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What are the earlier life contributions to reserve and resilience?

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ABSTRACT

The brain's structures and functions arise from a combination of developmental processes and interaction with environmental experiences, beginning in utero and continuing throughout the lifespan. Broadly, the process that we think of as "successful aging" likely has its foundation in early life and is continuously shaped as life experiences are programmed into the brain in response to a changing environment. Thus, individual lifestyle choices and interventions aimed at increasing cognitive reserve and resilience could change the course of cognitive aging. To determine the relative efficacy of these approaches, we will need to understand how the timing of these interventions (e.g., age, duration, frequency) influences cognitive capacity through the lifespan. Although analysis of age-related changes in cognitive function reveals a general decline at the population level, it has become clear that there is great individual variance in the extent to which cognitive function changes with advanced age. The factors responsible for the individual differences in cognitive decline are unclear, but uncovering them with new analytical tools, epigenetic approaches, and subpopulation studies will provide a roadmap toward enhancing reserve and resilience in the population at large and preserving cognitive function in a greater number of aging individuals.

1. Introduction

One's cognitive reserve capacity may be influenced by factors that impact brain development early in life, as well as by factors experienced during the lifespan. There is evidence that aspects of the intrauterine environment can influence brain growth and wiring at the anatomic and physiologic levels. In adulthood, lifestyle choices and environmental factors also seem to play an important part in the development and stockpiling of reserve. Individuals who exercise their minds and bodies, for example, seem to have a greater reservoir of cognitive reserve and resilience.

Many early-life factors appear to contribute to the accumulation of cognitive ability and reserve. Some of these factors are largely beyond an individual's control (e.g., family socioeconomic status), whereas others are somewhat within an individual's control (e.g., years of education) or largely within an individual's control (e.g., physical activity). These and other early-life factors have been shown in multiple observational studies to associate with cognition and cognitive reserve and resilience later in life, although the mechanisms of their influence remain unknown.

One challenge to interpreting data on early-life influences on later life cognitive function is that many of the variables that correlate with improved cognitive function also correlate with each other. This correlation makes it difficult to identify which factors are causal and thus potential targets for intervention and which are merely correlates or markers of the aging process. Still, characterizing the factors that contribute to an individual's cognitive capacity may provide important insights into strategies to promote the development of cognitive ability early in life and its retention into older age.

Ultimately, one's mental capacity seems to have a significant component that is either genetically influenced or is strongly influenced by the early-life experience, can be measured early in life, and persists to some degree throughout life but may also be amenable to modification through lifestyle choices made over the course of a lifespan. The presentations in this session of the Cognitive Aging Summit III, chaired by Carl Cotman, address these elements of cognitive reserve and resilience. The 4 authors analyze the life factors, including exciting perspectives on developmental

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origins on lifespan changes (Walhovd), the role of diet in protecting the neurovascular unit (Howell), predictors and mechanisms of cognitive aging (Ritchie), and early-life contributions to late-life accumulation of pathological burden (Staff). The discussion includes analyses of the state of the field and future challenges and offers recommendations, such as the development and application of statistical methods to combine data sets and to discover new factors that can maintain and even improve cognitive reserve and resilience in late life.

2. Neurodevelopmental origins of lifespan changes in brain and cognition

2.1. Kristine B. Walhovd

Brain structure and function change continuously over a lifetime; changes observed in late life reflect only part of this process. Many patterns of change that occur during aging are similar to those that occur during development. Although genetic and neurodevelopmental factors undoubtedly influence the brain and cognition, later life factors do as well.

For example, adults who report higher levels of physical activity show less thinning in their prefrontal cortex, suggesting that exercise may preserve brain function (Walhovd et al., 2014). Despite this finding, we cannot conclude that it is especially important to exercise while aging. Even if we could assume a causal link, such results may reflect either a lifetime of accumulated exercise or the fact that individuals who are currently physically active used to be so in childhood, which could be an important factor. Many studies of modifiable risk factors for neurocognitive decline have focused on individuals in late life or sometimes in midlife (Roberts and Petersen, 2014). As brain changes occur across the lifespan, it is reasonable to ask "When does the 'aging' process actually begin?"

We have used quantitative magnetic resonance imaging (MRI) scans to measure cortical thickness and surface area, white and gray matter volume, and other parameters in more than 1000 individuals across a wide range of ages. We have observed consistent patterns for several parameters in the general study population—such as a decline in white matter after midlife—but we have also noted wide variations among individuals, some of which is influenced by behavior or environment. We seek to identify the factors that contribute to this variation and the point during development at which they act.

Aging, in terms of accumulation of changes in brain structure or function over time, starts in the womb. For instance, long-term differences in brain structure and cognitive function observed in children exposed to opioids and other substances in utero suggest that the prenatal uterine environment can have a persistent influence (Nygaard et al., 2015, 2017; Walhovd et al., 2007, 2010, 2012b, 2015). The Helsinki Birth Cohort Study indicates the influence of early-life factors on cognition in adulthood, in that children born a few weeks before their full term (late preterm) showed increased risk of cognitive impairment in late adulthood (Heinonen et al., 2015). We and others have also observed relationships between normal variation in neonatal characteristics (e.g., birth weight) and later brain development in terms of cortical surface area (Raznahan et al., 2012; Walhovd et al., 2012a, 2016). Such relationships may originate both in prenatal environmental and genetic factors. The adult cortex can be divided into regions of shared genetic influence, and changes in cortical thickness during development and aging generally follow this genetic organization (Fjell et al., 2015). Hence, we see a similarity of patterns in development and aging.

Our longitudinal study of nearly 1000 individuals aged 4–88 years identified a broad cortical region where surface area correlated with general cognitive ability. This cortical surface area declined at similar rates over time for those with higher and lower cognitive ability, that is, those categorized as having "high" cognitive ability retained higher cortical surface area over time, compared with the lower half of the sample in terms of cognitive ability, but rates of cortical surface area decline were similar for those with higher and lower cognitive ability (Walhovd et al., 2016). Birth weight was moderately and positively related to extent of cortical surface area of the identified region. The observed cortical surface area trajectories could be part of the neural substrate for the relative stability of cognitive functioning across life. These findings point to neurodevelopmental origins of lifespan changes in brain and cognition.

Cognitive ability, however, is not solely controlled by early-life or genetic factors. In comparing the performance of younger and older adults, in their 20s and 30s, on an episodic memory test, the older adults on average performed worse on the test. After 10 weeks of memory training, however, the performance of the older adults improved on average, with many performing as well as their much younger counterparts during pretraining. We have found that such improvement in memory is accompanied by cortical as well as subcortical and white matter changes in the older adults' brains (de Lange et al., 2016, 2017; Engvig et al., 2010, 2012, 2014).

Together, these data suggest that early-life factors may impact brain and cognition throughout life, but environmental factors may influence brain and cognition also in older adulthood. A key remaining research question is determining the mechanisms by which these early- and later life factors interact to produce the continuum of brain and cognitive function across the lifespan.

3. Protecting the neurovascular unit to promote healthy aging

3.1. Gareth R. Howell

The brain contains a vascular network that supports the complex neural network. The functional interactions between the neurons and the blood vessels, that is, the neurovascular unit, may play an important role in cognitive aging. Because vascular health supports neuronal health, mechanisms that preserve the function of the neurovascular unit may protect cognitive function during aging. We aim to understand the effect of diet-related obesity and vascular dysfunction on cognitive function in the aging brain. This area is of particular importance because the number of individuals older than 65 years and the fraction of the population that is overweight or obese are both steadily increasing.

To study the relationship between aging and obesity, we compared young and aged mice that had been fed a standard diet of regular mouse food pellets with those fed a mouse equivalent of a western diet (i.e., richer in fats and sugars) and looked for physiological and cognitive changes. Not surprisingly, the mice that had been fed a western diet were heavier than the mice fed a standard diet; they also showed signs of persistent inflammation (Graham et al., 2016).

Aging and western diet–induced obesity were correlated with a decline in cognitive function and overall decline in neural and vascular health (Soto et al., 2015). Vascular decline, myelin loss, and cognitive decline were prevented if the animals exercised, even if they did not lose weight. Although obesity itself is associated with many adverse health outcomes, our observation suggests that consumption of a western diet was the primary driver of the observed pathologies, which could be ameliorated by physical activity.

In addition to diet and exercise, genetic predisposition may influence the relative robustness of the vascular system that might be considered as "vascular reserve," potentially predisposing some

individuals to dementias. *APOE* genotype, a well-characterized risk factor for Alzheimer's disease (AD) is also a risk factor for cardiovascular disease, suggesting that neural degeneration and cerebrovascular disease might work together to promote cognitive decline in AD. In mice lacking a functional *APOE* gene, exercise in midlife through old age had little to no effect on age-related neurovascular decline, suggesting that the benefits of exercise may be mediated at least in part through *APOE* (Soto et al., 2016). Experiments are under way to determine genetic factors that control vascular reserve and whether vascular health can be strengthened through activities such as exercise, to reduce the risk of or prevent cognitive impairment.

Ultimately, we aim to identify the mechanisms underlying cognitive and vascular decline in aging, obese mice to translate these findings into interventions in an aging, overweight, human population. Because many individuals begin to gain weight in midlife, future studies will address the best timing for any intervention related to obesity to preserve cognitive function over time.

4. Predictors and mechanisms of cognitive aging: evidence from the Lothian Birth Cohort of 1936

4.1. Stuart J. Ritchie

In 1947, nearly every 11-year-old child in Scotland took a mental aptitude test as part of that year's Scottish Mental Survey (Deary et al., 2009). The children living near Edinburgh were followed up over time and now comprise the Lothian Birth Cohort. Standardized performance data from the cohort's serial cognitive tests have allowed researchers to conduct detailed studies of the stability of intelligence over the lifespan and within older age, the role of genetics in cognitive aging, and epidemiologic factors that correlate with healthy and unhealthy cognitive aging.

Of the original cohort, 1091 individuals completed the initial follow-up cognitive testing at age 70 years; 550 completed cognitive testing at the most recent wave, age 79 years. Interim assessments were conducted at ages 73 and 76 years, at which points around 700 and 500 individuals, respectively, completed MRI brain scans alongside cognitive testing. During follow-up, the researchers assessed study participants in 4 cognitive domains: visuospatial reasoning, reading and verbal fluency ("crystallized" ability), verbal memory, and processing speed. Over time, the average score in all categories declined, but there were wide variations in the individual trajectories. Analyses revealed that 48 percent of the variation in longitudinal changes between individuals across different cognitive tests was shared. This observation suggests that a change in an as-yet-unknown, underlying, general factor may be responsible for nearly half of the change in individuals' broad cognitive performance over time (Ritchie et al., 2016).

Many of the variables that correlate with baseline cognitive level are well known—IQ score at age 11, educational duration, social class as a child and as an adult, and physical fitness, among others—but it is not clear whether these factors correlate with (i.e., predict variance in) subsequent cognitive change (Ritchie et al., 2016). A multivariate analysis of the data showed that most of the variables that correlated with baseline level were not found to correlate independently with change over time, with the exceptions of the *APOE ε4* genotype and physical fitness.

For the subset of volunteers for whom brain MRI data are available, significant variations in brain size were observed among individuals of the same age. Using white matter tractography to generate three-dimensional models of neural networks and architecture in the brain, researchers examined gray matter and healthy white matter volumes, white matter hyperintensity volume, general fractional anisotropy, and general mean diffusivity. Their analysis found that changes in these features were correlated longitudinally with the extent of cognitive decline: as gray matter and healthy white matter volume declined, and as white matter hyperintensity volumes increased, cognitive function declined (Ritchie et al., 2015, 2017).

Finally, there was an attempt to identify factors that might predict changes in brain structure over time. When the MRI data were analyzed alongside predictive data related to cognitive function, a correlation was seen between male sex and deterioration of brain fitness, and a positive correlation was seen between physical activity and preservation of brain health (Ritchie et al., 2017). Because sex is generally a nonmodifiable factor, increasing physical activity and improving fitness may be effective approaches to reduce the risk of future cognitive decline.

In conclusion, multivariate analyses of factors that correlate with cognitive aging find very few variables that are independently associated with cognitive function over time. Among factors that do correlate with cognitive function, those that predict ability at a given time do not necessarily predict its subsequent rate of change. The available data suggest that cognitive aging is likely caused by the accumulation of multiple small influences of a wide range of factors but also that physical fitness appears to be a predictor of both anatomic changes in the aging brain and in cognitive function. Physical exercise is thus an attractive approach for experimental studies aimed at the prevention of cognitive decline.

5. Early life conditions on late-life accumulations of pathological burden and cognitive decline: findings from the Aberdeen Birth Cohorts

5.1. Roger T. Staff

The University of Aberdeen in Scotland has followed up children born in Aberdeen in 1921, 1936, and 1950–1956. These individuals were tested as children for mental ability and then followed up as they aged. Collectively, they comprise the Aberdeen Birth Cohorts and have allowed researchers to explore important questions about health and aging across the lifespan.

To explain cognitive function and resilience over the lifespan, researchers have developed a conceptual model in which there is a tension between protective and risk factors. The balance between protective and risk factors can result in varying degrees of cognitive function and potential decline with age. Although it may be impossible to modify some of these factors, such as genetics, others, such as physical activity, may be easier to address through behavior changes.

Epidemiologic analyses of the Aberdeen Birth Cohort data suggest that some early-life factors are associated with outcomes in later life, such as brain pathology, cognition, and cognitive trajectory during aging (Whalley et al., 2011). These analyses found that childhood socioeconomic status is associated with differences in adult brain anatomy, with children from poorer families having lower hippocampal volume and higher white matter lesion load in later adulthood. These changes were seen even after adjusting for assessed childhood ability, sex, socioeconomic status as an adult, and education level (Murray et al., 2014; Staff et al., 2012).

The mechanistic relationship underling this correlation remains unclear: Does relative hardship early in life lead to differential development of brain function early in life or differential loss of brain function later in life, or both? Support for the former hypothesis is seen in some studies (Noble et al., 2015) of pediatric brain size (Walhovd et al., 2016). Support for the latter hypothesis comes from studies that show that the accumulation of white matter lesions with age is associated with cognitive ability late in

life but not with the rate of cognitive decline (Murray et al., 2012, 2005; Salarirad et al., 2011).

There is also evidence that emotional trauma early in life can lead to increased risk of dementia later in life. Losing a parent before age 11, for example, increases the risk of dementia (Whalley et al., 2013). Children who score low in early-life cognitive tests can, to some degree, overcome this disadvantage, especially if they have more years of education. However, among many variables, childhood mental ability is the primary influence on an individual's later life resilience, defined as cognitive function, physical impairment, and depressive symptoms. These data point toward a complex interplay between genetic and social influences on cognitive function over the lifespan.

6. Discussion

At a population level, we identify general declines in cognitive function with increasing age. At the individual level, however, there is great variance in the extent to which different individuals retain or lose cognitive function. The factors driving these differences remain poorly understood. Some studies suggest that one or a few variables present early in life play an outsize role in an individual's later life cognitive function. Other studies suggest that cognitive aging is influenced by many factors, each of which may be a potential target for intervention.

Differences between individuals likely reflect a complex interaction between genetic predisposition, early-life (including in utero) experiences, behavioral choices made across the lifespan (e.g., exercise and mental stimulation arising from employment or leisure activity), and to some extent avoidance of brain injury. Although researchers have identified many genetic risk factors for AD, most appear to contribute only a relatively small amount to one's risk of developing the condition. Moreover, genetic risk factors are themselves influenced by environmental and lifestyle factors. Thus, it seems likely that individuals can improve the likelihood of a healthy aging process by making healthy choices about diet and exercise, both physical and mental. In particular, numerous studies have shown that increased levels of physical activity are associated with better cognitive outcomes. Although it is not yet possible to say whether physical activity is a causal protective factor against development of AD, there are several plausible potential mechanisms through which exercise might promote brain health, such as improved vascular tone. In this context, exercise studies in animal models can help to identify cause versus effect relationships. Overall, the field would benefit from animal studies that model human early-life contributions to late-life cognitive reserve and resilience. Surprisingly, such studies are few and far between and would add to our knowledge base on early-life contributions to late-life cognition reserve and resilience.

Sex is a significant risk factor for AD: women have a higher risk of developing AD, whereas men have a higher risk of cognitive decline. The biological basis of these differences remains unclear. Other cognitive diseases, such as schizophrenia and Tourette syndrome, also exhibit sex-related differences in prevalence or disease course. Although sex is not a modifiable factor, understanding the underlying biological mechanisms that drive sex-related differences in AD risk and prognosis may point to potential therapeutic strategies.

The Scottish Mental Surveys provide important longitudinal data about the relative stability of mental acuity over time. However, these results must be interpreted with some caution, as there are multiple opportunities for selection or retention bias to influence the data collection, which is probably true of most longitudinal studies of this type. These studies have also shown that individuals who score higher on intelligence tests or have higher socioeconomic status are more likely to volunteer for such studies. In addition, they are also more likely to return for follow-up visits and testing. These factors could skew the results of the surveys and could overstate the degree of resilience in the general population and understate the effects of particular diseases and conditions on cognitive decline. In addition, although the survey data provide evidence on the stability of the relative rank of intelligence across the lifespan, they do not rule out the possibility of environmental influences that may change the mean level of function across the entire group.

Although it is important to exercise caution in the interpretation of these results, there are statistical techniques, such as imputation and simulations, which can help mitigate selection and retention biases. Development of new statistical techniques remains an active area of study and is likely to improve the robustness of results from longitudinal studies in the future.

Taken together, our data provide evidence that cognitive function and reserve vary among individuals. Identifying the factors that influence cognition early in life and that contribute to its maintenance across the lifespan would represent an important step forward in our understanding of cognitive aging.

Disclosure

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