

CONSIDERING CHILDHOOD ADVERSITY AS A RISK FACTOR FOR COGNITIVE AND MOOD DIFFICULTIES DURING PERIMENOPAUSE & BEYOND

C. Neill Epperson, MD

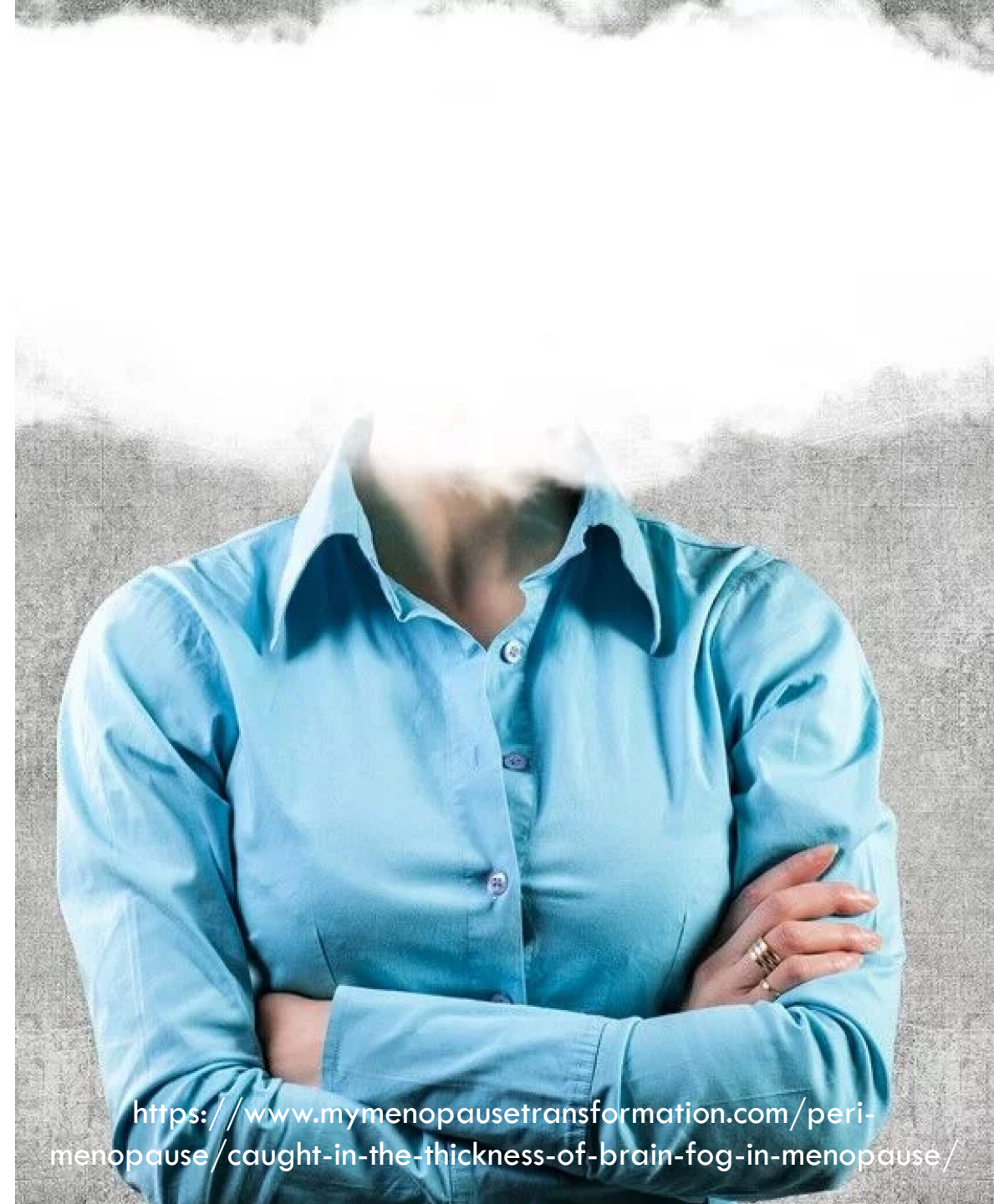
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National Academies of Science Engineering and Medicine
March 7, 2024



<https://www.mymenopausetransformation.com/perimenopause/caught-in-the-thickness-of-brain-fog-in-menopause/>

DISCLOSURES

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Sage Therapeutics | Consultant| Research
Babyscripts | Scientific Advisor
Skyland Trail | Consultant
EmbarkNeuro | Consultant
MycoMedica | Consultant



Department of Psychiatry

SCHOOL OF MEDICINE

UNIVERSITY OF COLORADO **ANSCHUTZ MEDICAL CAMPUS**



BRAIN HEALTH for all, for life.

KATHY'S CASE: NATURAL MENOPAUSE

Kathy is a 49 year-old executive who is in the **late perimenopause** and is worried about her “memory”. She is experiencing **vasomotor symptoms, sleep disruption, and moodiness**, but **her cognitive symptoms** are of utmost concern. She is worried that these symptoms are negatively impacting her **productivity** at work and her ability to care for her family. She knows that Alzheimer’s Disease is more common in females. She is **particularly frightened** as her 85 yo mother has dementia.



Shanmugan et al., 2017; Epperson et al., 2017; Gervais et al., 2017; Girard et al., 2017; Sullivan et al., 2016; Podcasy & Epperson, 2016

KATHY'S CASE: NATURAL MENOPAUSE

- Sustaining attention in meetings
- Recovering her train of thought after a distraction
- Forgetfulness
- Ability to complete tasks as quickly as before
- Word finding difficulties
- Decreased motivation for certain tasks



Shanmugan et al., 2017; Epperson et al., 2017; Gervais et al., 2017; Girard et al., 2017; Sullivan et al., 2016

PATIENT EXPERIENCE: SURGICAL MENOPAUSE

“When I was deciding at the age of 39 whether to undergo an oophorectomy to reduce my risk of cancer, my doctor told me that I may have problems with my metabolic, heart, and bone health. No one told me that I could lose my mind. I wish I had waited.”

**GAP: THE BRAIN IS NOT EVEN A CONSIDERATION IN THE RISK
BENEFIT DISCUSSION OF RRSO**



WHY FOCUS ON MENOPAUSE?

1.2 Billion perimenopausal individuals world-wide

6,000 females each day reach menopause in US

4 to 8 years = Duration of perimenopause

\$1.8 billion in lost work time each year

2- to 5-fold increase in risk for depression

44%-62% report cognitive complaints

7-10 yr duration of vasomotor symptoms

39%-60% report sleep disturbances

- Age at FMP
- Race/Ethnicity
- Education
- Health
- Lifestyle
- **Early life adversity**



LIFE EXPECTANCY AND YEARS POSTMENOPAUSE

Age at FMP

Female life expectancy 1924

Female life expectancy 2024

HOW COULD CHILDHOOD ADVERSITY HAVE ENDURING EFFECTS ON BRAIN HEALTH?

- **Alterations in**

- Gene expression
- Brain structure and function
- Stress responsiveness
 - HPA-A
 - Immune
 - Autonomic
- Microbiome
- Response to hormone dynamics



The three types of ACEs include

ABUSE



Physical



Emotional



Sexual

NEGLECT



Physical



Emotional



Sexual

HOUSEHOLD DYSFUNCTION



Mental Illness



Substance Abuse



Divorce



Incarcerated Relative



Substance Abuse

≥ 2 ACEs=High ACE

0-1 ACEs=Low ACE

WHAT IMPACT DO ACEs HAVE?

4+ ACEs females > males



BRAIN HEALTH for all, for life.

BEHAVIOR



Lack of physical activity



Smoking



Alcoholism



Drug use



Missed work

PHYSICAL & MENTAL HEALTH



Severe obesity



Diabetes



Depression



Suicide attempts



STDs



Heart disease



Cancer



Stroke



COPD



Broken bones

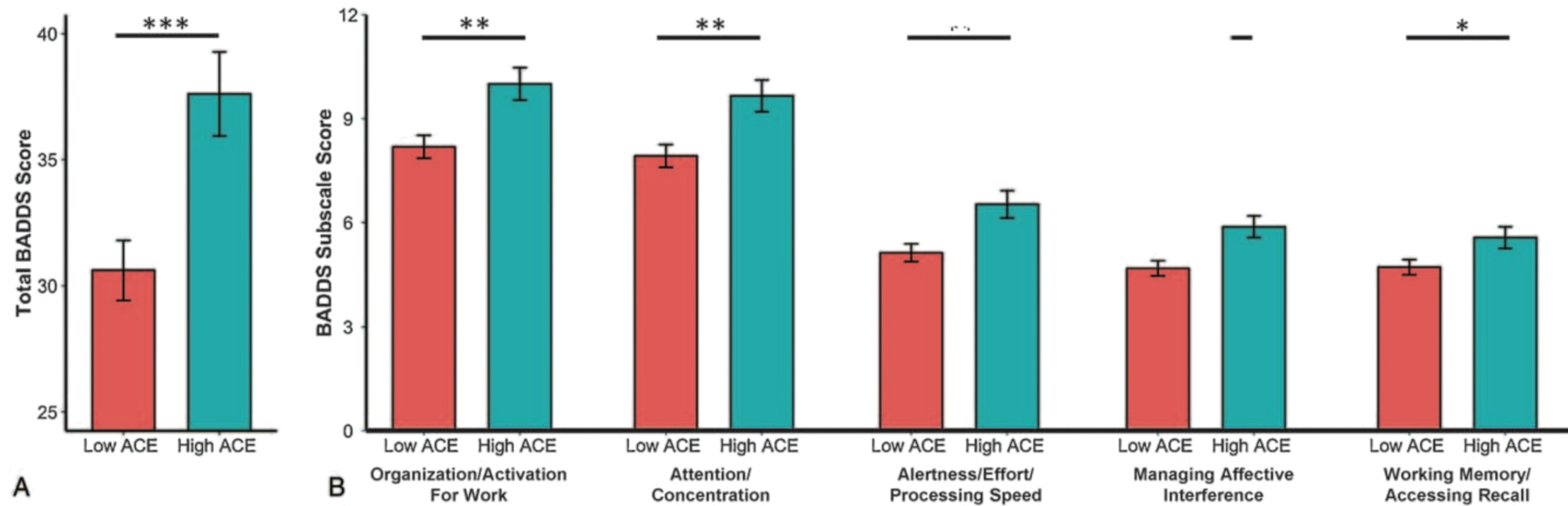
<https://www.cdc.gov/violenceprevention/acestudy/index.html>



2.6 X RISK OF DEPRESSION

2+ prepubertal ACEs are
Associated with a 2.6-fold
increase in first onset of
MDD during the
perimenopause

Epperson CN, Sammel MD, Bale TL, et al. Adverse Childhood Experiences and Risk for First-Episode Major Depression During the Menopause Transition. J Clin Psychiatry. 2017;78(3):e298-e307.



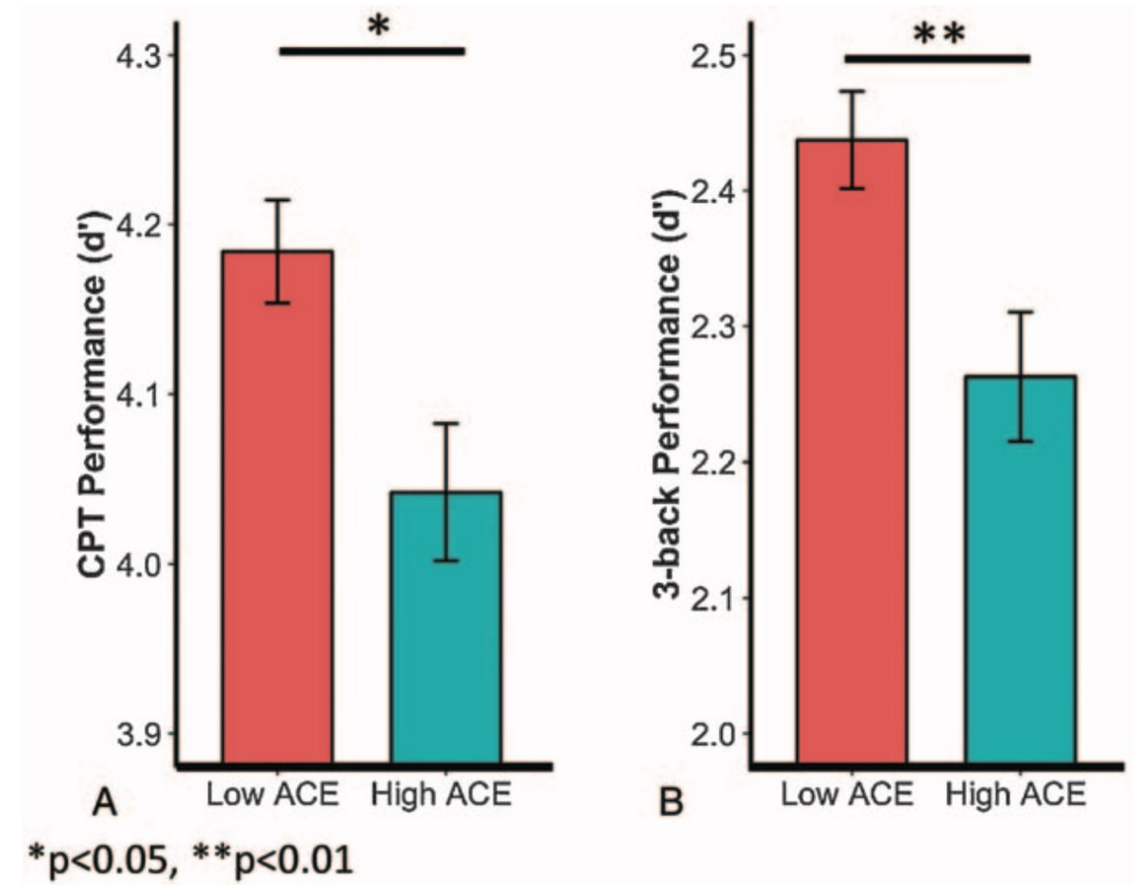
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

ACE ASSOCIATED WITH SUBJECTIVE EXECUTIVE FUNCTION DIFFICULTIES

- BADDS= Brown Attention Deficit Disorder Scale
 - Motivation & activation for work
 - Attention/concentration
 - Alertness/effort/processing speed
 - Managing affective interference
 - Working memory

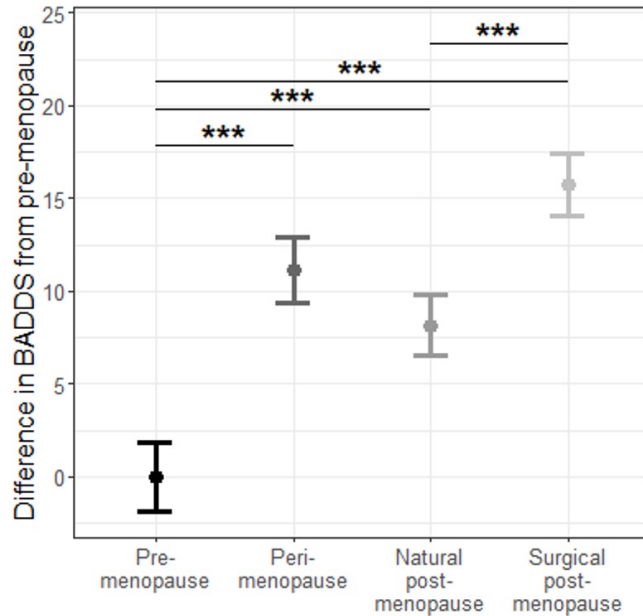
ACE ASSOCIATED WITH OBJECTIVE EXECUTIVE FUNCTION DIFFICULTIES

Negative affect (depression
& anxiety symptoms)
mediate part of the ACE
effect on sustained attention,
but not working memory.

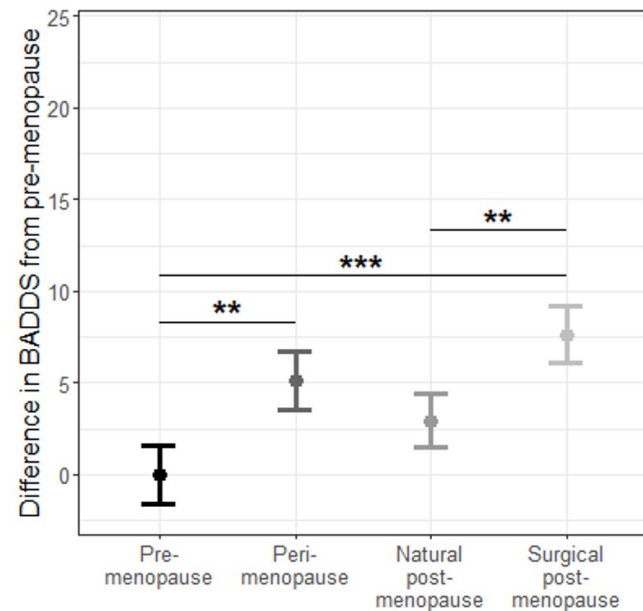


Shanmugan S, Sammel MD, Loughhead J, et al. Executive function after risk-reducing salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: does current mood and early life adversity matter?. *Menopause*. 2020;27(7):746-755.

Executive Function Across the Menopause Transition

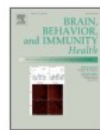


Adjusted for age, education, and self-reported ADHD diagnosis



Adjusted for age, education, ADHD, difficulty sleeping, meaningful anxiety and depression (based upon standard scales)

- 1,971 women 35-65 yo completed an on-line survey (Research Match, FORCE)
 - Premenopause N=597
 - Perimenopause N=331
 - Natural Postmenopause N=724 (FMP 50 yo)
 - Surgical post N=319 (FMP 41 yo)
- BADDS= Brown Attention Deficit Disorder Scale
 - Motivation & activation for work
 - Attention/concentration
 - Alertness/effort/processing speed
 - Managing affective interference
 - Working memory
- High education status, but not necessarily located near an academic research center



Short Communication

Influences of the Menopause Transition and Adverse Childhood Experiences on Peripheral Basal Inflammatory Markers

Christina A. Metcalf PhD¹, Rachel L. Johnson MS¹, Ellen W. Freeman PhD², Mary D. Sammel ScD¹, C. Neill Epperson MD¹✉



Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx



Adverse childhood experiences interact with inflammation and menopause transition stage to predict verbal memory in women



Christina A. Metcalf^{a,*}, Rachel L. Johnson^b, Andrew M. Novick^a, Ellen W. Freeman^c, Mary D. Sammel^{a,b}, Laura G. Anthony^a, C. Neill Epperson^{a,d}

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RESEARCH ARTICLE

WILEY

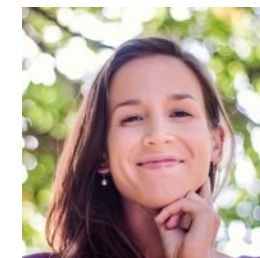
Depressed, stressed, and inflamed: C-reactive protein linked with depression symptoms in midlife women with both childhood and current life stress

Christina A. Metcalf¹✉ | Rachel L. Johnson² | Korrina A. Duffy¹ | Ellen W. Freeman³ | Mary D. Sammel^{1,2} | C. Neill Epperson^{1,4}



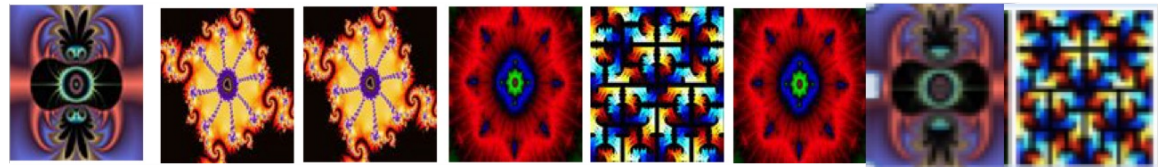
ACE, Menopause, & Immune Markers: *Cognition and Mood*

- ACEs are associated with greater increase in peripheral markers of inflammation across the menopause transition, particularly late transition.
- Among women reporting 2+ ACES, markers of inflammation are associated with worse verbal memory.
- Among women reporting 2+ ACES and high levels of current life stress, C-reactive protein is associated with clinically meaningful depressive symptoms (CES-D score ≥ 16).



CHRISTINA METCALF, PHD

Covariates included menopause stage, age at study baseline, body mass index, race, and smoking status

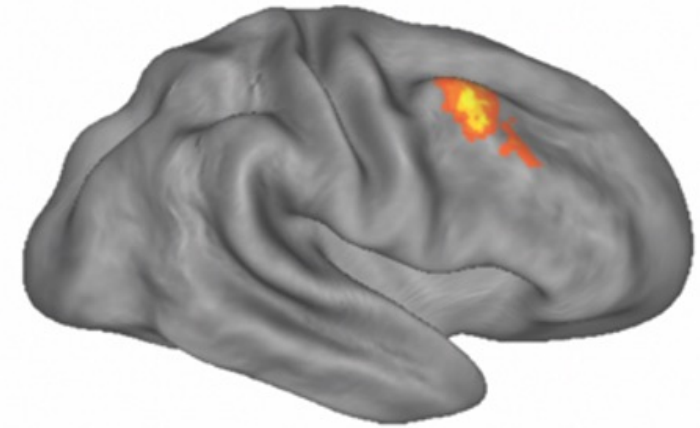


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3.1 Z 3.94

Shanmugan S, ... Epperson CN, Menopause. 2020;27(7):746-755.

Shanmugan S,...Epperson CN. Neuropsychopharmacology. 2017 Nov;42(12):2398-2406.

EARLY LIFE EXPERIENCE MATTERS



Sheila Shanmugan



James Loughead

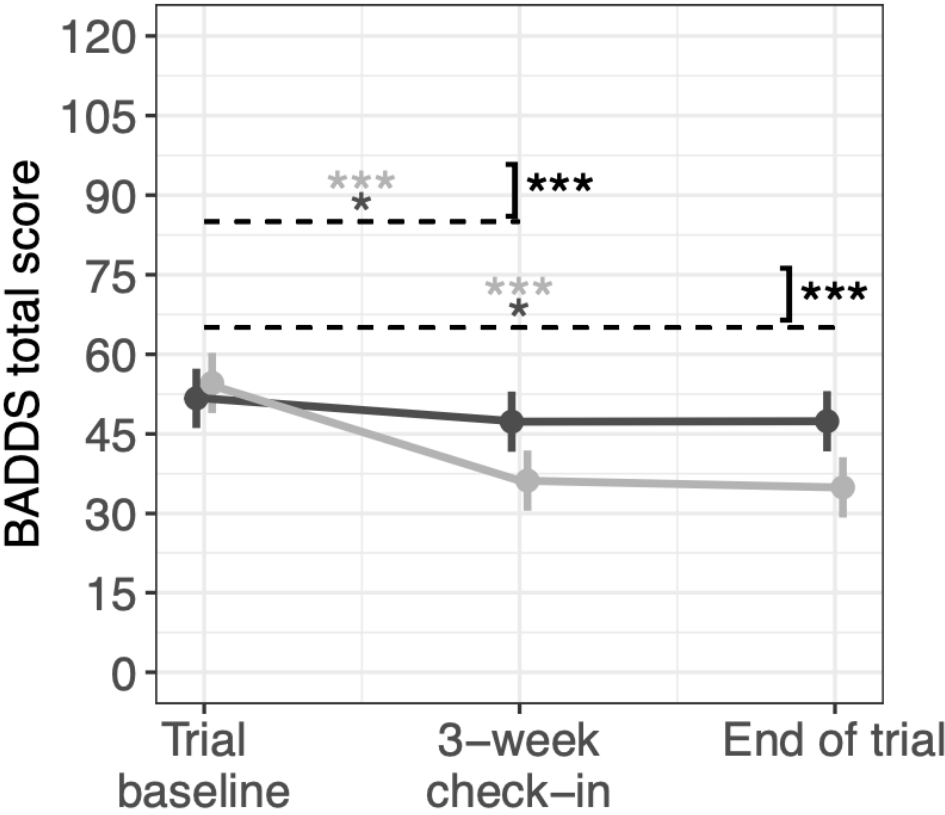
WHAT CAN WE DO FOR KATHY?

- Does Kathy report significant childhood adversity?
- How is her health? Does she have reason for having greater inflammation?
- Must evaluate and intervene to improve
 - Sleep disturbance
 - Low mood
 - High anxiety
- Treatment options for new onset executive function difficulties.



Shanmugan et al., 2017; Epperson et al., 2017; Gervais et al., 2017; Girard et al., 2017; Sullivan et al., 2016

Lisdexamfetamine vs Placebo: Executive Function Difficulties



- * = <0.05
- *** = <0.001
- Brackets indicate between group significance

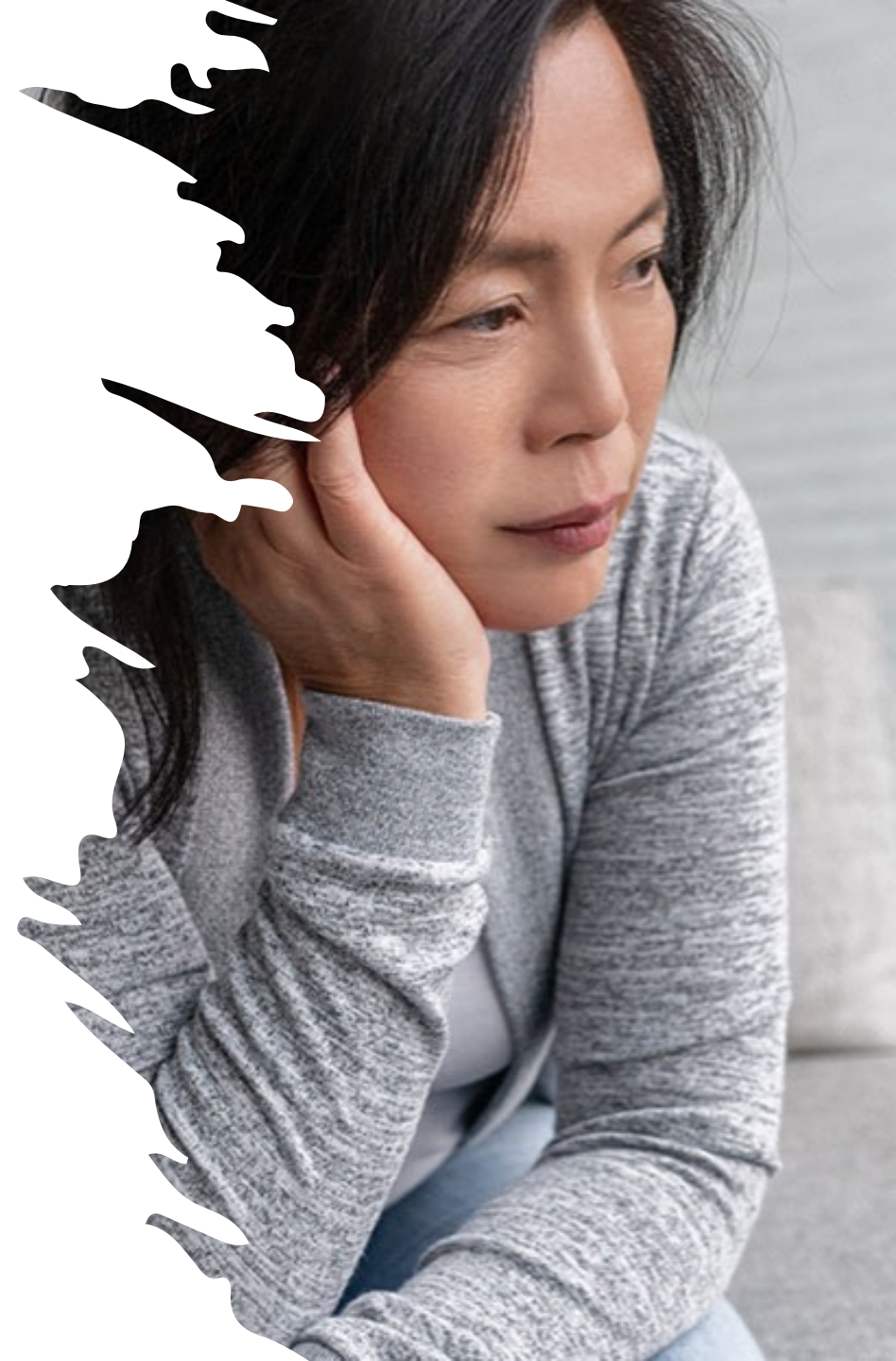
Subscale Results***

- Motivation and activation for work
- Attention/concentration
- Alertness/effort/processing speed
- Working memory

Outcome	Placebo: trial endpoint - study baseline estimate (95% CI)	p value	LDX: trial endpoint - study baseline estimate (95% CI)	p value	Difference in LDX vs. placebo change (95% CI)	p value
CPT accuracy	0.98 (0.15, 1.80)	0.021	1.29 (0.46, 2.12)	0.003	0.31 (-0.49, 1.10)	0.449
LNB accuracy	0.67 (-0.73, 2.06)	0.347	2.16 (0.77, 3.55)	0.003	1.50 (0.09, 2.90)	0.037
NYU Paragraph Recall accuracy	1.48 (0.58, 3.28)	0.001	1.39 (0.49, 2.29)	0.003	-0.09 (-0.88, 0.70)	0.826

SUMMARY

- Adverse childhood experiences are common
 - Females are more likely to fall into the 4+ category
- Even 2+ ACE status is associated with
 - Perimenopause onset of depression
 - Executive function difficulties
 - Alterations in brain activation during working memory task performance and
 - Response to estradiol
- Promising results with lisdexamfetamine
 - Whether this is the case for other stimulants is not known

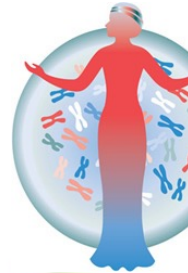


NEXT STEPS

- Screening for ACEs in primary care
 - Develop programs/interventions to identify high risk women prior to perimenopause and before surgical menopause
- Develop or adapt interventions aimed at reducing
 - Health problems (metabolic & immune)
 - Depression and anxiety
 - Sleep disturbances
 - Executive function difficulties
- Pharmacotherapies targeting prefrontal cortex function



And our Funding Sources!



National Institutes of Health
Office of Research on Women's Health

NIMH
National Institute
of Mental Health



**National Institute
on Aging**



An illustration of a diverse group of seven women from the chest up, arranged in a cluster. They have various hair colors (black, brown, blonde, grey) and styles (straight, wavy, curly, short, long). They are wearing different colored tops (teal, blue, orange, green, brown). The background is a solid dark purple. The text "QUESTIONS? THOUGHTS?" is overlaid in the center in a white, bold, sans-serif font. A thin white vertical line is positioned to the right of the text.

QUESTIONS? THOUGHTS?