Evolution of Concepts on Reserve and Resilience in Aging and Dementia

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Research Centers Collaborative Network Workshop
Austin, TX
Overview of the talk

- Evolution of the concept
- Recent workshop on research definitions for Reserve and Resilience in aging and dementia
- Open opportunities and challenges
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History of AD and Related Disorders
Pathology and Cognition

1906  1984

NINCDS-ADRDA Criteria
Clinical-Pathological Definition

Clinical Symptoms
Gold Standard – Pathological confirmation

Plaques
Tangles
HISTORY OF CONCEPTS

1984: NINCDS-ADRDA Criteria

1989
Katzman et. al.
Brain Reserve

Incipient AD (plaques) – larger brains - reserve

1990s
Satz 1993 – Brain Reserve Capacity
Mortimer 1997

End of 1990s

~29000 individuals
Higher brain reserve was associated with a 54% lower risk for incident dementia

Summary: Valenzuela and Sachdev 2006

Epidemiological studies
Evans et. al. 1993
Stern et. al. 1994
CRITICAL REVIEW

What is cognitive reserve? Theory and research application of the reserve concept

YAAKOV STERN
Cognitive Neuroscience Division, G.H. Sergievsky Center, The Taub Institute, and Departments of Neurology, Psychiatry, and Psychology, Columbia University College of Physicians and Surgeons
(RECEIVED AUGUST 22, 2000; REVISED February 26, 2001; ACCEPTED February 28, 2001)
Reserve: Passive vs. Active Models

2002
Stern
Construct of Reserve

Brain structure differences

A
B

Brain function differences

C
D

Subject D
More efficient use of networks
Recruitment of other networks
Compensatory mechanisms
Cognitive Reserve takes off ...

# of publications on PUBMED
Brain Maintenance

Reserve: Individual differences in the brain itself allow some people to cope better than others with brain pathology

Maintenance

- Successful memory aging (preserved structure and function)
- Absence of pathology

Nyberg L et. al. 2012
Consolidated Effort: PIA (AAIC) ~600 members
Slightly different view..

2018
Brain Reserve
Cognitive Reserve
Brain Maintenance

2018
Reserve
Compensation
Maintenance

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


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

Roberto Cabeza, Marilyn Albert, Sylvie Belleville, Fergus I. M. Craik, Audrey Duarte, Cheryl L. Grady, Ulman Lindenberger, Lars Nyberg, Denise C. Park, Patricia A. Reuter-Lorenz, Michael D. Rugg, Jason Steffener and M. Natasha Rajah
The 2000s-present: Changing Landscape
Biomarkers to measure two main pathologies

- **Aβ**
  - Amyloid PET Imaging
  - CSF Aβ
  - *Plasma Aβ*

- **Tau**
  - Tau PET Imaging
  - CSF p-tau
  - *Plasma p-tau*
Biomarkers in cognitively unimpaired individuals

Age 65

\[\text{A}\beta^+ \sim 20\%\]

Age 80

\[\text{A}\beta^+ \sim 50\%\]
Defining concepts based on biomarkers

Subject B
Unimpaired

Subject A
Unimpaired

Subject C
Impaired

• How can one be more like Subject B?
• How can one be more like Subject A and not C?
Resistance vs. Resilience to AD pathologies

Avoid vs. Coping

Resistance vs Resilience
Clarifying terminology for preclinical studies

Eider M. Arenaza-Urquijo, PhD, and Prashanthi Venkitaraman, PhD

Neurology® 2018;90:695-703. doi:10.1212/WNL.0000000000005303
Concepts for brain aging: resistance, resilience, reserve, and compensation

Thomas J. Montine, Brenna A. Cholerton, María M. Corrada, Steven D. Edland, Margaret E. Flanagan, Laura S. Hemmy, Claudia H. Kawas, and Lon R. White

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

- Evolution of the concept
- NIA Initiative: Recent workshop on research definitions for Reserve and Resilience in aging and dementia
- Open opportunities and challenges
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
GOAL
The three year, NIA supported Collaboratory on Research Definitions will provide a platform for the exchange of ideas on definitions for the concepts of Reserve and Resilience and related concepts. The goal of the Collaboratory is to come to a consensus across the research community on operational definitions to further a cohesive research goal encompassing age-related and disease related cognitive decline.

OBJECTIVES
1. ANNUAL WORKSHOP – A novel approach to workshop where researchers from diverse background will have the opportunity to brainstorm the concept of reserve and resilience with each other and bring about consensus driven operational definitions.
2. CREATE FOCUSED WORKGROUPS – Establishing workgroups that will develop strategies to address specific plan across scientific disciplines.
3. IDENTIFY AND FUND PILOT GRANTS – Committees to identify promising research themes and fund pilot studies.
4. DEVELOP DATA AND INFORMATION SHARING PLATFORMS – Creating database of datasets relevant to the definitions for collaborative analytical research.

EXECUTIVE COMMITTEE MEMBERS
Yaakov Stern, PhD, Chair
Columbia University

Marilyn Albert, PhD
Johns Hopkins University

Carol Barnes, PhD
University of Arizona

Roberto Cabeza, PhD
Duke University

Alvaro Pascual-Leone, MD, PhD
Institute for the Aging Brain and the Center for Memory Health at Hebrew Senior Life

Peter Rapp, PhD
National Institute on Aging
4 Panels with 6 experts each
Normative Aging I
Normative Aging II
Alzheimer's Disease and Related Disorders I
Alzheimer's Disease and Related Disorders II
Differing Opinions

- Reserve
  - Reserve (10/25)

- Resilience (10/25) – umbrella term

- Resistance (6/25)

- Compensation (6/25)

- (Brain) Maintenance (11/25)
Differing Opinions

➢ Reserve
  • Reserve (10/25)
  • Cognitive (3/25) vs. Brain Reserve (5/25)

➢ Resilience (10/25) – umbrella term

➢ Resistance (6/25)

➢ Compensation (6/25)

➢ (Brain) Maintenance (11/25)
Outcomes of the meeting

- Agreement on the disconnect between pathology and cognitive symptoms

- Variety of research paradigms
  - animals/humans
  - biomarkers/pathology/clinical designs
  - E x G

- Workgroups to address key programmatic issues and common definitions
Save the date (2020)
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Mayo Clinic Study of Aging

PI: Ron Petersen M.D., Ph.D.
Funded by National Institute of Health, GHR Foundation, Alexander Family Foundation

Population-based study of 5000+ (3200 active) persons – age 30-89 years
A. Risk factors for clinical AD

Pubmed Search: Alzheimer Risk+

- APOE4
- Sex
- Diabetes
- Hypertension
- Dietary Patterns
- Smoking
- High Cholesterol
- Obesity
- Excessive alcohol intake
- Low Education
- Physical Inactivity

Number of Publications
Sleep Disruption and Amyloid

Poor sleep quality and the risk for cognitive decline and AD

- Sleep drives metabolite clearance (Xie L Science 2013)
- Cross-sectional biomarker studies (Varga AW Sleep 2016; Spira JAMA Neuro. 2013; Sprecher KE NBA 2015)

Longitudinal Amyloid Deposition vs. Sleep

Carvalho DZ JAMA Neurology 2018
Tau Stress and Tau

- Chronic stress $\rightarrow$ increased risk of AD clinical syndrome (Wilson RS, Neurology 2003, Johansson L, Brain 2010)
- High glucocorticoid levels and tau
- Brief resilience scale (BRS) – Stress-coping ability
- A+ CU older adults with lower stress coping abilities showed higher tau
Vascular Health and Neurodegeneration

Vemuri P et. al. JAMA Neurology 2017
Risk Factors for Neurodegeneration

Role of Sex

- Tau levels are not different between men and women when controlled for age and amyloid levels.
- Tau-mediated metabolic dysfunction is higher in women compared to men.
- Brain architecture differences.

*Ramanan et al. JAMA Open 2019*
Clinical Syndrome

Age
APOE
Sleep
Sex
Diabetes
Hypertension
Dyslipidemia
Obesity
Smoking
Chronic Conditions

Alzheimer’s Disease Biomarkers

$\text{A}\beta$
Age, APOE, Sleep

$\text{Tau}$
Age, Amyloid, Hypertension(?), Stress (?)

Non-AD ND
Age, Sex, Diabetes, Obesity, Smoking, Hypertension, Chronic Conditions
A. Understanding Risk Factors

- Effect size estimation
- Appropriate end-points
- Better subject recruitment (subpopulation effects)

Examples of Specific Triggers, Accelerators, Decelerators

Amyloid: APOE, Sleep

Neurodegeneration: Vascular Health, Non-AD processes

Cognition: Intellectual Enrichment

See Summary: Vemuri P, Exceptional Aging: Triggers, Accelerators, and the Net Sum Game
Alz, Res & Therapy 2018
B. Mechanisms of Resilience

Shift in cognitive performance curves but not Amyloid (CSF or PET) and Neurodegeneration (CSF or FDG or MRI)

Low verbal IQ

High verbal IQ

Vemuri P et. al., Brain 2011
B. Mechanisms of Cognitive Resilience

- **Task Invariant Network**
  - Stern Y et. al. NeuroImage 2018

- **SuperAgers**
  - Gefen T et. al. Corex 2017

Arenaza-Urquijo EM et. al. Brain 2019
C. Better Prognostic Models

“Generalizable” learning models and methodologies that capture the “complexity” and “heterogeneity” of the disease

- Gene Expression
- Non AD - Pathologies
- Amyloid and Tau
- Risk of Cognitive Impairment
- Cognitive Resilience
- Neurodegeneration
- Systemic vascular Health
Resilience and Vascular Pathways

- Resilience and Vascular Pathway
  - Education/occupation differences associated with later life white matter health through systemic vascular health
- Pathways converge to brain shrinkage
Resilience and Vascular Pathways

Vemuri et al., Annals of Neurology 2019
Summary

- Evolving Concepts of Reserve and Resilience
- Open Challenges and Opportunities
  - Risk/Protective Factors
  - Mechanisms
  - Modeling Heterogeneity
- Public policy (IFA and WHO – Michael Valenzuela)
Acknowledgments

Study Participants and Families
Aging and Dementia Imaging Lab
Mayo ADRC
Mayo Clinic Study of Aging

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B. Mechanisms of Cognitive Resilience

Differences in the predicted time to cognitive impairment for an 80 year old APOE4 carrier subject

High education/occupation
High mid and late life cognitive activity

Low education/occupation
Low mid and late life cognitive activity

Vemuri P. et al. JAMA Neurology 2014