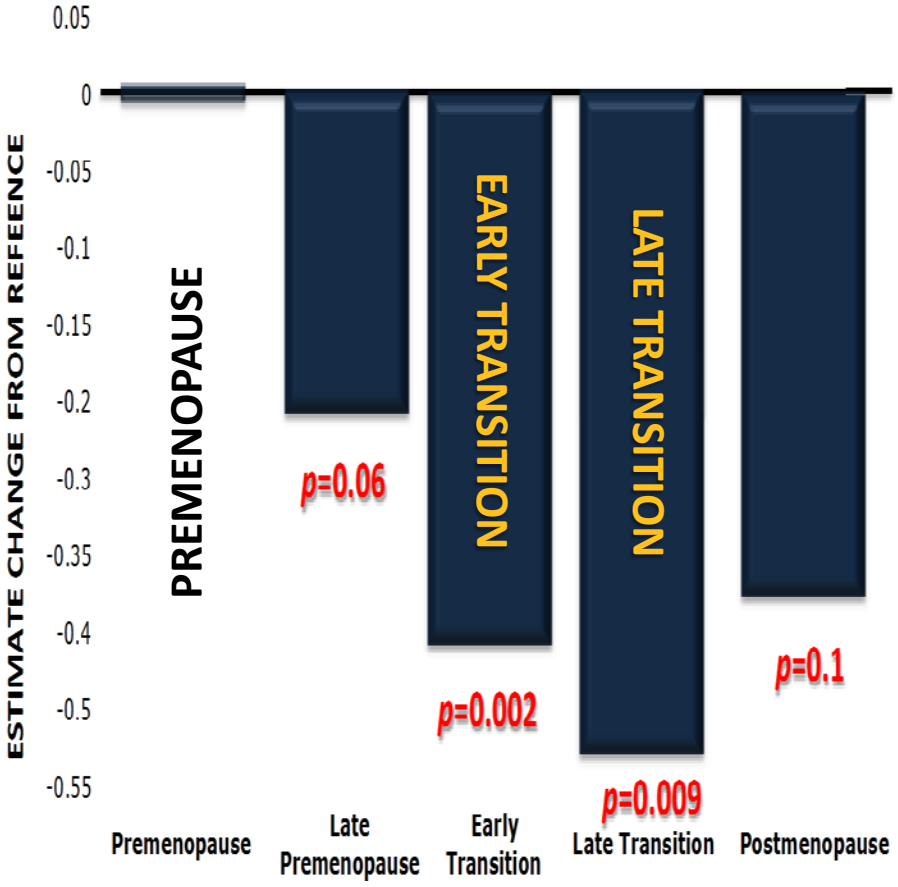


VERBAL MEMORY PERFORMANCE DECLINES ACROSS THE MENOPAUSE TRANSITION

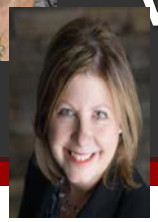
IMMEDIATE RECALL



DELAYED RECALL

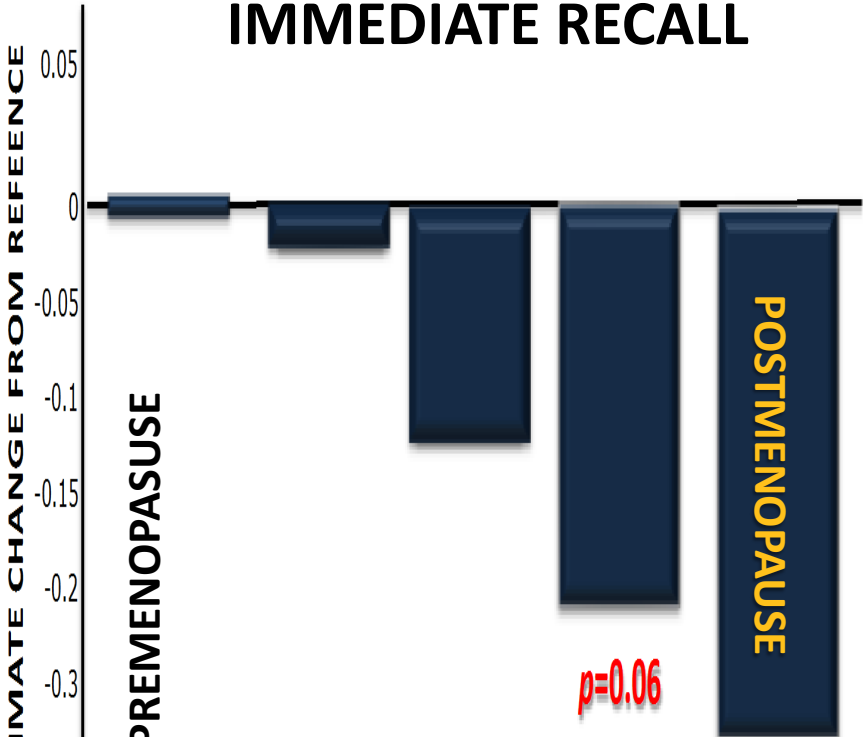


Epperson, Sammel, Freeman (2013) JCEM 98(9)3929-3838

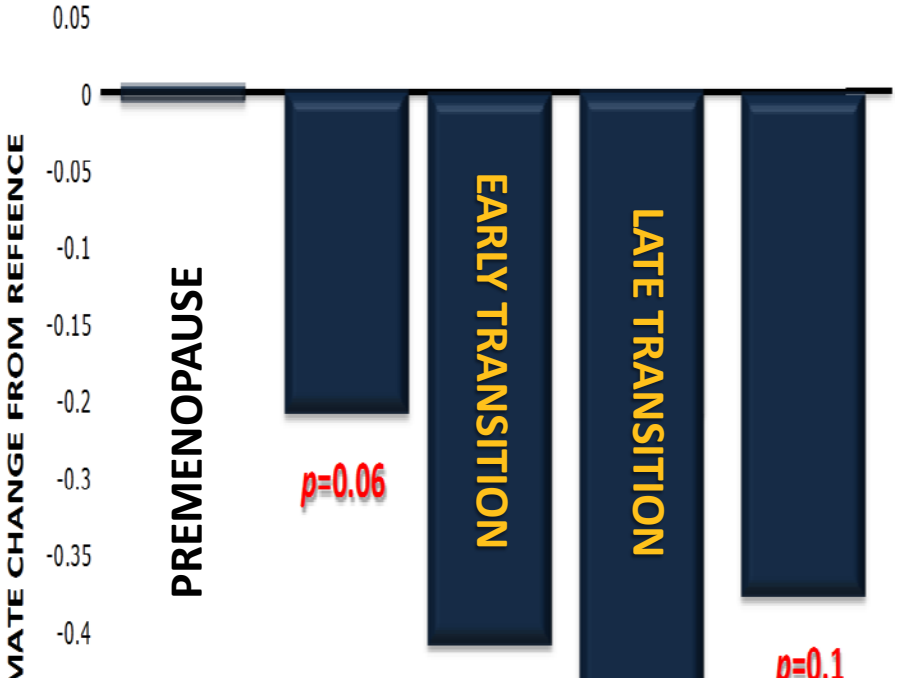


VERBAL MEMORY PERFORMANCE DECLINES ACROSS THE MENOPAUSE TRANSITION

IMMEDIATE RECALL



DELAYED RECALL



Early adversity contributes to increased risk.

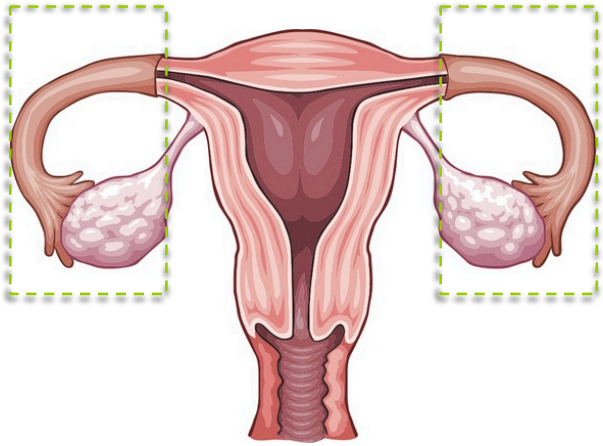
Sheila Shanmugan

Executive Function in Women after Risk Reducing Salpingo-Oophorectomy (RRSO)

- **800 women post-RRSO recruited primarily via internet through advocacy group *Facing our Risk of Cancer Empowered* (FORCE)**

Susan Domcheck

- **Completed online….**
  - Self-report of executive function using the Brown Attention Deficit Disorder Scale.
  - Objective measures of cognition using the Penn Computerized Neuro-cognitive Battery (CNB).
  - Adverse Childhood Experiences Questionnaire (ACE-Q)



Risk-Reducing Salpingo Oophorectomy (RRSO)

Assessing Executive Functions

Thomas Brown

- ✓ **BROWN ATTENTION DEFICIT DISORDER SCALE (BADDS)**
  1) **ORGANIZATION AND ACTIVATION FOR WORK**
  2) **ATTENTION AND CONCENTRATION**
  3) **MAINTAING ALERTNESS AND EFFORT AND PROCESSING SPEED**
  4) **MANAGING AFFECTIVE INTERFERENCE**
  5) **WORKING MEMORY AND ACCESSING RECALL**

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)**
  - ✓ **2 Questions regarding separation from parent/family member**
  - ✓ **3 Questions regarding household dysfunction (violence, substance abuse, parental mental illness**

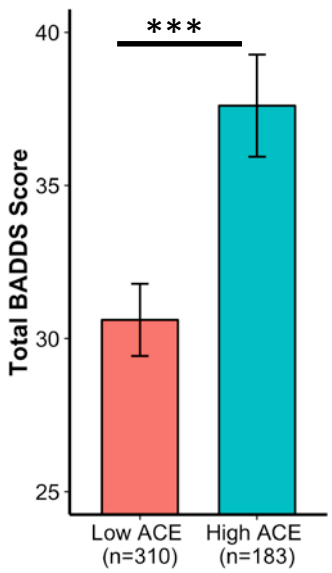
- ✓ **"Stressed" group are those with ≥ 2 ACEs**
- ✓ **Pre-pubertal period (birth to 2 years prior to menarche)**

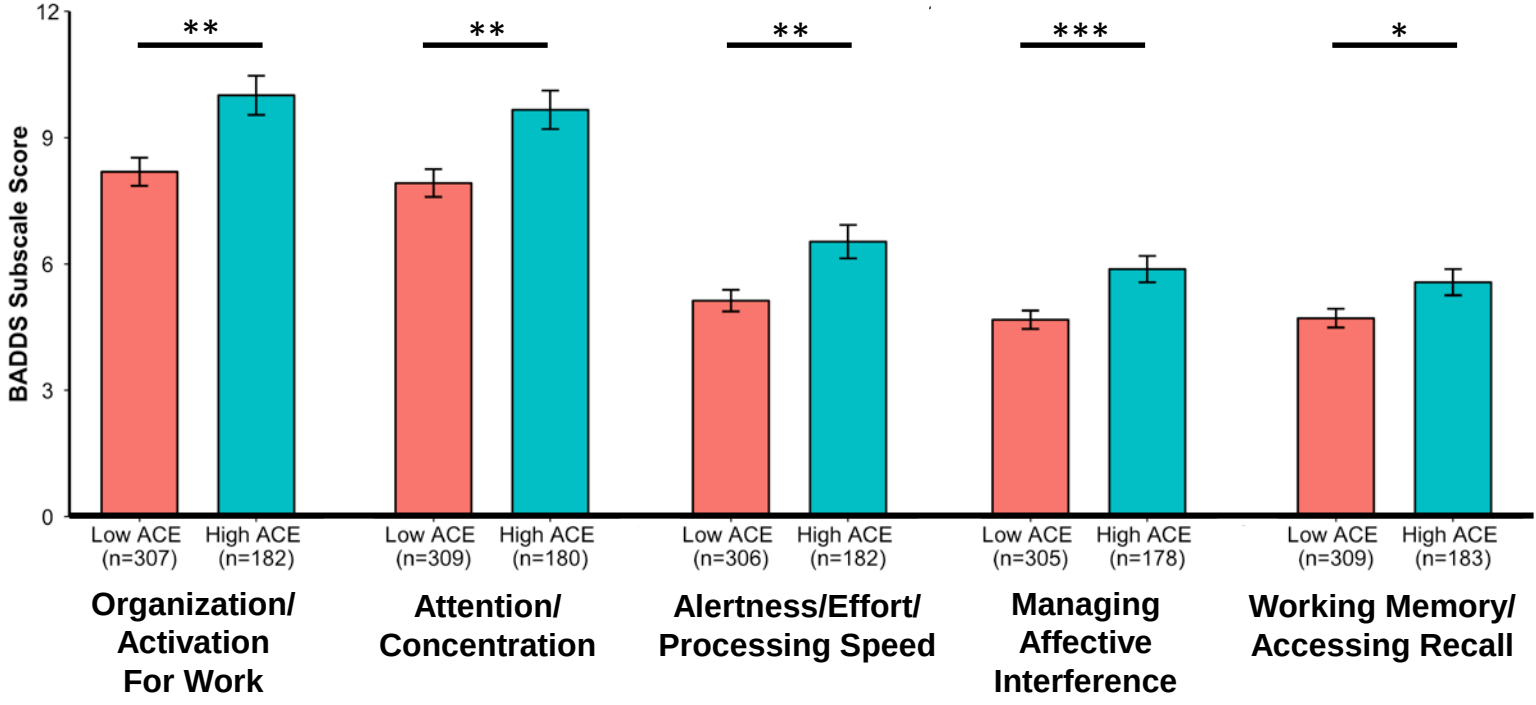
Russo SJ et al. (2012) Nat Neurosci. 12(11):1475-84
Felitti V. et al., (1998) Am J Prev Med, 14(4):245-258. .

Childhood Adversity Impact on Executive Function after Oophorectomy

a)

b)

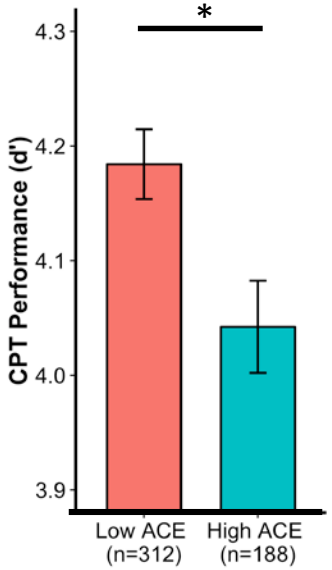




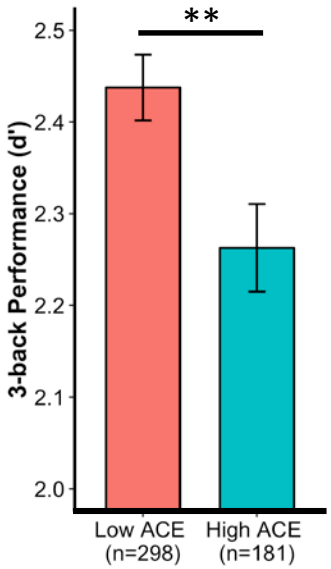
*p<0.05, **p<0.01, ***p<0.001

Objective Findings: Sustained Attention and Working Memory

a)

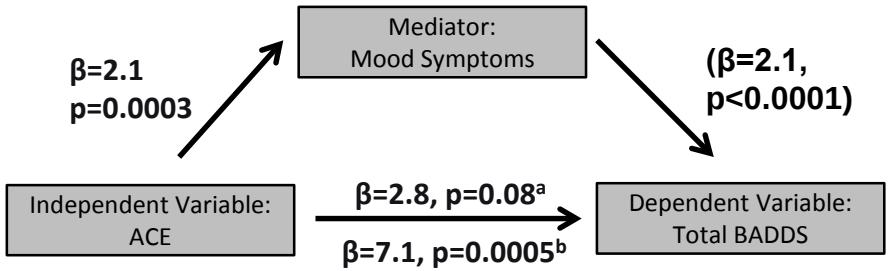


b)

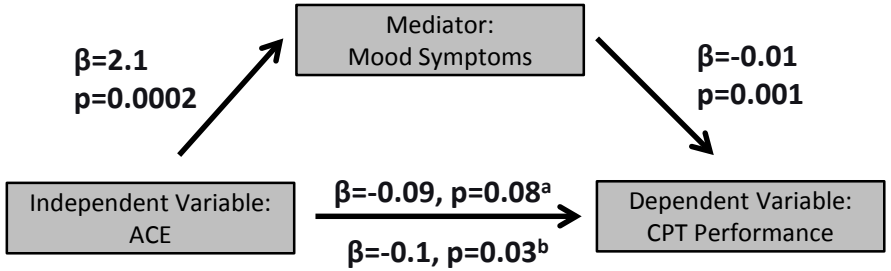


***p<0.05, **p<0.01, ***p<0.001**

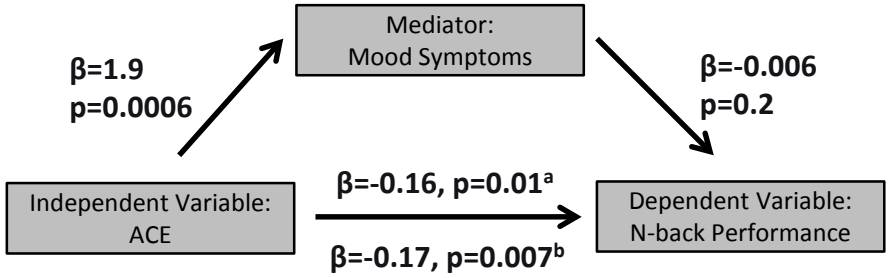
a)



b)



c)



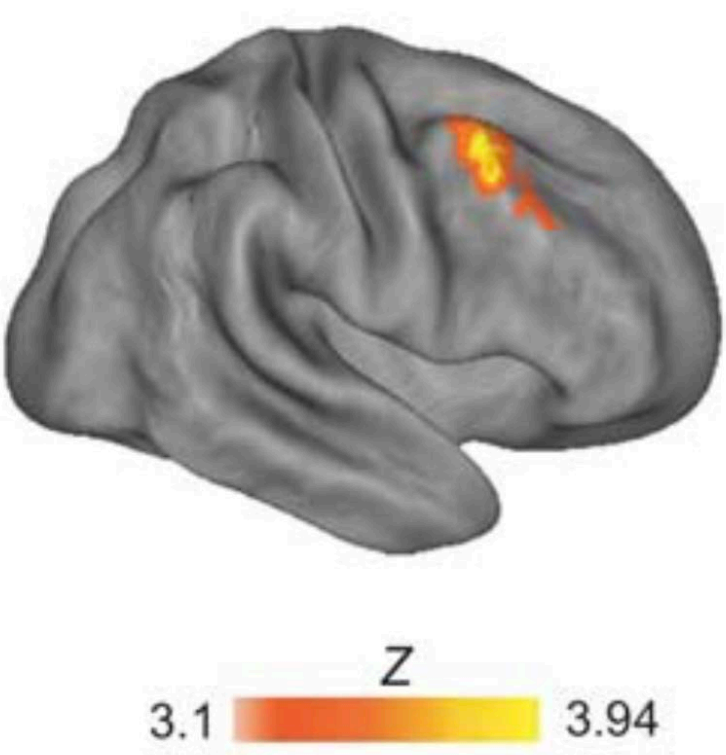
[a] **Direct effect of ACE on dependent variable**
[b] **Total effect of ACE on dependent variable**

MEDIATION ANALYSIS

MOOD (ANXIETY AND DEPRESSION) SYMPTOMS WERE SIGNIFICANT MEDIATORS OF THE EFFECTS OF ACE

- Subjective report of executive function difficulties (63%).
- Objective measure of sustained attention (21%).
- **But not, working memory.**

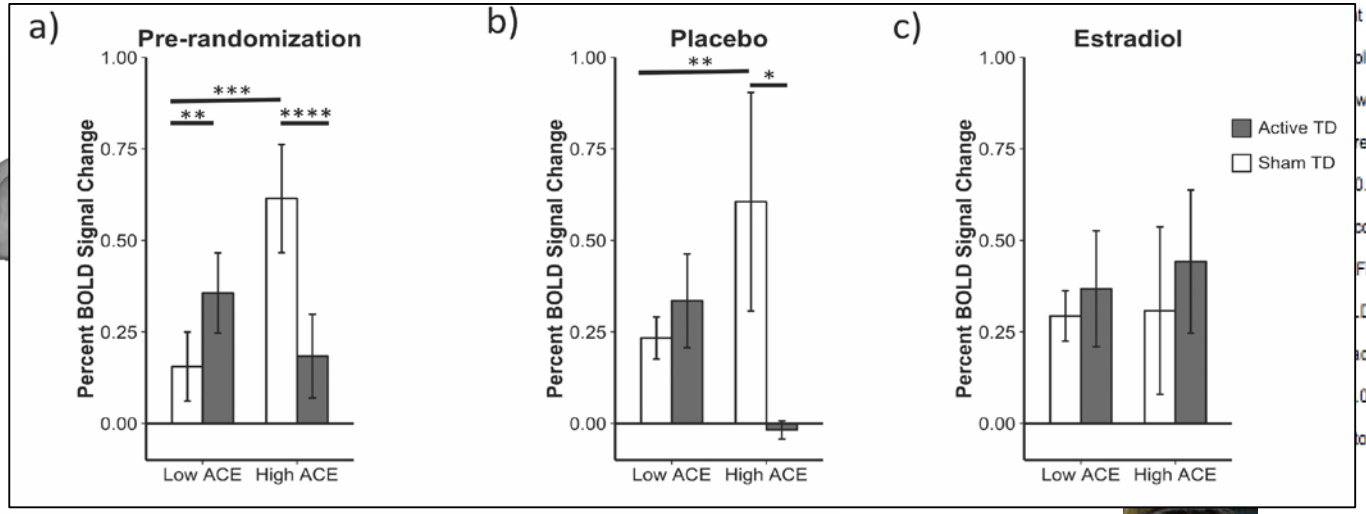
Enduring Effects on Brain?

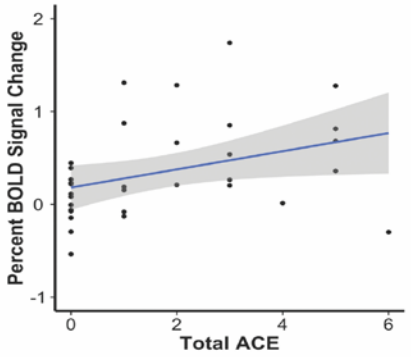


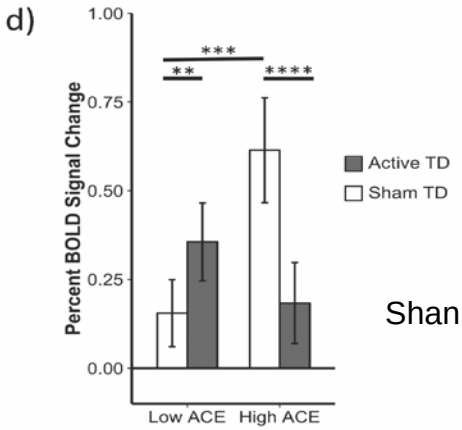
ACEs are associated with enduring effects on brain function, response to neurotransmitter and hormone manipulations

Figure 3-2. Phase 1 imaging results. a. A whole-brain mixed-effects 2 x 2 ANOVA
t DLPFC activation in high and low ACE
olume=108 mm³; peak z=3.94). **b.** BOLD
with true positive responses across all
emained significant when excluding the
0.30, p=0.02). **c.** During sham depletion,
correlated with total ACE score (r=0.41,
Figure 2a was extracted for visualization.
D relative to sham TD (β=0.20, 95% CI: -
ctive TD decreased activation relative to
.0003). During sham depletion, high ACE
o low ACE (β=0.49, 95% CI: 0.15 – 0.82,

a)





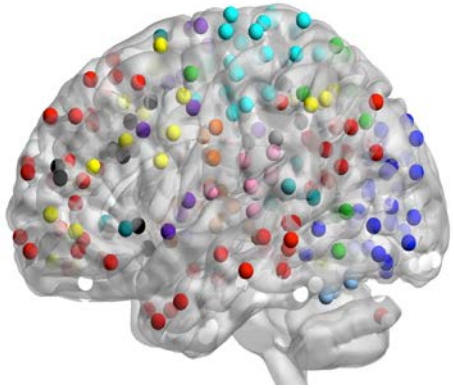


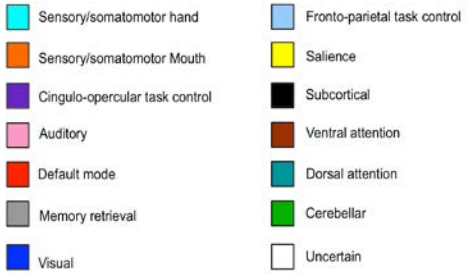
Sheila Shanmugan

James Loughead

Shanmugan S, Loughead J, Cao W, Sammel MD, Satterthwaite TD, Ruparel K, Gur RC, **Epperson CN**. Neuropsychopharmacology. 2017 Apr 12. doi: 10.1038/npp.2017.64. [Epub ahead of print]

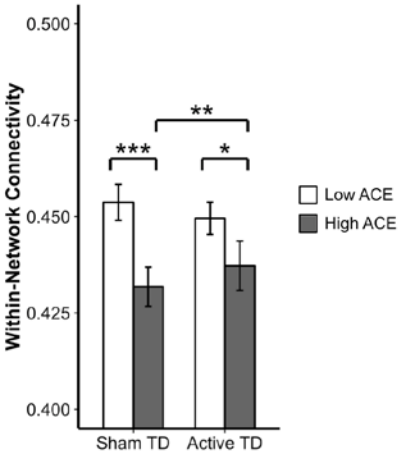
ACEs are associated with enduring effects on brain function, response to neurotransmitter and hormone manipulations





Sheila Shanmugan **James Loughead**

a)



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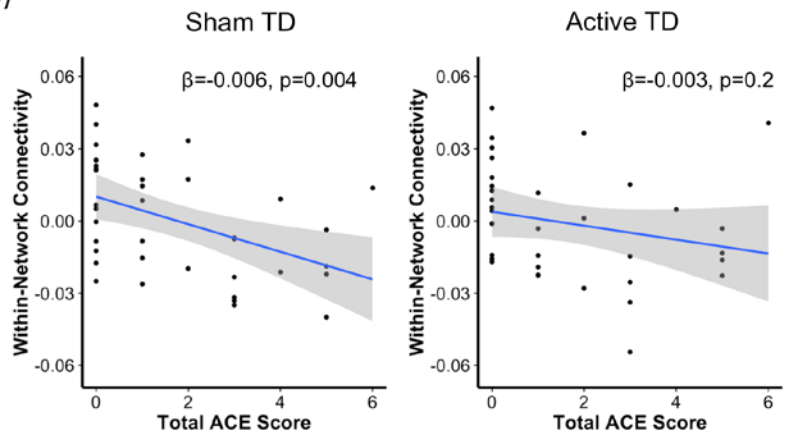
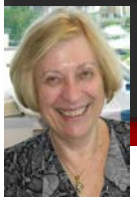
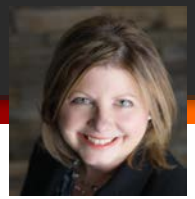


Shanmugan S, Satterthwaite TD, Sammel MD, Cao W, Ruparel K, Gur RC, **Epperson CN**, Loughead J. Psychoneuroendocrinology. 2017 Jul 14;84:197-205.

Could natural changes in inflammation unmask vulnerability?





- **Loss of estradiol at menopause is associated with a rise in pro-inflammatory cytokines.**
  - **Cardiovascular disease**
  - **Osteoporosis**
  - **Obesity**
  - **Depression**

Could loss of estradiol at menopause and rise in cytokines unmask vulnerability?

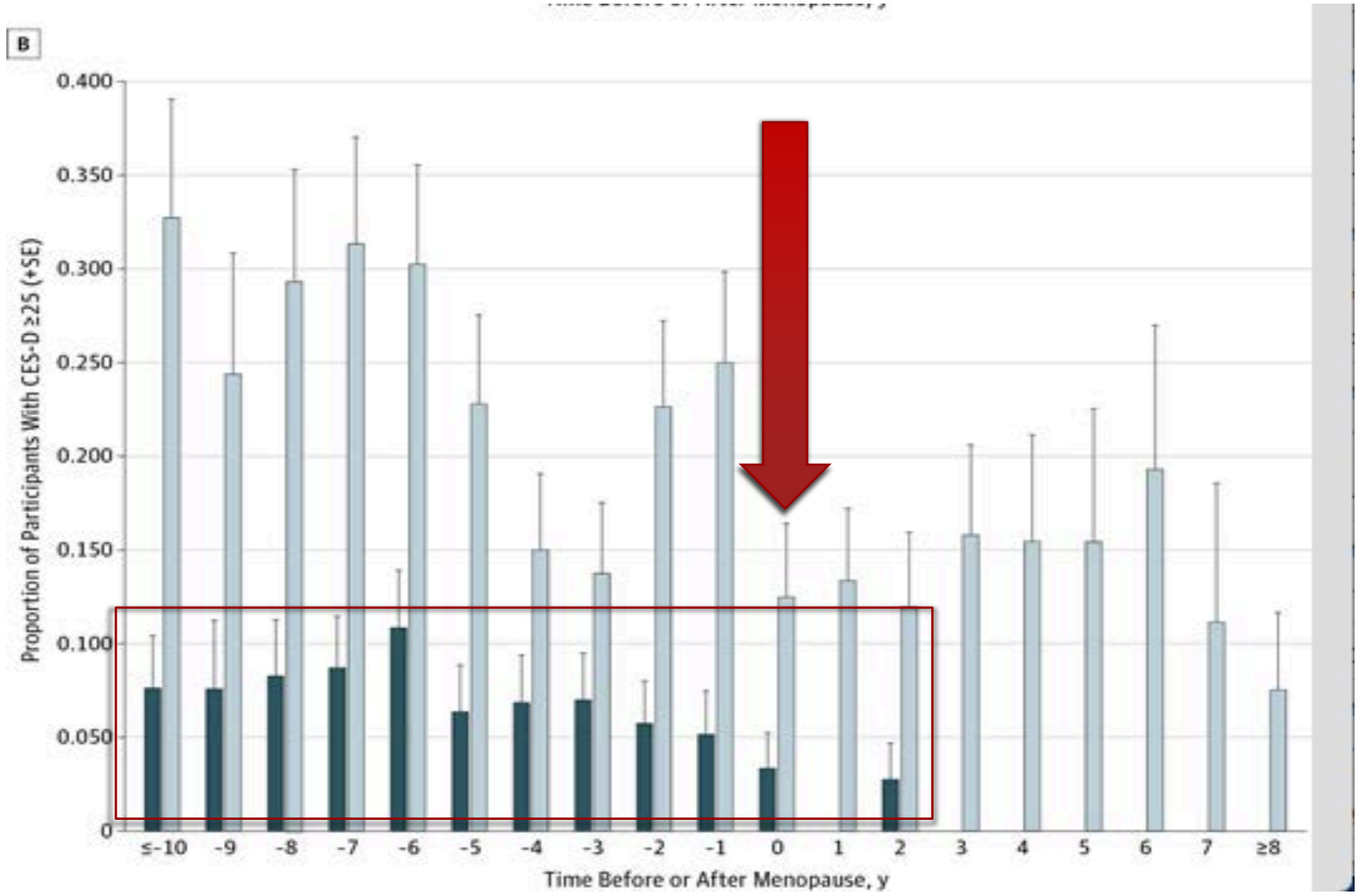
Prepubertal ACE x Cytokine x Menopause Stage: Impact on Cognitive Measures

	Processing Speed		Verbal Memory	
	DIGIT SYMBOL	**SYMBOL COPY**	**DELAYED RECALL**	**IMMEDIATE RECALL**
hsCRP	0.482	0.401	0.742	**0.023**
IL-1β	0.327	0.874	0.382	**0.027**
IL-6	**0.02**	**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

From: **Longitudinal Pattern of Depressive Symptoms Around Natural Menopause**

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



Ellen Freeman, Ph.D.

NIH National Institute on Aging

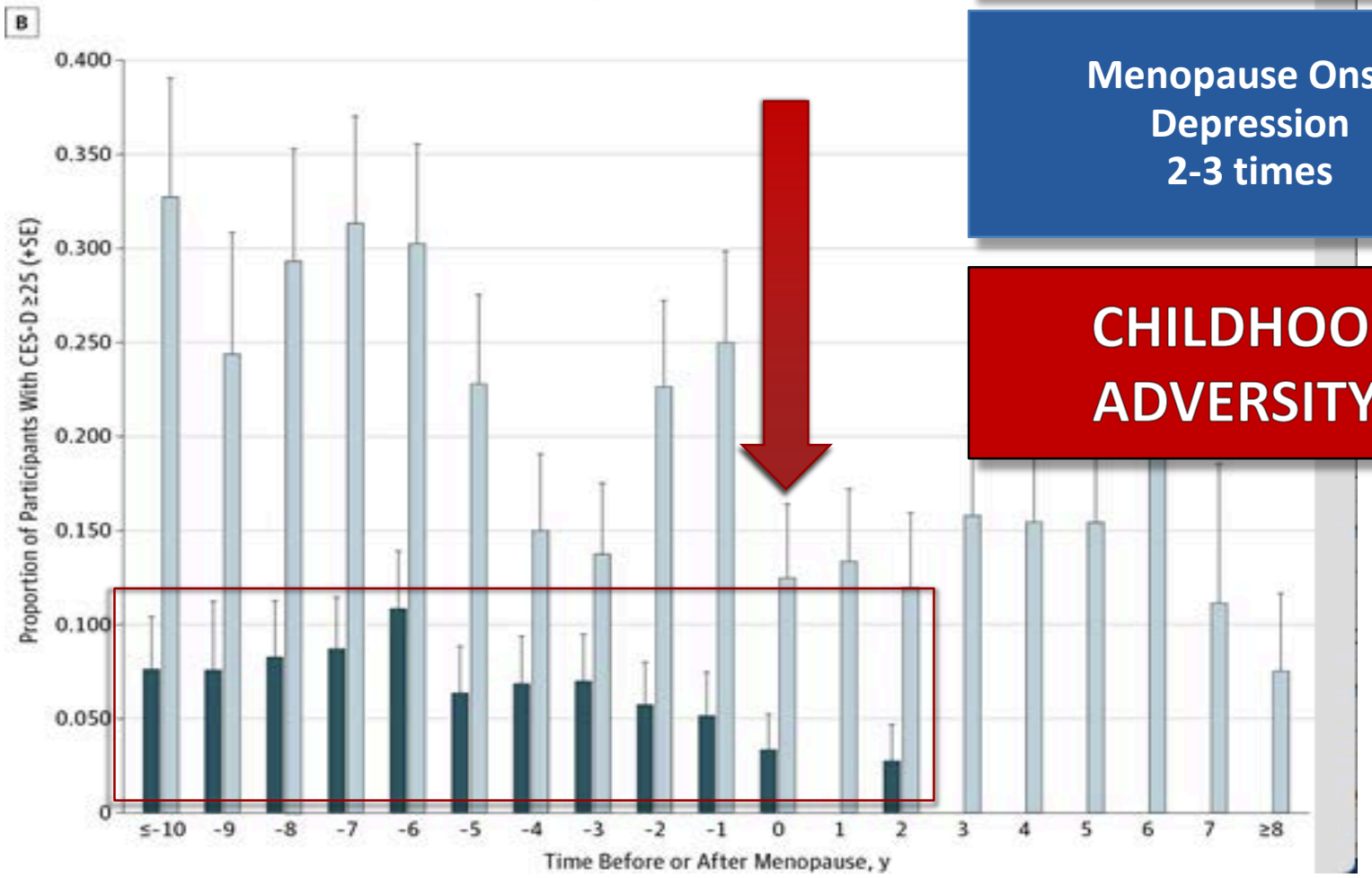
From: **Longitudinal Pattern of Depressive Symptoms Around Natural Menopause**

JAMA Psychiatry. 2014;71(1):36-43. doi:10.1001/jamapsychiatry.201

Recurrent Depression
4-5 times

Menopause Onset
Depression
2-3 times

CHILDHOOD ADVERSITY?



Ellen Freeman, Ph.D.

NIH National Institute on Aging

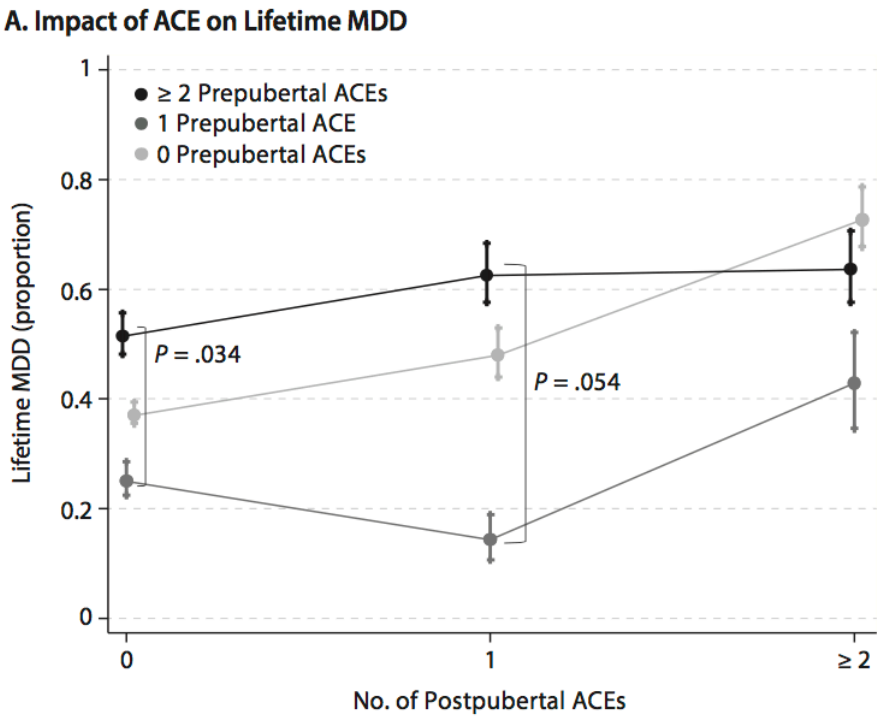
Adverse Childhood Experiences and Risk for First-Episode Major Depression During the Menopause Transition

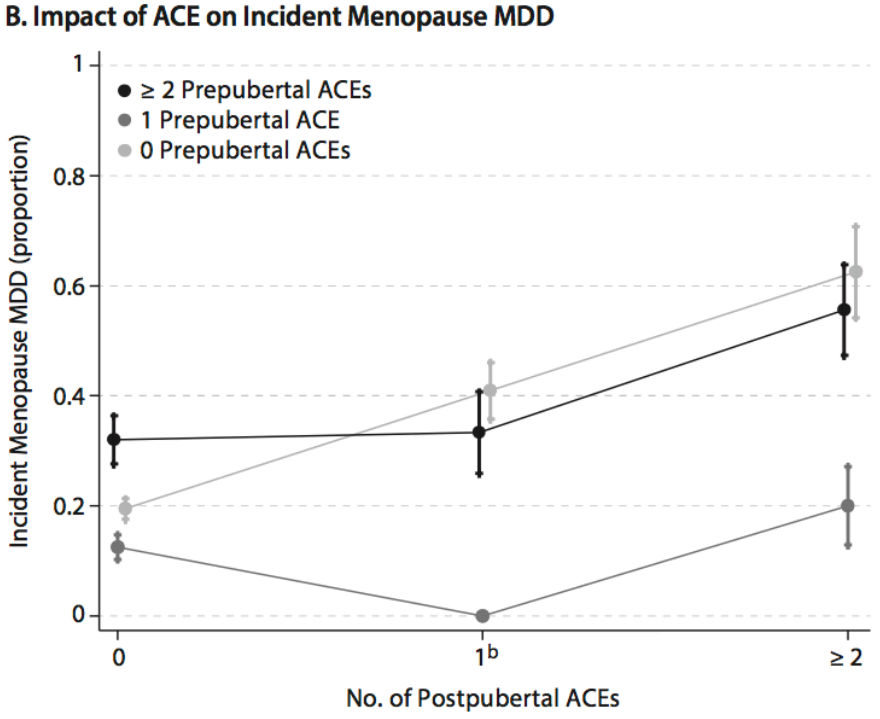
C. Neill Epperson, MD[a,b,c,*]; Mary D. Sammel, ScD[a,d]; Tracy L. Bale, PhD[a,e]; Deborah R. Kim, MD[a,b]; Sarah Conlin, BA[f]; Stephanie Scalice, MA[a]; Katharine Freeman, BA[a]; and Ellen W. Freeman, PhD[c]

- Can adverse childhood experiences lead to risk for first episode of major depressive disorder in the menopause transition.
- Contacted 243 original POAS Participants.
- Administered the ACE Questionnaire.
  - Lifetime
  - Incident Perimenopause Depression

THE JOURNAL OF CLINICAL PSYCHIATRY

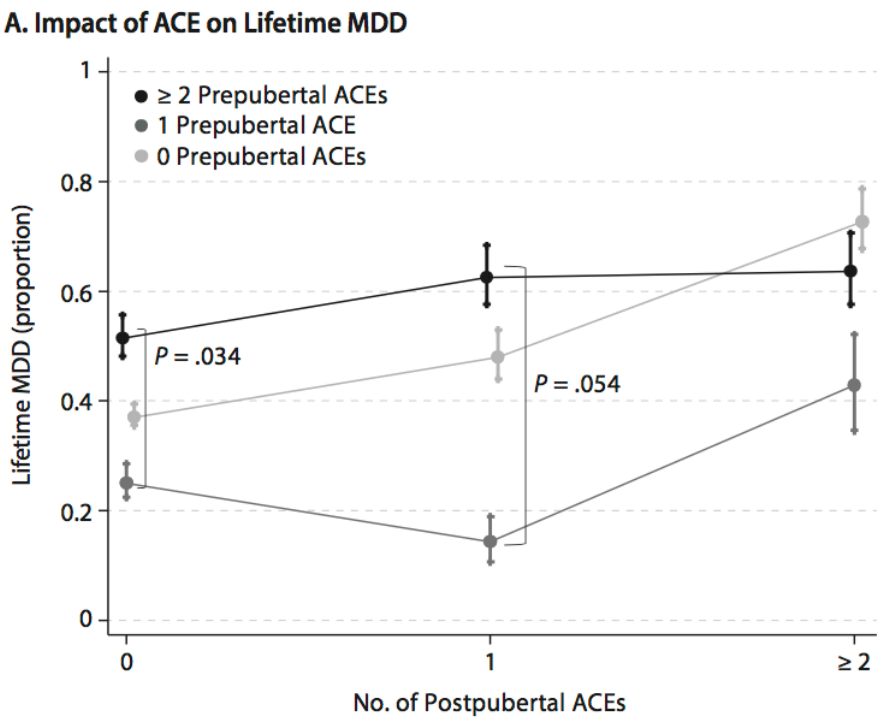
ACE & MDD: Impact of number and pubertal status

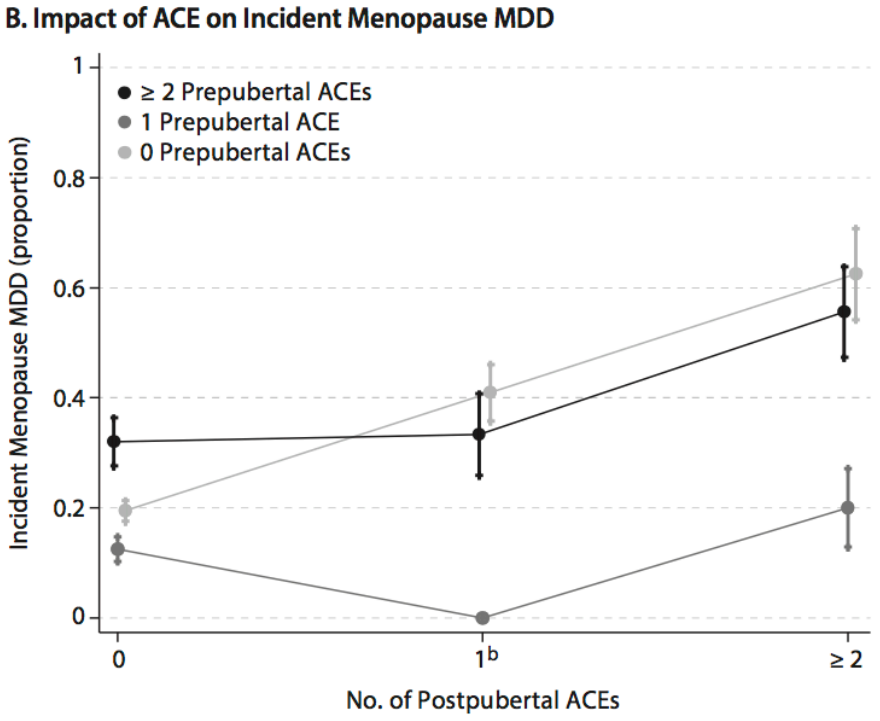




Epperson, et al. J Clin Psychiatry. 2017 Mar;78(3):e298-e307.

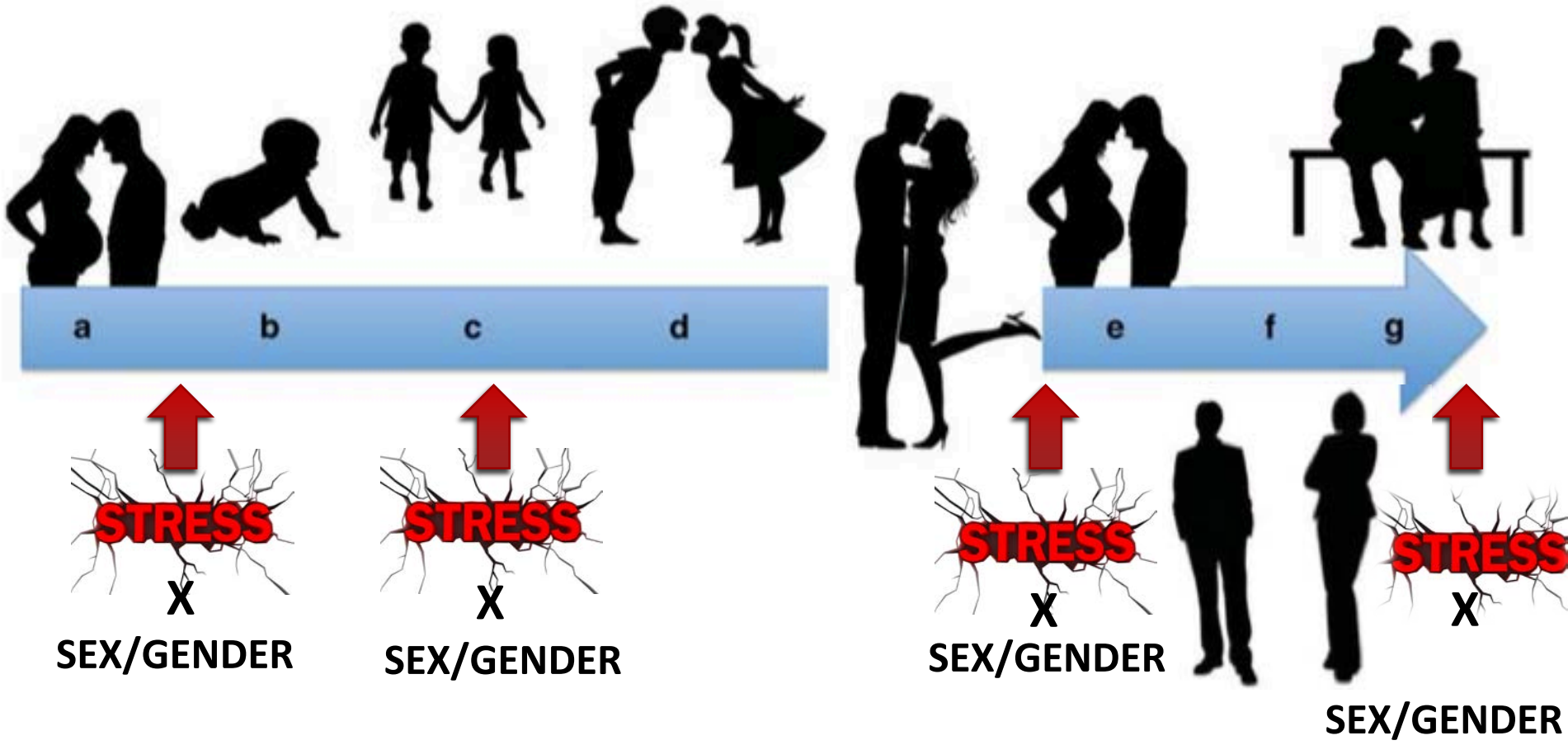
- In this sample, most commonly reported single ACE was…
  - Household substance abuse
  - Divorce Separation





Epperson, et al. J Clin Psychiatry. 2017 Mar;78(3):e298-e307.

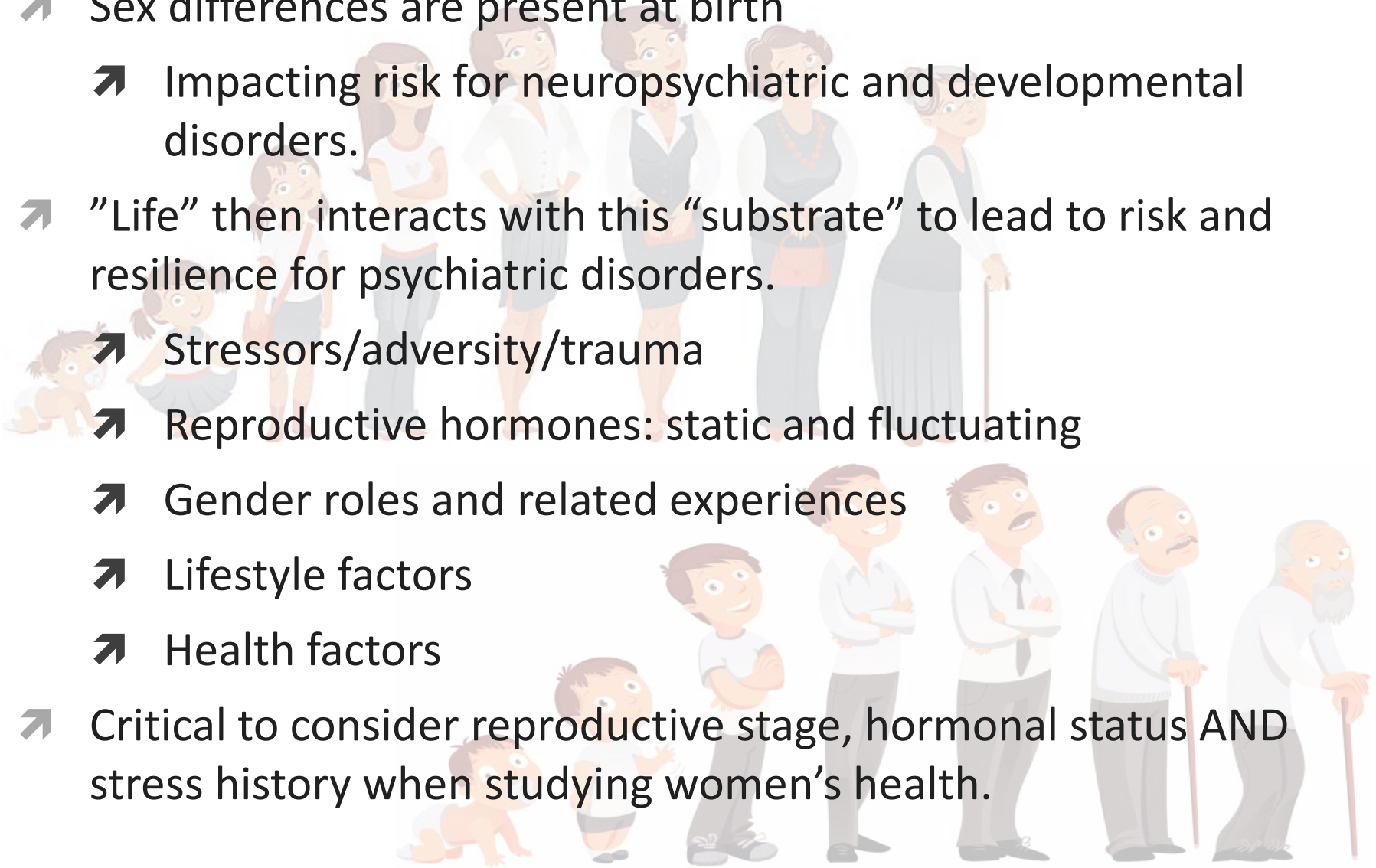
Critical Windows Across Development



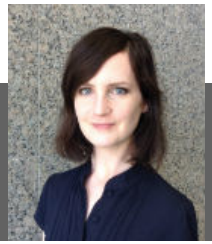
Bale & Epperson, Nature Neuroscience, 2015

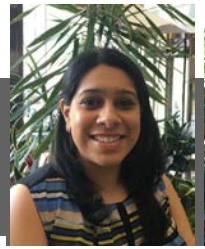
SUMMARY

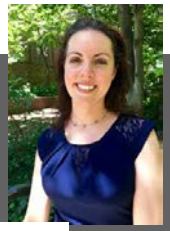
- Sex differences are present at birth
  - Impacting risk for neuropsychiatric and developmental disorders.
- ”Life” then interacts with this “substrate” to lead to risk and resilience for psychiatric disorders.
  - Stressors/adversity/trauma
  - Reproductive hormones: static and fluctuating
  - Gender roles and related experiences
  - Lifestyle factors
  - Health factors
- Critical to consider reproductive stage, hormonal status AND stress history when studying women’s health.

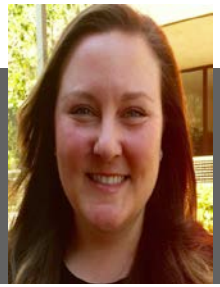



Grace Ewing


Liisa Hantsoo


Raisa Raina


nette dley


Claudia Iannelli

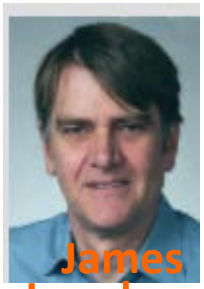

Ruben Gur


Gianna Melendez


Deb Kim


Allie Mott


Ellen Freeman


James Loughead


Joanna Marks


Emily Lipner


Brendan McGeehan

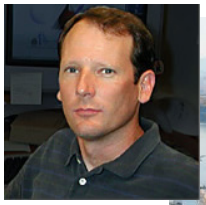

Susan Domcheck


Lindsay Sortor

Tom Brown


Andrew Siegel


Mary Sammel

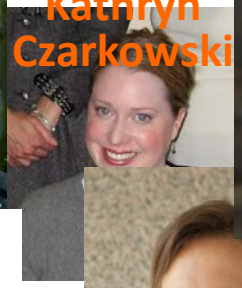

Mark Elliot


Kosha Ruparel


Stephanie Criniti


Sara Kornfield


Jessica Podcasy


Kathryn Czarkowski


Sarah Mathews


Ravi Reddy


Tracy Bale

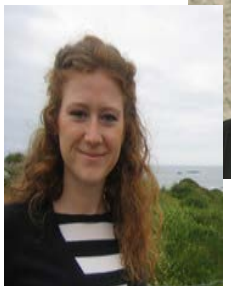

Sheila Shanmugam


Emily Lipner Ravi PNR


Hillary Nguyen


Carrie Malanga


Connie Brady


Katie Morrison

And our Funding Sources!

Questions and Answers