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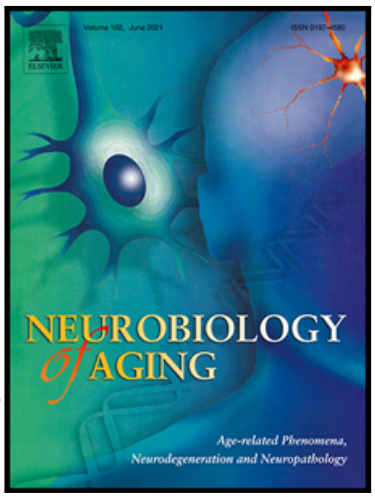

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A Framework for Concepts of Reserve and Resilience in Aging

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Abstract (not to exceed 170 words)

The study of factors, across species, that allow some individuals to age more successfully than others has important implications for individual wellbeing as well as health education, policy and intervention. Design of studies and communication across investigators in this area has been hampered by a diversity of terminology. The Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia was funded by the National Institute on Aging and established in 2019 as a three-year process of developing consensus definitions and research guidelines. The proposed Framework is based on an iterative process including three annual Workshops, focused workgroups, and input from numerous international investigators. It suggests the overarching term: resilience, and presents operational definitions for three concepts: cognitive reserve, brain maintenance and brain reserve. Twelve pilot studies that integrate these definitions are presented. The use of a common vocabulary and operational definitions will facilitate even greater progress in understanding the factors that are associated with successful aging.

Key words: resilience, cognitive reserve, brain maintenance, brain reserve

Introduction

The study of factors that allow some individuals to age more successfully than others, including for example genetics and life exposures, has important implications for individual wellbeing as well as health education, policy and intervention. Moreover, identifying factors that are relevant across species (i.e., humans and non-humans) is fundamentally necessary to facilitate studies of the neurobiological underpinnings of such factors.

In this context, overarching concepts like reserve and resilience are often invoked for capturing differential susceptibility to brain aging and disease. However, design of studies and communication across investigators in this area has been hampered by a diversity of terminology. Several groups have published proposed nomenclature and operational definitions for concepts including resilience, cognitive reserve, brain reserve, brain maintenance, compensation, scaffolding, resistance and resilience. Across these papers there are often disparate definitions for the same term. In addition, most of these papers focus on human studies, so the definitions and nomenclature are not optimally suitable for nonhuman studies.

The Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia was funded by the National Institute on Aging of the National Institutes of Health in the USA and established in 2019 as a three-year process of developing consensus definitions and research guidelines for cognitive reserve and related concepts. The present document is the result of an iterative process including three large annual Workshops, input from focused workgroups, and the extensive participation and consultation of over 40 selected, international expert investigators who utilize multiple research approaches and study both humans and nonhumans. Here we present a framework that includes definitions for three concepts, cognitive reserve, brain maintenance and brain reserve, along with suggested operational definitions to help guide the design of research investigating these concepts. We also include resilience as an overarching term that subsumes all of the concepts presented.

Our aim is to present a well-defined set of operational definitions in order to encourage, advance, and develop research on these concepts. At the same time, we want to encourage investigators who have different views or use a given concept differently to note how their definitions relate or differ with one of those described here. Similarly, this framework provides a basis for describing how the operational definition of another concept differs from those suggested here.

Our intention is not to limit the creativity or ingenuity of investigators, or to claim that the framework presents the only way to investigate these important concepts. We hope to encourage research that provides either evidence-based support for these concepts or that presents data that cannot be accommodated by the proposed operational definitions of these concepts. We also hope that referring to this framework will facilitate collaboration and comparison of findings across studies and species.

The Collaboratory also sponsored 12 studies that were intended to implement the suggested research guidelines and thus provide experimental examples of their operational utility. This disparate set of studies incorporates humans and nonhumans, as well as multiple approaches including epidemiologic, neuroimaging, and interventions. We include in the supplementary material descriptions of the pilot projects as wells as a table that summarizes the projects and how they incorporate the framework presented here. These provide useful real-world examples that illustrate how study designs can incorporate the suggested framework.

Our hope for this framework is that the use of a common vocabulary and operational definitions will facilitate even greater progress in understanding the factors that are associated with successful aging.

Resilience

The term resilience has been used in many contexts. Here we consider it a general term that subsumes any concept that relates to the capacity of the brain to maintain cognition and function with aging and disease. There can be substantial variability in the

mechanisms underlying resilience. Here, we present three, cognitive reserve, brain maintenance and brain reserve.

Cognitive reserve

1. Definition

Cognitive reserve (CR) is a property of the brain that allows for cognitive performance that is better than expected given the degree of life-course related brain changes and brain injury or disease:

- Property of the brain refers to multiple potential mechanisms including molecular, cellular and network levels. The working hypothesis is that these mechanisms help cope with or compensate for brain changes and the consequences of brain injury or disease.
- These mechanisms can be characterized via biological or cognitive-experimental approaches.
- Better than expected cognitive performance refers to differences ideally measured longitudinally.

CR can be influenced by multiple genetic and environmental factors, operating at various points or continuously across the lifespan.

2. Operational Definition: General considerations

Research aimed at further elucidating CR requires the inclusion of three components:

1. measures of life course-related brain changes, insults, disease, or risk factors that theoretically impact cognitive outcomes,

2. measures of associated change in cognition, and

3. a variable that influences the relationship between 1 and 2.

Ideally, the aim is to demonstrate that any proposed CR measure (e.g., a sociocultural or functional brain measure) moderates the relationship between 1 and 2.

For example, in an analysis where change in brain atrophy/pathology measures (component 1) predict change in cognition (component 2), and includes education as a hypothesized CR proxy (component 3), there is a statistical interaction between brain measures and education, such that level of education significantly moderates the association of brain measures with cognitive change.

Even without evidence for moderation, it can also be sufficient to demonstrate that a hypothesized CR proxy or measure is associated with cognitive performance over and above (e.g., after adjusting for) the effects of brain change, pathology, or insult. For example, in a multiple regression analysis of change in cognition that includes brain atrophy/pathology measures and a hypothesized CR proxy, the proxy should account for variance in cognitive performance. In this analysis, the CR proxy simply adds predictive information (a protective factor), a weaker form of CR evidence than moderation.

All three components are needed when investigating cognitive reserve. For example:

Demonstrating that expression of higher connectivity within a specific resting BOLD network is associated with slower cognitive decline is not sufficient to conclude that expression of this network reflects cognitive reserve. To make a claim about CR it must also include measures of age-related brain change, insult or disease that theoretically impact cognitive outcomes.

Similarly, a relationship between a particular genotype and rate of cognitive decline would not be sufficient to conclude that this genotype is associated with cognitive reserve. It would be important to demonstrate that the genotype's relationship to reduced rates of cognitive decline is expressed through moderation of age-related brain change or reduction of the expected impact on cognitive performance of a given brain insult or disease.

3. Specification of the 3 components needed to elucidate CR

3.1 Measures of life course-related brain developmental changes, injury or disease that theoretically impact cognitive outcomes.

This could consist, for example, of measures of anatomic changes such as loss of brain volume or white matter tract integrity, or onset and progression of disease pathology such as biomarkers of neurodegenerative disease.

These changes could be more extensively specified. Measures/mechanisms underlying aging that impact cognitive outcomes could include change in structure or function of synapses, oxidative damage/stress, impaired stress response signaling, Ca2+ dyshomeostasis and/or dysregulation, mitochondrial function, impaired waste disposal, inflammation, epigenetics, stem cell depletion, and altered neuronal activity/connectivity.

It is likely that unmeasured or unknown brain or pathologic changes contribute to inter-individual variance in the cognitive outcomes. Their eventual inclusion would increase the precision of elucidating CR.

3.2 Measures of cognition

This term encompasses measures of cognition and day-to-day function that change with aging and disease. When possible, it would be useful to adopt cognitive tests that show changes with age or brain disease, and that can be used across species. In this case, it is important to be mindful that formal operational similarity between human and nonhuman tasks is not sufficient, or even necessary; the tasks need to tap similar underlying neural systems.

3.3 Cognitive Reserve Proxy/Mechanism: A hypothesized variable that influences the relationship between 1 and 2

As the definition of CR states, these mechanisms can be characterized via biological or cognitive experimental approaches.

Proxies for cognitive reserve in human studies have included features associated with both endowment and experience, including early age IQ, cognitively stimulating exposures across the age span, education, occupational exposures, leisure activity,

social networks, or other exposures, hypothesized or to be discovered, that might impart cognitive reserve. Similar proxies such as behavioral training, physical exercise, environmental enrichment, social housing, or diet are applicable to nonhuman studies.

In addition, the nature of the cognitive reserve proxy or mechanism that influences the relationship between component 1 and 2 can be explored. For example, investigators might explore whether differential expression of a specific functional network is associated the degree of sustained cognitive function in the face of age-related brain changes that impact cognition. More generally, mechanisms underlying cognitive reserve could be specified at the molecular, cellular or network levels.

4. Example of studies of CR

In studies of CR, longitudinal designs optimally address the three features underlying the concept of CR. However, rich information can be gained from cross-sectional studies including discovering variables that appear to be critical for CR, establishing preliminary observations, providing insight into neurobiological mechanisms and developing research or conceptual approaches.

4.1 Longitudinal study incorporating measures of brain and cognitive change.

In a longitudinal study, one could explore whether some life exposure conceptually linked to CR moderates the relationship between change in brain status (e.g., volume, white matter tract integrity, white matter hyperintensity burden) and change in cognition. For example, one could establish a relationship between age-related changes in cortical thickness/surface area, brain volume, and white matter tract integrity with changes in cognition. The potential moderation by education of this relationship could then be explored. Such moderation would provide support for the idea that higher education is associated with cognitive reserve.

Some longitudinal studies may have no direct measures of brain change. Analyses that assume parity across all followed individuals or incorporate risk factors for brain changes could suggest hypotheses and guide subsequent studies.

4.2 Neural implementation of cognitive reserve:

Although variables such as IQ, education, occupational attainment etc. can be associated with cognitive reserve as described in 4.1, i.e., moderating between measures that theoretically impact cognitive outcomes (component 1) and measures of associated change in cognition (component 2), more insight into the mechanisms underlying cognitive reserve might be obtained from studies that directly examine neural mechanisms. In both human and nonhuman studies, imaging techniques including functional MRI (fMRI), spectroscopy, and EEG are uniquely suited for longitudinal measurements, providing in-depth assessments of brain structure, neural activity, and the chemistry in the aging brain. CSF, plasma/serum, and extracellular vesicle biology in blood are advancing rapidly and may provide a translatable fluid biopsy for relevant brain changes in this context.

Thus, one goal might be to identify functional networks or circuits, whose differential expression moderates the relationship between age-related brain changes that impact cognitive outcomes and the associated change in cognition. For example, longitudinal studies of aging or neurodegenerative disease can investigate how the relationship between changes in structure/function and cognition/clinical status can be moderated by proposed reserve-related networks. It would be of interest to determine whether differential expression of this network is related to life exposures such as education or occupational experience. This would create a relationship between a proxy for CR and a potential brain mechanism underlying that proxy.

4.3 Intervention studies and natural experiments

Intervention studies can most directly test whether some exposure or mechanism underlies CR by examining whether the intervention moderates the effect of age-related brain changes on cognitive outcomes. These studies can help explore mechanisms underlying CR.

Similarly, controlled perturbations such as transcranial magnetic or direct current stimulation could model brain insult, stressor or disease. Alternately, they could be used to modulate activity in networks/circuits associated with CR, and by suppressing it or

facilitating it, gain causal and mechanistic insights, and even potentially explore therapeutic interventions.

Sometimes, environmental changes can be used as natural experiments. A natural experiment is a situation when some change occurs in the environment that is not under experimental control and approximates random assignment. An example of such a natural experiment is changes to compulsory schooling laws. Conversely, animal models that feature increased individual differences in cognitive aging, under conditions of tightly controlled life-course exposures, can test for inherent genetic and biological moderators or mediators of CR. Quasi-experimental twin design is closest to this experimental design in humans. This design can utilize co-twins with different levels of exposures such as educational or occupational attainment.

Brain Maintenance

1. Definition

Brain maintenance (BM) refers to the relative absence of changes in neural resources or neuropathologic change over time as a determinant of preserved cognition in older age.

BM can be influenced by multiple genetic and environmental factors, operating at various points across the lifespan.

2. Operational Definition

BM is influenced by factors (genes, sex, early life influence or differential experiences) that slow or prevent brain changes associated with aging and disease. The emphasis centers on change over time. Thus, BM may be operationalized as minimal changes in brain markers of aging or disease associated with preservation of cognitive function.

Research aimed at further elucidating BM requires the inclusion of three components.

1. measures of age-related brain changes, injury or disease that theoretically impact cognitive outcomes,

2. measures of change in cognition.

Demonstrating a link between less change in 1 and less change in 2 would be evidence of brain maintenance.

To investigate potential mechanisms of individual differences in BM one could examine:

3. a hypothetical variable that influences 1.

This variable can encompass many of the same exposures potentially associated with CR. However, their impact on BM in this context would be specific to maintaining the structural and functional integrity of the brain.

3. Example studies of BM

BM is optimally ascertained in longitudinal designs. A single time point measurement cannot definitively differentiate people who have maintained their brain from those who did not but started at a higher baseline level. In both human and nonhuman studies this issue can be addressed to some degree by determining what level of brain status is expected for a particular age, or considering a given brain measure relative to the distribution seen in younger subjects. However, longitudinal designs are preferable to examine factors underlying interindividual differences in the change in neural resources that are in turn associated with differences in cognitive outcomes.

3.1 Longitudinal study of brain maintenance

A general approach to studying BM would be to examine longitudinally whether individual differences in the rate of age- or disease-related brain anomalies accumulated over time are related to individual differences in the rate of cognitive change.

3.2 Exposures related to brain maintenance.

An extension of study 3.1 would be to assess potential proxies or mechanisms (e.g., genetic, lifestyle, neural) that are associated with these different trajectories of brain maintenance/change.

In summary, BM and CR are complementary concepts. BM accounts for individual differences in cognitive trajectories that are associated with differences in rate of brain change. In contrast, CR addresses individual differences in cognitive trajectories controlling for changes in neural resources or neuropathology.

Brain Reserve

1. Definition

Brain reserve (BR) has been used to reflect the neurobiological status of the brain (numbers of neurons, synapses, etc.) at any point in time. BR does not involve active adaptation of functional cognitive processes in the presence of injury or disease as does CR.

2. Operational definition and Example Studies

Research aimed at further elucidating BR requires the inclusion of 2 components:

1. measures of brain features that theoretically are associated with cognition.
2. associated measures of cognition.

3. Example Studies of BR

Longitudinally, differences in BR at a point in time could account for the observation that individuals starting at a different level of cognition may show the same rate of age- or disease-related cognitive decline. This could reflect different initial levels (intercepts) due to variation in BR, but similar rates of change (slopes) due to similar depletion of BR. This is distinguished from brain maintenance, where slopes would differ as a function of the degree of brain maintenance.

BR has also been associated with individual differences in level of cognition given a specific amount of brain change, injury or disease, such as amyloid plaques and neurofibrillary tangles. This association could rely on a threshold model, where a specific amount of depletion of neurobiological capital results disease-related changes. Those who initially have a higher BR can tolerate more depletion before they show symptoms.

Conclusion

Here we present a framework that includes well defined operational definitions for three concepts: cognitive reserve, brain maintenance and brain reserve. We also propose the term resilience to subsume all of the concepts presented. The operational definitions were carefully designed to be applicable to both human and nonhuman studies.

We believe that the use of a common vocabulary and operational definitions will facilitate research design and communication. The framework also provides a basis for describing how the operational definition of another concept differs from those suggested here.

Our hope for this framework is that a common vocabulary and operational definitions will facilitate even greater progress in understanding the factors that are associated with successful aging and lifelong brain health.

Investigator	Human/Nonhuman	Cognitive Reserve (CR)				Brain Maintenance (BM)			
		Brain Change	**Cognitive change**	**Factor associated with CR**	**CR Hypothesis**	**Brain Change**	**Cognitive change**	**Factor promoting BM**	**BM hypothesis**
Lídia Vaqué-Alcázar	H	Structural MRI measures of age-related change	Episodic memory measures at least two timepoints	years of education and lifestyle associated measures	Factors associated with CR will moderate the relationship between change in multimodal MRI-based measures and change in episodic memory	Structural MRI measures of age-related change	Episodic memory measures at least two timepoints	years of education and lifestyle associated measures	Factor promoting BM will be related to age-related structural and/or functional brain change, resulting in preservation of episodic memory

r									
Daniel Gray	N	structural and diffusion-weighted MRI scans	cognitive assessment to identify high-, average-, and low-performing rats for an age group	2 proteins critical for synapse health and plasticity: neuronal pentraxin 2 (NPTX2) and perineuronal nets (proteoglycans)	Expression of proteins associated with synapse health will moderate the relationship between structural changes and levels of cognitive function				
Holly Hunsberger	N	senescent cells	contextual memory and memory trace	repeated acquisition training at early age	Early life training will be associated with more preserved memory trace cell activation and memory in the presence of senescent cells	senescent cells	contextual memory and memory trace	mouse strain or sex	Mouse strain or sex be associated with more preserved senescent cells, resulting in more preserved memory trace and contextual memory
Anna Marseglia	H	AD neurodegeneration and vascular changes (SVD)	global cognition	differences between predicted brain age and chronological age given the same level of cognition	The CR measure will moderate the relationship between AD/SVD and cognition				
Rory Boyle	H	AD neurodegeneration measured by a cortical thickness pattern and brain structure (WM hyperintensities, WM integrity, vascular health)	cognitive function	expression of a functional network that is correlated with a residual score. The residual score reflects the degree to which cognition is better or worse than expected given brain structure, age, and sex	The CR functional network will (a) be associated with longitudinal cognitive function above and beyond the effects of AD signature cortical thickness or (b) moderate the impact of the change in AD signature	AD neurodegeneration and brain structure	cognitive function	Life exposures	A brain-predicted age difference residual reflecting the deviation of an individual's MRI brain measures from healthy aging patterns will be associated with longitudinal cognitive function.

					cortical thickness on longitudinal cognitive function. Both effects ((a) or (b)) will remain statistically significant after accounting for brain structure measures.				
Colin Groot	H	Structural measures and AD pathology (CSF amyloid and tau)	cognitive change in: Study 1 nondemented individuals with AD pathology; Study 2: individuals with diagnosed AD	Education	Study 1: CR will be represented by higher initial performance. CR will moderate AD pathology resulting in a longer time until the beginning of cognitive decline. Study 2: there will be more rapid decline in individuals with higher education, driven by pathology being be more advanced at the time of diagnosis.	Structural measures and AD pathology (CSF amyloid and tau)	cognitive change in: Study 1 nondemented individuals with AD pathology; Study 2: individuals with diagnosed AD	Education	Study 1: differential rate of structural measures decline and AD pathology increase time influence the time to develop AD. Study 2: Differences in the rate of increase in AD pathology will account for differences in rate of cognitive decline. In both cases education could account for differences in BM
Gabriel Ziegler	H	hippocampal network atrophy, as a longitudinal measure of aging-related brain pathology	Cognitive battery	FADE score: A model of the degree to which older people show youth-like fMRI activity patterns	The impact of change in hippocampal network atrophy on rates of cognitive decline will be moderated by the FADE score.	hippocampal network atrophy	Cognitive battery	FADE score: A model of the degree to which older people show youth like fMRI activity patterns	The FADE score will change with hippocampal atrophy. Both will correlate with change in cognitive performance
Chr	H	aggregate of age related	cognitive summary scores	an fMRI pattern that correlates with task performance and is	Expression of the CR fMRI pattern will be				

istianHabeck		changes in regional cortical volume, regional cortical thickness, tract integrity		uncorrelated with brain structure	correlated with CR -related variable such as education, IQ, and life exposures. In external data, the CR fMRI pattern will account for cognitive performance beyond age and brain structure.				
MelisAnatürk	H	Brain age gap (BAG): a machine learning estimate of how much each individual's MRI brain measures deviate from healthy aging patterns	Cognitive age gap (CAG): machine learning metric of how much each individual's cognition deviates from healthy aging patterns	premorbid IQ, education and a lifestyle marker (composite measure of smoking status, physical activity and alcohol intake)	Changes in BAG on CAG trajectories will be moderated by factors associated with CR	Brain age gap (BAG)	Cognitive age gap (CAG):	premorbid IQ, education and a lifestyle marker	Less change in BAG will be associated less decline in CAG. BM promoting factors will be associated with lower BAG
Tom Foster	N	Senescence-related genes identified in this study	Spatial memory: Performance in watermaze	potential resilience genes defined as 1. expressed differently between unimpaired aged and young rats, but are not differently from young and aged impaired rats, genes associated with network efficiency or compensation	The identified potential resilience genes or networks will moderate the effect of senescence genes on spatial memory	Senescence-related genes identified in this study	Spatial memory: Performance in watermaze	potential maintenance-related genes: those that ae most different between young and aged impaired rats	The identified maintenance-related genes will delay the expression of senescence-related genes, thus preserving spatial memory
SaraJames	H/N	Multiple MRI measures, as well as molecular and cellular measures	Cognitive test or incidence of MCI/dementia	Human: Early age IQ, Early life circumstance, education, occupation, leisure activity, physical activity, social networks, vascular health, crystalized ability, personality/mental	Some measures associated with CR will modify the impact of age-related brain changes, insults or disease on cognition and cognitive decline of a	Multiple MRI measures, as well as molecular and cellular	Cognitive test or incidence of MCI/dementia	The same as factors associated with CR	Some exposures will be directly associated with the development and change of a range of measures indexing age-related brain changes, insults or disease. These brain changes will be directly associated

				health/psychological constructs and fMRI networks. Non-human: Behavioral training, Environmental enrichment, Social housing, Diet	range of measures indexing	measures	tia		with cognition and cognitive decline.
Erovuoksimaa	H	changes in relative cortical surface area and thickness in regions implicated in Alzheimer's disease	episodic memory tests from three time points (at ages 56y, 62y, 68y)	general cognitive ability at age 20 and lifetime years of education	Factors associated with CR will moderate the effects of cortical surface area / thickness change on cognitive trajectories	changes in relative cortical surface area and thickness in regions implicated in Alzheimer's disease	episodic memory tests from three time points (at ages 56y, 62y, 68y)	general cognitive ability at age 20 and lifetime years of education	Factors promoting BM will be associated with less brain change, resulting in better preserved cognition

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Disclosures

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