Some Methodological Challenges in Studying Resilience

Ravi Varadhan
Oncology Biostatistics & Center on Aging and Health
Johns Hopkins University
RCCN Austin Tx
November 13, 2019
Gratitude

• Drs. Bandeen-Roche, Walston, Buta, Xue

• NIA UH2/UH3

• The organizers of RCCN
Characterizing Resiliencies to Physical Stressors in Older Adults: A Dynamical Physiological Systems Approach

Johns Hopkins University
NIA Grant # UH2AG056933

PIs: Jeremy Walston, MD, Karen Bandeen-Roche, PhD, Ravi Varadhan, PhD, PhD
Conceptual Framework for Physical Resiliency

Baseline Determinants
- Age
- Psychosocial
- Health Behaviors
- Disease
- Molecular
  - Senescence
  - Epigenetics
  - Biophysics

Physical Resilience

Stressors
- Cognitive Function
- Physical Function / Activity
- Fatigability
- ADL/IADL

Phenotypic
- Mitochondrial dysfunction
- Angiotsensin System
- Cardiovascular & Neurologic

Physiologic
- Coagulation & Clotting
- Stress Response Systems
  - HPA Axis
  - Innate Immune System / Inflammation
  - Autonomic Nervous System

Outcomes

Surrogate measures of resilience
Dynamic stimulation tests
Key Methodological Challenges

• Recruitment of representative participants

• Ability to probe physiology of resilience with stimulus-response tests

• Ability to collect exquisite post-stressor longitudinal data

• Modeling and characterization of phenotypic trajectories

• Handling death
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Selection Bias in Recruitment

• This is a very difficult problem

• People are undergoing serious clinical stressors such as BMT and TKR
  • Our recruitment yields are around 50%

• Selection bias is inevitable and affects generalizability

• Through secondary data sources, we may be able to assess the impact of selection bias
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Stimulus-Response Testing Paradigm

• Resilience is a property of a complex, dynamical system

• Perturb the system with a finite stimulus and study its response (Varadhan 2008)

• Response is typically biphasic, i.e. stimulation and recovery phases

• Estimate magnitude and kinetics of response (e.g. characteristic time constants)
SRT Paradigm

- **Stimulation phase**: $t_0 < t \leq t_{\text{max}}$
- **Recovery phase**: $t_{\text{max}} < t \leq t_{\infty}$
- **Peaks response**: $y_{\text{max}}$
- **Stimulation**: $y_{\text{max}} / y_0$
- **Recovery**: $y_{\infty} / y_0$
Stimulus-Response Tests (SRT)

• SRTs potentially useful for probing resilience

• Unfortunately, we don’t know the optimal SRTs

• We need novel SRTs that are safe and yet probe the stress-response physiology

• Non-linear random effects models or non-parametric approaches may be used for analysis
SRTs in SPRING

- ACTH Stimulation
- Diurnal Salivary Cortisol Profile
- Oral Glucose Tolerance Test
- Treadmill fatigability assessment
- Holter Monitoring
- Dynamic ex-vivo response of immune cells to LPS stim
- Orthostatic Blood Pressure
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Longitudinal Sampling

• To study resilience, we need pre-, peri- and post-stressor measures

• Pre-stressor performance measures not possible for unplanned stressors (e.g., hip fracture)
  • is it possible to impute this?
  • self or proxy report measures may be useful

• Utility of peri-stressor measures needs to be examined
  • Changes in physiology during and 24-48 hours after stressor

• Post-stressor measures:
  • sampling time frame?
  • sampling frequency?
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• Handling death – competing risk or non-resilience
Modeling Phenotypic Response Trajectories

• Models of longitudinal response: well-established in biostatistics

• Conditional (mixed-effects) versus marginal (GEE) models
  • Pros and cons for each
  • choose depending on the goal

• Latent class or latent variable models (e.g., Colon-Emeric 2019)
Characterizing Phenotypic Trajectories

• Different forms of trajectories

• Within-person variability

• How do we utilize baseline function?

• How do we define resilience?
Pain-score-Increasing (N=6311, 89%) Pain-score-Decreasing (N=123, 2%)

Pain-score-Stable (N=465, 7%) Pain-score-Variable (N=169, 2%)

Unpublished Data from FORCE-TJR
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Latent Profiles
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Handling Death

• How to account for death?
  • Simple censoring is seldom appropriate
  • Mixed-effects model extrapolate phenotypes beyond death

• Is death a competing risk or does it denote lack of resilience?
  • Model death as a separate process – joint modeling
  • Death as part of resilience itself
  • Survival as resilience!
What Constitutes a Resilient Phenotype?

• Resilience is a rich, multi-dimensional concept
• Stressor-specific clinical outcomes
  • for example in bone-marrow transplantation for treating leukemia, major clinical outcomes are: graft failure, GVHD, relapse, and death
• Physical and cognitive function
• Quality of life
• Patient-reported outcomes
• Modeling and characterization is challenging
Thank you!