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Brain Reserve, Cognitive Reserve, Compensation, and Maintenance: Operationalization, Validity, and Mechanisms of Cognitive Resilience

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Abstract

Significant individual differences in the trajectories of cognitive aging and in age-related changes of brain structure and function have been reported in the past half-century. In some individuals, significant pathological changes in the brain are observed in conjunction with relatively well-preserved cognitive performance. Multiple constructs have been invoked to explain this paradox of resilience, including brain reserve, cognitive reserve, brain maintenance, and compensation. The aim of this session of the Cognitive Aging Summit III was to examine the overlap and distinctions in definitions and measurement of these constructs, to discuss their neural and behavioral correlates, and to propose plausible mechanisms of individual cognitive resilience in the face of typical age-related neural declines.

Keywords

Cognitive aging; measurement; animal models; MRI; functional connectivity

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1. Introduction

Typical aging is accompanied by declines in multiple cognitive skills, but trajectories of aging exhibit substantial individual differences. Some individuals show precipitous deterioration, while others maintain their cognitive performance to the end of life. Although multiple factors may determine individual paths of cognitive aging, some people appear more resilient than others to the detrimental effects of aging and the associated pathological changes. Although its origin remains obscure, the concept of individual resilience received empirical support in the late 1960s, after scientists observed a discrepancy between the burden of brain pathology and ante-mortem cognitive performance in a series of brain specimens (Blessed et al., 1968).

These findings, combined with later observations of recovery from brain injury (Satz, 1993) and noninvasive neuroimaging of patients with dementia (Stern et al., 1992) have led to the hypothesis that some individuals may possess a reserve that allows them to withstand the onslaught of cognitive aging and to mitigate the cognitive impairment expected from brain pathology. To explain this finding, scientists have invoked multiple constructs, including brain reserve, cognitive reserve, brain maintenance, and compensation. Brain reserve is a neuroanatomic resource that reflects structural properties of the brain that somehow afford a surplus capacity to maintain cognitive function despite substantial loss of their material substrate. With cognitive reserve, the cognitive skills and abilities that are acquired before the onset of neural deterioration serve as a hedge against—or even actively mitigate—loss of function inflicted by the progressive brain failure, while revealing significant individual differences in resilience and flexibility. Some people appear to be better than others in maintaining structural and functional properties of their brains while aging, with multiple factors contributing to variations in success. The mechanisms by which brain and cognitive reserve bolster individual ability to maintain intact cognitive performance over time and thus contribute to more successful cognitive aging remain a topic for ongoing research.

The relationship between brain reserve, cognitive reserve, maintenance, and compensation and their contribution to resilience is the focus of a lively debate within the research community. The arguments center on the core issues of definition and measurement of each construct, their differential validity, and their neural mechanisms, as well as their potential for guiding development of interventions to mitigate the effects of cognitive aging on behavior. Regardless of how the related and partially overlapping constructs are understood in the overarching notion of resilience, they are all theoretical entities that currently cannot be measured directly. Therefore, a problem of measuring resilience and evaluating the validity of its indicators needs to be addressed.

During this session of the Cognitive Aging Summit III, chaired by Naftali Raz, the speakers sought to define and describe these constructs to explain the phenomenon of resilience: brain reserve, cognitive reserve, maintenance, and compensation. They examined the fundamental definition and measurement issues facing the study of resilience and discussed models and mechanisms that describe brain adaptation to age-related changes, and, in principle, could guide interventions to alleviate age-related cognitive declines.

2. Reserve: An Evolving Concept

Yaakov Stern

The term reserve describes the difference between the degree of brain damage observed in an individual and the clinical manifestation of that damage. At least two models explain reserve.

The brain reserve model defines reserve as a physical trait: some people have larger brains, with more neurons and synapses, which may allow their brains to absorb more injury before cognitive function is affected (Katzman et al., 1988; Satz, 1993). Brain reserve may therefore be thought of as individual differences in the hardware of the brain. Brain reserve can be conceived as a passive entity, which reflects an overt expression of impairment only after an individual's capacity falls below a crucial threshold of loss of the brain substrate (Satz, 1993). People with greater initial brain capacity can therefore tolerate more neurological attrition in absolute terms before crossing into impairment. However, some people can maintain their brain better than others throughout the aging process as a function of genetics and life experience—a concept called brain maintenance (Nyberg et al., 2012). Thus, past life experience can influence the status of brain reserve at any time.

The cognitive reserve model posits flexibility and adaptability of cognitive/brain networks that allow the brain to actively resist the effects of age- or disease-related changes (Stern, 2002). The efficiency and capacity of individuals' cognitive networks may differ. Similarly, some individuals may be better able to compensate for brain damage by using alternate brain networks to maintain function (Cabeza, 2002; Stern, 2009). Cognitive reserve—with its focus on functionality, plasticity, and adaptability—may be thought of as software that carries out the calculations in the brain, which is influenced by all aspects of life experience (Stern, 2009). Thus, the cognitive reserve model can be considered active. Given the same amount of brain reserve, some people can better cope with age- or pathology-related brain changes than others, depending on their cognitive reserve capabilities.

Evidence supporting cognitive reserve includes epidemiologic data regarding lifestyle and clinical outcomes. Individuals with higher premorbid IQ, educational or occupational attainment, or engagement in late-life leisure activities have a reduced risk of developing dementia (Deary et al., 2004; Scarmeas et al., 2001; Stern et al., 1994; Valenzuela and Sachdev, 2006). and may have slower rates of age-related cognitive decline (Zahodne, 2015). The underlying assumption is that some aspect of these experiences has allowed people to better cope with age- or disease-related changes. Thus, these experiences have often been used as proxy measures for cognitive reserve. In addition, many studies have demonstrated that, in individuals with comparable clinical severity of mild cognitive impairment or Alzheimer's disease, those with higher levels of these cognitive reserve proxies have more advanced Alzheimer's type pathology (Bennett et al., 2003; Ewers et al., 2013; Stern et al., 1992). These observations indicate that individuals with higher cognitive reserve can better cope with the brain changes and can maintain higher function despite brain deterioration.

Cognitive reserve is typically measured via proxies that summarize experiences that affect reserve, such as educational and occupational attainment (Stern et al., 1999). Although these

measures moderate the relationship between brain changes and clinical status, they are not direct measures of cognitive reserve and do not reflect the underlying brain processes through which cognitive reserve operates. Many investigators have studied the “neural implementation” of cognitive reserve. As these relationships become better understood, proxies for cognitive reserve may be replaced with direct measures of specific brain processes that underlie cognitive reserve. For example, our group has recently described a pattern of brain activation that occurs when people are performing almost any task and that is expressed to a greater degree by people with higher IQ than those with lower IQ (Deary et al., 2004). Furthermore, expression of this pattern moderates the relationship between age-related brain changes and performance. Another group has described a resting BOLD pattern that seems to be associated with increased cognitive reserve (Franzmeier et al., 2017). Expression of such a pattern may be a more direct measure of cognitive reserve, and examination of the pattern may yield information about how cognitive reserve is neurally implemented.

Brain reserve and cognitive reserve are not mutually exclusive. Structural features and dynamic network capacity both play a role in how the brain functions in the face of age-related brain changes and pathology. Furthermore, the concept of brain maintenance suggests that life experiences can mitigate age-related brain changes. A better understanding of the brain’s adaptability will enable approaches to preserve or increase both brain and cognitive reserve to delay or reverse the effects of age-related cognitive decline.

3. Animal Models of Brain Adaptation and Compensation in Aging

Carol A. Barnes

Although humans are unique in developing Alzheimer’s disease, many animals display signs of neurodegeneration and cognitive decline as they age. Studies of aging, memory, cognitive reserve, and compensation in animals may therefore yield important insights into changes in brain function during normal aging in humans. Because it is possible to conduct much more detailed mechanistic studies in animals than in humans, animal studies are an important piece of the cognitive aging and decline puzzle.

With well-reasoned models, animal studies can provide powerful insights into the molecular, cellular, and neural mechanisms of human aging. To date, researchers have looked for elements of brain structure and function that are common across species and have tried to extrapolate insights gained from these studies to humans. Tests of spatial memory—the ability to recall where things are in physical or virtual three-dimensional space—are particularly useful when comparing data from studies of humans and other animals because language is not an essential aspect of that area of cognition. Spatial memory and spatial navigation strategies are linked to the functional and structural properties of brain structures that are common to all mammals: the hippocampus, the entorhinal cortex, and the striatum. Measurements of spatial memory and spatial navigation in classic laboratory paradigms—for example, the water maze—have been extrapolated into the human realm via virtual reality analogues (Daugherty et al., 2016; Moffat et al., 2001) to reveal individual differences in the associations between regional brain properties and cognition in humans and rodents (Lester et al., 2017).

Notably, spatial memory deficits have been observed across all animals at the ages at which they are considered to be “old,” for example, approximately 65 years for humans, 22 years for macaques, and 2 years for rats. The timing and extent of these memory differences and changes over time, however, exhibit substantial inter-individual variability. Animal studies helped to establish that age-related memory declines do not stem from cell death, which is not simply a part of normal aging. In fact, within the hippocampus, a brain region key to the formation of new memories, there is no age-related difference in abundance of its primary cell types—neither granule cells of the dentate gyrus, nor CA3 or CA1 pyramidal cells (Gray and Barnes, 2015; Keuker et al., 2003; Rapp and Gallagher, 1996; West, 1993).

Following these observations, scientists focused the animal models of human memory on the age-related loss of *function* of neurons, that is, their plasticity, adaptability, or connectivity, rather than the *number* of neurons. The overarching hypothesis is that older individuals with high cognitive ability would have more plastic, denser, or stronger connections among their neurons than would their lower-performing peers (Barnes, 1979; Barnes and McNaughton, 1980; Bondareff and Geinisman, 1976; Norris et al., 1996; Rogalski et al., 2012; Stoub et al., 2012).

Aging animals frequently show loss in the components of neuropil. They evidence thinner dendritic arbors and greater “axon pruning,” a loss of pathways carrying signals from neural cell bodies to other cells via synaptic connections. As the main components of neuropil, axons and dendrites are essential for formation of synapses and eventual arrangement of individual neurons into complex circuits. Their loss during aging is therefore a plausible explanation for impaired communication among neurons, regardless of the sheer number of communicating cells. Importantly, studies in rats revealed that older rats that display fewer granule cell synapses compared to their younger counterparts show increased strength of the individual signals transmitted across the remaining synapses (Barnes and McNaughton, 1980). Thus, an adjustment in synaptic strength may form a neural substrate of compensation, as far as it provides some degree of stability of function across the neural circuit.

Studies in aging rodents show that although synapses onto granule cells are stronger in older animals, the overall output from granule cells onto CA3 neurons is still reduced. Consistent with the idea that the brain may continuously adapt during the normative aging process, CA3 neurons that receive less input from their partner neurons with age are more sensitive to the input they receive, that is, they are hyper-excitable (Foster et al., 1991; Wilson et al., 2005). Studies in non-human primates also show increased excitability of single CA3 neurons, which suggests a possible mechanism for this change in circuit function: a decrease in the number of inhibitory neurons in the CA3 region that contain the neurotransmitter GABA effectively reduces levels of inhibition of CA3 cells (Thome et al., 2016). Consistent with this observation, magnetic resonance imaging (MRI) memory experiments in older humans show greater activation in the CA3 region (Yassa et al., 2011).

These studies underscore the brain’s adaptability in the face of reduced neural resources and relative increases in external demands, as outlined in a recent model of brain adaptability and plasticity (Lövdén et al., 2010). Elucidation of the molecular and cellular mechanisms

that control synapse numbers and function throughout the lifespan may provide important insights into the key mechanisms of cognitive decline. To advance this goal, we must improve translational strategies that bridge animal and human research on aging.

4. Age Differences in the Dynamic Flexibility of Brain Activity and Functional Connectivity

Cheryl L. Grady

The dynamic flexibility of the brain allows it to incorporate and react to new information in real time and to rebalance or form new neural connections to adapt to new circumstances (Garrett et al., 2013). In older adults (e.g., at least 65 years of age), several neural processes that are fundamentally associated with dynamic flexibility are altered. These include differentiation, defined as stimulus-related or task-related specificity of activity in various neural networks, and functional connectivity among brain networks.

Studies of task dynamics in older adults show dedifferentiation of brain activity during memory and other tasks (i.e., reduced selectivity). This observation has led to the hypothesis that selective brain activity is important for some subset of memory tasks; it further suggests that reduced selectivity may be a mechanism underlying the observed age differences. For example, a representative memory function that shows age-related differences is associative memory, which reflects the ability to bind together disparate pieces of information and to form a unified representation of the combined stimulus (Old and Naveh-Benjamin, 2008). In a typical experiment to test this memory skill, participants are shown pairs of unrelated images and later are asked to discriminate re-presented (“old”) pairs from new pairs that the participants have not seen. On average, older adults remember these paired stimuli more poorly than do younger adults. When the tests are administered as a part of a functional MRI (fMRI) experiment, older participants show reduced selectivity in brain regions that are specifically involved in encoding the paired images (Saverino et al., 2016), consistent with their reduced associative memory. This provides evidence that reduced selectivity (dedifferentiation) of brain activity during encoding, one type of dynamic brain activity, may be an important mechanism underlying reduced memory performance in older adults.

The past two decades saw a surge in studies of task-free (resting state) connection dynamics of brain activity in fMRI experiments, providing another measure of brain flexibility, that is, the functional connectivity within and between brain networks at rest. In this paradigm, time-dependent fMRI signals recorded in specific neuroanatomic locations are examined for coherent and covarying activity, with higher coherence signifying stronger functional connectivity. Three functional brain networks of particular interest are the default mode network, the dorsal attention network, and the frontoparietal control network, which have been linked to internal attention, external attention, and cognitive control, respectively (Spreng et al., 2013). In general, older adults have weaker connections within nodes of an individual network but stronger connections between different networks (Chan et al., 2014). Frontoparietal control network integration is inversely related to default mode network connectivity in older adults, with stronger between-network connections in the frontoparietal control network in those individuals with weaker connections within the default mode

network (Grady et al., 2016). In addition, frontoparietal control network integration is positively correlated with memory performance in older adults. These observations raise the possibility that more robust frontoparietal control network connectivity might be a source of cognitive reserve.

Both lines of research converge on the notion of robust age-related and individual differences in the dynamic range of brain activity. Age-related reduction in selectivity of task-related brain activity is linked to poorer associative memory, whereas increased integration of the frontoparietal control network at rest is associated with better memory performance in older adults. Importantly, dynamic brain activity is related to cognitive performance regardless of age, and therefore elucidating this aspect of brain function may advance understanding of cognition in general as well as age-related differences therein.

5. (Mis-) Measurement of Reserve

Richard N. Jones

The brain pathology that is often seen in demented individuals can also be present in cognitively normal elderly adults who show no or very limited signs of cognitive decline (Blessed, 1968; Satz, 1993). This observation has led to the hypothesis that some elderly adults may possess a *reserve* that allows them to continue to function well in the face of sometimes significant brain pathology. Although many researchers accept the concept of brain or cognitive reserve, it has proven difficult to define it specifically and to quantify it accurately. Several biological traits (e.g., brain size) (Satz, 1993) and social-demographic characteristics (e.g., years of education) (Stern et al., 1999) have been associated with reserve. Yet, it remains unclear whether and how these factors are fundamental to reserve as a construct.

The uncertainty surrounding the exact nature of reserve has led to approaches to measure reserve as a latent, or hidden, variable (Jones et al., 2011). Latent variables represent theoretical constructs that cannot be directly observed and measured. Their existence can be inferred through observation and modeling of other variables that can be directly observed and measured, that is, indicators. The uncertainty of the relationship between the construct and its indicators is a major theoretical issue in research on reserve and resilience, and it hinges on the distinction between the formative and reflective natures of the postulated entity. In the formative model, the latent variable is created by and is a consequence of the measurable variables. In the reflective model, the measurable variables are viewed as being caused by and reflecting one or more facets of the underlying, unseen but theoretically derived, latent variable. In either case, carefully identifying and reliably measuring the appropriate indicators is key, because they provide insights into the unknown, latent factor.

The distinction between formative and reflective constructs is not just a matter of classification. These two models lead to distinct interpretation of the empirical data and have very different implications for designing interventions to mitigate age-related cognitive decline. If the formative model is correct, then measured variables—such as education—*cause* the accumulation of reserve, and increasing years of education would make an individual less susceptible to cognitive decline. If the reflective model is correct, then some

yet-unknown factor influences education, reserve, and a host of other characteristics, and identifying appropriate reflective indicators is key. These theory-derived indicators would need to be tested in observational or experimental settings to determine whether they adequately account for lifetime cognitive ability, with formative vs reflective models explicitly compared in their fit to the data (Hagger-Johnson et al., 2011).

Reserve, as it is currently conceived, is an important modulating factor between brain decline (gradual or catastrophic) and cognitive outcomes. To understand and measure the impact of reserve on this relationship, it is important that researchers accurately assess the behavioral and cognitive indicators as well as accurately measure normal and pathological changes in brain structure and function. Measures of cognitive function are vulnerable to confounding variables, including possible selection bias in samples, the effect of practice and mere exposure to multiple testing, as well as artifactual effects related to floors and ceilings in cognitive performance. Defining the influence on cognitive aging of these variables and devising methods to measure them are important steps to improve our understanding of aging. In summary, fine-tuning theoretical concepts and developing reliable and valid indicators should go together in promoting our understanding of resilience and harnessing its power for improving the cognitive trajectories of older adults.

6. Discussion

No single approach will fully reveal how cognitive resilience is implemented in the brain. The emphasis should be on multimodal neuroimaging studies that will combine noninvasive neuroimaging methods geared to simultaneously evaluate neuropil volume, myelin content, white-matter connectivity, and axonal integrity, as well as functional organization and key neurotransmitters over multiple occasions throughout lifespan. More studies should address the neuroenergetic (Raz and Daugherty, 2017) and vascular (Raz and Rodrigue, 2006) correlates of age-related changes in brain structure and function.

The limitations of cross-sectional designs and their inability to capture the dynamics of aging even in a single modality, not to mention the brain-cognitive relationship, has been highlighted by many methodologists (Hofer and Sliwinski, 2001; Lindenberger et al., 2011; Maxwell and Cole, 2007). Overcoming this limitation is a daunting task, and it is made even more challenging by the fact that researchers' lifespans are commensurable with that of the subjects of their study. Thus, there is a need for long-term longitudinal studies with multiple measurement occasions. Moreover, refinement of the existing animal models and development of new ones that optimize the demands for manageable lifespan, sufficient neuroanatomical and neurofunctional homology, and comparable pattern of age-related diseases and risk factors is a critical need.

The challenges notwithstanding, animal models are of critical importance. Only in well-controlled animal studies can we examine synaptic and cellular indicators of resilience with a full range of invasive techniques. To optimize this path of investigation, it is necessary to take a *translational harmonization* approach. That is, traditional techniques of animal research (e.g., intracellular recordings, genetic and epigenetic manipulations, radiolabeling) should be supplemented with noninvasive neuroimaging that replicates in the closest

possible manner human methods of brain mapping. Existing studies of this type have already yielded important insights into the nature of regional volume changes observed on MRI in humans; for example, a recent study of rodents demonstrated the parallelism between stress-induced changes in dendritic arborization and MRI-derived volumes of the hippocampus and anterior cingulate gyrus (Kassem et al., 2013).

The challenges posed by the extraordinary complexity of the brain can be ameliorated by adopting the mathematical methods that have been developed in other disciplines that study complex systems (Gu et al., 2015). Adopting the framework of control theory to analyze age-related differences and changes in configuration of brain networks may help elucidate the mechanisms of resilience through understanding of preservation and maintenance of fundamental connectivity as well as (potentially compensatory) response of the aging brain to structural deterioration in the context of cognitive reserve.

Because resilience is by all accounts built over a lifetime, it is important to address its developmental roots and the risk factors that modify its expression over time. Thus, lifespan longitudinal studies are essential for elucidating how brain reserve emerges, how cognitive reserve is built, how brain maintenance is implemented, and how compensation is applied. In that context, lifespan changes in plasticity and the ability to meet systemic and environmental challenges that come with aging are particularly important (Lövdén et al., 2010). Attention should be paid to multiple factors shaping the trajectories of brain aging and potentially acting as modifiers of resilience, such as physical fitness (Hillman et al., 2008); social engagement; as well as vascular (Raz and Rodrigue, 2006), metabolic, and neuroinflammatory risk factors, including risk-associated genetic variance (Raz et al., 2015); as well as socioeconomic deprivation (Johnson et al., 2013) with associated high levels of stress (McEwen, 2013); and environmental pollution exposure (Woodward et al., 2017).

Whatever the source of resilience, while it is associated with a reduced risk of developing dementia, it is—perhaps paradoxically—also associated with a faster rate of cognitive decline and mortality once Alzheimer’s disease is diagnosed (Stern et al., 1999). This rapid decline may be because, in Alzheimer’s disease, the brains of more highly educated people exhibit relatively greater functional and structural damage than those of less educated individuals. This discrepancy between brain state and cognitive performance suggests superior maintenance and, possibly compensation, mechanisms that are being stretched to the breaking point before they fail.

One of the central challenges is the difficulty in clearly defining the terms and confronting the fallacy of concreteness: the belief that something exists only because it can be measured. As a corollary, just because something can be measured does not mean that it is the most important thing to measure. If reserve is a real thing, then it should manifest itself in multiple contexts, if researchers can find ways to detect it in different circumstances. Multiple sightings of reserve in action make its existence highly plausible and inspire continued efforts to improve understanding of this potential key factor in ameliorating age-related cognitive impairment.

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Highlights

- People vary in their ability to maintain good cognition despite significant neuropathology.
- Reserve, maintenance, and compensation may explain the paradox of resilience.
- These constructs may have passive (structural) or active (functional) brain basis.
- Identification of reliable reflective indicators will boost validity of reserve construct.
- Progress requires integrating animal and human neuroimaging in longitudinal designs.