Neurobiology of Aging 83 (2019) 130–134

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

What are the threats to successful brain and cognitive aging?

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ARTICLE INFO

Article history:
Received 31 March 2019
Accepted 23 April 2019

Keywords:
Resilience
Reserve
Compensation
Maintenance
Pathology
Modifiable factors

ABSTRACT

The structure and function of the brain change over the life span. Aged brains often accumulate pathologic lesions, such as amyloid plaques and tau tangles, which lead to diminished cognitive ability in some, but not all, individuals. The basis of this vulnerability and resilience is unclear. Age-related changes can alter neural firing patterns and ability to form new memories. Risk factors for cognitive decline include male sex and apolipoprotein E genotype. Physical activity seems to be protective against cognitive decline. Longitudinal studies have shown that, although the onset of amyloid pathology and associated cognitive decline can vary greatly, once it begins, the rate of deposition is similar among affected individuals. This session of the Cognitive Aging Summit III explored fixed and modifiable factors that can threaten cognitive function in aging adults and approaches to modulate at least some of these risks.

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1. Introduction

Brain structure and function change across the life span. The extent to which these changes are malleable over the life span, the factors that influence these changes, and the extent to which they can be modified is the subject of much investigation.

Many individuals with brain pathology sufficient to cause cognitive impairment in some individuals nevertheless maintain high levels of cognitive function. Age- and pathology-related cognitive decline are, therefore, not inevitable. Studying individuals with preserved cognitive function may yield important insights into mechanisms broadly applicable to the general population. Understanding these processes may uncover ways to promote healthy brain aging as well as to mitigate cognitive decline in the presence of significant brain pathology.

Cognitive decline during aging arises from a complex interplay of biological factors, social influences, and life choices. Understanding the extent to which any of these might be modifiable could provide important tools for investigators and clinicians to develop interventions to prevent or reverse age-related cognitive decline and impairment.

In this session of the Cognitive Aging Summit III, speakers addressed issues related to the mechanisms that threaten or support preserved cognition in the face of brain aging. Although much remains to be learned, it is becoming clear that successful cognitive aging involves a process of adaptive neural change rather than avoidance of the neurobiological effects of aging.

2. Contributions of neurocognitive aging to risk and resilience (in rats)

2.1. Michela Gallagher

A current understanding of neurocognitive aging is grounded in laboratory research using rodents to study specific circuits in the hippocampal formation that underlie its specialized contribution to episodic memory. In young adult rats, recordings of neurons show that representations of new information are rapidly encoded to distinguish current input from similar experiences in the past. By contrast, hippocampal neurons in aged rats with memory impairment fail to exhibit this property, generating interference among current and previous memories. The neurons contributing to this encoding impairment also exhibit elevated firing rates, producing an imbalance in excitation and inhibition in the key circuits that ensure optimal function in episodic memory (Wilson et al., 2003, 2005).

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0197-4580/$ – see front matter Published by Elsevier Inc.
https://doi.org/10.1016/j.neurobiolaging.2019.04.016

The circuits that mediate these memory processes involve 2 key areas of the hippocampal formation—the dentate gyrus and the CA3 region. The dentate gyrus implements pattern separation, referring to the encoding of distinctive representations to reduce interference, whereas the CA3 retrieves previous encoding, referred to as pattern completion (Leutgeb et al., 2007; Neunuebel and Knierim, 2014). In age-related cognitive impairment, the performance of these neural circuits is shifted away from pattern separation with augmented pattern completion. Interestingly, in studies of outbred rodents, this aging phenotype is not inevitable, and a substantial proportion of aged cohorts exhibit encoding properties and memory performance on a par with young adults (Wilson et al., 2003). Thus, rodents exhibit individual differences in the effects of aging on memory similar to those observed in the human population.

The molecular mechanisms that underlie aberrant elevated neural activity in aged, impaired animals are not completely understood. However, an analysis of mRNA expression profiles comparing aged unimpaired rats to aged impaired rats showed a relative increase in expression of genes related to GABA signaling in aged animals with preserved memory function (Haberman et al., 2013). Because GABA is one of the primary inhibitory neurotransmitters in the brain, this finding and other recent results support the hypothesis that although elevated excitation is associated with memory loss in aging, an adaptive increase in inhibition contributes to maintenance of memory function (Branch et al., 2019). Indeed, drugs that target signaling pathways to restore excitatory/inhibitory balance may represent a promising avenue for therapy, mimicking an adaptive mechanism associated with successful aging.

Notably, this concept has received some support from studies in humans with age-related memory impairment and in a condition of amnestic mild cognitive impairment in which memory loss is greater than would be expected for an individual's age. The use of functional magnetic resonance imaging (MRI) has revealed overactivation in the DG/CA3 regions of the hippocampal formation associated with memory deficits in those populations (Bakker et al., 2012; Yassa et al., 2011). Therapeutic treatment to reduce the overactivity has also demonstrated cognitive improvement in memory tasks sensitive to the computation functions of pattern separation and pattern completion in memory performance (Bakker et al., 2012, 2015).

3. Aerobic fitness and genetics contribute to resilience in Alzheimer's disease

3.1. Ozioma C. Okonkwo

The risk and severity of Alzheimer's disease (AD) is associated with age and apolipoprotein E (*APOE*) genotype, with older individuals and those homozygous for the ε4 allele at highest risk: 86 percent of ε4 homozygotes will show signs of AD at age 75 years (Corder et al., 1993). Among this high-risk population, however, there is evidence that disease onset and severity can be attenuated by some form of cognitive resilience. We seek to understand the mechanisms of resilience. Physical activity and aerobic exercise may contribute to this resilience in individuals who are older or those who carry one or more copies of the *APOE ε4* allele. In one study, we were particularly interested in the relationship between physical activity, age, and several biomarkers of AD: amyloid-β burden, glucose metabolism, hippocampal volume, and episodic memory. All 4 of these variables are risk factors for the development of AD that are independent of age, although all are more common in the elderly.

We compared these 4 biomarkers in adults who were physically active to those who were physically inactive. Physical activity was defined as 30 minutes of moderate exercise for 5 days each week. Those who were physically active had a relatively steady amyloid burden as they aged from 45 to 75 years, whereas those who were inactive had increased amyloid burden over this period. Similarly, glucose metabolism was relatively constant in active individuals over time and declined in inactive ones. Physically inactive individuals had a greater loss of hippocampal volume over this period compared with those who exercised. Finally, the memory test scores of physically inactive individuals declined more rapidly than those of active individuals (Okonkwo et al., 2014). All of these observations suggest a correlation between physical activity and better biologic and physiologic brain health as individuals age.

We next investigated the influence of known genetic risk factors for AD in individuals who exercised regularly compared with those who did not. Regular physical activity was indexed by cardiorespiratory fitness. Volunteers were genotyped for variants in the *APOE4*, *CLU*, and *ABCA7* genes—all of which are involved in cholesterol metabolism and are thought to play a role in AD susceptibility—to generate a polygenic risk score. Not surprisingly, individuals whose score suggested a higher risk of AD showed lower ratios of amyloid-β_{42} to amyloid-β40, higher ratios of total tau protein to amyloid-β_{42}, and higher ratios of phosphorylated tau to amyloid-β_{42}. When the volunteers were separated into groups by level of habitual physical activity, higher cardiorespiratory fitness attenuated the hazard associated with higher genetic risk scores (Schultz et al., 2017). This observation suggests that physical fitness can attenuate, at least to some degree, the genetic susceptibility to AD.

The precise mechanism through which physical activity and fitness might influence AD risk is not known. It is also unclear whether it is mediated through vascular, neurotrophic, genetic, or epigenetic processes or is a consequence of improved overall fitness. One possible mediator of the beneficial effect of exercise may be the *KLOTHO* gene. Mutations in this gene are associated with aging, and some studies have shown that a life span–extending variant of the human *KLOTHO* gene, *KL-VS*, is associated with enhanced cognition in heterozygous carriers independent of aging and AD pathophysiology (Dubal et al., 2015). Data suggest that individuals who carry one copy of the protective *KLOTHO* gene may be somewhat protected from the risk associated with aging or the *APOE ε4* allele. Preliminary data suggest that physical activity may increase klotho in serum, suggesting a possible mechanism through which physical fitness might have a direct effect on AD neuropathology. Strategies aimed at modulating the effects of the *KLOTHO* gene or enhancing circulating klotho may be a promising avenue for future research.

4. Cognitive resilience in the face of pathology

4.1. Susan M. Resnick

One of the central questions facing researchers who study cognitive decline is understanding how some individuals can maintain cognitive function despite the presence of pathologic lesions in their brains. We have focused on a longitudinal cohort of individuals whose cognitive and physical function have been assessed on a regular basis. We seek to identify potential threats to successful cognitive and brain aging (i.e., the preservation of cognitive function over time); potential modifiers and predictors of successful cognitive aging; and strategies to identify the factors that may preserve cognitive function and promote cognitive resilience in the presence of brain pathology.

Since 1958, the Baltimore Longitudinal Study of Aging (BLSA) has studied normal aging by repeatedly evaluating the same

individuals over time (Shock et al., 1984). A subset of these volunteers—nearly 160 men and women aged 55 years and older who did not have neurologic or severe cardiovascular disease at the time that they enrolled—have undergone regular neuroimaging studies as part of their BLSA evaluations since 1994 (Resnick et al., 2000) and amyloid positron emission tomography (PET) since 2005 (Resnick et al., 2010). In addition, since 2009, MRI assessments were expanded to a larger sample of BLSA participants, with more than 900 participants evaluated to date.

In the BLSA, we have found that one of the more significant threats to successful cognitive aging is being male. Cross-sectionally, men in our study show lower scores on tests of verbal memory and some measures of executive function at a given age compared with women; however, they have higher visuospatial performance. In addition, over time, men show a greater decline in mental status, executive function, and—despite their higher initial scores in this area—a greater rate of decline in visuospatial performance compared with women (McCarrey et al., 2016). Men also show faster total brain volume loss with age in both white and gray matter, as well as faster loss in hippocampal volume.

In addition to male sex, another threat to successful cognitive aging is the presence of an *APOE ε4* allele. Individuals with this AD risk allele have higher amyloid burden overall in their brains and begin accumulating amyloid approximately a decade earlier than noncarriers. However, once amyloid deposition begins, it proceeds at roughly the same rate in cognitively normal individuals. Longitudinal studies show that once an individual crosses a threshold of detectable amyloid accumulation, he or she is fated to continue amyloid accumulation and the amyloid pathology progresses. In addition, amyloid deposition generally proceeds in a consistent way across brain regions in older adults (Bilgel et al., 2016; Resnick et al., 2015).

Personality traits may also play a role in susceptibility to the clinical symptoms associated with AD. BLSA studies of asymptomatic AD (i.e., individuals who are cognitively normal at autopsy despite the presence AD pathology) have shown that these individuals score lower on measures of neuroticism and higher on conscientiousness years before death compared with those who have clinical manifestations of AD (Terracciano et al., 2014). Similarly, higher neuroticism and lower conscientiousness are associated with an increased risk of AD in a meta-analysis of community-dwelling samples (Terracciano et al., 2014).

Other insights into factors that promote cognitive resilience come from the Women's Health Initiative Memory Study. In one report, the Women's Health Initiative Memory Study investigators examined women aged 80 years and older to identify predictors of preserved high cognitive function. As in other studies, cognitive resilience was associated with more years of education, higher income, higher emotional well-being, and higher than average physical function (Goveas et al., 2016). Although absence of the *APOE ε4* AD risk allele was associated with preserved cognitive function compared with cognitive impairment, the *APOE* risk allele was not associated with preserved high cognitive function among those who remained free of cognitive impairment.

Unfortunately, a definitive comprehensive assessment of brain pathology is available only on autopsy. Still there exists a group of clinically asymptomatic individuals whose brains show pathology consistent with AD. In contrast to in vivo associations between higher amyloid PET levels and greater longitudinal decline in verbal memory, individuals with asymptomatic AD do not show accelerated antemortem memory decline. This paradox likely reflects the fact that the in vivo studies include both individuals who will ultimately develop clinical dementia as well as those who will remain asymptomatic during their lifetime (Resnick et al., 2010; Resnick and Sojkova, 2011). A better understanding of the factors that allow these individuals to continue to function at a high level could help researchers identify the factors that contribute to resilience as well as potential interventions to preserve or enhance this cognitive health.

5. Age-related pathology, cognition, and resilience

5.1. William J. Jagust

The current model of AD is that amyloid-β peptide (Aβ) accumulates and aggregates into plaques. Soluble forms of Aβ are associated with synaptic alterations that contribute to cognitive decline. As part of the Aβ pathological cascade, the protein tau becomes hyperphosphorylated, inhibiting its function and leading to the disruption of the neuronal cytoskeleton and the formation of neurofibrillary tangles. In most studies, approximately 30 percent of cognitively normal individuals in their 70s and older have substantial amyloid accumulation in their brains as measured by PET scans. Virtually all individuals who reach 90 years of age have neurofibrillary tangle tau pathology in their brains—with deposition preferentially occurring in specific areas—that are a classic marker of AD (Braak and Braak, 1997; Schöll et al., 2016). Although the amount and location of tau pathology appears to be strongly related to the level and type of cognitive dysfunction, the amount of amyloid pathology is more weakly associated with cognition.

Amyloid deposition generally demonstrates weak associations with cross-sectional measures of cognition such that individuals with higher levels of amyloid deposits in their brains perform more poorly on tests of episodic memory compared with those with lower level (Hedden et al., 2013). However, longitudinal data suggest that both change in cognition over time and change in amyloid over time show closer relationships (Leal et al., 2017). The discordance between cross-sectional data (i.e., snapshots of performance of a group of individuals who have varying levels of AD-like brain pathology at a given point in time) and longitudinal data (i.e., information gathered about specific individuals who are followed up over time) raises questions about the best way to think about the relationship among age, brain pathology, and cognitive function.

In considering the subset of individuals with amyloid deposits in their brain but normal cognition, researchers are seeking to identify a mechanism that might allow the brain to preserve cognitive function in the face of sometimes significant brain pathology. Such a mechanism might provide a biologic basis for the widely observed but poorly understood cognitive compensation, resilience, and reserve exhibited by these individuals.

To investigate this possibility, we conducted a memory encoding test in which volunteers in their mid-70s were shown images and then asked to recall details of the images (Elman et al., 2014). When compared with same-aged adults without Aβ deposition, those with amyloid deposits who were cognitively normal showed reduced deactivation in task-negative (default mode network) regions of their brains but increased activation in task-positive regions, which are typically activated in response to tasks requiring direct attention. In individuals with Aβ deposition, greater activation was associated with more detailed recall of the stimuli. These differences in relative brain activity suggest that Aβ-related hyperactivation may be one way that the brain can compensate in the presence of pathology (Elman et al., 2014).

Individuals who maintain normal cognition despite Aβ accumulation may also show differences in brain structure. A small study of cognitively normal individuals at high risk for developing AD (over age 70 years with either an *APOE ε4* allele or a family history of AD, and positive for amyloid deposition) found that these individuals had more gray matter volume and higher glucose metabolism than individuals at low risk for AD. The "high-risk"

group also scored better than the "low-risk" group on an episodic memory test. However, over time, the cognitive function of the high-risk group declined faster than the low-risk group. This suggests that, despite the anatomic and physiologic features that may protect them from the onset of cognitive decline, these individuals face steep odds when trying to maintain cognitive function.

These data suggest that both Aβ and tau are likely to be related to—and, in some cases, causative of—age-related cognitive decline. However, in the presence of amyloid deposits, both neural compensation and pre-existing neural reserve may confer resilience in these individuals.

According to the Centers for Disease Control and Prevention, the number of Americans aged 90 years and older tripled during the past 30 years, reaching nearly 2 million in 2010 (U.S. Census Bureau, 2011). Although the number of these individual remains small relative to the overall aged population, studies of the very old may yield important insights into the normal aging process and the preservation of cognitive function.

6. Insights from the Dominantly Inherited Alzheimer Network

6.1. Tammie L. S. Benzinger

The Dominantly Inherited Alzheimer Network (DIAN) is a study of more than 400 participants worldwide with autosomal dominantly inherited AD (Bateman et al., 2012; Morris et al., 2012). Participants undergo extensive clinical, cognitive, and biomarker evaluations and are divided into 2 groups: genetic carriers and noncarrier siblings. The course of dominantly inherited AD is predictable, with symptom onset occurring around the same age as it did in the affected parent—typically in the 40s. Although the genes that cause dominantly inherited AD have about 99 percent penetrance, some carriers do exhibit resilience. The mechanisms of resilience remain unknown. Although resilient carriers have normal brain MRI scans and are asymptomatic well past the expected age of onset, they do exhibit many typical signs of AD, including very-high amyloid burden, positive tau PET scans, and hypometabolism as measured with fluorodeoxyglucose PET (Benzinger et al., 2013; Gordon et al., 2018). Through DIAN and other studies, researchers are investigating potential mechanisms of resilience and their implications for predicting, diagnosing, and treating all forms of AD.

7. Discussion

The brain changes over the course of a life span as it encounters new situations, incorporates new information, and adapts to an ever-changing environment. This adaptation continues into old age, even in the face of increasing brain pathology that has the potential to compromise cognitive abilities. The factors that promote resilience despite the presence of AD risk factors remain poorly understood. Efforts to study high-risk yet resilient individuals, such as those under way by the DIAN investigators, are promising but not mature.

Studies of neural firing and pattern formation in rats have shown that the brain seeks to strike a balance between forming new memories based on new experiences and drawing from a reservoir of old memories based on previous, similar experiences. These activities are localized in particular brain regions, and the appropriate sorting of neural signals is predicated on proper functions of the underlying neural processes. In aging rats, this internal routing system sometimes seems to break down, leading to intrusion of older memories into newer ones. Our research suggests that the molecular underpinning of this process may be an imbalance between excitability and signal inhibition in the brains of aging animals. There is some evidence of mitochondrial dysfunction in the development of AD pathology (Lustbader et al., 2004)—suggesting a metabolic component of brain injury—although the precise mechanism connecting the 2 remains a mystery.

Across multiple studies, increased physical fitness seems to be an important protective factor against cognitive decline and AD. This factor is particularly important in midlife or younger, when individuals may be best positioned to incorporate more physical activity into their lifestyles. One implication of this finding is the existence of one or more exercise-induced circulating factors that may be protective against cognitive decline, at least in some individuals. Although it is clear that exercise promotes vascular health, more research is needed to understand the mechanisms by which exercise mediates other AD risk factors.

Once initiated, global levels of amyloid accumulation seem to occur at approximately the same rate in all cognitively normal individuals. This finding suggests that approaches to delay the onset of amyloid accumulation may represent a valid approach to delaying—if not preventing—the development of debilitating cognitive decline. Other studies indicate that individuals who reach the age of 80 years without developing significant amyloid deposits in their brains are likely to retain cognitive function longer, suggesting that approaches to shift the onset of amyloid accumulation to later in life could have a significant impact on cognitive outcomes.

Whatever their early-life or midlife experiences, many individuals will accumulate significant brain pathology (i.e., Aβ deposits and phosphorylated tau protein) as they age. Yet, many of these individuals retain normal cognitive function, perhaps owing to a yet unknown reserve or compensation mechanism. The speakers in Session I sought to define and characterize cognitive reserve in biologic and physiologic terms. They discussed the theorized existence of innate reservoirs of cognitive capacity that can be expanded over the course of a life span to contribute to observed resilience in some individuals. Notably, many different potential concepts of reserve and resilience exist. Multiple concepts may not be mutually exclusive. Nonetheless, determining the mechanisms of cognitive resilience and devising methods to measure reserve and resilience will be a key focus for the field. In this session, participants expanded on these ideas, exploring ways in which these innate abilities might respond to challenges over the course of the life span. The research discussed here suggests that the brain has an ability to rewire its connections—recruiting regions typically involved in different processing activities to contribute to more immediate needs—in an attempt to overcome these insults.

In addition, the chain of molecular events that is thought to cause AD has several stages, each with high variance that may provide multiple opportunities for resilience, which may be mediated by multiple environmental or genetic factors. Although the molecules involved in the development of AD may differ from those involved in normal cognitive aging processes, the concepts of resilience may be common and the mechanisms diverse.

Finally, all studies of older adults face the question of survivor bias: What is the appropriate way to interpret studies of the elderly when those who are most likely to be available for follow-up studies are those who have lived the longest, been the healthiest, have the most robust social support networks, and have the readiest access to health care? Post hoc analyses of data can correct for this bias somewhat, but this remains an issue in the field of longitudinal studies. Nevertheless, a close examination of the changes in cognitive function over time can provide important insights into normal and pathological aging. Careful study of this process may uncover heretofore unknown opportunities to intervene much

earlier in life to prevent the initiation or slow the progression of cognitive aging and decline.

Disclosure

M.G. is the founder of AgeneBio and director of its Board of Directors. M.G. also holds an ownership equity interest in AgeneBio. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies. W.J.J. has served as a consultant to Bioclinica, Biogen, Novartis, and Genentech. T.L.S.B. has investigator-initiated research support from Avid Radiopharmaceuticals (Eli Lilly). In addition, TLSB is part of the Dominantly Inherited Alzheimer Network Trial (DIAN-TU), which is supported in part by corporate partners Eli Lilly, Roche, and Jaansen. TLSB additionally collaborates as a site investigator in clinical trials sponsored by Biogen. All other authors report no conflicts of interest.

Acknowledgements

The authorship order reflects the order of presentations in the session, with the session Chair (P.R.R.) listed last. The Cognitive Aging Summit III was supported by a grant from McKnight Brain Research Foundation, United States to the Foundation for the National Institutes of Health. David Miller, Samuel Thomas, and Nancy Tuvesson of Rose Li and Associates, Inc. provided writing and editorial support for the preparation of this article. The authors gratefully acknowledge our sources of funding: National Institutes of Health, United States grants P01 AG009973 and RC2 AG036419 to MG; National Institutes of Health, United States grants K23 AG045957 and R21 AG051858 to OCO; National Institutes of Health, United States grant R01 AG034570 to WJJ; National Institutes of Health, United States grants R01 AG053267, R01 AG046179, U01 AG042791, and UF1 AG032438 to TB; and in part by the Intramural Research Program of the National Institute on Aging to SMR and PRR.

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