I Don’t Bounce Back Like I Used To: 
Age-related Changes in Resilience

HEATHER E. WHITSON, MD, MHS
PROFESSOR OF MEDICINE (GERIATRICS), OPHTHALMOLOGY, NEUROLOGY, HEAD & NECK SURGERY AND COMMUNICATION SCIENCES
DIRECTOR, DUKE AGING CENTER
DUKE SCHOOL OF MEDICINE/DURHAM VA GRECC
Disclosures

National Institute on Aging: P30AG028716-11, UH3AG056925, P30-AG064201-02, R01-AG062623-01A1, U13 AG054139, R33-AG057806, P30AG072958-01

Veterans Administration – Durham VA GRECC

AGS Board of Directors
Objectives

1) The importance of **resilience to stressors** in overall human health
2) The role of aging in resilience
3) How do we measure “resilience” after a stressor?
4) Can we get better at predicting and promoting resilience to health stressors?
“I don’t bounce back like I used to”
A Brief (and surely incomplete) History of Resilience in Aging Research

- Wagnild & Young 25-item Resilience Scale (1993)
- Barbara Resnick's Physical Resilience Measure (2011)
- NIA Workshop on Measuring Resilience in Laboratory Animals (2014)
- Cognitive reserve elaborated by Yaakov Stern (2012)
- 1st Workshop on Research Definitions for Reserve and Resilience in Cognitive Aging & Dementia (2016)
- Many tools in psychosocial literature
- NIA Workshop on Measures of Physiologic Resiliencies in Human Aging (2019)
- AGS/NIA Workshop on Overview of the Resilience World (2022)
Consider two patients being evaluated as candidates for total knee replacement.

76 year old woman who is a caregiver for her husband. She has obesity, depression, sedentary lifestyle, and history of coronary artery disease treated with a stent in 2015. She had gall bladder surgery and a hysterectomy, each more than 10 years ago.

75 year old man with well-controlled hypertension and glaucoma who plays golf and tennis weekly and has a supportive wife and two daughters nearby. He has never had a surgery.
Much of Successful Aging Depends on "Bouncing Back" After Stressors
Every person is a complex dynamic system

**Interconnected Systems and Sub-systems** constantly moving, transitioning, and adapting to changing environments and new stressors

Image by: Institute for Systems Biology, Seattle, WA
With age, our ability to respond briskly and adaptively to perturbation declines.
Diseases can diminish biologic resilience… and lower resilience makes us vulnerable to the next disease…
Geroscience: Biological resilience has a molecular basis

Resilience

- Response to Damage & Toxins
- Mobilizing Energy Stores
- Regulating Inflammation & Immune Response
- Cellular Damage Control
- Protein Folding & Recycling
- Stem Cells & Regeneration
- Genetics & DNA Repair

...and all of these molecular pathways exhibit decline with age (over time), even in the absence of serious disease.

Adapted from Kennedy et al. Cell 159; 2014
But the rate of decline is not the same for everyone. Why?

And sometimes our patients really surprise us…
Can we get better at predicting and promoting physical resilience to health stressors?

Step 1: We have to decide what to measure
Duke Pepper Center Conceptual Model of Physical 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
How might we quantify “resilience” after a stressor?

Two Key Clinical Questions

1. What is the pattern of recovery my patient will experience across health measures that matter?

2. How much better/worse will my patient do than expected, given their age and pre-stressor status?
Recovery Phenotype Approach

- Descriptive
- Can quantify multiple parameters (slope, % recovery, etc)
- Can summarize multiple outcomes simultaneously
  - Latent Class Trajectory Analysis
  - Factor Analysis
  - Principle Components Analysis
- Driven by age, comorbidities, pre-stressor function

Example: Recovery phenotype approach after hip fracture

Latent Profile Analysis trajectory group

- Lowest resilience
- Medium resilience
- Highest resilience
What Factors Were Associated with the Phenotype of High Resilience after Hip Fracture?

Model Predicting High vs. Low/Medium Resilience

- **Stressor Factors**: AUC = 0.6
- **Environment**: AUC = 0.6
- **Psychosocial**: AUC = 0.67
- **Comorbidities**: AUC = 0.61
- **Demographics**: AUC = 0.67
- **Pre-stressor function**: AUC = 0.84
**Expected Recovery Differential (ERD) Approach**

- Quantifies how observed outcomes differed from expected
- Requires predictive model from large cohort
- Accounts for baseline status, stressor factors, environment etc.

---

**Figure B. Expected Recovery Differential**

- Stressor
- Variable Score
- Baseline  2 mo  6 mo  12 mo
- Actual Outcome
- Expected Recovery Differential
- Predicted Outcome

---

Proof of Concept Study: Are “Pillars of Aging” markers linked to Resilience after Hip Fracture?

Metabolism
- Acylcarnitine, branched chain amino acids, IGF-1

Gene expression miRNA Panel associated with stress response

Inflammation
- Senescence associated secretory phenotype (SASP) panel, IL6, IL10, V-CAM, TNF R1&2
This panel of biomarkers explained 38% of the observed variability in recovery differential after hip fracture.

Daniel Parker, MD

Are there feasible, safe tests that can predict physical recovery after big health stressors?
Enrolling 200 Duke patients scheduled for elective knee replacement surgery

**Baseline Visit**
- Consent
- Covariates (Demographics, education, social support, environment)
- Cognitive Reserve Tests
- Physical Reserve Tests
- Provocative Tests (dual task gait/cognition, fNIRS reactivity tests, PBMC reactivity tests)
- Blood for biomarkers
- 7 day Step Counts

**Surgery Week**
- Provocative test (ECG variability)
- Covariates (surgery characteristics, complications, length of stay)
- Pain intensity and interference (daily)
- 3D-CAM Attention Items
- Blood for biomarkers
- 7 day Step Counts

**1, 2, 4 Month Phone Calls**
- Pain intensity and interference
- LE PADs
- Cognitive Change Index (subject, informant)
- 7 day Step Counts
- Intercurrent events, Rehabilitation received

**6-Month Visit**
- Cognitive Reserve Tests
- Physical Reserve Tests
- Provocative Tests (dual task gait/cognition, fNIRS reactivity tests, PBMC reactivity tests)
- 7 day Step Counts

Provocative Tests: Baseline and 6 months

- **Gait Speed Dual Task Test** walking while performing a speech generation task
- **Near-Infrared Spectroscopy (NIRS)** cerebrovascular reactivity before and after cognitive task, orthostatic challenge
- **In vitro PBMC response** influenza vaccine/virus and LPS stimulation
A sneak peak at PRIME-KNEE data

Do self-reported psychosocial measures collected before elective total knee arthroplasty predict pain trajectories in older adults?

- PHQ9 Depression Scale
- Brief psychosocial resilience scale
- Emotional support questionnaire
Predicting Pain Trajectories in PRIME-KNEE

How is pain recovery different for people with depressive symptoms?

How is pain recovery different for people with low psychosocial resilience?
Duke Pepper Center Resilience Leadership Team

Duke Claude D. Pepper OAIC

Leadership and Administration Core
Kenneth Schmader, Director

External Advisory Board

Independent Review Panel
Internal Operating Committee

Data Integration Working Group
William Kraus

Research Education Core
Cathleen Colon-Emeric (CL)
Kim Johnson (CL)

Pilot Exploratory Studies Core
Heather Whitson (CL)
William Kraus (CL)

Molecular Measures Core RCI
Virginia Kraus (CL)
James Bain (CL)

Health & Mobility Measures Core RC2
Kathrina Hall (CL)
Amy Pastor (CL)

Analysis Core RC3
Carl Pieper (CL)
Jane Pendergast (CL)

REC Scholars
2022 Awards
Leah Acker
Sonali Advani
Kim Hreha

2020 Awards
Brian Andonian
Ming-Feng Hsieh
Daniel Parker

Pilots
2022 Awards
Nicole DePasquale
Krista Haines
Tina Yang
1-yr Seed Project
Laura Petrosimone & Trevor Lentz

2020 Awards
Gurpreet Batli
Elaine Guevara
Gentzoy Hall
Adam Devore

Emerging Discovery/Health Innovation
Sheng Liu
Lisa Hobson-Webb
Jaime Hughes
Kevin Caves
Marty Woldoff
What populations are we studying?

- Sickle cell anemia
- Hemodialysis
- Glomerulosclerosis
- Rheumatoid arthritis
- Bone marrow transplant
- ECMO
- Osteoarthritis
- Fracture
- Dementia
- Urinary tract infections
- Vaccination
- Elective abdominal surgery
- Anesthesia/POCD
- Lemurs!
Goal: Promoting Resilience Before and During Health Stressors

**Predict Recovery Trajectory**
- Clinically feasible provocative tests
- Biomarkers

**Current Interventions**
- “Prehabilitation”
- Decision support tools
- Nutrition
- Psychosocial support

**Future Interventions**
- Resilience in a pill?
The Era of Resilience Medicine

- Disease Focused Medicine
- Preventive Medicine
- Resilience Medicine
Thank you and Questions

Duke Collaborators:
Cathleen Colon-Emeric, Ken Schmader, Kim Huffman, Bill Kraus, Virginia Kraus, James Bain, Micah McClain, Miles Berger, Marty Woldorff, Daniel Parker, Janet Bettger, Harvey Cohen, Miriam Morey, Carl Pieper, Rick Sloane, Mary Cooter, Jody Feld, Patrick Smith, Katherine Hall

U. Maryland Collaborators:
Jay Magaziner, Denise Orwig, Ann Gruber-Baldini

U. Connecticut Collaborators:
George Kuchel, Jacques Banchereau, Janet McElhaney

Harvard Collaborators:
Lew Lipsitz, Junhong Zhou

NIA Collaborators: Giovanna Zappala, Basil Eldadah, Chhanda Dutta
Molecular Measures of Resilience – Cartilage Regeneration

Humans may have innate cartilage regeneration ability

“Analysis of “old” proteins unmask dynamic gradient of cartilage turnover in human limbs”

Illustrations created in BioRender and in part by Alisa Wegundt.
M-F Hsueh, P. Oomenford, V.B. Kraus et al. Science Advance, 2019