Thinking About Reserve from a Genetic and Lifespan Perspective

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• MRI, IQ, and academic achievement in 389 economically diverse children ages 4-22 years.

Smaller volume in:
- Frontal Lobes
- Hippocampus
- Temporal Lobes
The developmental brain differences explain as much as 20% of achievement deficits in low income children (and achievement deficits are associated with reduced occupational attainment).

From Hair et al., *JAMA Pediatrics*, 2015

Do education and occupational complexity influence later cognitive outcomes?

Or

Reverse causation? Do cognitive ability level and brain development influence educational and occupational attainment?
Average $h^2$ of environmental measures = .27
The heritability of general cognitive ability increases linearly from childhood to young adulthood

Additive genetic influences

Unique environmental influences

Common environmental influences
Gene-Environment (G-E) Correlation

- When people with a genetic propensity for some trait also live in an environment that supports expression of that trait.

- **Passive G-E Correlation**: When the environments are not sought out or selected.

- **Active G-E Correlation**: When the environments are sought out or selected.

- **Evocative (Reactive) G-E Correlation**: When genetic propensities evoke responses from the environment.

From Plomin et al., *Psychological Bulletin*, 1977
# Age 62 Cognitive Outcomes in VETSA

[N = 1009]

<table>
<thead>
<tr>
<th></th>
<th>Childhood SES</th>
<th>Lifetime Education</th>
<th>Occup. Complexity</th>
<th>Cognitive Activities</th>
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Type III Effects

Adjusted for age and race/ethnicity
## Age 62 Cognitive Outcomes in VETSA

\[N = 1009\]

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**Type III Effects**

Adjusted for age and race/ethnicity
Age 62 Cognitive Outcomes in VETSA: 12 Years Education at Age 20

[\text{N} = 711]

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<th></th>
<th>Childhood SES</th>
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Type III Effects
Adjusted for age and race/ethnicity
# Age 62 Cognitively Normal (N=774) vs. Amnestic MCI (N=126)
[MCI defined based on scores adjusted for age 20 GCA*]

<table>
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<th>Predictors</th>
<th>Effect Size (Cohen’s d)</th>
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Age 20 GCA
(based on MCI not adjusted for age 20 GCA)

≈ .52
475 VETSA Participants with Exactly 12 Years of Education
Genome-wide association meta-analysis of 78,308 individuals identifies new loci and genes influencing human intelligence


Intelligence is associated with important economic and health-related life outcomes. Despite intelligence having substantial heritability (0.54) and a confirmed polygenic nature, initial genetic studies were mostly underpowered. Here we report a meta-analysis for intelligence of 78,308 individuals. We identify 336 associated SNPs (MAGMA P < 5 × 10^-8) in 16 genomic loci, of which 15 are new. Around half of the SNPs are located inside a gene, implicating 22 genes, of which 11 are new findings.

Genome-based analyses identified an additional 30 genes (MAGMA P < 2.7 × 10^-9), of which all but one had not been implicated previously. We show that the identified genes are predominantly expressed in brain tissue, and pathway analysis indicates the involvement of genes regulating cell development (MAGMA P < 3.5 × 10^-8). Despite the well-known difference in twin-based heritability for intelligence in childhood (0.45) and adulthood (0.80), we show substantial genetic correlation \( r_G = 0.89 \), LD score regression \( P = 5.4 \times 10^{-20} \). These findings provide new insight into the genetic architecture of intelligence.

We combined genome-wide association study (GWAS) data for intelligence in 78,308 unrelated individuals from 13 cohorts (Online Methods). Of these individuals, full GWAS results for intelligence on \( n = 48,698 \) have been published in two different studies (\( n = 12,441 \) and \( n = 36,257 \), respectively), while GWAS results for the remaining 29,610 individuals have not been published previously. Across the different cohorts, various tests to measure intelligence were used. Therefore, following previous publications on combining intelligence phenotypes across different cohorts—the cohorts either calculated Spearman’s r or used a primary measure of fluid intelligence (Supplementary Table 1), which is known to correlate highly with \( r_P \). Previous research has shown that many different aspects of intelligence are highly correlated to each other and that Spearman’s r captures the latent general intelligence trait, irrespective of the specific tests used to construct it.

All association studies were performed on individuals of European descent; standard quality control procedures included correcting for population stratification and filtering on minor allele frequency (MAF) and imputation quality (Online Methods). As of the 13 cohorts consisted of children (aged <18 years, total \( n = 19,059 \)) and 5 consisted of adults (\( n = 58,790 \), aged 18–78 years), we first performed meta-analysis of the children- and adult-based cohorts separately using METAL software and subsequently calculated \( r_G \) using LD score regression. The estimated \( r_G = 0.89 \) (s.e.m. = 0.08, \( P = 5.4 \times 10^{-20} \)), indicating substantial overlap between the genetic variants influencing intelligence.

\[ r_G (\text{Educ.-Intell.}) = 0.70 \]
Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve

Daniel Barulli and Yaakov Stern
Cognitive Neuroscience Division, Department of Neurology, Columbia University College of Physicians and Surgeons, New York, USA

Cognitive reserve (CR) is a concept meant to account for the frequent discrepancy between an individual’s measured level of brain pathology and her expected cognitive performance. It is particularly important within the context of aging and dementia, but has wider applicability to all forms of brain damage. As such, it has intimate links to related compensatory and neuroprotective concepts, as well as to the related notion of brain reserve. In this article, we introduce the concept of cognitive reserve and explicate its potential cognitive and neural implementation. We conclude that cognitive reserve is compatible with established, and compatible with established, and conceptual boundaries in order to truly explain preserved cognitive function in the face of aging or brain damage.

The reserve concept

CR (see Glossary) has been proposed to account for the frequent discrepancy between a person’s underlying level of brain pathology (or age-related changes) and the observed functional and/or cognitive deficits that are expected to result from that pathology [1,2]. There is extensive epidemiological and experimental evidence for the existence of such reserve: life experiences, such as educational and occupational attainment, and engagement in leisure and social activities have each been associated with decreased risk of developing dementia [3-6], more successful aging [7], and reduced clinical changes in several other conditions, including traumatic brain injuries [8], Parkinson’s disease (PD) [9], multiple sclerosis (MS) [10], and HIV-related dementia [11] (Figure 1).

The status of CR as a concept has been debated since via [8] other related concepts, such as brain reserve (BR) [12] and more recently brain maintenance (BM) [13]. Several other related concepts have also been proposed [14]. In this review, we discuss recent work on these and related concepts, and attempt to delineate the subtle distinctions between them. We argue that, although the concepts differ in important respects, they are complementary as opposed to competing.

Models of reserve

Below we outline some of the dominant theories of preserved cognitive function in the face of advanced age, dementia, and/or brain damage. These theories focus either on compensatory mechanisms (emphasizing adaptations to diminished function or impaired brain structure), neuroprotective mechanisms (emphasizing factors which prevent diminished function and impaired structure), or some combination of both. The main models we discuss are BR, CR, BM, and neurocognitive scaffolding.

Glossary

Brain reserve (BR): Differences in brain size and other quantitative aspects of the brain that explain differential susceptibility to functional impairment in the presence of pathology or other neurological insult.

Cognitive reserve (CR): Differences in cognitive processes as a function of lifetime intellectual activities and other environmental factors that explain differential susceptibility to functional impairment in the presence of pathology or other neurological insult.

Neural reserve: One proposed neural basis of cognitive reserve that involves cognitive networks used by impaired individuals. Individual differences in network efficiency/capacity or the use of alternative strategies may provide reserve against the impact of brain damage.

Efficiency: The degree to which a task-related brain network must become activated in order to accomplish a given task.

Capacity: The degree to which a task-related brain network can be activated maximally to keep performing a task even in the face of increasing demands.

Neural compensation: One proposed neural basis of cognitive reserve involving the utilization of alternative networks not typically used by healthy individuals in order to maintain or improve cognitive performance.

Brain maintenance (BM): Individual differences in susceptibility to pathology, particularly in the context of aging, whereas reserve theory emphasizes compensatory mechanisms and maintenance theories emphasize neuroprotective mechanisms.

Scaffolding theory of aging and cognition (STAC): Scaffolding is the recruitment of additional neural circuits or networks when the primary networks become inefficient or damaged due to age, pathology, or even some normal task-related challenge. This process is in theory a general and lifelong property of the brain.

Compensation-related utilization of neural circuits hypothesis (CRUNCH): The theory that, as a task becomes more difficult, a network will be recruited to an increasing degree. At some point, increased difficulty overcomes the network, which ceases to function effectively.
“Cognitive reserve (CR): “Differences in cognitive processes as a function of lifetime intellectual activities and other environmental factors that explain differential susceptibility to functional impairment in the presence of pathology or other neurological insult.”

“These theories focus either on compensatory mechanisms (emphasizing adaptations to diminished function or impaired brain structure), neuroprotective mechanisms (emphasizing factors which prevent diminished function and impaired structure), or some combination of both.”

Barulli & Stern, *Trends in Neuroscience*, 2013
“CR is often estimated using proxy variables for lifetime exposures and cognitive activity…”

- Years of education
- Measures of crystallized intelligence (e.g., vocab)
- Literacy level
- Intellectually stimulating leisure activities
- Occupational complexity
- SES

Barulli & Stern, *Trends in Neuroscience*, 2013

Are these processes, mechanisms, or adaptations?
Is cognitive reserve a process or a variable?

Is cognitive reserve a dynamic phenomenon or a static measure?

Is it a verb or a noun?
Figure 1. Representation of how CR may mediate between AD pathology and its clinical expression based on epidemiological and imaging studies. The x-axis represents AD pathology, slowly increasing over time. The y-axis represents cognitive function. We assume that AD pathology increases over time at the same rate in two individuals with high and low reserve. The amount of pathology needed before cognitive function is affected is greater with higher CR, leading to a later change point. It follows that more pathology will be needed for the person with higher CR to meet clinical diagnostic criteria for AD, thus delaying the onset of the disease. Also, at any level of cognitive performance, AD pathology will be more severe in the individual with higher CR. Once cognitive decline begins, it is more rapid in the person with higher CR.
AD Pathology

Cognitive Reserve

Cognitive Status
- Weak form of reserve (Stern)
- Differential preservation (Tucker-Drob)
- Passive form of CR (Zahodne, Stern)
- Main effect
High Reserve

Low Reserve

Age

Cognitive Function

*Stronger form of reserve (Stern)
*Differential preservation (Tucker-Drob)
*Active form of CR (Zahodne, Stern)

*Post-MCI or post-dementia (Stern)

• Moderation (interaction) effects
Figure 1. Representation of how CR may mediate between AD pathology and its clinical expression based on epidemiological and imaging studies. The x-axis represents AD pathology, slowly increasing over time. The y-axis represents cognitive function. We assume that AD pathology increases over time at the same rate in two individuals with high and low reserve. The amount of pathology needed before cognitive function is affected is greater with higher CR, leading to a later change point [60,61]. It follows that more pathology will be needed for the person with higher CR to meet clinical diagnostic criteria for AD, thus delaying the onset of the disease. Also, at any level of cognitive performance, AD pathology will be more severe in the individual with higher CR [27,62]. Once cognitive decline begins, it is more rapid in the person with higher CR [61,63].
Cognitive reserve and long-term change in cognition in aging and preclinical Alzheimer's disease

Anja Soldan a,*, Corinne Pettigrew a, Qing Cai b, Jiangxia Wang b, Mei-Cheng Wang b, Abhay Moghekar a, Michael I. Miller c, Marilyn Albert a, the BiOCARD Research Team

Education: 17.0 (2.4)  
NART IQ: 119.6 (7.9)  
-2 SD = 12.2  
-2 SD = 103.8
Differing Effects of Education on Cognitive Decline in Diverse Elders With Low Versus High Educational Attainment

Laura B. Zahodne, Yaakov Stern, and Jennifer J. Manly
Columbia University

Low Educ. Group (0 – 8 years)  High Educ. Groups (9 - 20 years)
A Slightly Different Viewpoint
Cognitive Reserve:
• Intellectual Capacity (usually maximum, but could be current)
• Best approximated by IQ/GCA/g; second best is “hold” tests.
• Tends to decline with age
• May be maintained or decline may be slowed via activities that stimulate brain and cognition.
Cognitive reserve
• Intellectual capacity (early GCA, current NART, WRAT reading, Vocab)

Factors that may maintain/enhance cognitive reserve (≠ CR)
• Occupational Complexity
• Engagement in Cognitive Activities
• SES

“In between”
• Education ≈ CR as a weak proxy for intellectual capacity, but also may maintain/enhance CR.

Resilience (≠ CR)
• The ability or capacity to adapt to or recover from adversity.
What’s the relationship between resilience and reserve?

• Degree of resilience may differ as a function of differences in cognitive reserve.
Higher CR confers greater resilience with respect to memory in the face of brain adversity.
Concluding Thoughts

• What look like environmental exposures that enhance CR may actually be largely determined by genes and GE correlation.

• In epidemiological studies, education, occupational complexity, and engagement in cognitive activities appear to be more “neuroselective” than “neuroprotective.”

• Much of the education differences related to older adult outcomes may really be a function of longstanding IQ/GCA differences.
• People are *not* randomly assigned to their amount of educational exposure, occupational complexity, or engagement in cognitive activities.
  • Causal inferences are very limited, without random assignment to conditions.

• *Policy implications:*
  • If the effect is primarily reverse causation, then recommendations for increasing exposure to these activities may be of little benefit.
  
  • A key to enhancing CR as a protective factor against cognitive decline and dementia may be very early intervention to improve conditions that will allow for adequate brain development during sensitive periods.
On a More Optimistic Note...

- Interventions to enhance CR during later life:
  - There is growing evidence that interventions in later life can be effective.
  - Random assignment is critical.
  - The extent of engagement that people do on their own may not be enough.
  - Engagement may need to be intensive and lengthy.
Sending Your Grandparents to University Increases Cognitive Reserve: The Tasmanian Healthy Brain Project

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University of Tasmania

Mathew J. Summers
University of the Sunshine Coast and University of Tasmania

Nichole L. Saunders
University of Tasmania, Hobart

Jeffery J. Summers
University of Tasmania, and Liverpool John Moores University

David D. Ward
University of Tasmania, Hobart

Karen Ritchie
INSERM, Montpellier, France

James C. Vickers
University of Tasmania

Objective: Increasing an individual’s level of cognitive reserve (CR) has been suggested as a nonpharmacological approach to reducing the risk for Alzheimer’s disease. We examined changes in CR in older adults participating over 4 years in the Tasmanian Healthy Brain Project. Method: A sample of 459 healthy older adults between 50 and 79 years of age underwent a comprehensive annual assessment of current CR, neuropsychological function, and psychosocial factors over a 4-year period. The intervention group of 359 older adults ($M = 59.61$ years, $SD = 6.67$) having completed a minimum of 12 months part-time university study were compared against a control reference group of 100 adults ($M = 62.49$ years, $SD = 6.24$) who did not engage in further education. Results: Growth mixture modeling demonstrated that 44.3% of the control sample showed no change in CR, whereas 92.5% of the further education participants displayed a significant linear increase in CR over the 4 years of the study. These results indicate that older adults engaging in high-level mental stimulation display an increase in CR over a 4-year period. Conclusion: Increasing mental activity in older adulthood may be a viable strategy to improve cognitive function and offset cognitive decline associated with normal aging.

Keywords: aging, education, cognitive reserve, age-related cognitive decline
Research Article

The Impact of Sustained Engagement on Cognitive Function in Older Adults: The Synapse Project

Denise C. Park1,2, Jennifer Lodi-Smith3, Linda Drew1, Sara Haber1, Andrew Hebrank1, Gérard N. Bischof1,2, and Whitley Aamodt1
1Center for Vital Longevity, University of Texas at Dallas; 2School of Behavioral and Brain Sciences, University of Texas at Dallas; and 3Department of Psychology, Canisius College

Abstract

In the research reported here, we tested the hypothesis that sustained engagement in learning new skills that activated working memory, episodic memory, and reasoning over a period of 3 months would enhance cognitive function in older adults. In three conditions with high cognitive demands, participants learned to quilt, learned digital photography, or engaged in both activities for an average of 16.5 h a week for 3 months. Results at posttest indicated that episodic memory was enhanced in these productive-engagement conditions relative to receptive-engagement conditions, in which participants either engaged in nonintellectual activities with a social group or performed low-demand cognitive tasks with no social contact. The findings suggest that sustained engagement in cognitively demanding novel activities enhances memory function in older adulthood, but, somewhat surprisingly, we found limited cognitive benefits of sustained engagement in social activities.

Keywords
cognitive aging, intervention, engagement, cognitive training, aging cognition, episodic memory, cognitive reserve, working memory

Received 12/16/12, Revision accepted 7/2/13

Despite the tremendous strides made in scientifically based recommendations for promoting physical health in adulthood, less is known about what one should do to maintain cognitive health. As baby boomers age, the issue of maintaining healthy cognitive function has become a problem of increasing social urgency. There is a considerable amount of correlative data suggesting that individuals who are engaged in intellectual and social activities in middle and late adulthood fare better cognitively than their less active peers. For example, self-reports of higher participation in cognitive, leisure, and social activities are related to better cognitive ability in middle-aged adults (Singh-Manoux, Richards, & Marmot, 2005) and are even associated with a decreased risk of being diagnosed with Alzheimer's disease (Wilson et al., 2002; Wilson, Scherr, Schneider, Li, & Bennett, 2007).

Such results are intriguing, but there is surprisingly little evidence that lifestyle engagement maintains or improves cognitive function (Hertzog, Kramer, Wilson, & Lindenberger, 2008). No doubt the reason is the difficulty of translating this hypothesis into an experimental design in which volunteers agree to be randomly assigned to conditions that significantly alter their daily experiences for a sustained period. Two studies to date have approached this issue. In one study, participants in the Senior Odyssey program engaged in diverse problem-solving activities in a group-based competition that spanned approximately 5 months and showed small but reliable improvements in speed of processing, inductive reasoning, and divergent thinking skills when compared with no-treatment control participants (Stine-Morrow, 2001).

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E-mail: dcpark@utdallas.edu
“Brain Reserve: Differences in brain size and other quantitative aspects of the brain that explain susceptibility to functional impairment in the presence of pathology or other neurological insult.”

“Brain Maintenance: Individual differences in susceptibility to pathology, particularly in the context of aging; whereas reserve theories emphasize compensatory mechanisms, maintenance theories emphasize neuroprotective mechanisms.”

Barulli & Stern, Trends in Neuroscience, 2013
Experience induces structural and biochemical changes in the adult primate brain

Yevgenia Kozorovitskiy, Charles G. Gross*, Catherine Kopil, Lisa Battaglia, Meghan McBreen, Alexis M. Stranahan, and Elizabeth Gould

Department of Psychology, Princeton University, Princeton, NJ 08544

Contributed by Charles G. Gross, October 7, 2005

Primates exhibit complex social and cognitive behavior in the wild. In the laboratory, however, the expression of their behavior is usually limited. A large body of literature shows that living in an enriched environment alters dendrites and synapses in the brains of adult rodents. To date, no studies have investigated the influence of living in a complex environment on brain structure in adult primates. We assessed dendritic architecture, dendritic spines, and synaptic proteins in adult marmosets housed in either a standard laboratory cage or in one of two differentially complex habitats. A month-long stay in either complex environment enhanced the length and complexity of the dendritic tree and increased dendritic spine density and synaptic protein levels in the hippocampus and prefrontal cortex. No differences were detected between the brains of marmosets living in the two differentially complex environments. Our results show that the structure of the adult primate brain remains highly sensitive even to modest levels of experiential complexity. For adult primates, living in standard laboratory housing may induce reversible dendritic spine and synapse decreases in brain regions important for cognition.

dendritic spine | enriched environments | hippocampus | marmoset | prefrontal cortex

Experience can change the structure of the adult mammalian brain. A large body of evidence documents that exposing laboratory rodents to complex or “enriched” settings enhances multiple aspects of brain structure, including the size and weight of brain regions, the number and size of neurons and glia, the prefrontal cortex (PFC), and raised the expression levels of several synaptic proteins in the same areas. Dendritic architecture and spine and synaptic measures did not differ between monkeys living in the two environments of varying size and intricacy.

Materials and Methods

Animal Care and Treatment. Adult male and female marmosets, weighing 250–500 gm, 1.5–5.5 years old, were used for these studies. All of the animals were sexually mature and would be classified as young to middle-aged adults. Animal procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

At the start of the experiment, male–female pairs were assigned to move to either a new standard laboratory control cage (n = 10), a complex single cage (n = 10), or a complex double cage (n = 4). One pair of animals was housed in each cage. The distribution of ages for animals in different groups did not differ statistically, with the average age of 2.6, 3.4, and 3.7 years for animals in the control and complex single- and complex double-cage conditions, respectively.

Control animals lived in cages (29 × 30 × 32 inches) without enriching objects and received food in bowls. This cage size, the smallest used in the study, is almost double the minimum National Institutes of Health mandated standard for primates of this size. Animal pairs assigned to the complex single-cage condition lived in larger cages (48 × 30 × 66 inches) equipped with branches, hay, paste, vegetation, and 15 unique objects.
Resilience in Relation to Cognitive Reserve

• Hippocampal volume as an index of brain burden or advantage.

• *Cross-sectional*: Predict a memory x hippocampal volume interaction, i.e., the correlation will be higher in people with low CR than in people with high CR.
• Education, occupational complexity, and engagement in cognitive activities are often considered to be cognitive reserve proxies.

• All are associated with reduced risk for cognitive decline and dementia.

• Therefore...

  Increasing these things should be neuroprotective.