AGS-NIA Bench to Bedside Conference

Stress Tests and Biomarkers of Resilience

March 4-5, 2024

Hyatt Regency, Bethesda
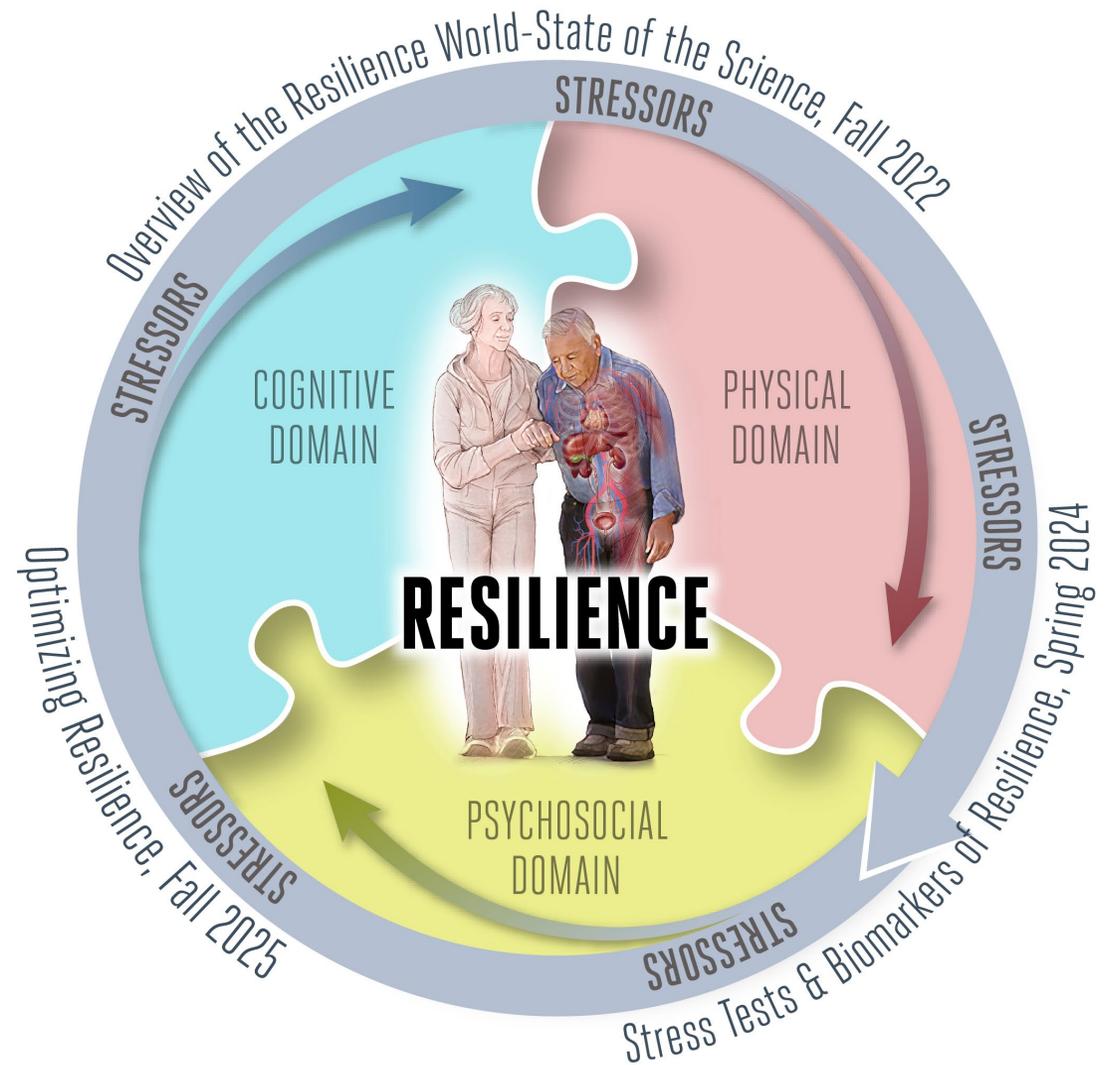
Who are We? Please Stand Up if you are:

- A Conference Planning Committee member

- An AGS representative

- A NIH representative

- A Rising Star Attendee

Who are you?

https://www.polleverywhere.com/free_text_polls/RpWzQg9WwY3bQ4w9Nhau8

- Your specialty/discipline
- Where you live
- A favorite pastime
- Context/condition in which you study resilience

Conference Topics

First U13 Workshop
Branches = Resilient outcomes in different domains (cognitive, physical, psychological)
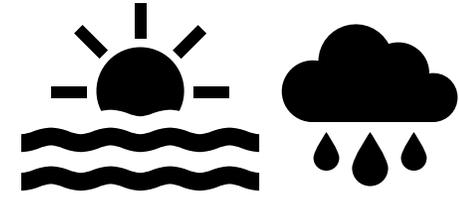
Acute Stressors

Final U13 Workshop
Resilience Promoting Interventions
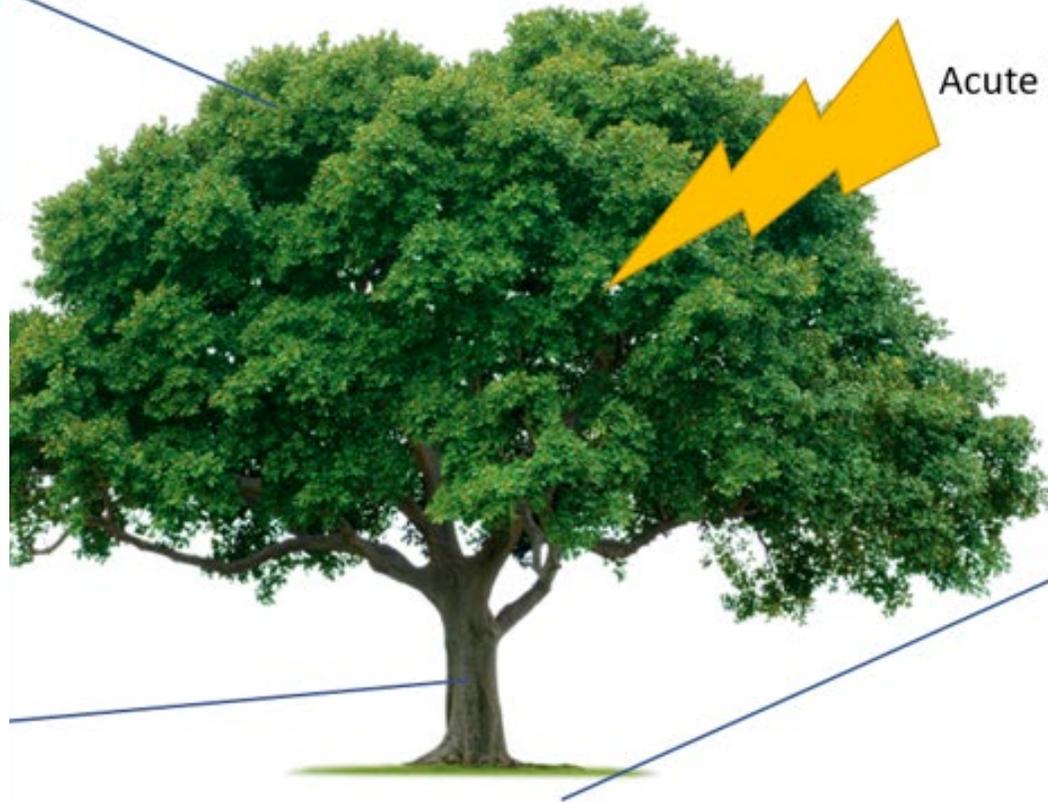
Conference Flow: Monday

- Introduction and Orientation

- **Plenary:** Dr. James Herman

- **"State of Science" Brief Talks + Moderated Discussion**
  - Topic 1: **Resilience Biology**
  - Topic 2: **Mediators and Moderators of Resilience**

    (Networking lunch)
  - Topic 3: **Stress Tests and Biomarkers**

- **Small Group Sessions**

- Dinner reception
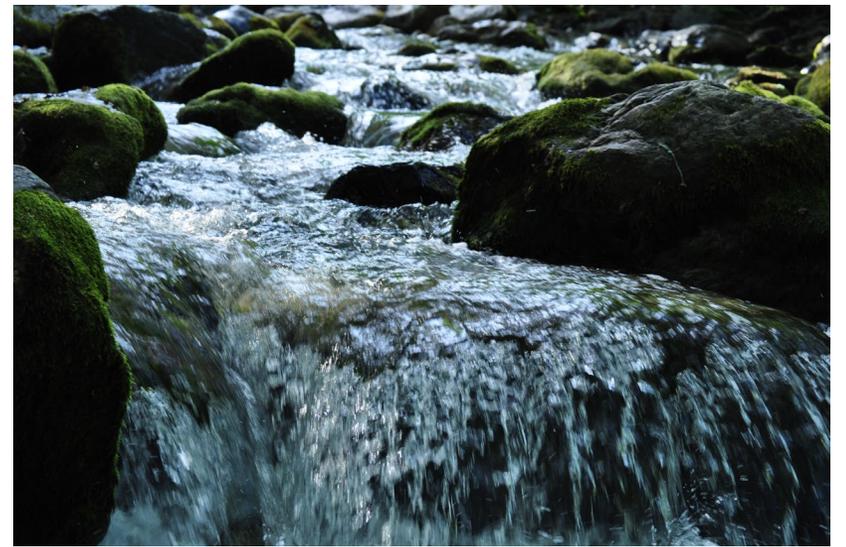
Conference Flow: Tuesday

- Mentoring Breakfast

- **Small Group Report-outs** and Discussion
  - **Research priorities, agenda setting**

- Wrap up and evaluation

- Lunch with NIA representatives

- **Rising Star Session**
  - Consultancy Tables for challenges in Resilience Research
  - Panel Discussion: Writing a compelling Resilience Grant
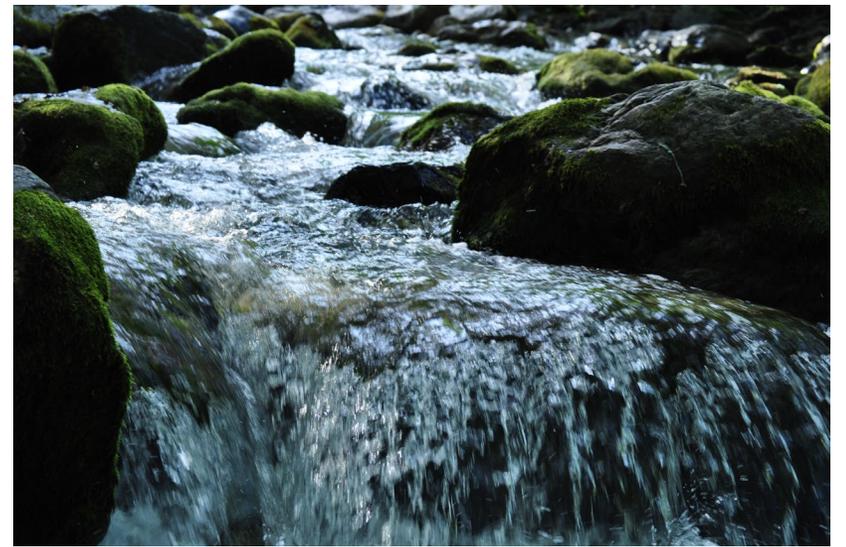
Making this conference magical

- Share your perspective
- Be curious and open
- Respect others' ideas
- Be mindful of time
- Ask questions
- Meet new collaborators

Conference 1 Summary: Dr. Abadir
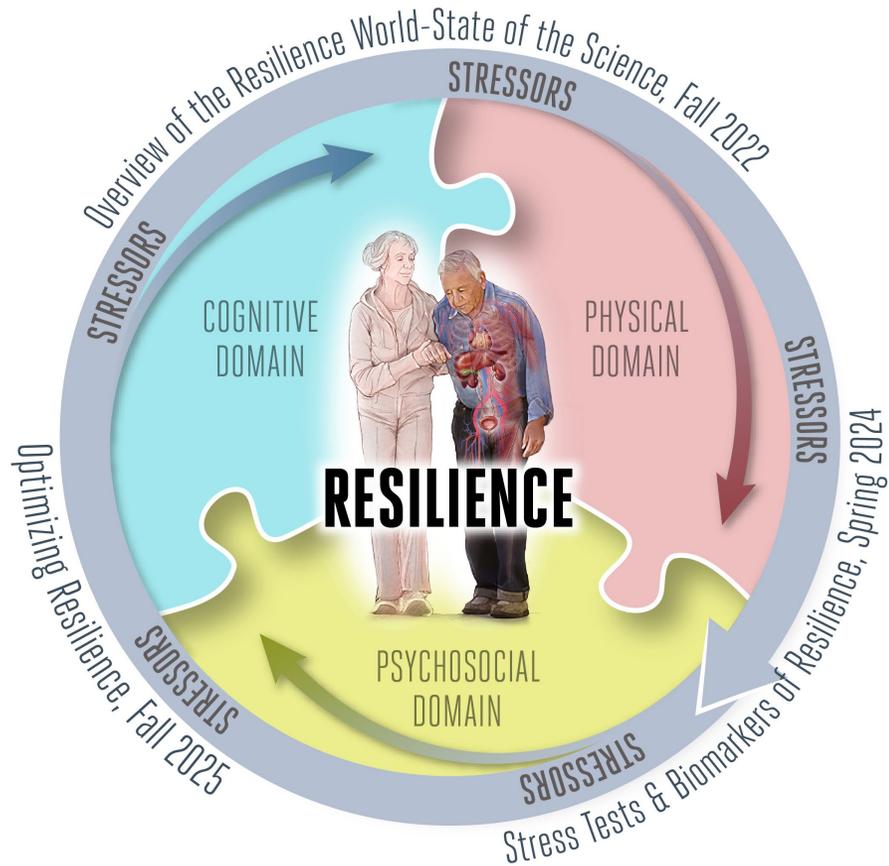
Sir William Osler

- "It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has."

Understanding Resilience in Older Adults: An Overview of the Resilience World

Peter M. Abadir, M.D.

Associate Professor of Medicine

Nathan Shock Scholar in Aging

Division of Geriatrics Medicine and Gerontology
Johns Hopkins University

Questions being asked

1. What are the common core elements that define "resilience" across physical, cognitive, and psychosocial domains in older adults?

2. Is resilience changeable? Does it vary with day-to-day exposures and stressors?

3. How does the exposome—encompassing all lifetime exposures—influence resilience in the context of systemic inequities and social determinants of health?

4. What are the high-priority research gaps in understanding resilience in older adults, and what types of studies are recommended to fill these gaps?

Why Does This Matter?

A clearer definition(s) could enhance our understanding of resilience and lead to more effective and equitable strategies to promote resilience in older adults.

"All our work, our whole life is a matter of semantics, because words are the tools with which we work, the material out of which laws are made, out of which the Constitution was written. Everything depends on our understanding of them."
Felix Frankfurter

Understanding Resilience in Older Adults

Resilience Domains: Interconnected and Interdependent
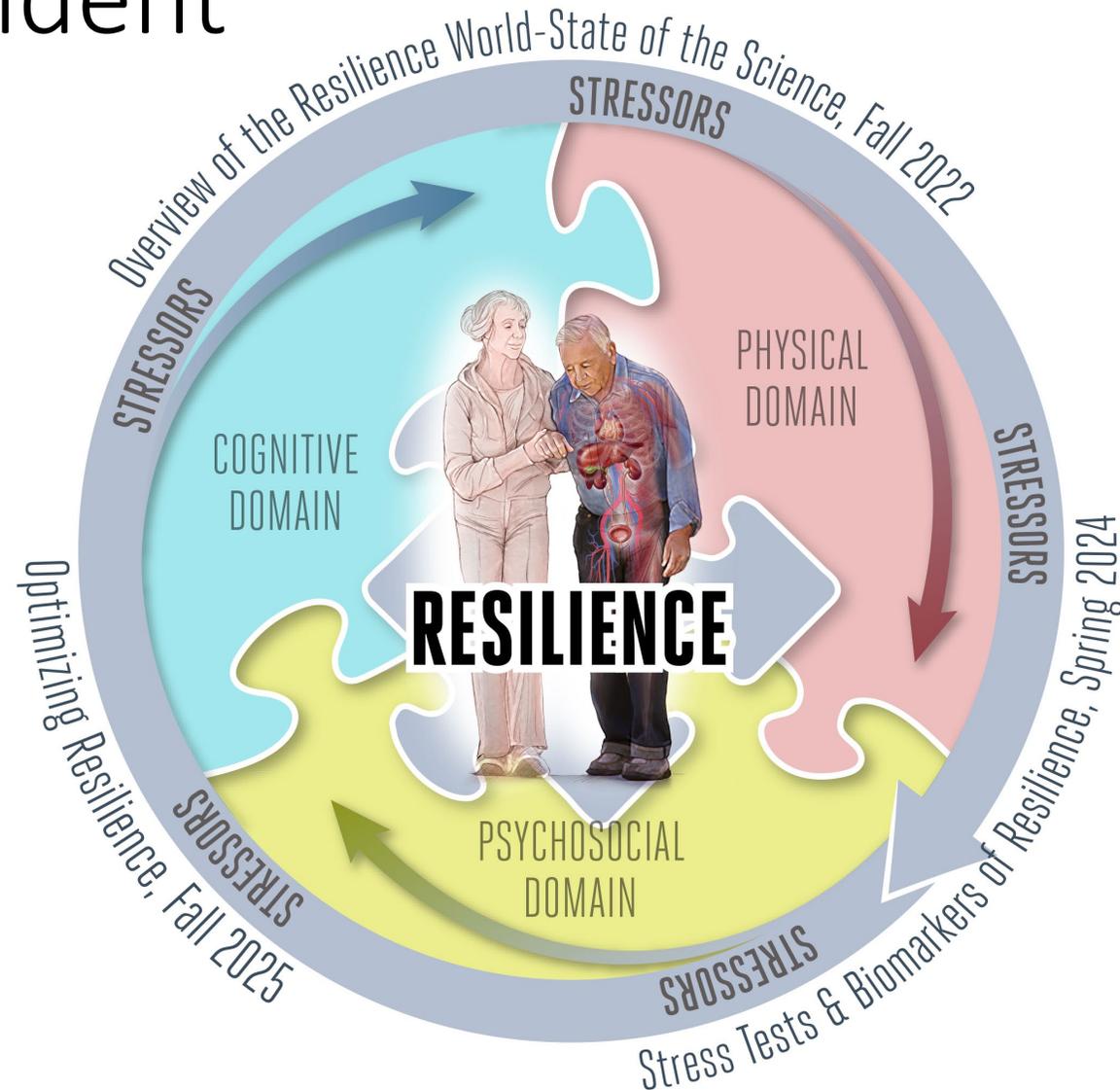
Key points to remember

Resilience, which relates to <u>one's ability to respond to stressors</u>, typically declines with age and the development of comorbid conditions in older organisms, but health-related disciplines have differed in their conceptualizations of resilience in older adults and its multicomponent dimensions in response to <u>physical, cognitive, and social stressors</u>.

Social support

Resilience reservoir

Wasted resources

Definition (Lifespan Psychology):

- "capacity of a dynamic system to adapt successfully to disturbances that threaten system function, viability, or development".

Suits multidisciplinary use.
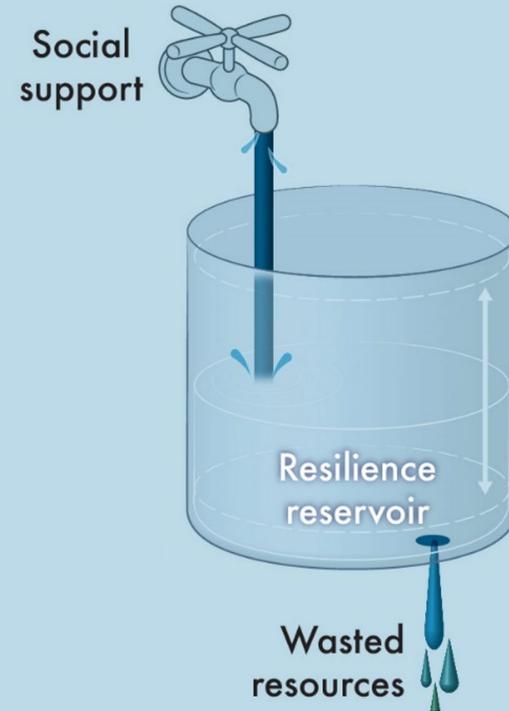
Factors Defining Psychosocial Resilience:

Challenges to the system:

- Acute (e.g., getting lab tests).
- Major events (e.g., loss of loved ones).
- Chronic (e.g., ongoing health conditions).

Outcomes:

- Recovery: Bouncing back from stressors.
- Sustainability: Absorbing disturbances with minimal effect.
- **Growth: Enhanced coping for future stressors**.

Often studied on frail older adults with low reserve capacity.

But Even non-frail older adults vary in resilience to health stressors.

Frailty vs. Resilience:

Frailty is influenced by the <u>resources available to a system</u>, whereas resilience is the extent to which this complex system <u>can recruit those resources</u> when challenged by a stressor.
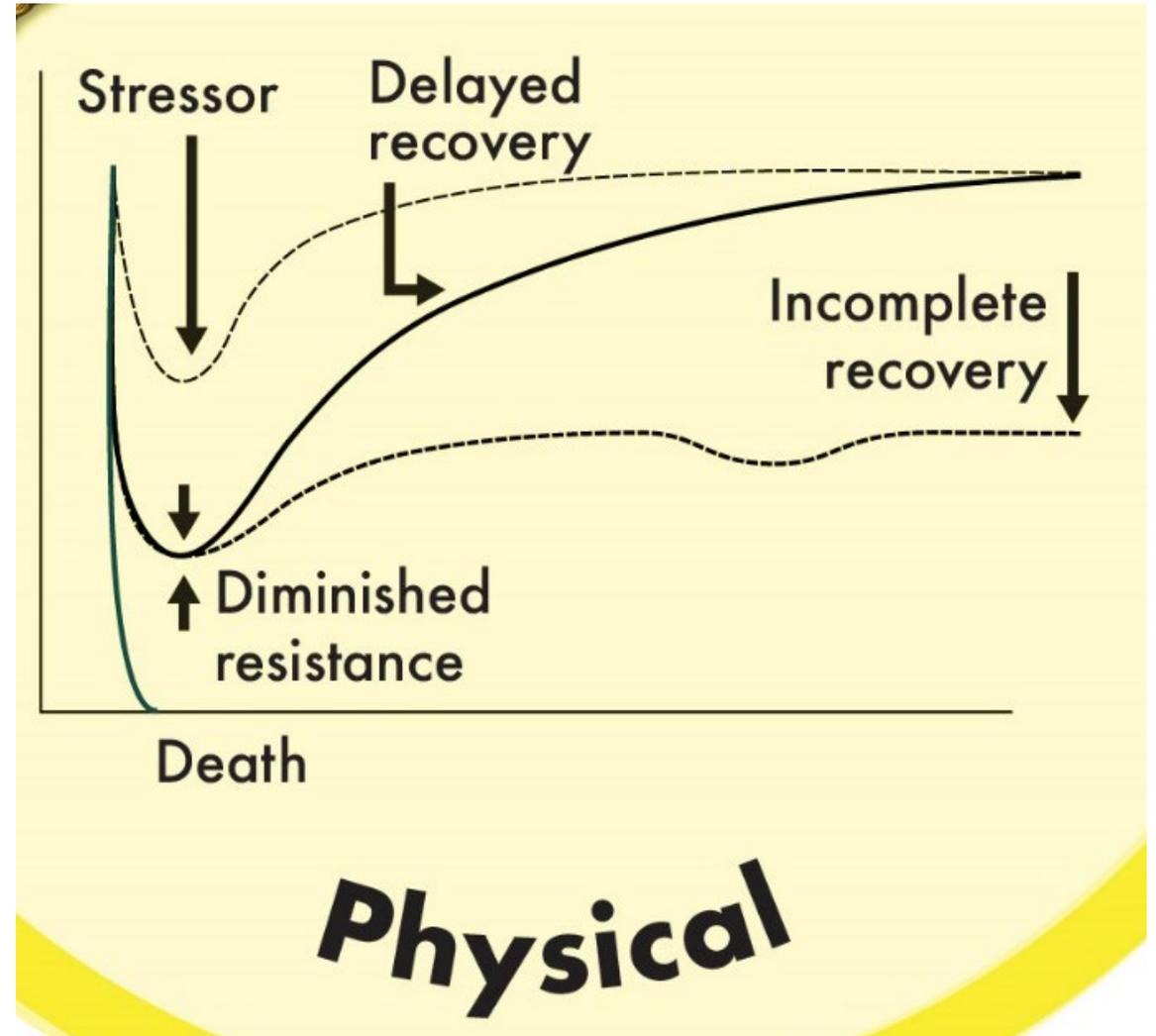
Cognitive Resilience

- **Cognitive Reserve**:
  - Property allowing superior cognitive performance despite brain aging or injuries.
  - Helps cope with:
    - Age-related brain changes.
    - Neuronal damage (e.g., Alzheimer's).
  - Factors boosting reserve:
    - Higher education.
    - Occupational attainment.
- **Brain Maintenance**:
  - Absence of changes in neural resources.
  - Preserves cognition in older age.
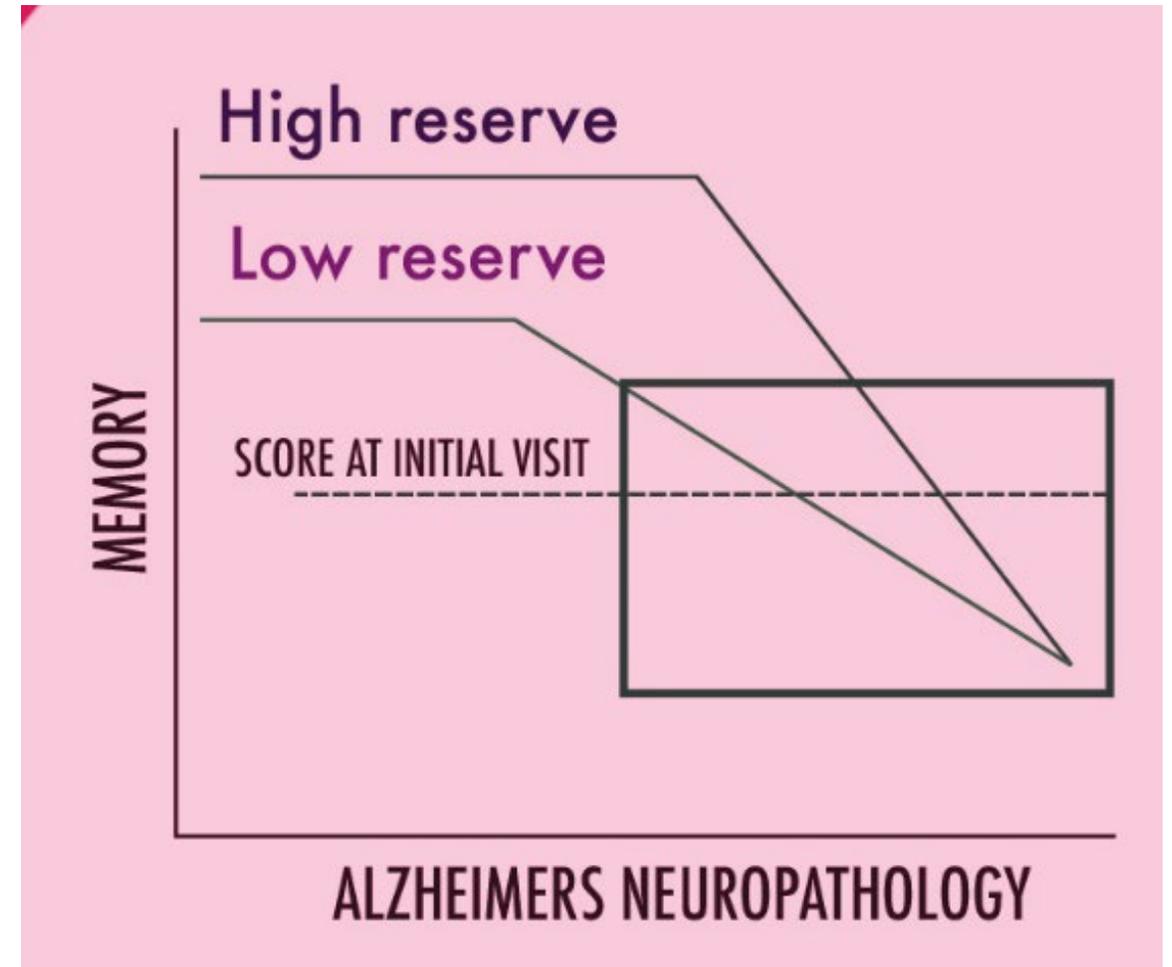
Toward a Holistic Concept of Resilience

- The "warp" and "woof" (terms used in weaving) of developmental dynamics
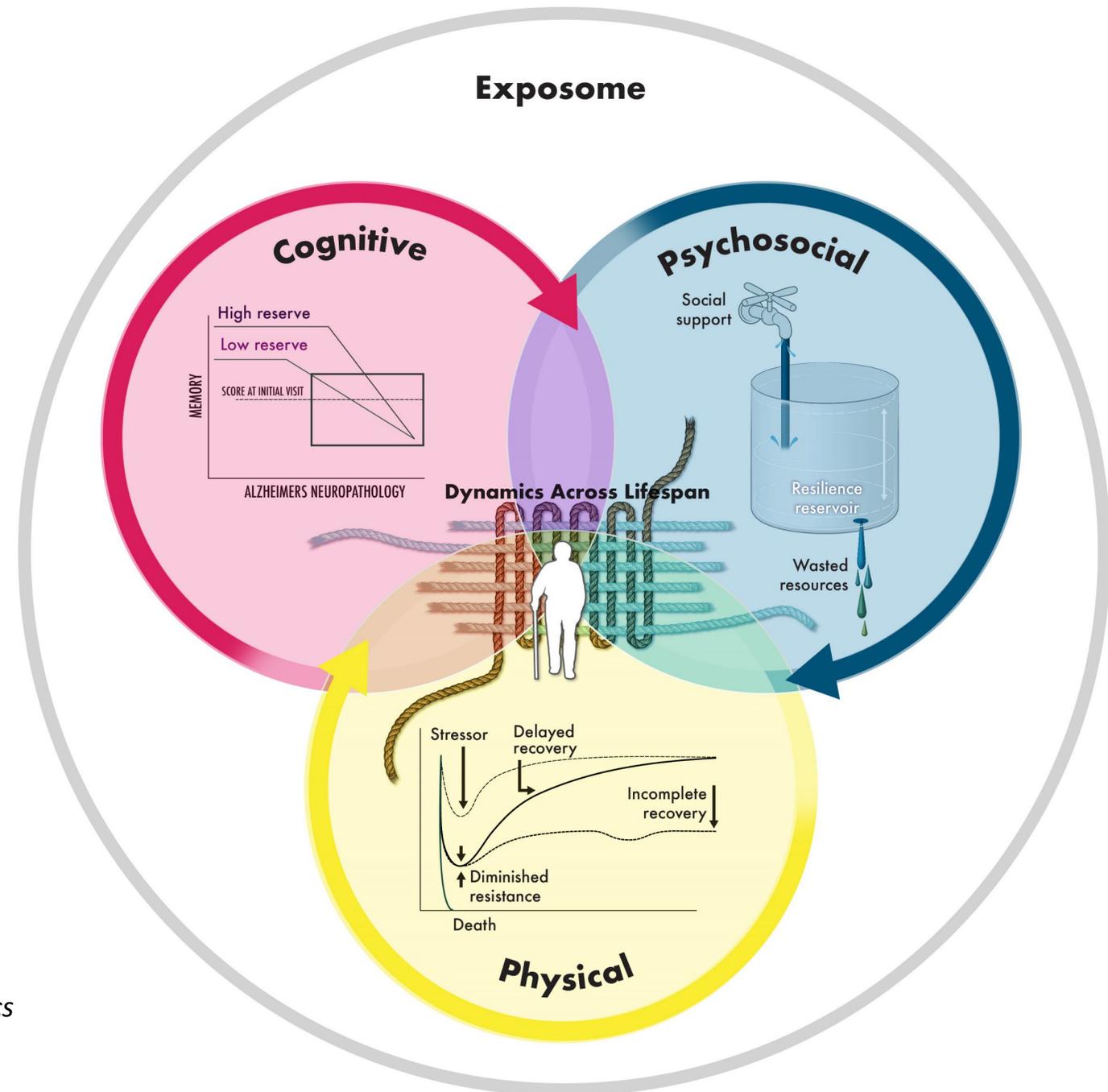
John Nesselroade (1990) introduced measurement bursts to depict the "warp" and "woof" (terms used in weaving) of developmental dynamics

Key Gaps-No consensus on definition: Attempt at Defining Resilience

- **Definition of Resilience**:
  - No consensus on a single definition.
  - Common core elements:
    - A stressor.
    - Response to the stressor.
    - Valuable response outcomes.
- **Research Recommendations**:
  - Longitudinal studies on impact of stressors.
  - Use new/existing cohort study data.
  - Incorporate natural experiments (e.g., COVID-19).
  - Employ preclinical models.
  - Translational research for patient care.

Putting it all together

We declined to offer a single definition.

Many research teams or fields have already operationalized their own definitions and frameworks. We simply encourage resilience investigators to:

1) specify definitions
2) recognize that their use of resilience is a "branch" in a larger tree.

The "big idea", or trunk, of resilience: Individuals differ in response to hardships or perturbations. This variation has significant implications for health.

Thoughts on defining resilience

Unitary definitions are challenging because resilience inherently extends across single units, systems, or domains of health

However, common core (trunk) elements:

     temporal dynamics needs longitudinal measures

     quantification of stressor *and* response (even if these are measured in a static fashion)

Definition must operate at multiple levels, across discrete domains. The same stressor may impact different domains/levels differently

Thoughts on defining resilience

- Ability to recover some function of value (or maybe resistance to loss of function, rather than "recovery")
- Following a meaningful stressor to the system
- Quantified through dynamic measures

➢ General feeling that term "resilience" connotes positive response

➢ But who is the judge?

➢ Need more of an emphasis on those who do surprisingly well for their level of vulnerability, even if they do suffer some loss

Possible over-arching definition of "resilience" with relevance to health:

Attainment of a valued outcome following an exposure that is expected to diminish that outcome

Overview of the Resilience World-State of the Science. Fall 2022

STRESSORS

PHYSICAL DOMAIN

COGNITIVE DOMAIN

RESILIENCE

PSYCHOSOCIAL DOMAIN

Optimizing Resilience. Fall 2025

Stress Tests & Biomarkers of Resilience. Spring 2024

IMAGE OF THE MONTH

Domains of Resilience in Older Adults. For full details, see "An overview of the resilience world: Proceedings of the American Geriatrics Society and National Institute on Aging State of Resilience Science Conference" on page 2381.

EDITOR'S CHOICE ARTICLE

A Study of Physical Resilience and Aging (SPRING): Conceptual framework, rationale, and study design

Jeremy Walston, Ravi Varadhan, Qian-Li Xue, et al.

FULL TABLE OF CONTENTS INSIDE

WILEY | AGS Geriatrics Healthcare Professionals
Leading Change, Improving Care for Older Adults.

Thank you

Developing a Common Framework for Discussion - A brief tour of:

- Current Conceptual Models of Resilience

- Approaches for Quantifying Resilience

- Categories of potential resilience predictors

Conceptualization of Resiliency
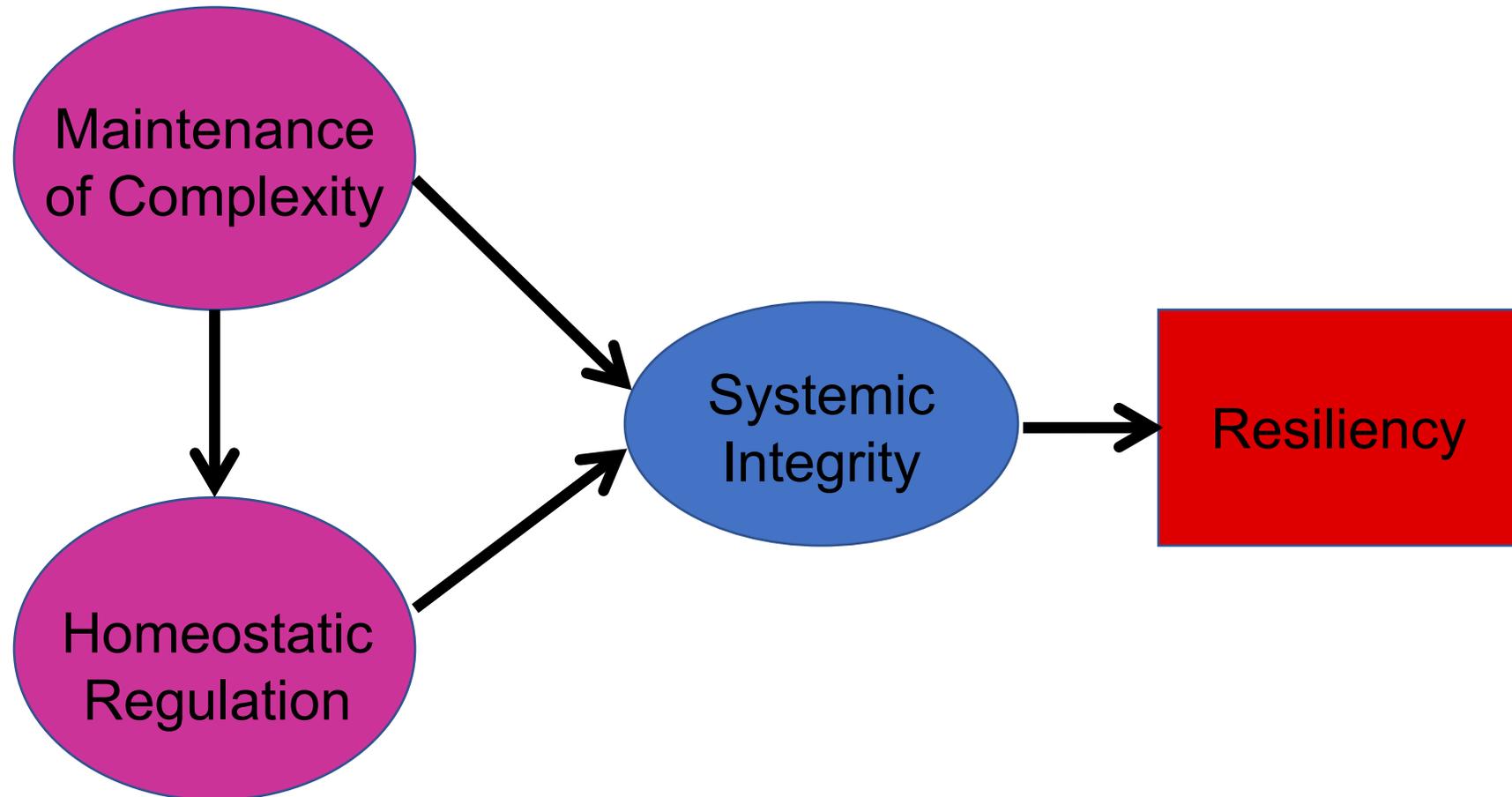
Theories of Resiliency

- Resiliency as the ability to rebound from stressors and the capacity to withstand stress (Buchner and Wagner 1992)

- Resiliency as maintenance of complexity (Lipsitz 2002)
  - Complexity of homeostatic mechanisms (e.g. inter-connectedness, feedback/feedforward)
  - Reactive tuning
  - Loss of complexity => vulnerability to stressors

Stimulus-Response Paradigm

- A key common notion is embedded in theories of physical frailty and resilience
  - vulnerability to stressors results from impaired homeostasis
  - identification of the homeostatic systems and poor performance measures has been often not available in aging research
  - Baseline measures without stressors can be helpful, but not very informative when considering potential clinical outcomes from stressful procedures

- A dynamical systems approach: stimulus-response experiments
  - To find out what might happen to a complex system when it is disturbed, you have to disturb it, not merely observe it passively
  - Older adults get many procedures that stress many systems
  - Figuring out how best to test them before procedures is not common in clinical practice except perhaps in cardiovascular testing

(Varadhan R et al., MAD 2009)

Conceptual Framework for Complex Stimulation

Gijzel SMW., et al J Am Geriat Soc. 2019
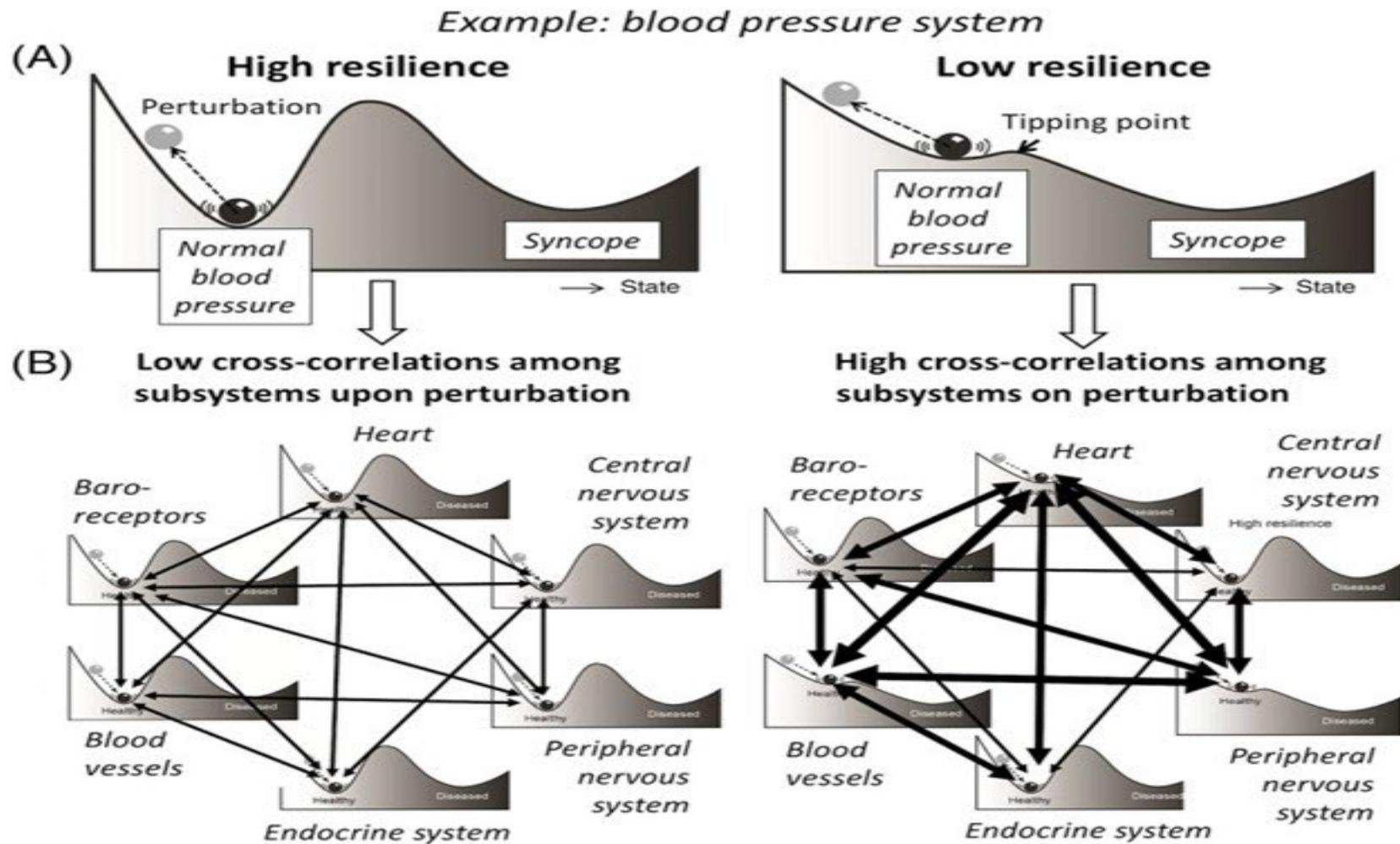
Conceptual Framework for Overall Resilience

Whitson H. et al, J Am Geriat Soc. 2021
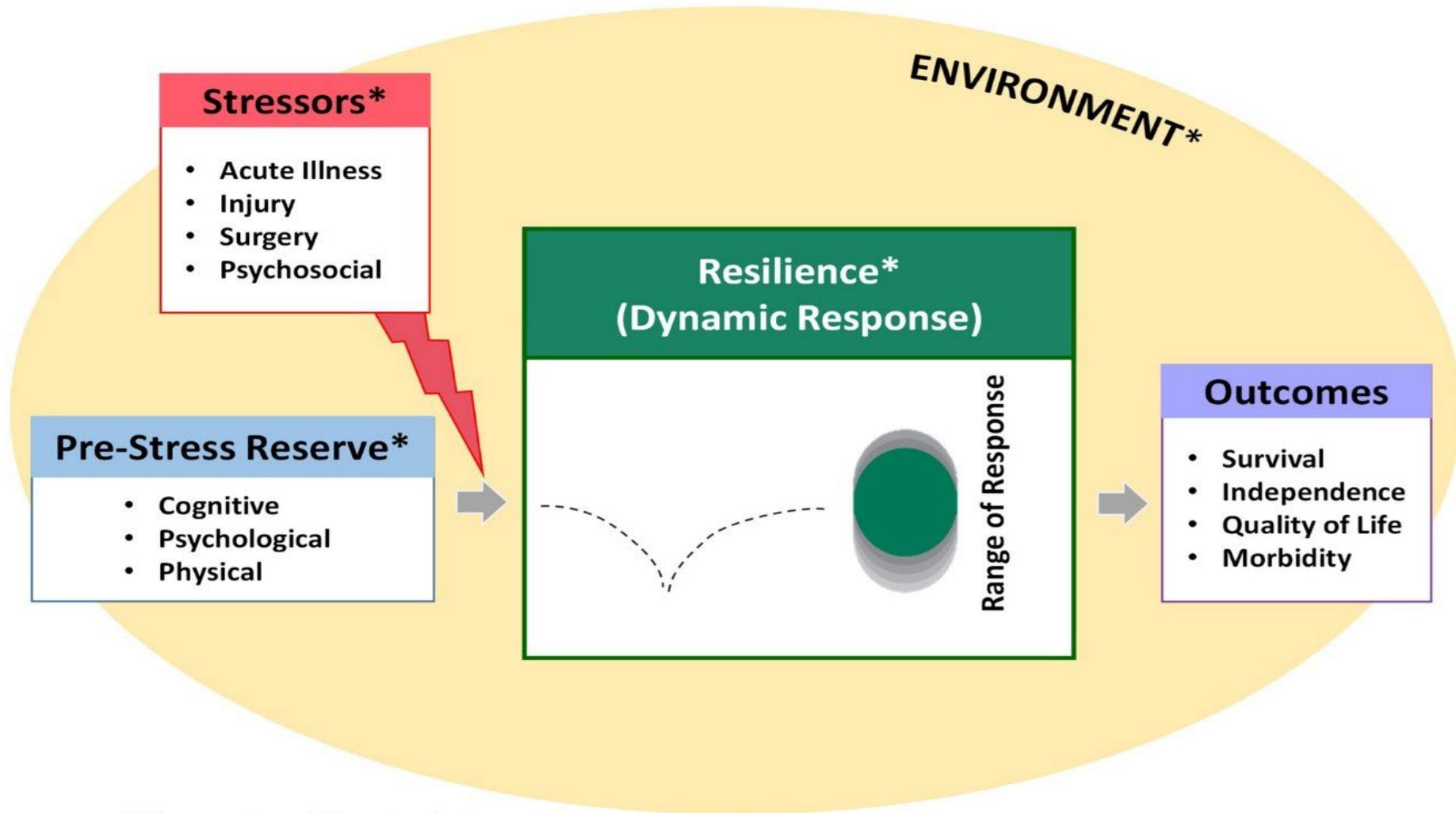
Conceptual Framework for Physical Resilience

Baseline Contributors
- Age
- Psychosocial
- Health Behaviors
- Disease
- Baseline biological and functional markers
- Molecular
  - Senescence
  - Epigenetics
  - Biophysics

SPRING
STUDY OF PHYSICAL RESILIENCE AND AGING

REBOUND RESILIENCY

REDI RESILIENCY

RESTORE RESILIENCY

Stressor → Physiologic Resilience Capacity → Resilience Phenotypes → Clinical Outcomes

Cognitive and Social Function

ADL/IADL

Physical Function / Activity

Biologic Markers
- Inflammatory cytokines
- Hemoglobin
- Albumin

Fatigability

Dynamic stimulation test as indicators of resilience

Static surrogate measures of resilience

Walston J, et al. J Am Geriatr Soc. August 2023

Complexity and Conceptual Framework

First U13 Workshop
Branches = Resilient outcomes in different domains (cognitive, physical, psychological)

Topic 3
Biomarkers, Provocative tests, imaging that reflect resilience biology and predict resilient outcomes

Topic 1
Trunk = Resilience biology (i.e., molecular, cellular, and systems biology underlying resilient outcomes

Acute Stressors

Topic 2
Soil = Social, environmental, genetic and psychological factors that impact resilience biology

Why Predict Resilience?

- Improve risk stratification
  - Shared decision-making
  - Targeting interventions
  - Selection for clinical trials

- Develop mechanistic understandings of resilience biology
  - Identify physiologic subsystems most involved in a particular resiliency
  - Generate hypotheses about cellular and molecular mechanisms which can be further tested in the laboratory

What do we want to Predict?

Descriptive Approaches: What will the recovery trajectory look like?
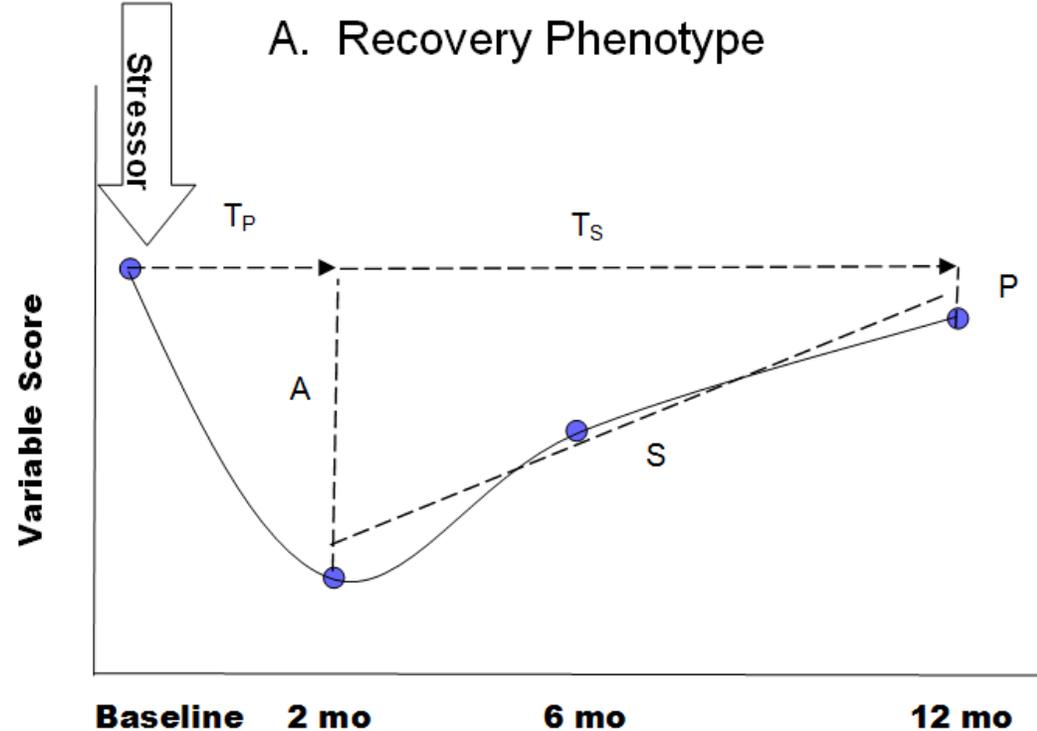
Residual Approaches: How much better/worse will recovery be than expected?

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7328208/
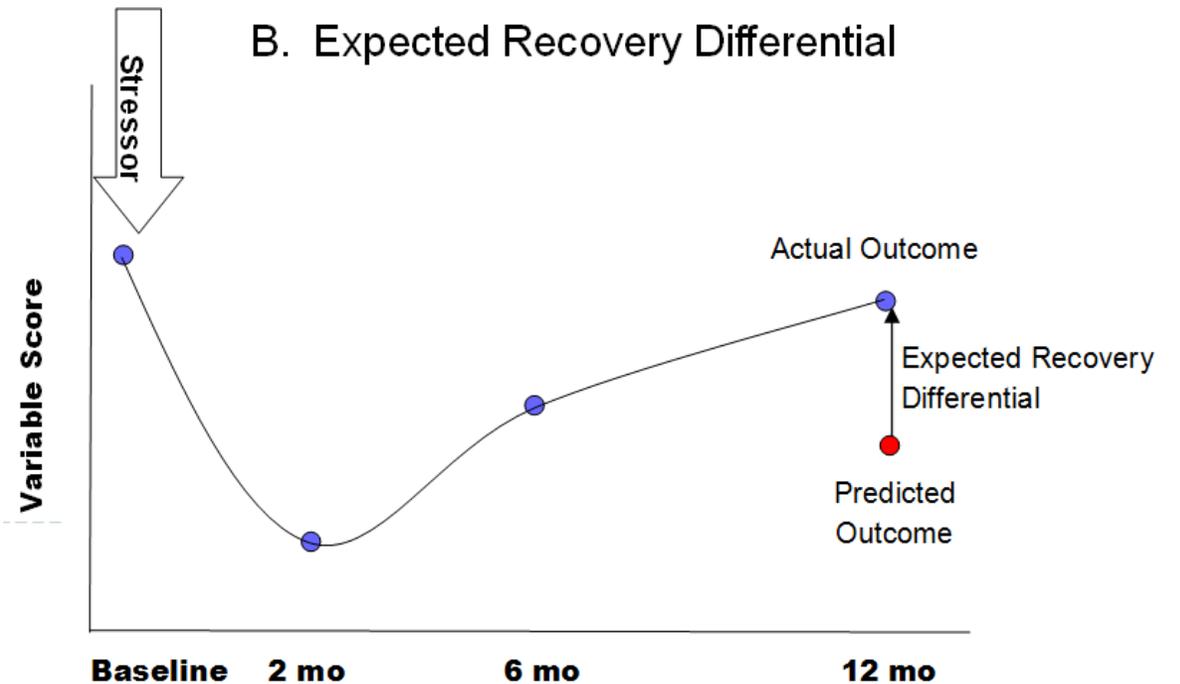
Static Measures that May Predict Resilience

Predictor Type	Examples
Functional and cognitive measures	Gait speed, SPPB, 6-minute walk, Independent Activities of Daily Living scales
Psychological Resilience Scales	Physical Resilience Scale
Biomarkers	Associated with hallmarks of aging
Genetic profiling	Whole genome sequencing, single cell RNA sequencing
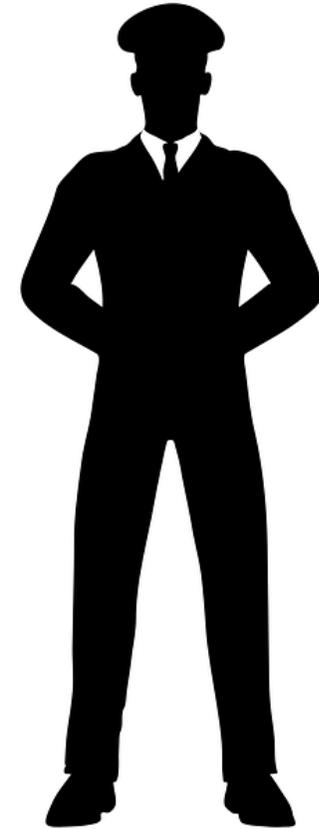
Dynamic Measures that May Predict Resilience

Predictor Type	Examples
Response to mild clinical challenge	Vaccine response, healing after punch biopsy
Continuous/ repeated physiologic data	Entropy or Dynamic Resilience Indicator measures using Heart Rate monitoring, actigraphy, postural sway, EEG
Dual task test	Gait speed with and without a cognitive challenge
Physiologic stimulation tests	Oral glucose tolerance test, ACTH stimulation test, movement evoked pain
Functional imaging	fMRI, fNIRS during cognitive or orthostatic challenge
In vitro stimulation tests	PBMC stimulation with LPS, influenza virus

Let's Get Started!

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