Cognitive Reserve: An Evolving Concept
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What is reserve?

Brain Damage → Outcome

Reserve

Reserve may explain the disjunction between the degree of brain damage and the clinical manifestation of that damage.

Mechanisms underlying reserve

- Brain reserve:
  - More neurons/synapses to lose
  - Brain maintenance: Direct effect of lifestyle/activities on the brain

- Cognitive Reserve:
  - Resilience/plasticity of cognitive networks in the face of disruption

Passive, threshold model of reserve

Brain reserve: association between head circumference and Alzheimer’s disease

Satz, Neuropsychology 1993

Schweisfield, et al, 1997
Brain reserve is not so simple

The literature suggests that exercise and environmental stimulation can activate brain plasticity mechanisms and remodel neuronal circuitry in the brain. They can increase:

- Vascularization (exercise)
- Neurogenesis in the dentate
- Brain volume/Cortical thickness
- Neuronal survival and resistance to brain insult
- Brain-derived neurotrophic factor (BDNF) -- benefits brain plasticity processes

Memory aging and brain maintenance

- Relative lack of brain pathology is the biggest contributor to heterogeneity of cognitive aging
- Various lifestyle factors contribute to resisting the advent of pathology
- Brain maintenance could account for the current level of brain reserve

Incident dementia in the Washington Heights study

<table>
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<th>Group</th>
<th>N</th>
<th>Incident Cases</th>
<th>Relative Risk</th>
<th>95% CI</th>
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<td>High Occupation</td>
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</tbody>
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Stern et al, JAMA 1994
Literacy and memory decline in non-demented elders

Manly et al, JCEM 2003

Association of education with cognitive decline in the Washington Heights study

Zahodne et al, in press

More rapid memory decline in AD patients with higher educational attainment


Bronx Aging Study

**Education and rCBF**

Controlling for clinical disease severity, there is an inverse relationship between education and a functional imaging proxy for AD pathology.

*Stern et al, Ann Neurol 1992*

**Interaction of AD pathology and education**

The role of education and verbal abilities in altering the effect of age-related gray matter differences on cognition.

*Steffener et al, PLoS ONE 2014*
Using Functional Imaging to Study CR

- **Goal:** To understand how cognitive reserve may be neurally implemented.
  - Emphasis on networks mediating CR, not task performance
- **Working hypothesis:** CR operates through individual differences in how tasks are processed in the brain.
- **Basic approach:** Challenge participants with a demanding task and investigate differences in task-related activation between individuals with high and low CR.
- **Assumption:** Because CR modulates most aspects of cognitive performance in the presence of pathology, this approach should work with most demanding tasks.

Modified Sternberg Task

“Load-related” activation: the change in activation as set size increases

We focus on load-related activation because CR might be more related to the coping with increases in task demand than to task-specific features.

Load-dependent Activation During Retention:

Neural Reserve and Neural Compensation

- Two patterns were expressed during retention
- The primary network was expressed by both groups, but more efficient in the young
- The second network was expressed only by the elders
  - Higher expression was associated with poorer performance
  - Elders with greater volume loss in the primary network were more likely to express it
- Thus this is a compensatory pattern

Areas with significant mediated moderation

Mediated moderation sample result

Modified Sternberg Task

“Load-related” activation: the change in activation as set size increases

We focus on load-related activation because CR might be more related to the coping with increases in task demand than to task-specific features.
A generalized “task-invariant” neural representation of CR

- CR allows people to better maintain function in multiple activities and cognitive domains in the face of brain pathology.
- If a particular brain network subserves CR, it should be active across tasks with varying processing demands.
- Goal: Can we identify a pattern of CR-related brain activity:
  - that is common to 12 different tasks
  - whose expression in other tasks correlates a CR proxy
  - whose expression moderates the relationship between cortical thickness and task performance

Expression of the task-invariant CR network in a different fMRI activation task (in different people) correlates with NART

Expression of the task-invariant CR network moderates between cortical thickness and task performance

Clinical Implications: Cognitive reserve, aging and AD

- Two individuals who appear the same clinically, whether demented of non-demented, can have widely divergent levels of underlying age-related neural changes or AD pathology.
- Thus, the clinical diagnosis of normal aging, MCI or AD may be accompanied by very minimal pathology or more than enough to meet pathological criteria for AD.
- Measuring CR therefore becomes an important component of diagnosing and characterizing aging and dementia.

Clinical implications: Cognitive reserve, aging and AD

- Optimal clinical evaluation of age-related cognitive change or AD should include:
  - A measure of pathology
    - age-related atrophy, amyloid imaging
  - A measure of an individual’s CR, that is, the ability the ability to cope with this pathology:
    - Proxies for CR such as education or IQ
  - fMRI measured expression of “CR networks”
- This type of evaluation is important for:
  - early diagnosis and characterization
  - prognosis
  - measuring progression over time
  - assessing the effect of interventions

Deriving a task-invariant CR network

- 255 subjects from RANN study, age 20-80, with complete neuroimaging for 12 different tasks
- Randomly divide data into training sample of 200 observations and test sample of 41 observations
- In derivation sample, use scaled Subprofile modeling (SSM) to derive best fit NART pattern
- Project derived pattern into test sample and estimate NART in all 12 tasks
- Repeat steps 500 times, each time storing the derived patterns and the test prediction quality
- Compute weighted Z-map of pattern loadings for the 500 patterns
How would reserve-based interventions work?

Aging/AD Pathology → Clinical Disease

? → Brain Reserve

Brain Reserve → Cognitive Reserve

Cohrane Review: Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment

Eight out of 11 studies reported that aerobic exercise interventions resulted in ... improvements in cognitive capacity.

The largest effects on cognitive function were found on motor function and auditory attention (effect sizes of 1.17 and 0.50 respectively).

Moderate effects were observed for cognitive speed (effect size 0.26) and visual attention (effect size 0.26).

Physical Activity, Diet and Risk of Alzheimer’s Disease

Problems with cognitive interventions in aging

• Small effect size
• Poor generalization to other cognitive domains (far vs near transfer)
• Poor generalization day-to-day functions or IADLs
• Questionable sustainability of effects
• Relation to rate of aging or dementia onset not established

Space fortress intervention study

• Emphasis Change Training:
  – Subjects perform the whole task during training, but are required to systematically change their emphasis on major sub-components of the task.
  – Encourages subjects to explore the response alternative space
  – Promotes executive control
  – Is associated with improved transfer of training

• Our study had 3 groups: 12 weeks of game play with and without emphasis change training, and a no gameplay control group

Space Fortress: Fortress Destruction
Space Fortress: Cognitive Outcome

What will the large-scale project to enhance CR look like?

- Healthy elderly population
- Intensive, extensive, combined interventions
- Long-term follow-up
- Outcomes:
  - Rapidity of cognitive/functional decline
  - Incident dementia

Conclusions

- Epidemiologic and imaging evidence support the concept of reserve
- Reserve is malleable: it is influenced by aspects of experience in every stage of life
- Two forms of reserve:
  - Brain reserve: passive, supported by brain maintenance
  - Cognitive reserve: active
- The concept of cognitive reserve is applicable to a wide range of conditions that impact on brain function at all ages
- Imaging studies can help clarify the neural implementation of reserve
- Influencing reserve may delay or reverse the effects of aging or brain pathology