The National Academies of Science, Engineering and Medicine

➢ The Forum on Neuroscience and Nervous System Disorders

➢ The Forum on Mental Health and Substance Use Disorders

➢ The Staff:

Sheena Posey Norris, Eva Childers, Kimberly Ogun, Ashley Pitt, and Shay Shuaib

➢ The Planning Committee

➢ The Speakers

➢ The Participants

FIVE OBJECTIVES

➢ Review scientific evidence on the **global rise of stress**, disparities among populations, and the relationship between stress and development of systemic disorders (e.g., psychiatric, neurological, metabolic, cardiovascular, autoimmune).

➢ Examine recent discoveries illuminating the **neurobiological mechanisms of stress susceptibility, distinct mechanisms of resilience**, **and individual differences** in responses to stress and building resilience.

➢ Consider the role of **childhood neurodevelopment and neuroplasticity across the lifespan** in building early-life and lifelong resilience (as opposed to stress susceptibility) and discuss effective approaches for optimizing resilience during critical and sensitive periods of neurodevelopment.

➢ Explore how these findings could inform **public health programs and education** to promote resilience to stress.

➢ Discuss **research gaps and opportunities** for studying resilience across research, clinical, and public settings.

DAY 1

Welcome & Introductory Remarks

Workshop Overview

Keynote Presentation: The Science of Stress and Resilience

A Lived Experience: Perspective on Resilience

Session 1:   Neurobiological Mechanisms of Stress Susceptibility and Resilience

Concluding Remarks

Some Housekeeping

- Throughout the day, there will be opportunities for **attendees to ask questions**, and we encourage you to do so using the microphones located throughout the meeting room, and for those **online through the Q&A box** located below the livestream.

  Please introduce yourself first and keep your questions concise.

- The **recording and presentations** from this workshop will be available for viewing on the National Academies website in a week of two.

- A **"proceedings" document** of the presentations and discussions from the workshop will be prepared to reflect what transpired at the workshop. It will be published by the National Academies Press and will be publicly available.
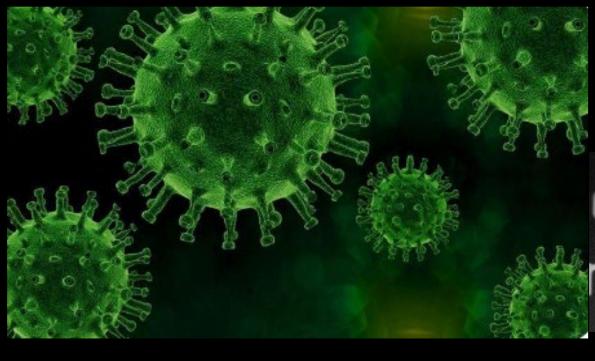
  All views presented in the report will be those of workshop participants; the report will not contain consensus recommendations.

The Science of Stress & Resilience

Huda Akil, PhD
Eric Nestler, MD, PhD
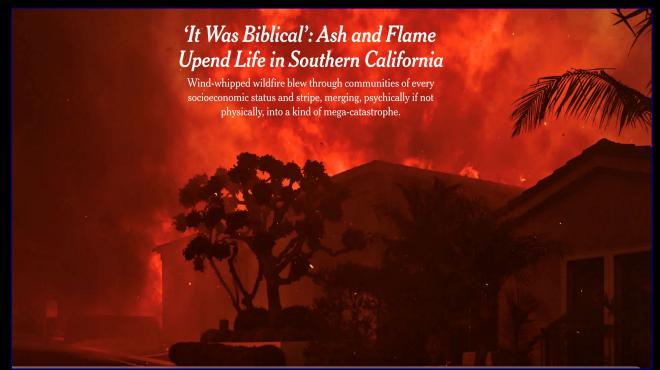
NO CONFLICTS OF INTEREST

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rknes

‘It Was Biblical’: Ash and Flame
Upend Life in Southern California

Wind-whipped wildfire blew through communities of every
socioeconomic status and stripe, merging, psychically if not
physically, into a kind of mega-catastrophe.

HOMELESS
PLEASE
HELP

The Second Pandemic

Globally
***25%** Increase in Depression & Anxiety Disorders During the **First Year** of the Pandemic Ongoing*

When the Darkness comes.

Chronic Disease, Chronic Pain And Long Covid

*The **Opioid Crisis** and Other Substance Use Disorders*

Major Upheavals around the Globe :
Wars, Political Instability, Economic Challenges, Refugees and Migrations

The Mental Health Crisis

Some Evidence

- Prior to the Covid-19 Pandemic, Major Depression and Anxiety disorders were already among the leading health burdens globally.

- Within the first year of the pandemic, **~25% Increase** in the incidence of these disorders: **53 million** cases of MDD and **76 million** cases of anxiety disorders (1).

- The magnitude of increase in affective disorders in any given country was highly correlated with the magnitude of the impact of the Covid-10 pandemic on that country (1).

- **Younger people and females** in particular have been more profoundly impacted by the pandemic than other groups (1).

- Individuals in certain professions, such as **health care workers** were highly affected (2).

- Individuals confronting **economic and social challenges or experiencing discrimination**, were especially hard hit (3).

1. *COVID-19 Mental Disorders Collaborators. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic.* **Lancet. 2021**.

2. *Zhu H, Yang X, Xie S, Zhou J. Prevalence of burnout and mental health problems among medical staff during the COVID-19 pandemic: a systematic review and meta-analysis.* **BMJ Open. 2023.**

3. *Eboigbe LI, Simon CB, Wang YS, Tyrell FA. The compounded effect of the dual pandemic on ethnic-racial minority adolescents' mental health and psychosocial well-being.* **Curr Opin Psychol. 2023.**

Rising Trends: Lifetime and Current Depression Rates

Has a doctor or nurse ever told you that you have depression?

Do you currently have or are you currently being treated for depression?

— % Yes, lifetime depression   — % Yes, current depression

GALLUP

2024 KEY FINDINGS

23% OF ADULTS EXPERIENCED A MENTAL ILLNESS IN THE PAST YEAR. EQUIVALENT TO NEARLY 60 MILLION AMERICANS.

5% OF ADULTS **&** **13%** OF YOUTH

REPORTED EXPERIENCING SERIOUS THOUGHTS OF SUICIDE.

2022 HAD THE HIGHEST NUMBER OF DEATHS BY SUICIDE EVER RECORDED IN THE U.S.

1 IN 5 YOUTH HAD AT LEAST ONE MAJOR DEPRESSIVE EPISODE (MDE) IN THE PAST YEAR.

OVER 1/2 (NEARLY 3 MILLION YOUTH) DID NOT RECEIVE TREATMENT.

OF THOSE WHO DID RECEIVE TREATMENT, ONLY **65%** SAID IT HELPED THEM.

18% OF ADULTS IN THE U.S. HAD A SUBSTANCE USE DISORDER IN THE PAST YEAR.

77% OF THEM DID NOT RECEIVE TREATMENT.
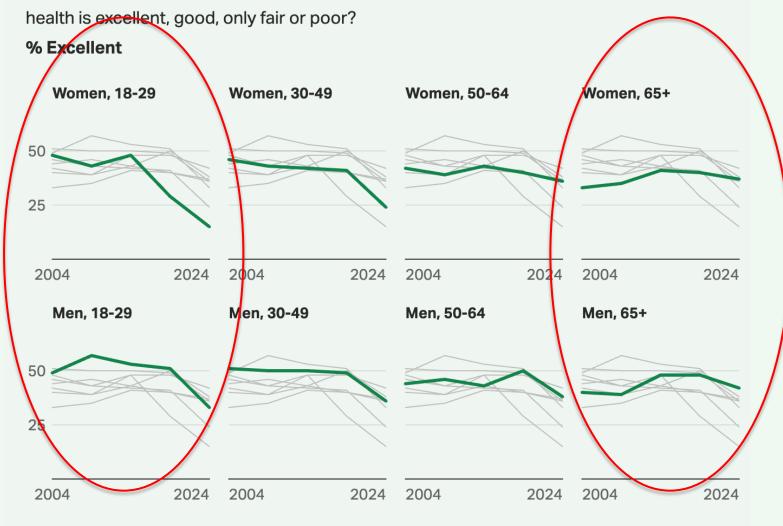
1 IN 4 ADULTS WITH FREQUENT MENTAL DISTRESS COULD NOT SEE A DOCTOR DUE TO COST, A 2% INCREASE OVER THE LAST REPORT.

Mental Health America
2024 Report
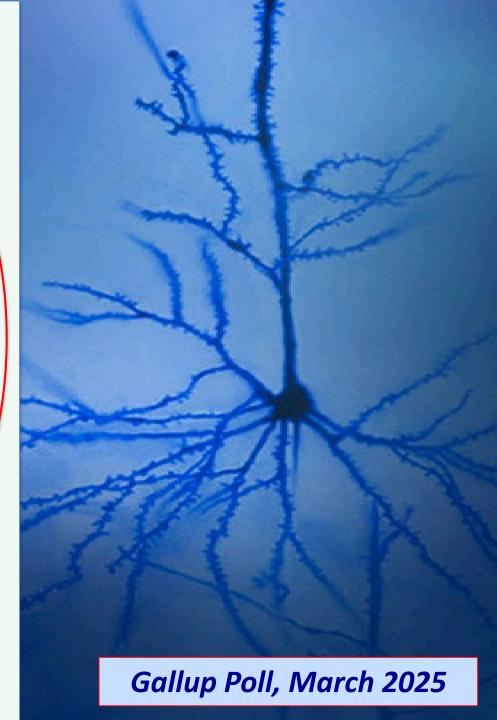
Mental Health Ratings by Gender/Age

How would you describe your own mental health at this time? Would you say your mental health is excellent, good, only fair or poor?

% Excellent

Gray lines represent all other age and gender groups, shown to facilitate direct comparison

Date ranges are 2001-2004, 2005-2009, 2010-2014, 2015-2019, 2020-2024.
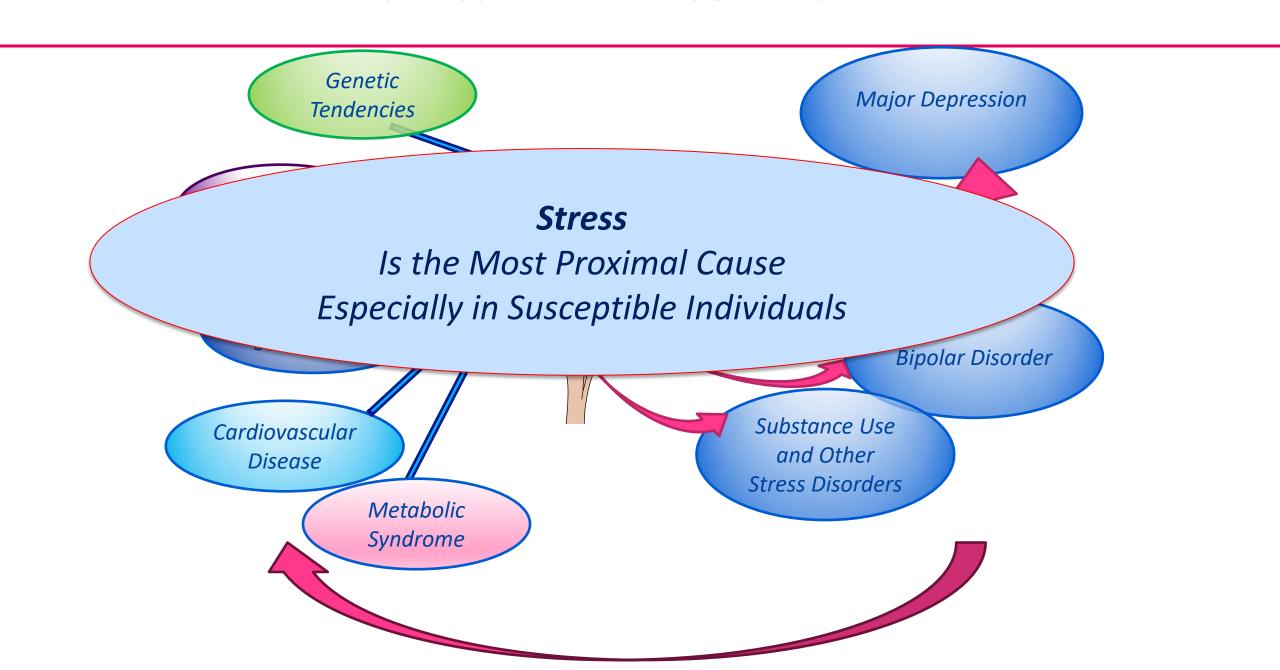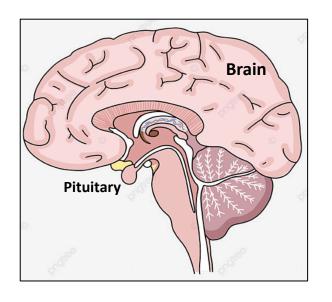
Get the data • Download image

GALLUP

Gallup Poll, March 2025
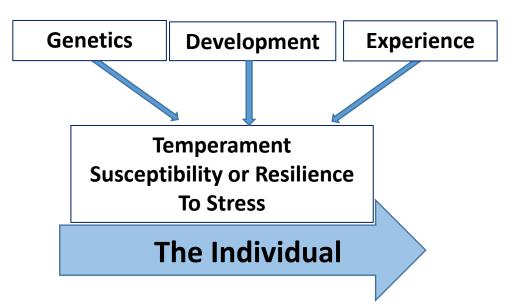
STRESS- RELATED DISORDERS
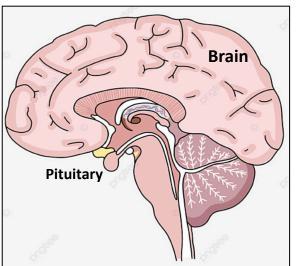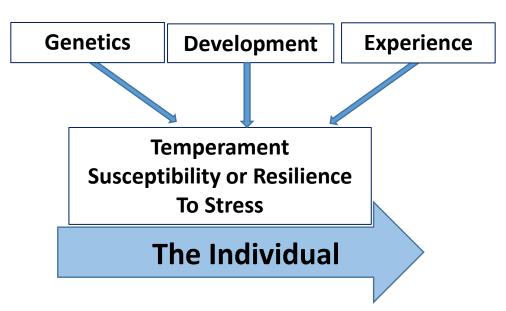
The Individual
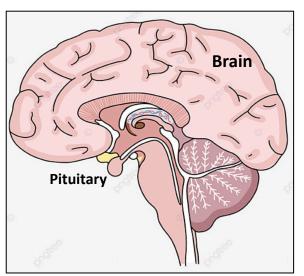
The Stressors

Brain

Pituitary

Genetics   Development   Experience

Temperament
Susceptibility or Resilience
To Stress

The Individual

Brain

Pituitary

The Stressors

Genetics **Development** **Experience**

Temperament
Susceptibility or Resilience
To Stress

The Individual

Brain

Pituitary

Threat and Uncertainty:
Acute or Chronic
Trauma and Life Events:
Divorce, Abuse, Death
Social Context:
Aggression, Poverty, Isolation
Physiological Stress:
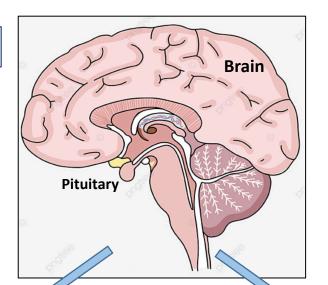Metabolic,Inflammation
Cardiovascular Disease

The Stressors

Genetics **Development** **Experience**

**Temperament
Susceptibility or Resilience
To Stress**

The Individual

Brain

Pituitary

Threat and Uncertainty:
Acute or Chronic
Trauma and Life Events:
Divorce, Abuse, Death
Social Context:
Aggression, Poverty, Isolation
Physiological Stress:
Metabolic,Inflammation
Cardiovascular Disease

The Stressors

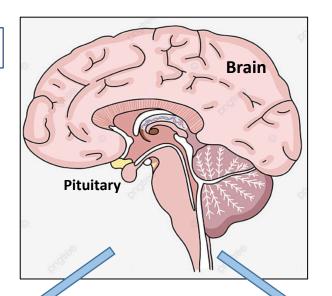**Physiological Stress Response**
"Good Stress" or "Bad Stress"

Behavioral Coping:
Adaptive or Maladaptive

Genetics Development Experience

Temperament
Susceptibility or Resilience
To Stress

The Individual

Brain

Pituitary

Threat and Uncertainty:
Acute or Chronic
Trauma and Life Events:
Divorce, Abuse, Death
Social Context:
Aggression, Poverty, Isolation
Physiological Stress:
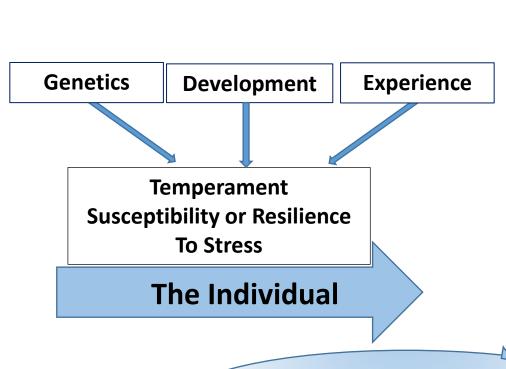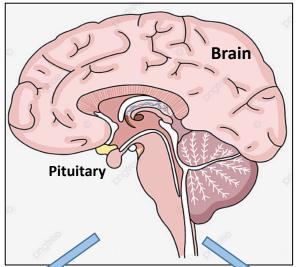Metabolic, Inflammation
Cardiovascular Disease

The Stressors

Physiological Stress Response
"Good Stress" or "Bad Stress"

Behavioral Coping:
Adaptive or Maladaptive
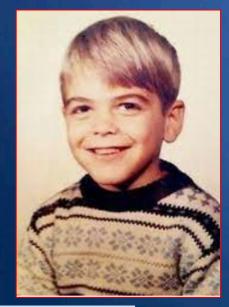
Experience-Induced
Neuroplasticity

Genetics **Development** **Experience**

Temperament
Susceptibility or Resilience
To Stress

The Individual

Brain

Pituitary

Threat and Uncertainty:
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The Stressors

Physiological Stress Response
"Good Stress" or "Bad Stress"

Behavioral Coping:
Adaptive or Maladaptive

Experience-Induced
Neuroplasticity

Positive:
Enhanced Resilience
to Future Stressors

Negative:
Enhanced Susceptibility to
Stress Disorders

A Multi-Scale Approach to Stress, Resilience and Mental Health
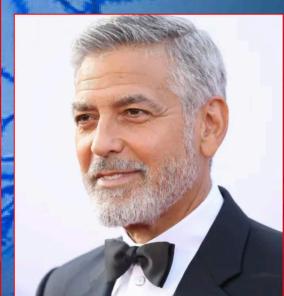
A Life Span Perspective
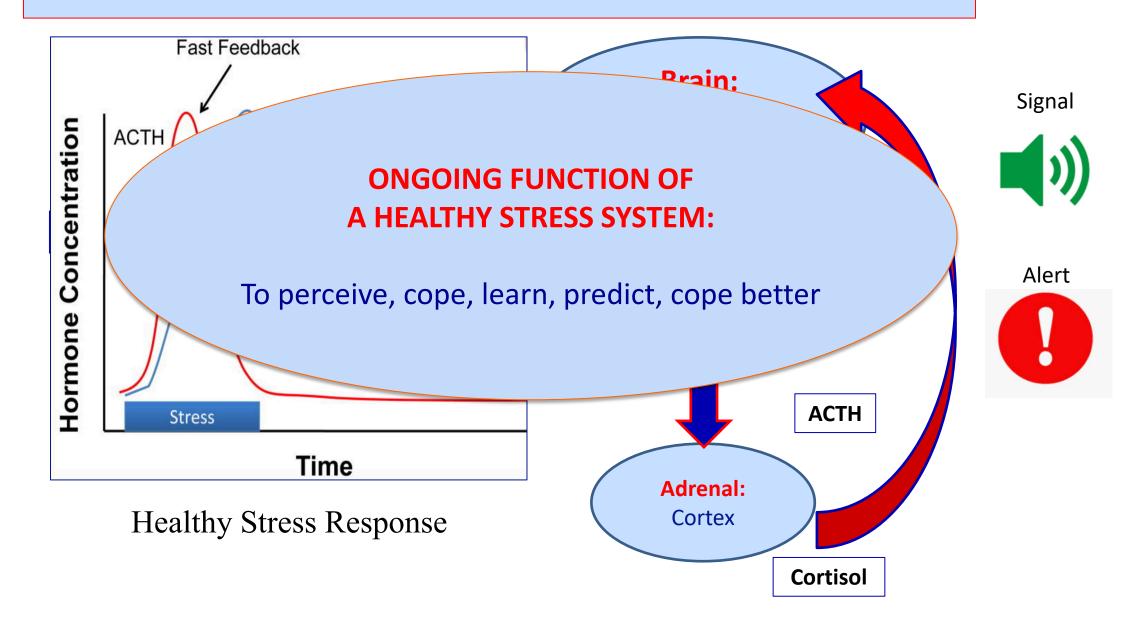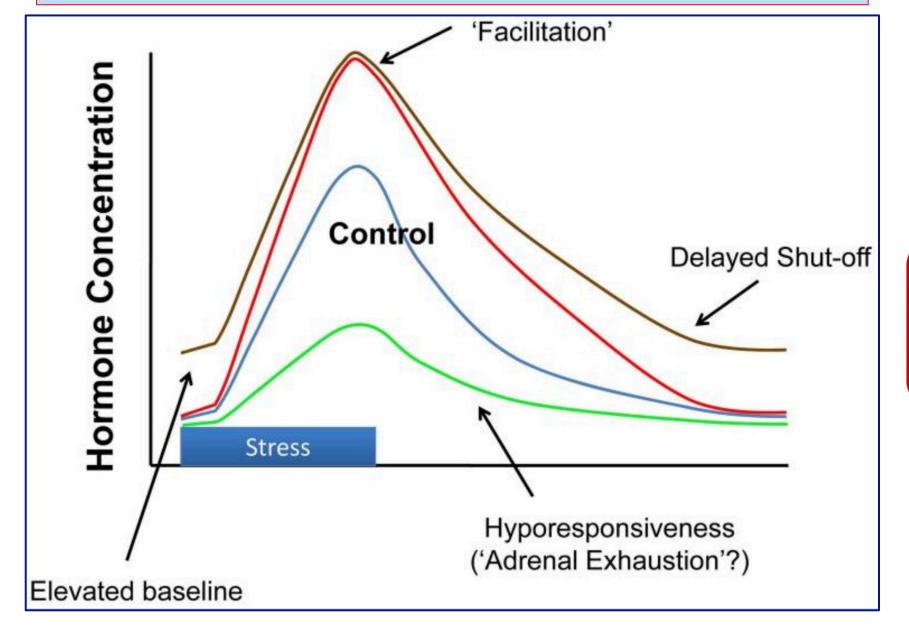
Critical Period

Critical Period

Neuroplasticity + or -

TWO KEY CONCEPTS

- *"Stress Fitness"*
- *Resilience is not the Absence of Vulnerability*

A Healthy Stress Response

Healthy Stress Response

ONGOING FUNCTION OF A HEALTHY STRESS SYSTEM:

To perceive, cope, learn, predict, cope better

Fast Feedback

ACTH

Hormone Concentration

Stress

Time

Brain:

Signal

Alert

ACTH

Adrenal: Cortex

Cortisol

Chronic Stress Disrupts the Biological Stress Response
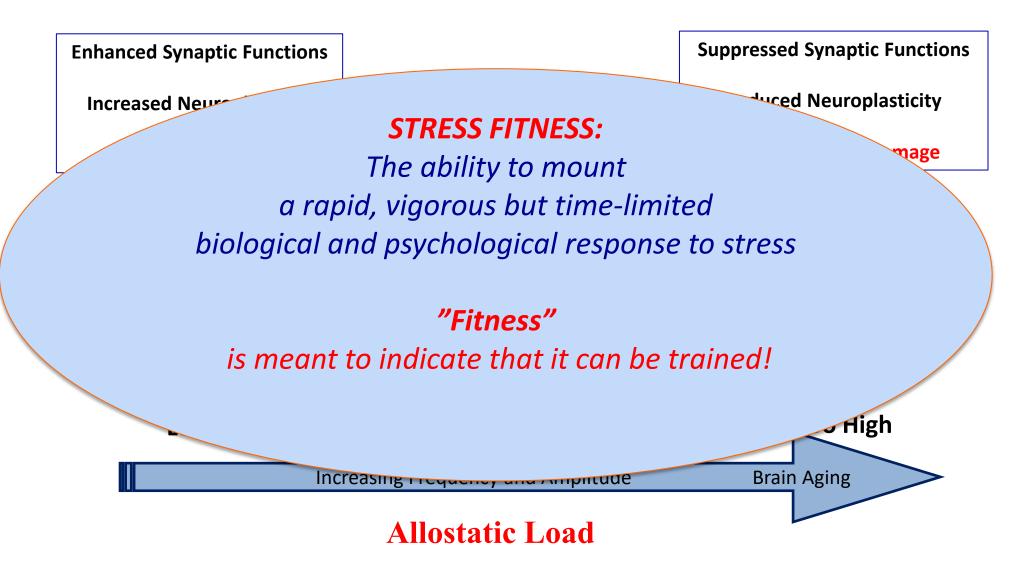
Biphasic Effects of Stress Steroid Hormones
Impact on Synaptic Function and Neuroplasticity

Enhanced Synaptic Functions

Increased Neur...

Suppressed Synaptic Functions

...duced Neuroplasticity

...mage

STRESS FITNESS:
The ability to mount
a rapid, vigorous but time-limited
biological and psychological response to stress

"Fitness"
is meant to indicate that it can be trained!

High

Increasing Frequency and Amplitude

Brain Aging

Allostatic Load

McEwen & Akil, J. Neuroscience, 2020

What is Resilience?

Not the Absence of Vulnerability.
A Positive Countervailing Force.
Especially Important in Vulnerable Individuals:
Propose the Concept of *Biological Stress Fitness*

Kintsugi
金継ぎ
Treating Breakage and Repair as Something to Highlight Rather than Hide

**SEVERAL GROWTH FACTORS
ARE CRITICAL FOR RESILIENCE:**

ROLE OF NEUROPLASTICITY

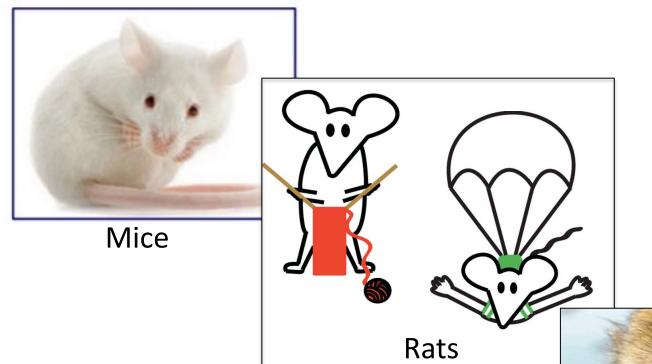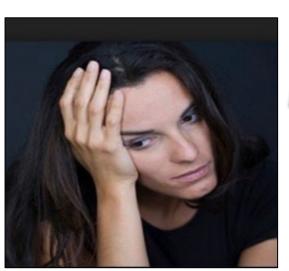*Natural* ... *ety and*
Anti-Depres... ... *...sant Factor*

Evans et al , PNAS, 2004
Turner et al , Biol Psych, 2006
Turner et al , Neuron, 2012
Aurbach et al , PNAS, 2015

The Buffering Power of Positive Personal Experiences and Social Interactions Throughout Life

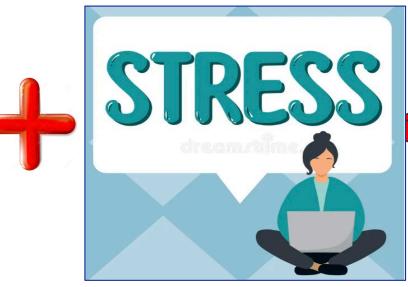*How Do we Study the Biology of Resilience?*

Mice

Rats

Monkeys

Human Adults

Children & Teens
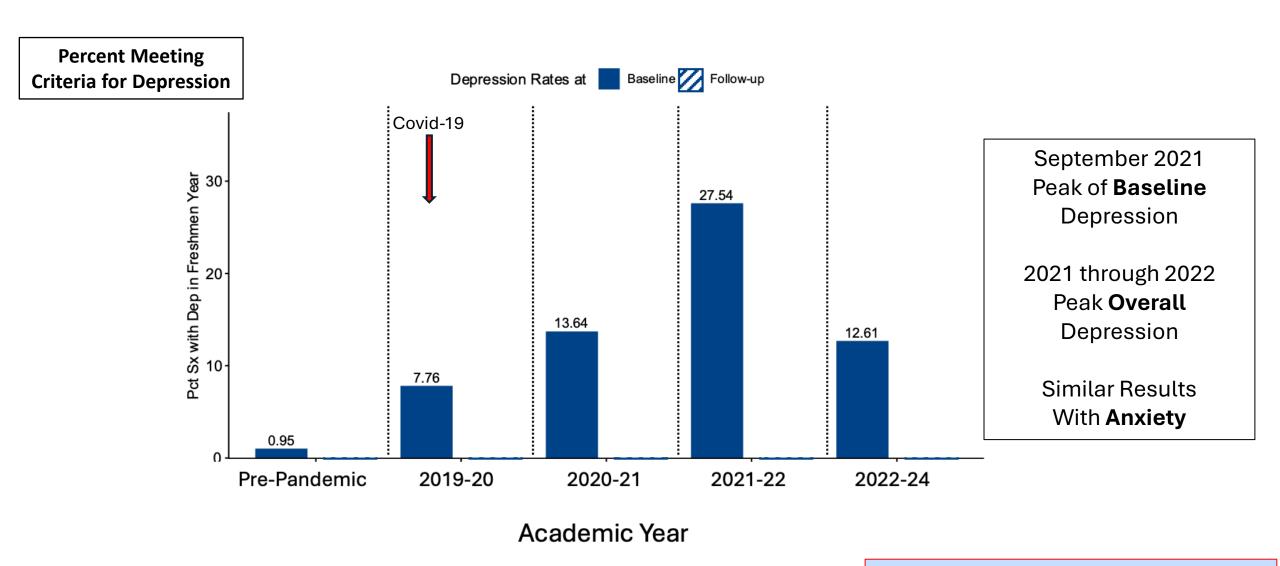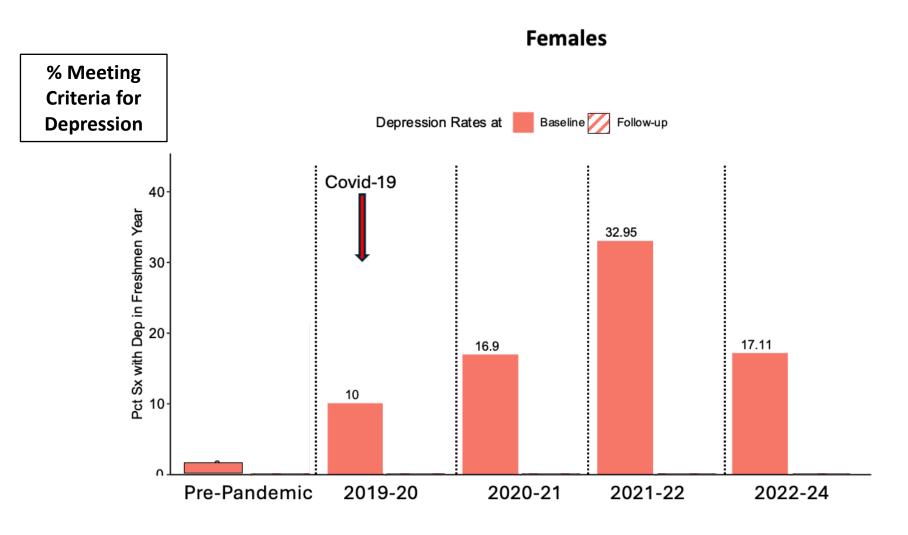
Michigan Freshman Project:
Larger Impact on Females

Females

% Meeting Criteria for Depression

- ➢ **42%** of Females experienced depression in 2020-2021

- ➢ **33%** of Females from the next cohort in the fall of 2021 were depressed at baseline

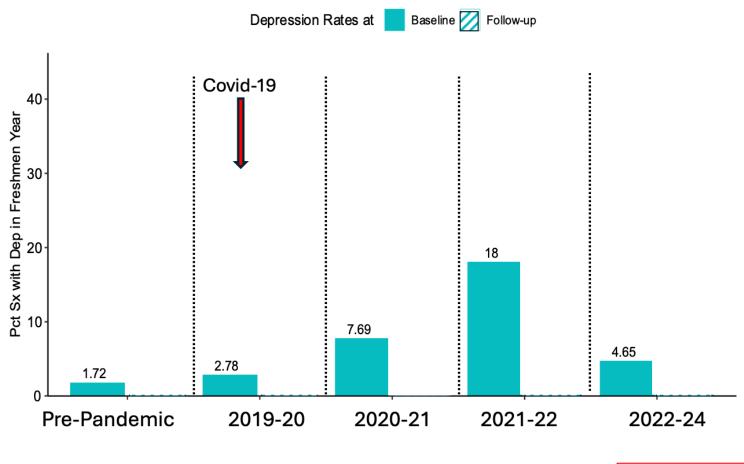- ➢ Depression in females occurs earlier, is more severe and more chronic- Continues into Junior Year.

Freshman Study Team- In Preparation

Michigan Freshman Project:
Lesser Impact on Males

% Meeting Criteria for Depression

Males

Depression Rates at ▮ Baseline ▨ Follow-up

Covid-19

Pct Sx with Dep in Freshmen Year

Pre-Pandemic	2019-20	2020-21	2021-22	2022-24
1.72	2.78	7.69	18	4.65

Academic Year

Freshman Study Team- In Preparation

Can We Predict Risk for Depression?

Used Machine Learning to Identify an

"Affect Score"

*Which is **Highly Predictive***

Can Genetics Help Us Predict?
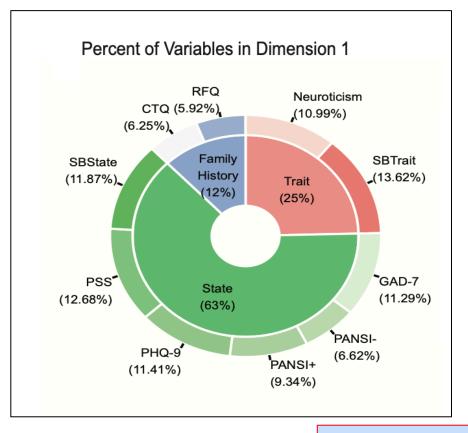
Yes and No

Polygenic Risk Score for Depression

➢ Was predictive <u>before</u> the pandemic
➢ Stopped being predictive during the pandemic
➢ Is now trending back towards prediction

Conclude: It only works under certain types of stress

Percent of Variables in Dimension 1

Turner et al, PNAS 2023

Affect Score Predicts Risk for Depression

Original Cohort

Replication Cohort

Correlation r = 0.67
p < 2.2e−16

Odds Ratio = 10.77
p < 1e−17

Correlation r = 0.71
p < 2.2e−16

Odds Ratio = 11.07
p < 1e−17

Follow−up PHQ−9

Affect Score

Original Cohort

Replication: 2022-2024

> **Baseline Affect Score** (measured in September) predicts depression during rest of the freshman year.
> Highly significant on any given year
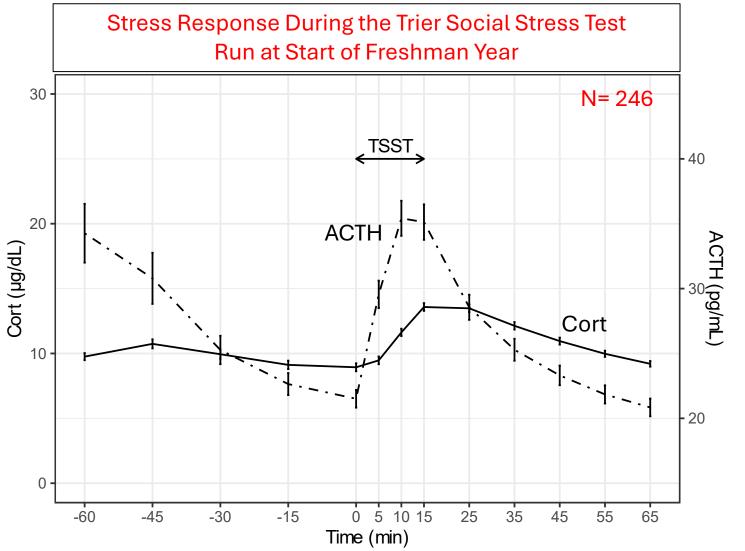> Still highly significant if we eliminate all subjects with a history of depression

Freshman Study Team- In Preparation

What Protects Against Risk for Depression?

Regardless of Genetic Susceptibility,

"Perceived Social Support" was Most Clearly Associated Protective Factor Against Depression

Its Importance Grew During the Pandemic

Biological "Stress Fitness"
And Relationship to Future Vulnerability or Resilience to **Stress**

Stress Response During the Trier Social Stress Test Run at Start of Freshman Year
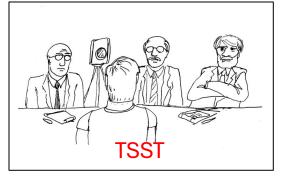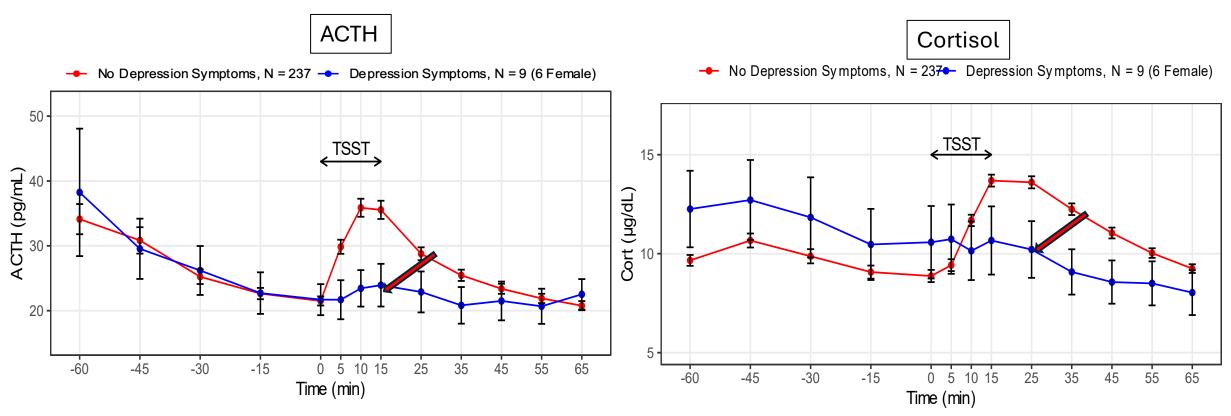

N= 246

TRIER SOCIAL STRESS TEST- TSST

➤ Across a group of 246 Subjects, we measure a healthy stress response to social stress (the TSST), with a peak of ACTH followed by Cortisol Increase.

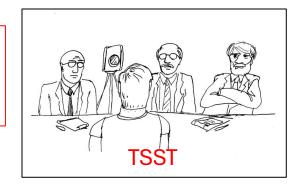➤ ACTH but not Cortisol show a stress anticipation effect.

Freshman Study Team- In Preparation
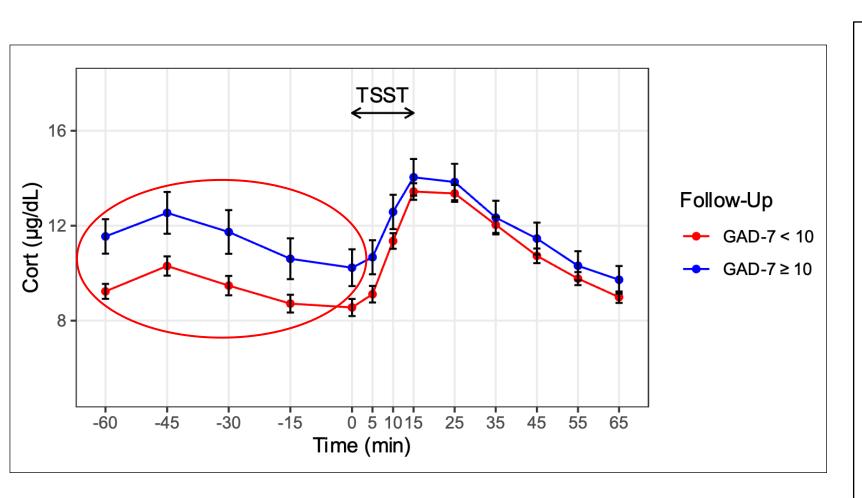
A Higher Endocrine Response During the Anticipatory Period Of the TSST **Predicts** Future Anxiety during Freshman Year

TSST

Total N: 212
Female: 113 (24 Follow-up Anxiety)
Male: 99 (12 Follow-up Anxiety)

➢ We excluded all subjects who were anxious at baseline

➢ We asked: In this normal subjects, does TSST predict future anxiety?

➢ A high anticipatory response to social stress was strongly predictive of future anxiety

➢ In a parallel analysis, high anticipatory response to social stress was *moderately* predictive of future depression

Freshman Study Team- In Preparation

Can We Decrease the Risk for Depression & Anxiety with Online CBT?

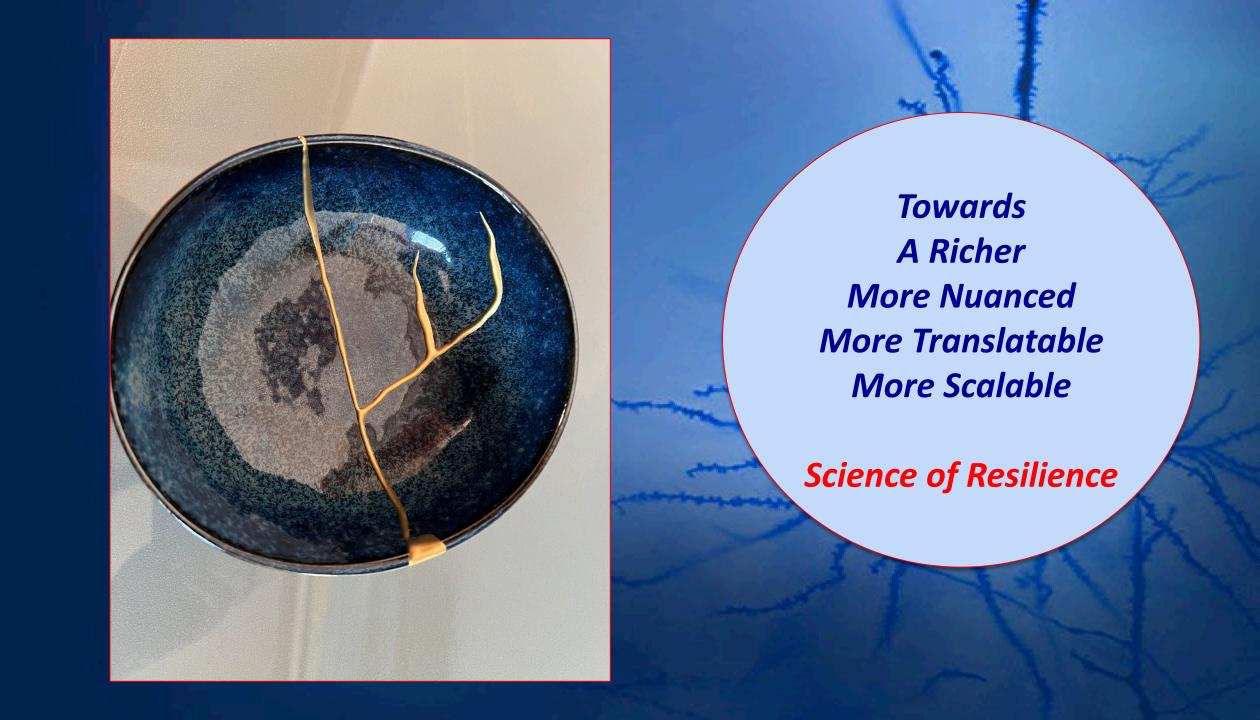*A Pilot Study (N=70: 40 CBT & 30 Control)*

The MAYA App

> In collaboration with Faith Gunning and Francis Lee at Weill Cornell, we are using a **well validated CBT App**: The MAYA App.

> **Pilot Study** is encouraging

> *In FEMALES, MAYA App decreased the symptoms of depression and anxiety throughout the Freshman year and into the start of the Sophomore year.*

> In **MALES:** No Effect (N is small due to lower partipation rates).

> Currently running a study with **N=~150** to determine efficacy of MAYA App and relation to Affect Score.

Multiple Types of Resilience:
Genetic & Non-Genetic

Context Matters: Pre- and Post- Pandemic

Social Support Matters

It is Not Destiny:
It is Possible to Predict & Prevent

Towards
A Richer
More Nuanced
More Translatable
More Scalable

Science of Resilience

Keynote & Introductory Lectures

Keynote Presentation: ***State of Science on Stress and Resilience***	Huda Akil, University of Michigan
A Lived Experience Perspective on Resilience	Jon Nelson, Pulverize the Stigma