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What are the later life contributions to reserve, resilience, and compensation?

Sara N. Burke [a], Elizabeth C. Mormino [b], Emily J. Rogalski [c], Claudia H. Kawas [d], Robert J. Willis [e], Denise C. Park [f,*]

[a] McKnight Brain Institute and Department of Neuroscience, University of Florida, Gainesville, FL, USA
[b] Department of Neurology and Neurosciences, Stanford School of Medicine, Stanford, CA, USA
[c] Department of Psychiatry and Behavioral Sciences, Mesulam Center for Cognitive Neurology and Alzheimer's Disease, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
[d] Departments of Neurology and Neurobiology & Behavior, University of California, Irvine, CA, USA
[e] Department of Economics and Research Professor, Institute for Social Research at the University of Michigan, Ann Arbor MI, USA
[f] Center for Vital Longevity, School of Behavioral and Brain Sciences, University of Texas at Dallas, Dallas, TX, USA

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ABSTRACT

Many studies have shown that early-life experiences can contribute to later life cognitive reserve and resilience. However, there is evidence to suggest that later life experiences and lifestyle choices can also play a vital role in the brain's ability to respond to and compensate for neural insults associated with aging. Engaging in a diversity of behaviorally, socially, and cognitively rich activities may forge new neural pathways that can perhaps provide greater flexibility in confronting the challenges associated with accumulating brain pathology. Studies of cognitively normal individuals with pathology and of individuals who have aged exceptionally well may provide insights that are generalizable to the overall elderly population.

1. Introduction

As individuals age, they experience declines in brain structures and in cognitive performance. There is considerable variability in rates of decline, and, somewhat surprisingly, the burden of brain pathology that an individual carries does not necessarily relate to cognitive performance. For example, there are cognitively normal older adults who harbor amyloid proteins in their brains at a level congruent with a diagnosis of Alzheimer's disease (AD), and yet they still maintain a high level of cognitive function. Why some older adults with AD-like brain pathology show normal cognitive function, whereas others with the same pathology show frank memory decline and progression toward AD remains a mystery. A leading possibility is that the maintenance of good cognition in the face of pathology arises from the plasticity of the brain and an accumulation of experiences over a lifetime that allows some individuals to overcome a pathological burden that leaves the cognitive function of others diminished.

Individuals who show resilience to pathology may be drawing from a reservoir of brain resources that accrued during early and mid-life and is further influenced by factors that occur in later life. Identifying and understanding these influences may lead to interventions that will build reserve and preserve cognitive function. Many of the mechanisms of cognitive resilience and decline are more easily studied in animals, which—due to their shorter lifespan and our ability to manipulate them experimentally—offer opportunities to examine, at a molecular level, the specific genes and brain regions that confer cognitive resilience with age. Insights gained from these nonhuman animal studies can potentially provide insights into physiological and pathological processes in humans.

Although most studies of aging assess cognitive performance cross-sectionally, it is increasingly recognized that longitudinal studies of adults that implement serial cognitive testing over many years can help identify individuals with preserved cognitive function, as well as those who show disproportionate decline. Ultimately, the goal of these efforts is to identify factors that confer brain resilience and protect cognition as the individual ages.

Speakers in this session of the Cognitive Aging Summit III, chaired by Denise Park, discussed the state of the research on factors that create cognitive reserve. Identifying these factors, perhaps

* Corresponding author at: Center for Vital Longevity, School of Behavioral and Brain Sciences, University of Texas at Dallas, Dallas, TX 75080, USA. Tel.: +1 2144708673; fax: 972-883-3250.
E-mail address: denise@utdallas.edu (D.C. Park).

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through some type of compensatory brain processes, might lead to novel prevention and treatment strategies that would benefit all.

2. An animal model of cognitive aging: do compensatory neural processes confer resilience?

2.1. Sara N. Burke

The study of cognitive aging in animals can provide important insights into this process in humans. Increasing evidence suggests that late-life experiences in rodents can enhance cognitive reserve, as evidenced by increased resilience, and brain compensation. We use various memory tests in rats to determine the effect of age on their ability to learn and recall new objects and tasks.

The Object-Place Paired Association test (OPPA) is an associative learning task in which rats are placed in a box with 2 corridors. At the end of each corridor is an object. Rats are required to alternate between each corridor, which requires working memory. To receive a reward, the rat must choose one object at the end of the first corridor and then the other object at the end of the second corridor. Thus, the reward is conditional on the rat's spatial location. Completion of this task requires the rat to integrate information about each corridor with the objects therein to make the correct selection (Jo and Lee, 2010). Young rats (4–7 months) begin to successfully complete the task after approximately 1 week of training; almost all rats do so after 2 weeks. (Success is defined as selection of the correct object greater than 81 percent of the time on 2 consecutive days.) In contrast, old rats (>24 months) require more time and make more unsuccessful attempts before they can reliably complete the task. In old rats, success in learning takes 9 days to 3 weeks. Old rats also have significantly more incorrect trials before they successfully complete the task (Hernandez et al., 2015).

Young and old rats were also tested for their performance in a spontaneous object recognition task. This test involves an environment that contains a familiar object and a novel object. Typically, rats spend more time exploring new objects compared with familiar ones. Young rats spend more time exploring the novel object than old rats, suggesting that old rats are not able to discriminate new objects from ones previously experienced (Burke et al., 2010). The OPPA and spontaneous object recognition tasks both require activity in the perirhinal cortex, a brain region involved in memory and vulnerable in old age and AD. Importantly, some old rats with impairment at spontaneous object recognition performed the OPPA task comparable with young rats, suggesting compensation when the perirhinal cortex is compromised.

To further investigate potential compensatory mechanisms in old rats, we examined gene expression patterns in the brains of rats after they received a series of memory tests and they were allowed to rest and then were retested in a control environment. After each stage of the experiment, the brains of some rats were analyzed for activation of the Arc gene, which is believed to play a critical role in learning and memory-related molecular processes. The data indicate that Arc activation in the perirhinal cortex in aged rats decreased compared with young rats (Burke et al., 2012). However, increased activity was seen in the aged rats' medial prefrontal cortex, which could indicate compensation for diminished function in the perirhinal cortex through the recruitment of other brain regions into the memory task. These findings are strikingly similar to the tendencies of older humans to recruit additional prefrontal cortex to perform memory encoding tasks.

Functional magnetic resonance imaging of an individual at rest allows scientists to view the connectivity of neural networks in the brain. The brains of young rats typically have more network connections than those of old rats. However, after 2 weeks of OPPA testing, the resting state connectivity of old rats was much more extensive and complex, suggesting that their brains created new connections in response to new stimuli. This observation suggests that neural connections can be bolstered by some type of memory training or enriching experience, providing a possible avenue to increasing brain resilience in rats and, perhaps, in humans.

3. Cognition and amyloid in healthy adults: who is resilient and who declines?

3.1. Elizabeth C. Mormino

Cognitively healthy older adults whose brains have measurable levels of AD-related pathology represent a valuable population in whom to study resilience and reserve. Our group is examining aged individuals (60 years and older) who have amyloid deposits in their brains but retain clinically normal cognitive function. The pathology of AD begins before clinical symptoms. First, there is distributed amyloid throughout cortex and focal tau deposition within the medial temporal lobe. This is followed by the spread of tau to other brain areas, possibly resulting in neuronal, subtle cognitive impairment and ultimately clinically detectable impairment.

Older individuals with detectable amyloid deposits but normal cognitive function show subtle AD-like differences in brain structure and function, such as reduced gray matter thickness (Dickerson et al., 2009) and diminished connectivity within the default mode network (Mormino et al., 2011). Within these groups, individuals with elevated levels of amyloid show greater declines over time in multiple cognitive domains, including episodic memory and executive function. By studying these individuals, we can characterize early changes associated with AD pathology and cognitive function over time. Amyloid-positive individuals with elevated tau deposits show the greatest decline in memory over time, and groups more vulnerable to amyloid-related cognitive decline include females and carriers of the *APOE ε4* genotype (Mormino et al., 2014).

An enriched environment, which has long been recognized as a contributor to cognitive reserve, may enhance brain function by contributing to increased brain thickness, enhanced neuronal efficiency, and possibly reduced amyloid deposition. Many other factors might have an impact on the physical, anatomic structure of the brain as well, including exercise, cognitive training, and sustained performance of cognitively demanding activities. These factors should be related to markers of AD pathology and cognitive outcomes over time, to establish mechanisms underlying these protection factors.

We have observed heterogeneity in long-term cognitive trajectories among amyloid-positive older individuals, highlighting the importance of additional risk and protective factors in the prediction of future decline. Although the amyloid-positive group is at greater risk of cognitive decline over time compared with the amyloid-group, many amyloid-positive individuals retain high levels of cognitive performance. One participant in our study, a 72-year-old amyloid-positive male with many years of education and a protective *APOE* allele showed high levels of cognition at baseline with slight declines over time, but given the higher baseline levels, these declines remained significantly above clinical thresholds for impairment. In that situation, protective factors such as education may mask the clinical expression of AD. Another individual, a 79-year-old amyloid-positive female with few years of education and a higher risk *APOE ε3/4* heterozygous genotype, remained cognitively normal for more than 7 years with no indication of decline. Although she possessed many AD risk factors (elevated amyloid, *APOE ε4*, female, low education), she may possess yet-unknown factors that preserve her cognitive function.

Ultimately, it will be important to follow individuals over longer time periods to identify those who are able to remain resilient to

cognitive decline despite elevated levels of AD pathology. The ability to identify these resilient outliers—who may be overlooked in cross-sectional studies—may reveal unknown protective factors that contribute to reserve and provide insights into mechanisms underlying this form of resilience.

4. Neurobiologic features of SuperAgers: is it resistance, resilience, or just luck?

4.1. Emily J. Rogalski

At a population level, average performance on tests of episodic memory declines over the lifespan. This average, however, can mask significant variability among individuals: a very few very old individuals have cognitive performance like that of individuals decades younger (McDaniel et al., 2008). We call these outliers "SuperAgers"—individuals who show little or no age-related cognitive decline and remain highly functional at an advanced age. We are studying these SuperAgers to understand how they maintain their youthful cognitive function—sometimes in the presence of significant brain pathology—to gain insights into mechanisms of resistance and resilience.

We define SuperAgers as individuals aged 80 years and older whose episodic memory performance is at least as good as cognitively average 50- to 65-year-olds and whose performance in other cognitive domains is at least average for their age (Rogalski et al., 2013). After an initial evaluation, the SuperAgers return for follow-up visits every 18–24 months and agree to donate their brains for analysis after death. As of April 2017, 55 female and 19 male SuperAgers had enrolled in the study. Preliminary results suggest that most SuperAgers have been, so far, able to maintain their superior cognitive performance over the course of follow-up visits, some taking place over many years (Gefen et al., 2014; Rogalski et al., 2018).

The SuperAgers do not show the cortical thinning that is typically seen in 80-year-olds; rather, their brains—much like their cognitive performance—appear to be largely identical to those of 50- to 65-year-olds (Harrison et al., 2012). A region of left anterior cingulate cortex, which is involved in attention and memory, was significantly thicker in the SuperAgers than in the 50- to 65-year-old comparison group. Comparison of cortical volume loss over an 18-month period shows that SuperAgers lose cortical volume at a significantly slower rate than age-matched, cognitively normal individuals who do not meet the criteria for SuperAgers (Cook et al., 2017b).

In looking at the brain histology of deceased SuperAgers, we initially focused on von Economo neurons (VENs) in the anterior cingulate cortex. The brains of SuperAgers showed more than 4 times as many VENs as normal elderly individuals (Gefen et al., 2015; Rogalski et al., 2013). This type of neuron is thought to play a role in more complex cognitive functions, and loss or abnormal development of VENs has been implicated in autism (Santos et al., 2011), schizophrenia and bipolar disorder (Brüne et al., 2010, 2011), and frontotemporal dementia in humans (Seeley et al., 2006). Genetic factors may contribute to the robust cognitive function in SuperAgers but have yet to be established in this group. Initial evidence suggests slightly lower frequency of the *APOE ε4* genotype; however, these individuals do not seem to have an elevated frequency of the protective *ε2* genotype.

SuperAgers seem to possess a combination of biologic and psychosocial characteristics that allow them to retain cognitive function much later in life than most individuals (Cook et al., 2017a). SuperAgers may therefore benefit from a combination of resistance, resilience, and good luck that has preserved their cognitive function. Studies of these individuals may provide important insights in ways to improve the quality of life for the normal aged population and to prevent age-related cognitive decline and AD.

5. Cognitive and brain resilience: is it present in the oldest old?

5.1. Claudia H. Kawas

In 1981, surveys were mailed to every resident of a large retirement community in California—nearly 14,000 individuals (Kawas and Corrada, 2006). In 2003, we launched the 90+ Study to characterize more than 1700 of these individuals who were 90 years of age or older to better understand factors related to cognition in the oldest old. Although dementia and cognitive impairment were prevalent, affecting 2/3 of the participants, a subset of individuals displayed cognitive resilience.

We defined "resilient" as individuals who were 90 years or older, completed at least 2 assessment visits, and scored 28 or higher on the Mini-Mental State Examination. Using these criteria, nearly half of the volunteers were classified as demented, 38 percent were neither demented nor resilient, and 13 percent were "resilient." Examination of various lifestyle factors collected as part of the original survey revealed that individuals classified as resilient reported being more active, getting more sleep, watching less TV, and having a more positive attitude than those who would become nonresilient or demented.

In the 90+ Study, 60 percent of demented individuals and 40 percent of nondemented individuals had high levels of AD pathology at autopsy (Corrada et al., 2012). Although the prevalence of AD pathology in resilient individuals is lower, it is still found in 20 percent of these individuals. Thus, these factors do not reliably differentiate between the resilient and the nonresilient, nondemented groups. The presence of vascular disease, however, does seem to distinguish between these groups: resilient individuals were less likely to have lacunae or large infarcts in their brains and to have moderate to severe brain atherosclerosis.

APOE genotype seems to be related to dementia but does not seem to correlate with brain pathology. Individuals with at least one *ε4* allele are more likely to be demented than those without. The *APOE ε2* protective genotype did not seem to play a significant role in determining cognitive status; in fact, the frequency of the *APOE ε4* allele was higher in the resilient than in the nonresilient, nondemented individuals. These results have led some researchers to speculate as to whether the observation of AD-like pathology in cognitively normal individuals represents resilience or preclinical AD.

Postcollege education was associated with resilience; resilient individuals reported the most years of school and demented individuals the least. In an imaging study of 103 participants whose average age was 96 years, we found that those without a college degree were 4 times more likely to have impaired cognition in the presence of high levels of amyloid on positron emission tomography scan when compared to those with a college degree or more.

It remains unclear whether individuals who display clinically normal cognitive function in the presence of significant brain pathology are the beneficiaries of significant cognitive reserves or are simply displaying a mild form of AD that is not yet detectable using current testing methods. If it is the former, a better understanding of the components of resilience may lead to changes much earlier in life that could impact its accumulation. If it is the latter, approaches to preventing AD in amyloid-positive individuals through earlier interventions, that is, before clinical disease is detected, may expand the number of individuals whose cognitive function can be retained.

6. Occupational complexity, retirement, and cognition

6.1. Robert J. Willis

Retirement is associated with a decrease in cognitive function as measured by word recall tests, even when accounting for reverse causation (Rohwedder and Willis, 2010). The negative effect of retirement on cognition is consistent with the joint hypothesis that greater mental stimulation promotes brain health and that working life is typically more cognitively stimulating than retired life. However, data from the Health and Retirement Study suggest that the effects of retirement on cognition are not the same in all individuals. Individuals whose careers were highly cognitively complex show much less cognitive decline in retirement compared with individuals who worked less cognitively complex jobs (Fisher et al., 2014).

This observation provides a potential biological parallel of the economic theory of human capital, wherein individuals accumulate cognitive capital through their fluid intelligence, learning effort, and knowledge base over their lifetime. Greater accumulation of cognitive capital may provide more cognitive flexibility later in life, thereby mitigating the effects of aging on cognitive decline.

7. Discussion

There is growing evidence that the brain retains some plasticity at older ages and that it is capable of some reorganization that helps maintain cognitive function into old, and in some cases, very old age. Studies of old animals suggest that brain regions not typically involved in memory can be recruited on a memory task, suggesting that the brain may be compensating for an overall decline in memory circuitry that was responsible for these functions at earlier ages. Identification of the genes involved in this brain reorganization could provide new targets for interventions, especially if they could be implemented early in the process of cognitive decline. In designing such interventions, it would be helpful to identify which individuals are likely to face such decline and thus require an intervention and to sort them into groups that are most likely to benefit from a given approach. Cognitively normal individuals who carry the *APOE ε4* gene or who have amyloid deposits on their brain are examples of high-risk individuals.

It is important to recognize that the individuals who show some loss of brain integrity do not necessarily have poor cognitive health because the resilience of the cognitive system to age-related brain pathology is quite remarkable. Some older adults show significant declines in brain integrity, yet maintain normal cognitive function. It has proven to be difficult, even after prolonged longitudinal study, to determine what lifestyle factors such as marital status, prior caregiving experience, and other sustained and complex behaviors lead to such cognitive resilience. It is not even clear whether those who maintain good cognition into old age represent a distinct group whose experiences might be generalizable to the overall population, or whether, instead, they are simply members of the "long tail" of the cognitive function distribution curve. Studies of the elderly who have retained good cognitive function may yield important insights into the ways that their brains continue to function at a high level. More needs to be known about their earlier life activities to shed light on a mechanism that may have preserved the cognitive function that led to late-life resiliency. Studies of high-performing oldest old may yield important information about the ways that their brains are able to overcome accumulated pathology and continue to function at a high level.

Studies of SuperAgers (i.e., those at the extreme end of high-functioning elderly) have revealed that 87 percent of SuperAgers reported engaging in regular physical activity. Other studies have shown that physical activity is associated with improved brain health and neural functioning. Although the SuperAgers were, on average, 68.5 years old when they retired, 18 percent report that they are still working in some capacity for many years beyond that. It is possible, therefore, that continued mental engagement and physical activity contribute to their cognitive function, even at an advanced age. Just as cognitive decline is believed to arise from the accumulation of multiple small neural insults—most of which, alone, would not be significant enough to cause measurable impairment—it is likely that continued cognitive health is a consequence of many, seemingly small factors that, together, contribute to overall resilience. Identifying these factors, and finding ways to address them through therapeutic interventions, may represent a promising strategy to preserve cognitive function in aging individuals.

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