Cognitive Reserve: From Theory To Intervention

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What is 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
  – Anatomic changes on the basis of experience

• Cognitive Reserve:
  – Resilience/plasticity of cognitive networks in the face of disruption
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
• Neuronal survival and resistance to brain insult
• Brain-derived neurotrophic factor (BDNF) -- benefits brain plasticity processes
• Serotonin, dopamine, IGF-1
Advancing AD Pathology

Initiation Factors

Promoting Factors

Clinical Symptoms Appear

Diagnosis

Death
## Incident Dementia in The Washington Heights Study

<table>
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<tr>
<th>Group</th>
<th>N</th>
<th>Incident Cases</th>
<th>Relative Risk</th>
<th>95% CI</th>
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Stern et al, JAMA 1994
<table>
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<tr>
<th>Study (first-named author)</th>
<th>High activity (n/N)</th>
<th>Low activity (n/N)</th>
<th>OR (95% CI random)</th>
<th>Weight (%)</th>
<th>OR (95% CI random)</th>
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<td><strong>Premorbid IQ</strong></td>
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<td><strong>Total (95% CI)</strong></td>
<td>1733/21456</td>
<td>2574/21468</td>
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<td>100.0</td>
<td>0.54 (0.49-0.59)</td>
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Test for heterogeneity $\chi^2 = 55.62$, df=32, $p=0.006$
Test for overall effect $z=-2.30$, $p<0.00001$
Reserve, AD Pathology, and Clinical Diagnosis

Clinical Severity

Mild AD

Mild

MCI

normal

severe AD

Low reserve

High reserve

Diagnostic Threshold

Mild

Moderate

AD Pathology

Stern, JINS 2002
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

Education $\times$ AD path = 0.088, $p<.01$

Summary Measure of AD Pathology

Bennett DA et al, Neurology 2003
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.
Scheme for Studying Neural Implementation of Cognitive Reserve

Volume
Cortical Thickness
WMH Burden
WM Tract integrity
Resting CBF
Resting connectivity
Amyloid burden

Measured IQ
Education/Literacy
Leisure Activity
CR Network

Task or NP performance, Clinical Outcome

Activation Task Performance
Cognitive Domains
Function / ADL
Cognitive decline over time/
Incident MCI/AD

Task-related network expression

Age-or AD-related pathology

Measured CR or CR-specific network

Activation Task Performance
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How Would Reserve-based Interventions Work?

Aging/AD Pathology  \(\rightarrow\) Clinical Disease

\[\text{Brain Reserve}\quad ? \quad \text{Cognitive Reserve}\]
Father’s occupation

Cognition at 8 years

Education by 26 years

Own occupation at 43 years

NART at 53

Richards, JCEN 2003
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).
Problems With Cognitive Interventions to Date

- Small effect size
- Poor generalization to other cognitive domains
- 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

The Space Fortress Game
Space Fortress: Cognitive Outcome

Stern et al, Aging, Neuropsychology and Cognition, in press
Ongoing Intervention Trials

We have two ongoing intervention trials in healthy, cognitively intact individuals:

- **Combined space fortress and aerobic exercise**
  - Age 60-75
  - 3 conditions (N=30/condition): space fortress + aerobic exercise; SF + stretching/toning; computer games + S/T
  - 3 months with 12-month followup

- **Long-term aerobic exercise**
  - Ages 30-45 and 50-65 (N=130 for each)
  - 2 conditions: aerobic exercise vs. stretching/toning
  - 6 months with 12-month followup
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 cognitive reserve
• Reserve is malleable: it is influenced by aspects of experience in every stage of life
• Imaging studies can help us understand the neural implementation of cognitive reserve
• The concept of cognitive reserve is applicable to a wide range of conditions that impact on brain function at all ages
• Influencing cognitive reserve may delay or reverse the effects of aging or brain pathology