### Title

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### Authors

White, Lon R
Boyle, Patricia A
Foster, Thomas C
et al.



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# How Do We Validate Approaches That Aim to Harness Reserve to Improve the Aging Brain?

**Lon R. White**[a], **Patricia A. Boyle**[b], **Thomas C. Foster**[c], **Adam H. Gazzaley**[d], **John F. Disterhoft**[e,*]

[a]Pacific Health Research and Education Institute, Honolulu, HI, 96819

[b]Department of Behavioral Sciences, Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL 60612

[c]Department of Neuroscience, University of Florida, Gainesville, FL 32611

[d]Department of Neurology, University of California, San Francisco, CA 94158

[e]Department of Physiology, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611

## Abstract

An accurate assessment of the impact of reserve on cognitive functioning in older individuals with brain pathology requires careful measurement of each and an assessment of the extent to which each influences the other. Studies to integrate information about molecular biology, neuropathology, behavioral aspects of cognitive decline, and cognitive resilience will be of particular importance. Additionally, more work is needed to improve our understanding of the effect of systemic factors on brain health and function. It seems likely that, even in later life, the brain's plasticity may allow for a positive response to stimulation. The ultimate goal of this research is to create a validated set of variables and interventions—and to understand the biology underlying them—that are useful not only in describing an individual's cognitive state but also in identifying promising paths for treatment and prevention of cognitive decline.

### Keywords

Reserve; resilience; interventions; neuropathology; assessment

[*]**Corresponding Author**: Department of Physiology, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, jdisterhoft@northwestern.edu.



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## 1. Introduction

There are few quantitative measures of brain reserve, cognitive reserve, resilience, and compensation, which are hypothesized mechanisms that allow for normal cognitive function in the presence of significant brain pathology. Development of an integrated measure of cognitive resilience that includes both brain pathology and cognitive reserve would benefit the research and clinical communities. However, uncertainty regarding which variables to measure, how best to quantify them, and how to relate them to pathology presents a significant challenge.

A better understanding of the ways that age-related neuropathology interacts with cognitive reserve and resilience could illuminate how different factors contribute to an individual's overall likelihood of cognitive decline. Quantifying this risk might allow researchers to compare multiple groups of patients and to draw conclusions based on larger, more diverse data sets.

Whatever its underlying biological basis, the factors that contribute to cognitive reserve coexist with the factors responsible for cognitive decline. A better understanding of the factors that underlie reserve and how they interact with each other and with neuropathology could provide important insights to researchers and clinicians. Some of these factors may alter gene expression in the brain and have lasting effects on functional output such as behavior. An improved ability to define, quantify, and track cognitive reserve in individuals is particularly important, because researchers could better identify the factors that play important roles in the dynamic balance between reserve and neuropathology that influences cognitive decline. In turn, researchers could move from cross-sectional characterization of groups at various ages to a sequential view that allows for a more accurate description of what causes some individuals to preserve their youthful cognitive capacity as they age.

Studies done in animal models of normal aging are especially useful within this context. Through the use of behavioral tasks that have direct translational relevance to aging humans, aging animals can be classified as learning-impaired or learning-unimpaired as compared to young animals. Spatial and temporal behavioral tasks that rely upon the hippocampus and associated temporal lobe regions and/or the prefrontal cortex are most informative in this regard. The cellular and molecular characteristics of neurons of animals from the various groups can then be functionally characterized. Alterations in calcium handling and in neuronal characteristics of neuronal excitability have been shown to be biomarkers of learning ability in aging animals. Pharmacological or molecular genetic manipulations designed to reverse these neuronal changes to a young-like state have been shown to reverse age-associated learning impairments. This approach, conceptually the study of "super aging" animals, has considerable promise for defining and then addressing changes in aging brain that can lead to cognitive impairments. Importantly, the life span of species such as rodents that are under study in laboratories investigating normal aging is short enough that it will be possible to begin longitudinal studies that follow animals from a young to very old age. Such studies offer the possibility of identifying those factors that predispose some individual animals to maintain their cognitive capacity as they age. These insights can be readily translated to humans (Disterhoft and Oh, 2006; Oh et al., 2013; Oh and Disterhoft, 2015).

Even in the face of cognitive decline, there is evidence that late-life activity (e.g., mental engagement and social interaction) can have a significant impact on short- and long-term cognitive function. In general, it seems that various forms of engagement, including reading and curiosity about learning new things, are associated with improved cognitive outcomes. Studies in animals that characterize the effect of behavioral learning and environmental enrichment on brain structure and function converge with these observations in humans and give insight into the effects that can be expected in human brain from maintenance of these activities. They may also allow the design of manipulations that lead to neurobiological changes that contribute to the preservation of cognitive capacity. If these activities can be shown to contribute to reserve—as opposed to simply correlate with it—then interventions that aim to promote these activities could delay or prevent cognitive decline.

Speakers in this session of the Cognitive Aging Summit III, chaired by John Disterhoft, highlighted ongoing efforts to better quantify and measure cognitive reserve and resilience. A better understanding of these concepts should provide a framework to identify targets for interventions in a growing at-risk population of older individuals.

## 2. Brain Reserve, Cognitive Reserve, and Brain Comorbidity Burden Together Determine Resilience to Neuropathologic Alzheimer's Disease

### Lon R. White

Our group is developing an approach to measure and quantify a given person's cognitive resilience, which is defined as the ability to sustain or recover cognitive functioning despite accumulated brain injury or degeneration. This approach requires quantification of the extent of brain pathology and cognitive performance in the same individuals over time. If we could quantify an individual's resilience, we could search for factors that contribute to it—possibly including physiologic, immunologic, metabolic, psychologic, and other factors. It might then be possible to target improvements in measured cognitive reserve as part of a prevention strategy.

As part of the Nun Study and the Honolulu-Asia Aging Study, we identified five common types of brain lesions that are strongly associated with dementia: AD-related neuropathologic changes, the presence of neocortical Lewy bodies, hippocampal sclerosis, microinfarcts, and low brain weight (White et al., 2016). We assigned a numerical score to each of these lesions that was related to its impact on dementia. We found a correlation between patients' cumulative scores and their performance on cognitive tests—individuals with higher brain pathology scores performed more poorly on various cognitive assessments.[1] Importantly, individuals who had multiple lesions of any type were more likely to be demented or severely impaired. This observation suggests that dementia may arise from an accumulation of multiple, individually small lesions.

Using these data, we recently generated a "resilience index" by combining information regarding brain pathology and cognitive test scores. A key consideration was that the index

[1] https://www.ncbi.nlm.nih.gov/pubmed/26888993

should relate the degree of brain pathology to the degree to which cognitive ability was preserved—those individuals with the greatest pathology who maintained the highest cognitive ability would score the highest.

Approximately two-thirds of the volunteers showed resilience in varying degrees. Individuals with a higher resilience index score were more likely to have greater educational attainment or occupational complexity. There was no significant correlation with other factors such as age at death, *APOE* genotype, or diabetes or heart disease. Our studies suggest that cognitive resilience is largely determined by the degree to which the mind is engaged in complex tasks over the course of the lifespan. Efforts to promote this sort of mental exercise could be a promising avenue for strategies aimed at delaying or preventing cognitive decline in old age.

## 3. Cognitive Aging: A Balance between Neuropathology and Resilience

### Patricia A. Boyle

Researchers and clinicians often classify older people into one of three groups: those whose cognitive function is largely intact and are considered “normal”, those who suffer minimal cognitive problems and are referred to as having “mild cognitive impairment”, and those who are impaired and meet criteria for dementia. While these categories provide a helpful framework to think about cognitive aging, the phenomenon of cognitive aging is considerably more complex and heterogeneous than these labels suggest. To effectively combat cognitive impairment in old age, we need to understand the factors that lead to cognitive decline, particularly the accumulation of age-related neuropathology; identify factors that provide resilience even in the face of accumulating neuropathology; and appreciate the potential implications of an increased focus on resilience factors for the prevention and treatment of age-related cognitive decline.

The data discussed here come from the ongoing epidemiologic, clinical-pathologic studies of aging, the Rush Memory and Aging Project and the Religious Orders Study. These studies began in the 1990s and comprise over 3,000 older people in their 80s who did not have known dementia at the time they enrolled. All volunteers undergo detailed annual clinical evaluations, neurological exams, cognitive assessments, and extensive behavioral testing. All participants have also agreed to donate their brains and other organs for post mortem evaluation. Currently, pathologic data are available from over 1,200 autopsies.

In recent years, we have learned a lot about what drives cognitive aging. Studies by our group and others have shown that neuropathology is nearly ubiquitous in brains of older individuals (Boyle et al., 2013). We know that virtually all older persons exhibit at least one type of neuropathology, but most have mixed neuropathologies. Rates of decline in cognitive function are greater among individuals with multiple pathologic lesions—particularly Alzheimer’s disease (AD) pathology, cerebrovascular disease, and Lewy bodies (Boyle et al., 2013). The presence of these pathologies also contributes to an earlier initiation and more rapid progression of cognitive decline. However, there is considerable variability in cognitive trajectories, even among individuals with a similar burden of neuropathology. We recently showed that, together, the most common pathologic causes of dementia account for

only about 40 percent of the observed variability in cognitive decline. Thus, even if we eliminated these common neuropathologies, considerable variability in cognitive decline would remain (Boyle et al., 2013). To complicate matters even further, these neuropathologies occur in different combinations across individuals and their impacts vary greatly depending on the combination and burden of neuropathology present (Boyle et al., 2017).

Since neuropathology is ubiquitous, the question becomes: what factors might protect against cognitive decline even in the face of accumulating neuropathology? One such factor is cognitive activity: individuals who report reading, playing games, and learning new things are about half as likely to develop AD as those who do not (Wilson et al., 2007). Furthermore, cognitive activity during both early and later life slows the rate of cognitive decline in later life, and, importantly, this effect persists even after controlling for neuropathology (Wilson et al., 2014). Additionally, individuals who have a greater sense of purpose in life (i.e., they are focused and intentional) are much less likely to develop AD compared to those with less purpose (Boyle et al., 2010). Importantly, individuals with greater purpose in life also have a considerably slower rate of decline in cognitive function despite their burden of pathology. Furthermore, and strikingly, individuals with greater purpose also have a considerably reduced risk of cerebral infarcts. Together, these findings suggest that behavioral engagement and psychological factors such as purpose in life can provide resilience independent of neuropathology, by buffering its deleterious effects, or by influencing it directly.

Cognitive aging occurs in the context of a complex relationship between neuropathology and resilience factors, some of which have been identified and many others which have not. The identification of modifiable resilience factors that act to preserve cognitive function in the face of accumulating neuropathology could offer novel therapeutic targets that provide meaningful protection against late-life cognitive decline. An increased focus on resilience factors may offer a powerful new strategy to reduce the burden of cognitive aging and may have broad implications at the population level.

## 4. On Biomarkers, Animal Models, and Senescence

### Thomas C. Foster

One of the earliest signs of cognitive decline is a change in episodic memory, with individuals who exhibit decreased ability to recall autobiographical events showing diminished activity in the hippocampus during memory encoding or retrieval. In animal models, an early decline in episodic memory is related to a loss of neuroplasticity preceding a loss of synapse number.

This loss of plasticity may be related to elevated levels of oxidative stress very early in cognitive decline (Kumar et al., 2017). This stress results in disruption of redox signaling that leads to changes in calcium signaling, including diminished function of the NMDA receptor, neuron polarization, and, ultimately, changes in gene expression. Evidence suggests that exercise, cognitive engagement, and other protective factors can lessen the impact of oxidative stress.

In addition, epigenetic mechanisms interact with age, environment, and lifestyle choices to influence transcription, resiliency, and variability in aging. DNA methylation is a well-studied epigenetic mechanism that is involved in maturation and the development of chronic diseases. Our studies have identified sets of synaptic genes in the cortex that exhibit hypermethylated DNA in aging animals that exhibit cognitive impairments (Ianov et al., 2017). It is not clear whether these methylation patterns and their attendant changes in gene expression patterns are causing the changes in synaptic activity or are a consequence of them.

Our more recent work has focused on biomarkers that can be translated across species including neural imaging (Febo and Foster, 2016) and microRNAs (miRNAs) that are found in circulating microvesicles (exosomes) (Rani et al., 2017). Exosomes can cross cell membranes and deliver miRNAs to silence genes by inhibiting translation. Intercellular communication from tissue to tissue by exosomes is a potential mechanism that would connect peripheral activity, exercise, and systemic inflammation to overall brain health. In turn, exosomes produced by and released from the brain may represent biomarkers of brain function. Many miRNA that are associated with impaired cognition are relatively specific to the brain, and the level of these miRNAs in the plasma change with age. Thus, exosomal RNA could provide information on mechanisms for reserve, offering a simple and relatively inexpensive way to monitor the progression of cognitive decline as well as to monitor the effectiveness of treatments.

Animal models of cognitive aging can provide insight into the mechanisms that underlie variability in brain neuroimaging associated with cognitive decline in humans. Combining human and animal studies to examine blood markers (such as markers of oxidative stress and exosomal miRNA) and neuroimaging could allow researchers to monitor the progression of cognitive decline and the effects of interventions that contribute to resiliency.

## 5. Technology Meets Neuroscience: A Vision of the Future of Brain Fitness

### Adam H. Gazzaley

Many diagnostic tests used to assess cognitive function have significant limitations. It is often difficult to determine the underlying cause of cognitive decline, and many insights from experimental studies are difficult to apply in the clinical setting. The current therapeutic approach of using small molecules to treat cognitive decline has not proven effective, perhaps because any given molecule may be poorly targeted, address only a single aspect of disease, or be insufficiently tailored to an individual’s physiology.

The goal of our research is to develop a targeted, personalized, multi-model, closed-loop approach to treating cognitive decline. We develop customized video games to engage individuals in cognitively challenging activities. Our games collect data on individuals’ performance in real-time and adjust the difficulty of the game to sustain maximal engagement relative to a person’s abilities. Our first game, Neuroracer, required the player to drive a car while responding to increasingly complex challenges. After 1 month, players

showed improved performance that persisted for about 6 months—even in the absence of additional practice. They also exhibited improvements on tasks of working memory and sustained attention, although these skills were not directly targeted by game play (Anguera et al., 2013). These findings demonstrated that experience in executing a complex cognitive task in a game environment could create meaningful and durable benefits, even if it occurs in the context of a fun activity.

Our studies incorporate both technology development and scientific research (Mishra et al., 2016). These complementary efforts require a development team to identify the appropriate target and to design, develop, and test a game that addresses it, coupled with a research team to identify the target population and develop experiments with the appropriate controls, measure the appropriate outcomes, and collect all the data necessary to draw valid conclusions. We are currently developing six new games, each of which targets a separate aspect of cognition, and are using them in longitudinal research in healthy older adults (60–90 years of age). During these tests, we are also exploring the real-time visualization of brain activity, providing feedback on the games' impact on neural pathways. We hope to validate and understand the impact of these games on cognitive function and to couple the data with information on eye and body movement to help foster cognitive resilience.

We are particularly interested in determining the transferability of any seen effects. We would like to know to what extent improvement in game performance is associated with improvement in overall cognitive performance, as well as how long any improvements last. We also seek to determine the mechanism by which these effects are mediated and to characterize any heterogeneity in response across individuals. We hope to develop new video game-based approaches to measure and improve cognitive function in older individuals and to better understand the mechanisms that drive these improvements.

## 6. Discussion

It is clear that late-life cognitive function is affected by a complex interplay of factors across the lifespan. These include early-life influences such as those discussed in Session III (e.g., socioeconomic status and years of education) and later-life influences such as those discussed in Session IV (e.g., cognitive and social engagement during older age). Cognitive, social, and physical activity have been shown to play a role in reserve and resilience. Many of these factors act to preserve cognition in the presence of sometimes significant brain pathology. These observations underscore the cross-talk between cognition and experiential factors that modify biology and vice versa. They also implicate lifestyle factors as attractive targets for intervention designed to preserve cognitive function. However, approaches to identify, quantify, and harness cognitive reserve in the aging brain must begin with an accurate assessment of it and an understanding of how it interacts with the brain pathology that is commonly found in the elderly.

One challenge to developing and validating interventions to maintain or increase cognitive function in aging adults is that the mechanisms of proposed interventions are poorly understood. For example, although there is evidence that playing certain video games improves cognitive function in older adults, it is not clear whether playing games improves

cognition by providing general mental stimulation, by presenting the brain with a novel situation, or by some other mechanism. Understanding the mechanism of action is important, because it will inform which types of video games or other interventions are likely to be most successful. If novel experiences are important for brain health, for example, then it would be necessary to play new video games or seek other novel experiences. If, on the other hand, games work through a mechanism of increased stimulation, then more complex games would be favored over simpler games for maximum effect.

Studies in animals are ideal for determining mechanism. Longitudinal studies may help determine the relative contribution of genetic predisposition as compared to behavioral experience to later life cognitive health. Animal studies have demonstrated biomarkers such as enhanced neuronal excitability that is related to learning and learning capacity in both young and aging animals. Pharmacological and molecular genetic manipulations that enhance neuronal excitability lead to improved learning in aging animals. It is important to determine how these manipulations enhance learning to determine whether the effects can be translated to humans (Disterhoft and Oh, 2006; Yu et al., 2017).

Similarly, gaining a better understanding of the mechanisms by which early-life factors affect late-life cognition may point to more effective intervention strategies. Although educational and occupational attainment are clearly associated with late-life cognitive outcomes, the mechanisms of these relationships are unclear. One hypothesis is that educational and occupational experiences improve the ability to respond to challenges with cognitive flexibility, which could confer greater cognitive resilience even in the aging brain. If this hypothesis were correct, it would suggest that diversity in education, occupations, and life experiences might lead to better cognitive outcomes in older age. An alternative hypothesis might be that the collective learning from fluid intelligence over a lifetime of experiences crystallizes as one ages, and that older individuals who develop greater crystallized intelligence (or wisdom) are better able to draw on their past experiences to solve current challenges. Testing these hypotheses, however, is a challenging endeavor. In addition, although educational and occupational attainment are often considered to be types of environmental exposures, researchers must account for a wide range of covariates when studying the effects of education and occupation on cognition. Animal studies may be particularly informative here. The lifespan of some animal models is short enough that it is possible to design manipulations such as multiple learning tasks in various cognitive domains, enhanced social interaction, and sensorimotor training at a young age that test various hypotheses for what factors lead to cognitive reserve and determine the effects on individual animals as they age (Curlik et al., 2014; Weiss and Disterhoft, 2015). This approach also would allow the possibility of comparing the impact of concentrated and relatively isolated bouts of intellectualor social activity at a relatively early age as compared to lifelong learning and social interaction on cognition in aging.

Another challenge facing researchers is how to integrate data from animal and human studies, particularly when measuring the impact of engagement with technology and the extent of social interactions. For example, social interactions are important in animals, and many show poorer health when raised alone but better health in pairs or groups. There is evidence in humans that having a large social network is important in preserving cognitive

health. However, relatively little is known about effective interventions to enlarge social networks, or the degree to which different individuals have unique needs. For example, some individuals may enjoy a wide circle of casual acquaintances, while others prefer a smaller group of closer friends, which necessitates a personalized approach to any intervention aimed at modifying social interactions. Although animal studies may help elucidate the mechanisms by which social engagement affects cognition, human studies are needed to fully capture the appropriate context.

Ultimately, all of these studies must confront the dilemma of integrating data from cognitive tests and pathological assessments with basic biologic studies that aim to define the molecular changes associated with cognitive decline. Ideally, measures of cognitive resilience would be incorporated into randomized clinical trials of AD and other neurodegenerative diseases. However, at present, it is not possible to accurately measure neuropathology in living individuals, let alone cognitive resilience. Before measures of resilience can be developed and deployed in clinical studies, a better understanding of the biomarkers of neurodegenerative diseases is needed.

In the meantime, one promising approach is to examine the extent to which later life interventions can provide cognitive reserve. Older animals and humans can learn and change. Understanding what kinds of learning lead to the greatest positive change at the neurobiological level in animals may provide insight into which activities in humans are most likely to lead to enhanced cognitive health. It seems clear that choices made across the lifespan influence cognitive function in later life. A better understanding of how these decisions impact reserve and resilience could provide important insights into the biologic and physiologic basis of cognitive function and point the way toward new prevention and treatment strategies.

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## Highlights

- Modifiable correlates of cognition are attractive targets for interventions.
- Engagement in complex cognitive tasks over a lifetime appears to promote resilience.
- Cognitively challenging video games show promise as interventions.
- Neuroimaging, epigenetic, and other biomarkers could help assess efficacy.
- Understanding the mechanisms of resilience may lead to better interventions.