1ST WORKSHOP ON RESEARCH DEFINITIONS FOR RESERVE AND RESILIENCE IN COGNITIVE AGING AND DEMENTIA

SEPTEMBER 9-10, 2019 | BETHESDA, MD

CHAIR: YAAKOV STERN

RESERVE & RESILIENCE

HTTPS://RESERVEANDRESILIENCE.COM

Collaboratory on research definitions for reserve and resilience in cognitive aging and dementia

- The request for applications from the NIA:
  - Organize three cross-discipline workshops to facilitate the development of definitions and research guidelines
  - Establish focused work groups that will address key programmatic issues
  - Develop a data sharing and information exchange platform
  - Support pilot studies to validate and clarify proposed definitions and concepts
  - Disseminate network resources to the field at large

- Our thanks to Drs. Molly Wagster and Jonathan King for both developing this RFA, and their unceasing guidance in developing this 1st Workshop

Funding for this workshop was made possible in by a grant (R24 AG061421) from the National Institute on Aging.

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Significant Support

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Emrah Düzel, MD, DZNE
Michela Gallagher, PhD, Johns Hopkins University
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Kristine Walhovd, PhD, University of Oslo
Lawrence Whalley, PhD, University of Aberdeen
Lon White, PhD, Pacific Health Research and Education Inst
Robert Willis, PhD, University of Michigan

** Chair*

Special thanks to:

- Kulbir Kaur, PhD: Columbia University
- Nico Stanculescu and Leanne Gustie: World Events Forum

The goal of this meeting

- Develop a set of well accepted operational definitions and research approaches that can be disseminated to the field at large
- Create synergy across the broad research field that will result in findings that will clarify our understanding of mechanisms that may delay or prevent the onset of ADRD, and slow or prevent cognitive decline
- Words have intuitive definitions; this can be misleading. In science, we develop operational definitions that go beyond this, e.g., significance, normal distribution
- For example, with regards to reserve:
  - dictionary definition: a supply of a commodity not needed for immediate use but available if required
  - Cognitive reserve, theoretical definition: use of cognitive processes developed over time and influenced by lifestyle factors to better cope with age- and disease-related brain changes
- The terms we are working with are labels for concepts that can often be complex
- We need shared definitions that include how they are operationalized in research

Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance

- Workgroup of 31 researchers from the Reserve, Resilience and Protective Factors PIA
- Consensus definitions and potential measures for several concepts:
  - Resilience is treated an overall descriptor for all concepts
  - Cognitive reserve, brain reserve, brain maintenance, compensation, efficiency, capacity
- Research guidelines, i.e. operational definitions, of each concept
- Points out the challenge of applying these concepts to animal or basic neuroscience research

- The Whitepaper serves as a model for an eventual product of our efforts

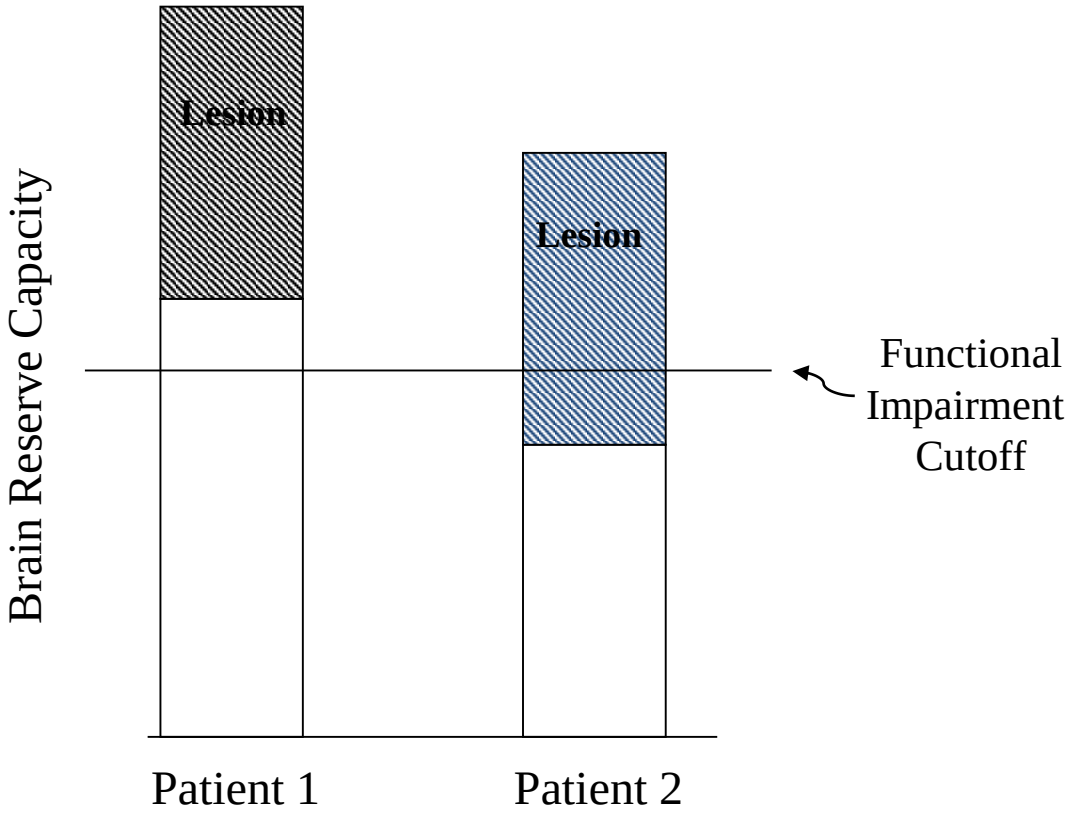
Stern et al, Alzheimer's and Dementia 2018

Brain Reserve : Whitepaper definition

- Brain reserve is commonly conceived as neurobiological capital (numbers of neurons, synapses, etc.). BR implies that individual variation in the structural characteristics of the brain allows some people to better cope with more brain aging or pathology than others before clinical or cognitive changes emerge.
- Brain reserve is a passive form of reserve
- One key concern with using this concept (and differentiating it from cognitive reserve) is that cognition must have a biological basis
  - Brain reserve is a passive form of reserve; cognitive reserve is active
  - In human studies structural measures have often represented BR, and functional measures CR
  - In any case, we need to account for structural measures when studying functional mechanisms, such as compensation, that might be associated with CR.

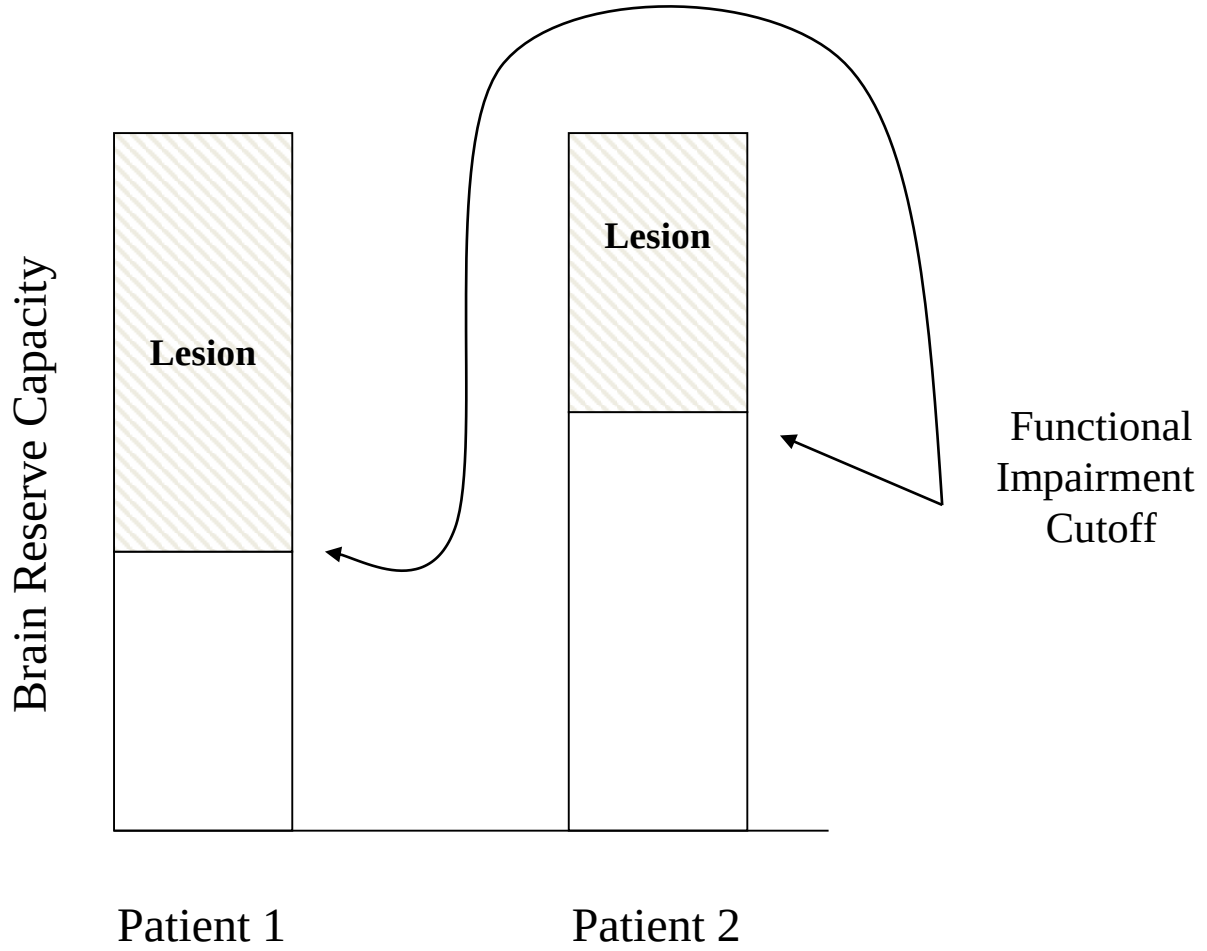
Passive vs active models of reserve

Brain Reserve



Satz, Neuropsychology 1993

Cognitive Reserve



Stern, JINS 2002

Cognitive reserve: Whitepaper definition

- Cognitive reserve refers to the adaptability (i.e., efficiency, capacity, flexibility) of cognitive processes that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult.
- Differences in CR are influenced by the interaction of innate (e.g., in utero, or genetically determined) individual differences and lifetime exposures.
- Research on cognitive reserve should include:
  - the status of the brain (reflecting brain change or pathology)
  - clinical or cognitive performance outcomes
  - a measure of reserve: either a sociobehavioral proxy (i.e., an index of lifetime exposure/premorbid ability) or a functional brain measure.

How is cognitive reserve “neurally implemented”?

- The Whitepaper suggested 3 concepts for studying the neural implementation of CR:
  - Efficiency: as the degree to which a given task-related brain network must become activated to accomplish a given task.
  - Capacity: the maximum degree to which a task-related brain network can be activated to keep performing a task in the face of increasing demands.
  - Compensation: In response to brain changes, individuals may recruit brain structures or networks (and thus cognitive strategies) not normally used by individuals with “intact” brains.
- Individuals with greater CR should have greater efficiency and capacity, and be able to compensate more effectively, and thus cope more effectively with age- and AD-related changes
- Many other “implementations” of CR are likely

Feature Review

Memory aging and brain maintenance

Lars Nyberg[1,2,3,7], Martin Lövdén[4,5,6], Katrine Riklund[1,3], Ulman Lindenberger[5] and Lars Bäckman[4]

- Brain maintenance: Individual differences in the manifestation of age-related brain changes and pathology allow some people to show little or no age-related cognitive decline
- Relative lack of brain changes and pathology is the biggest contributor to heterogeneity of cognitive aging
- Various genetic , environmental and lifestyle choices can play a role in maintaining brain integrity and cognitive performance
- Brain maintenance is complementary to cognitive reserve

Trends in Cognitive Sciences May 2012, Vol. 16, No. 5

OPINION

Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing

- Reserve: cumulative improvement, due to genetic and/or environmental factors, of neural resources that mitigates the effects of neural decline caused by ageing or age-related diseases
  - Reserve, instead of brain and cognitive reserve, since all cognition is in the brain
- Maintenance: the preservation of neural resources, which entails ongoing repair and replenishment of the brain in response to damage incurred at the cellular and molecular levels owing to ‘wear and tear’.
- Compensation: cognition-enhancing recruitment of neural resources in response to relatively high cognitive demand. Enhances cognitive performance.
- *Reserve* is used to refer to the accumulation of brain resources during the lifespan, *maintenance* to the preservation of these resources via constant recovery and repair, and *compensation* to the deployment of those resources to task demands.
- Reserve and the capacity for compensation may interact. For example, highly educated individuals may show different activation patterns than individuals with lower educational attainment because their greater reserve allows them to deploy more effective compensatory processes.

Cabeza et al, Nature Reviews, Neuroscience 2018

VIEWS & REVIEWS

Resistance vs resilience to Alzheimer disease

Clarifying terminology for preclinical studies

Figure Relation between the concepts of resistance and resilience, brain mechanisms, and contributing factors

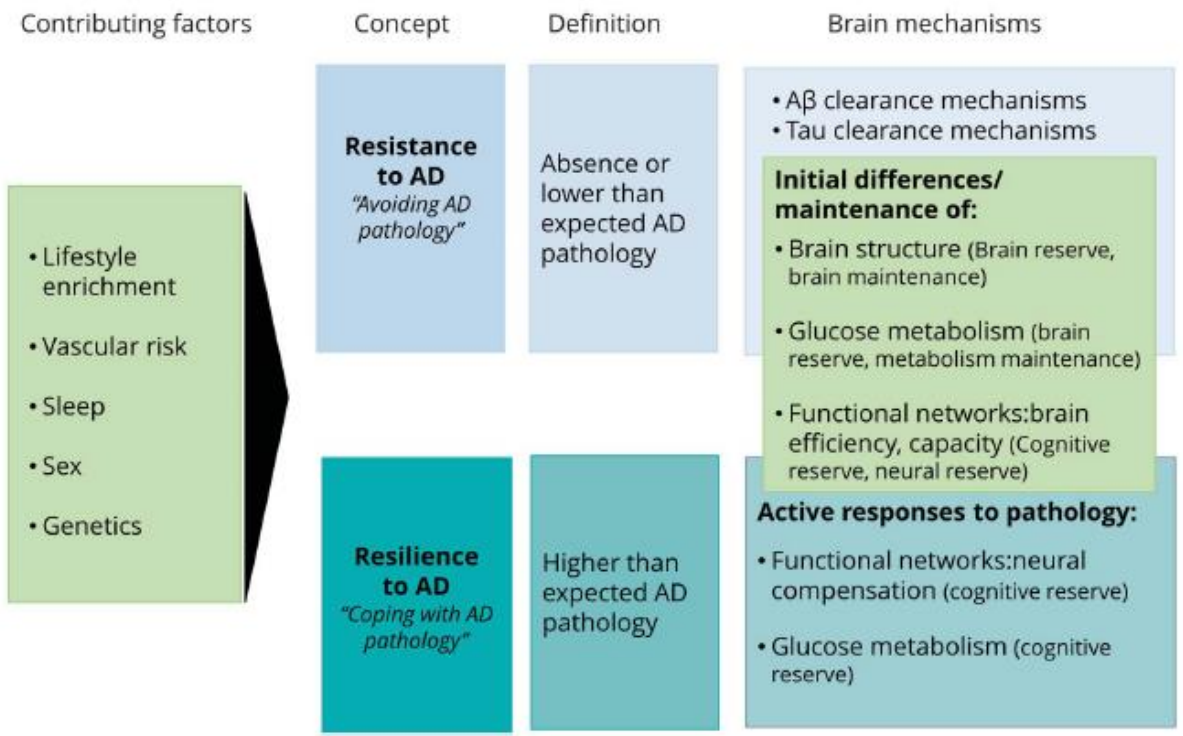


Table 3 Previous theories/concepts as defined in original articles under the umbrella terms of brain resistance and brain resilience

Brain resistance	Brain resilience
(Neuro)protection	Compensation
Brain maintenance	Metabolism maintenance[a]
	Structure maintenance[a]
Neural efficiency	Brain reserve (threshold model)
Cognitive reserve (neural reserve)	Cognitive reserve (neural compensation)

[a] Aspects related to brain maintenance that have been shown to be useful in preclinical Alzheimer disease research, considering the maintenance of brain structure and metabolism in the setting of Alzheimer disease pathology, instead of maintenance in an absolute way, as considered in the original article.

Arenaza-Urquijo & Vemuri, Neurology 2018

Montine et al. Alzheimer's Research & Therapy (2019) 11:22
https://doi.org/10.1186/s13195-019-0479-y

Alzheimer's Research & Therapy

COMMENTARY Open Access

Concepts for brain aging: resistance, resilience, reserve, and compensation

Thomas J. Montine[1], Brenna A. Cholerton[1], Maria M. Corrada[2], Steven D. Edland[3,7*], Margaret E. Flanagan[4], Laura S. Hemmy[6], Claudia H. Kawas[2] and Lon R. White[5]

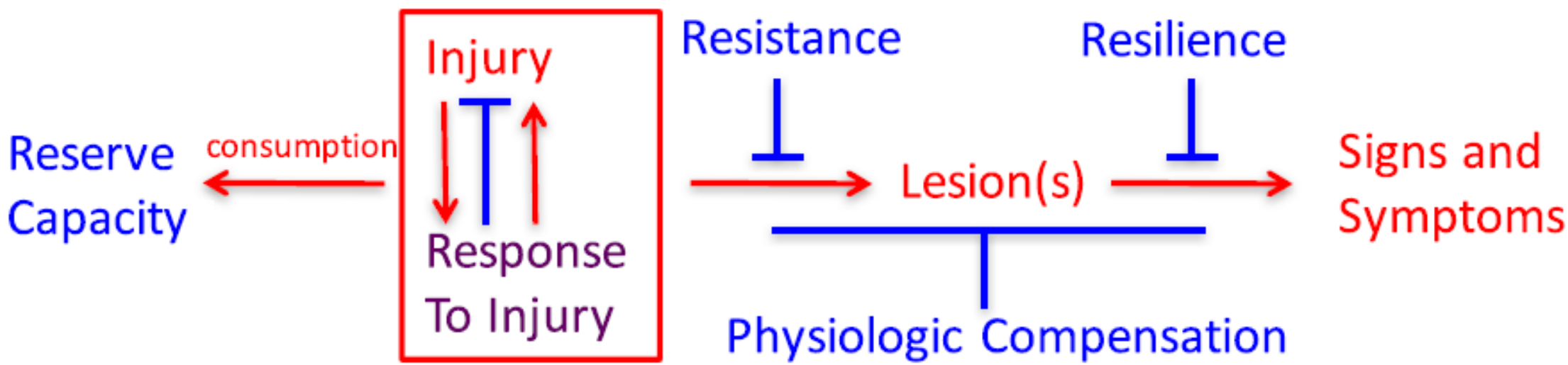


Fig. 1 Relationships among adverse (red), protective (blue), and mixed (purple) processes that culminate in signs and symptoms of neurodegenerative diseases

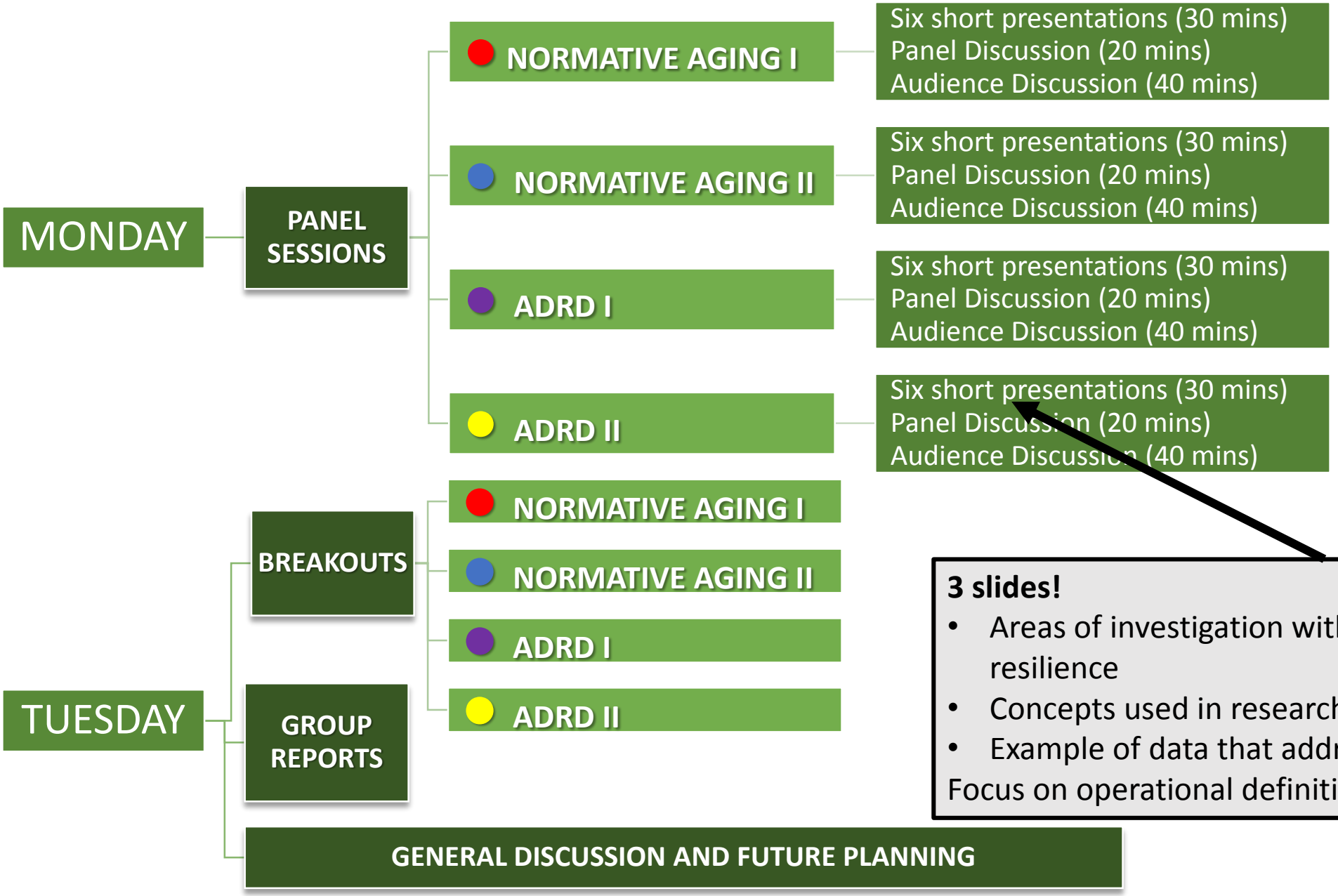
Other terms used by panelists in this Workshop

- Neural adaptation
- Neuroadaptation
- Neuroplasticity
- Plasticity
- Developmental plasticity
- Cognitive enrichment
- Cognitive resilience
- Cognitive resilience
- Global resilience
- Brain resilience
- Physiologic compensation
- Brain modulation

The promise of animal studies

- A unique feature of this Workshop is the desire to create definitions and research approaches applicable to both human and animal/basic science research
- There is a clear need for a conceptual counterpart to the reserve/ resilience concepts at the neurobiological levels of molecules, cells, and systems.
- Characterization of the biology supporting cognitive processes allows more direct study these concepts
- Longitudinal animal studies can directly test antecedents to, and study changes in BR, BM and CR

Format and Breakout group assignments



3 slides!

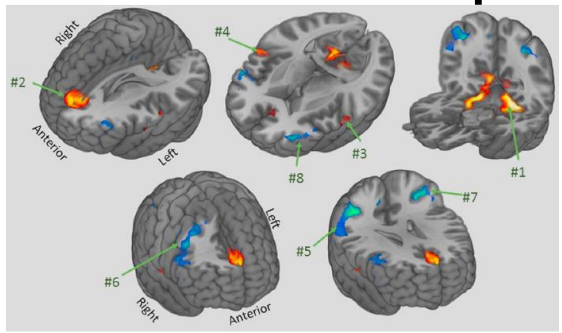
- Areas of investigation with respect to reserve and resilience
- Concepts used in research
- Example of data that address one concept

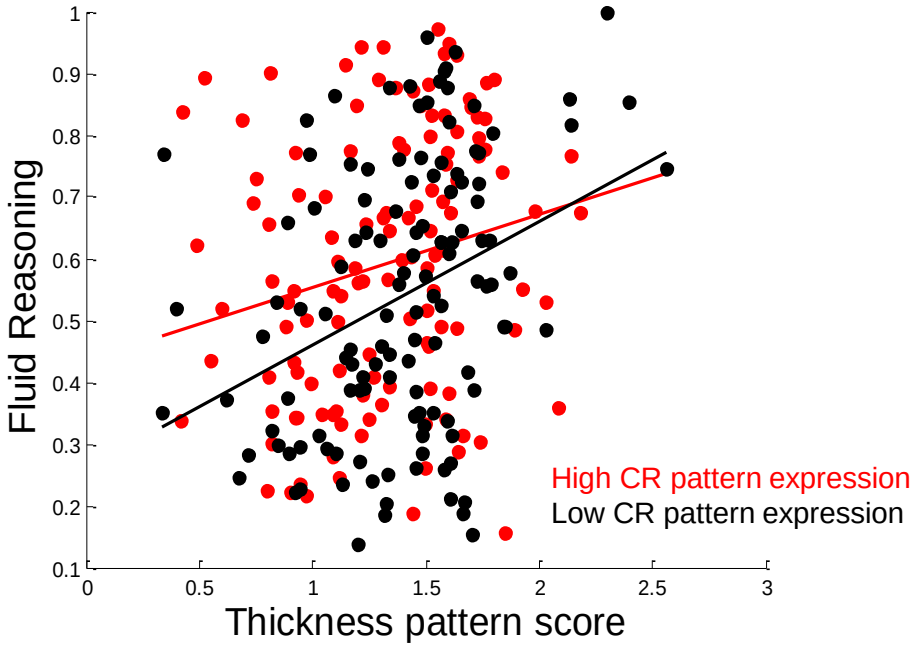
Focus on operational definitions, not findings

Example of Data that Address One Concept

- Concept: Cognitive reserve
- Measures: fluid reasoning, IQ-related functional activation, cortical thickness
- Operational definition: life exposures influence current cognitive processes, which moderate between brain change and cognitive status
- This approach includes
  - a brain change: cortical thickness
  - cognitive outcome
  - exposures that enhances reserve

Task-invariant, IQ-related activation pattern expressed during performance of 12 different tasks



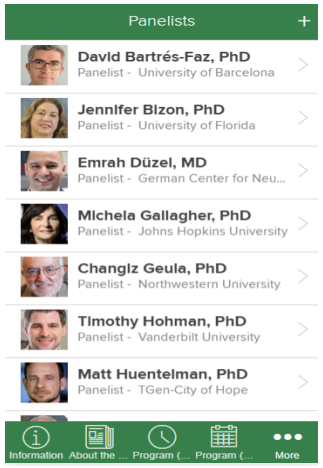


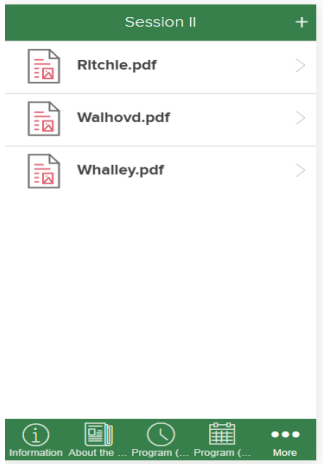
Expression of a task-invariant, IQ-related activation pattern moderates the relationship between cortical thickness and fluid reasoning

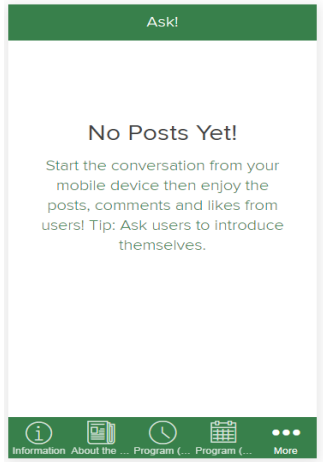
Stern et al, Neuroimage 2018

Some guidelines

1. The sessions will be recorded and posted on our website
2. All slides are available on the website and the mobile app
3. The audience Q&A for each of the four panel sessions will be coordinated by the Chair
   - For all questions/comments, please approach either one of the two aisle microphones and wait for the Chair to invite you to speak.
   - Please precede your questions/comments by your first and last name, and affiliation.
   - You can also submit comments/questions in writing using the mobile app's "ASK!" tab.
     - *To post, like, or comment, a user will need to identify themself. In order to do so, you will be asked to sign up or login to a Yapp account.*







MONDAY, September 9, 2019

8:30-9:00	**Welcome and Introduction: Current Definitions for Reserve, Resilience & Related Concepts**	Yaakov Stern, PhD, *Columbia University*
PANEL SESSIONS: Definitions and Research Paradigms for Reserve, Resilience & Related Concepts		
9:00-10:30	**Session 1: Normative Aging I** CHAIR: Gerd Kempermann, MD, *DZNE* Six cross-disciplinary speakers (9:00-9:30) Panel Discussion (9:30-9:50) Audience Discussion (9:50-10:30)	*Panelists:* Michela Gallagher, PhD, *Johns Hopkins University* William Jagust, MD, *Univ. of California, Berkeley* Richard Jones, ScD, *Brown University* Lars Nyberg, PhD, *Umea University* George Rebok, PhD, *Johns Hopkins University* Emily Rogalski, PhD, *Northwestern University*
10:30-11:00	Break	
11:00-12:30pm	**Session 2: Normative Aging II** CHAIR: Sylvie Belleville, PhD, *University of Montreal* Six cross-disciplinary speakers (11:00-11:30) Panel Discussion (11:30-11:50) Audience Discussion (11:50-12:30)	*Panelists:* Jennifer Bizon, PhD, *University of Florida* Denise Park, PhD, *University of Texas at Dallas* Marcus Richards, PhD, *University College London* Stuart Ritchie, PhD, *King's College London* Kristine Walhovd, PhD, *University of Oslo* Lawrence Whalley, MD, *University of Aberdeen*
12:30-1:30	Lunch	
1:30-3:00	**Session 3: Alzheimer's Disease and Related Disorders I** CHAIR: Nikolaos Scarmeas, MD, *Columbia University* Six cross-disciplinary speakers (1:30-2:00) Panel Discussion (2:00-2:20) Audience Discussion (2:20-3:00)	*Panelists:* David Bartrés-Faz, PhD, *University of Barcelona* Changiz Geula, PhD, *Northwestern University* Timothy Hohman, PhD, *Vanderbilt University* Matt Huentelman, PhD, *TGen-City of Hope* Catherine Kaczorowski, PhD, *Jackson Labs* Prashanthi Vemuri, PhD, *Mayo Clinic*
3:00-3:30	Break	
3:30-5:00	**Session 4: Alzheimer's Disease and Related Disorders II** CHAIR: William Kremen, PhD, *UCSD* Six cross-disciplinary speakers (3:30-4:00) Panel Discussion (4:00-4:20) Audience Discussion (4:20-5:00)	*Panelists:* Emrah Düzel, MD, *DZNE* Thomas Montine, MD, PhD, *Stanford University* Dan Mungas, PhD, *University of California, Davis* Dorene Rentz, PsyD, *Harvard Medical School* Lon White, MD, *Pacific Health Res. and Ed Inst.* Robert Willis, PhD, *University of Michigan*
5:00-7:00	Networking Reception	

TUESDAY, September 10, 2019

7:30am-8:30	Registration and Breakfast
8:30-8:45	**Breakout Group Activity: Instructions**
8:45-10:15	**Breakout Groups will address the following questions:** **1. Is there consensus on some concepts discussed?** **2. Are there any concepts that can be combined?** **3. What conceptual issues remain to be resolved?** **4. What studies are needed to help move the field forward and what type of pilot data would establish feasibility?** **5. What types of data would be useful to share in the near term?**
10:15-10:45	Coffee Break
10:45-11:45	**Group reports**
11:45-12:45	**General discussion and future planning**
12:45-1:45pm	Lunch and Networking Session

The key questions

1. Is there consensus on some concepts discussed?

2. Are there any concepts that can be combined?

3. What conceptual issues remain to be resolved?

4. What studies are needed to help move the field forward and what type of pilot data would establish feasibility?

5. What types of data would be useful to share in the near term?

Remember: Our hope is to identify ways to increase reserve/resilience, so the role of antecedent factors to the concepts is important