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)

Final U13 Workshop
Resilience Promoting Interventions

Acute Stressors
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 one's ability to respond to stressors, 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 physical, cognitive, and social stressors.
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:

<table>
<thead>
<tr>
<th>Challenges to the system:</th>
<th>Outcomes:</th>
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<tbody>
<tr>
<td>• Acute (e.g., getting lab tests).</td>
<td>• Recovery: Bouncing back from stressors.</td>
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<tr>
<td>• Major events (e.g., loss of loved ones).</td>
<td>• Sustainability: Absorbing disturbances with minimal effect.</td>
</tr>
<tr>
<td>• Chronic (e.g., ongoing health conditions).</td>
<td>• <strong>Growth</strong>: Enhanced coping for future stressors.</td>
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</table>
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 resources available to a system, whereas resilience is the extent to which this complex system can recruit those resources 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.
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

- Maintenance of Complexity
- Homeostatic Regulation
- Systemic Integrity
- 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

(A) High resilience
- Perturbation
- Normal blood pressure
- Syncope

(B) Low resilience
- Tipping point
- Normal blood pressure
- Syncope

Low cross-correlations among subsystems upon perturbation

High cross-correlations among subsystems on perturbation

Conceptual Framework for Overall Resilience

Stressors*
- Acute Illness
- Injury
- Surgery
- Psychosocial

Pre-Stress Reserve*
- Cognitive
- Psychological
- Physical

Resilience*
(Dynamic Response)

Outcomes
- Survival
- Independence
- Quality of Life
- Morbidity

*Opportunities to intervene

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

**Physiologic Resilience Capacity**

**Resilience Phenotypes**
- Cognitive and Social Function
- ADL/IADL
- Fatigability

**Clinical Outcomes**

**Dynamic stimulation test as indicators of resilience**

**Static surrogate measures of resilience**

**Biologic Markers**
- Inflammatory cytokines
- Hemoglobin
- Albumin

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

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

*Acute Stressors*
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?

A. Recovery Phenotype

Residual Approaches: How much better/worse will recovery be than expected?

B. Expected Recovery Differential

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

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

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

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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)

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

Acute Stressors
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<td>Heather Whitson, MD, MHS</td>
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