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COMMENTARY

Resilience to aging drives personalized intervention strategies for Alzheimer's disease

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Abstract

There has been little progress in reducing the incidence and mortality of Alzheimer's disease (AD). Prevention of onset, more accurate diagnostic tools, and prediction of health outcomes have all been identified as critical issues, but more and better basic research approaches are needed. The single greatest risk factor associated with AD is aging. It follows that if aging can be delayed, there should be an equivalent delay or even prevention of the onset of AD neuropathology. Therefore, targeting multiple pathways of aging would be a powerful way to enhance resilience to aging and slow or prevent the onset of AD neuropathology and dementia in a personalized manner. More effective and predictive animal models, such as the aging pet cat that spontaneously develops neuropathology similar to human AD patients, are necessary to help validate noninvasive and inexpensive biomarkers for identifying individuals at risk. Resilience to aging and its ability to delay or prevent the onset of age-related diseases should be the focus for preventing brain aging and enhancing resistance to AD.

Keywords: Alzheimer's disease, resilience to aging, brain aging, pet cats and Alzheimer's disease, drug cocktails, geroscience, aging pathways

Alzheimer's disease (AD) is a complex neurodegenerative condition characterized by the onset of amyloid-beta plaques and tau tangle neuropathology and subsequent cognitive impairment. While the understanding of the disease has made progress in recent years, there has not been an increase in the abilities of risk factors and biomarkers to reduce incidence or mortality. A recent article by van der Flier *et al*. proposed that AD should be approached clinically through prevention of onset, more accurate diagnostic tools, and prediction of health outcomes [1]. These goals are correctly identified, but a deeper platform is needed to direct basic research so that clinical and patient aspects can be practically addressed.

The single greatest risk factor associated with AD is aging. Aging is a complex and multifaceted process with multiple contributing pathways. As further research is being conducted, more pathways are being identified [2]. The geroscience concept states that delaying aging and its associated phenotypes should delay the diseases associated with increasing age [3]. It follows that if aging can be delayed, there should be an equivalent delay or even prevention of the onset of AD neuropathology.

Van der Flier makes an excellent point about the importance of lifestyle changes. Individual lifestyle changes have been shown to have effects even at the genetic level [4]. Despite the positive effects these changes can have, an individual's inherent resilience to the onset of aging is incredibly variable and a point of concern. Resilience is defined as the ability to experience stress and quickly return to homeostasis, and is an effective indicator of biological age. Recently, it was shown that by modulating the pathways of aging through a drug cocktail consisting of rapamycin, acarbose, and phenylbutyrate, middle-aged mice were more resilient to the onset of aging phenotypes [5]. Following that study, these mice were found to have reduced cognitive impairment and less brain aging when given the same drug cocktail [6]. In both cases, mice treated with the three-drug cocktail had less severe aging phenotypes than mice treated with any drug individually. With these results, it seems that targeting multiple pathways of aging may be a powerfully effective strategy to slow or prevent the onset of AD neuropathology and dementia.

Additional studies could focus on effective ways to increase resilience to a number of age-related diseases. Van der Flier argues well for personalized medicine. While the ability to create a resilience profile may not be ready for clinical application, the ability to generate pathway knowledge and its effect on various age-related diseases

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may have a compounding effect on treatment development. Ongoing studies are currently determining if resilience can reverse AD neuropathology, further supporting the need for early preventative care. Prevention of brain aging will be reliant on the ability of basic research to generate resilience altering interventions.

One of the challenges in addressing the shortage of diagnostic capability is a suitable translational animal model. Transgenic mice and rats are commonly used, as well as dogs and non-human primates. However, none of these animals develop naturally occurring AD neuropathology similar to human patients. This leads to shortcomings in not only the ability to follow the onset of characteristic phenotypes, but also in the lack of understanding of the underlying pathways responsible for relevant neuropathology. Additionally, assessments for cognitive decline may not be sensitive to the early stages of the disease. This makes the hunt for relevant biomarkers more difficult and unreliable.

The most promising candidate for a model of AD is the domestic cat [7]. Amyloid plaques can be histologically detected in the brain of pet cats as early as 7 years of age [8, 9]. Multiple aggregates of tau can also be detected [10, 11], making the cat unique compared to other non-human mammalian species that do not express tau tangles. Pet cats share the same environment as their owners and are therefore exposed to the same environmental stressors. These pets not only allow for tracking of potential risk factors, but also provide the ability to detect and follow early stages of AD to determine changes in the pathways of aging and validation of biomarkers. Current work is underway to characterize the neuropathology of pet cats to better determine how cats age and the translational viability of intervention testing [12].

Better diagnostic sensitivity needs to be found. Van der Flier points out that by the time cognitive impairment is evident, the neuropathology has developed past the point of reversing the disease. Digital formats for detection of cognitive decline may be helpful in finding it earlier, but again, symptoms may present too late. The most effective way forward will be to use a spontaneous model, such as the pet cat, to study longitudinal data and create translational profiles of biomarker-based cognitive decline in a species with a much shorter lifespan than humans.

Lastly, it is important to consider the prediction of health outcomes and the determination of disease risk. One of the most important aspects of resilience to aging, and a critical consideration for choosing an animal model, is being able to predict health outcomes. Current confirmation of AD is through autopsy after the patient is deceased. Radio-imaging and blood biomarkers are being studied, but can be expensive and sometimes unreliable. It is therefore necessary to find non-invasive and accurate predictors of aging phenotypes. One example is wound healing, which has long been associated with the ability to indicate physical aging. Recent work has shown that a 2 mm ear punch taken in the center of the ear of a middle-aged mouse can be monitored for the amount of wound closure after two weeks [6]. This observation correlates with the DNA methylation clock observed when DNA is isolated from the biopsy core (Ladiges *et al*., unpublished data). These DNA methylation clocks are compared to a bank of many DNA methylation results from the same mouse strain. While DNA methylation assays are still expensive, this type of correlation does warrant further investigation not only for translational impact but ability to serve as a reduced-cost proxy for resilience. A simple skin biopsy is relatively non-invasive, and signatures can be compared with signatures of blood samples collected from the same person, making it possible to evaluate resilience for the purposes of preventive care. Van der Flier makes an excellent point that epigenetics could hold some of the most promising answers. The more valuable aspect of epigenetics could be its correlation with aging. When these types of data sets are correlated with non-invasive assays that measure resilience and health outcomes, drug cocktail diets and personalized aging interventions may be able to be assigned not just to AD, but across the board for age-related diseases.

Clinically, much of the findings of enhancement to resilience to aging and resistance to AD neuropathology are not quite ready for prime time. Van der Flier paints an elegant picture of AD evaluation and treatment, but to reach it, basic science will have to generate effective interventions. Resilience to aging and its ability to delay the onset of age-related diseases should be the focus for preventing brain aging and cognitive impairment. Further diagnostic capability will rely on the use of an appropriate and accurate model, for which this commentary nominates the household pet cat. Simple yet meaningful assays will need to be introduced to follow and evaluate aging at a biochemical level. There is a future for the prevention of AD and other age-related diseases, and it starts with resilience.

Declarations

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