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Brief Commentary

Healthy foods, healthy brain? Mediterranean diet is associated with changes in inflammatory pathways affecting brain and behavior in a monkey model

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In a recent Brain, Behavior, and Immunity publication, Frye et al. (2024) utilize a nonhuman primate model to examine the effects of Western versus Mediterranean-like diets on primate brain and behavior measures. Over the past two decades, the Mediterranean diet has received attention from both the scientific community and general public due to a wide range of potential health benefits. This largely plant-based diet, which is rich in healthy oils, complex carbohydrates, and dietary fiber, has anti-inflammatory properties and has been strongly associated with reductions in cardiovascular disease, obesity, diabetes, and certain cancers (Guasch-Ferré and Willett, 2021). Mounting evidence suggests that adherence to a Mediterranean diet in humans may also be associated with better cognitive performance, slower rates of cognitive decline, and reduced risk of neurodegenerative diseases, including Alzheimer's Disease (AD) (Wu and Sun, 2017). However, it is challenging to establish causal associations based solely on observational studies in humans, and it is not clear which aspects of the diet are driving the potential neuroprotective effects and how other lifestyle factors associated with the diet (i.e., exercise, etc.) might contribute. Moreover, while anti-inflammatory diets, such as the Mediterranean diet, are uniquely positioned to influence inflammatory pathways and aging, the underlying mechanisms are poorly understood (Saavedra et al., 2023).

Preclinical (animal) models provide an opportunity to systematically explore associations between diet, inflammation, and behavior in a controlled environment. Rodent experiments have begun to provide mechanistic insight into the impact of the Mediterranean diet on the gut-microbiome-brain axis (Park et al., 2024) and will continue to provide foundational knowledge that drives the field forward. Although mice and rats are essential for studying conserved biological processes, it is also important to consider the substantial differences between humans and rodents in microbiome, metabolism, immune function and neurocognitive abilities (Perlman, 2016). The choice of which model organism to utilize in any given experiment must ultimately balance many experimental design considerations, including ethical concerns, infrastructure resources, cost, and translational utility. Interventions with high translational potential, such as the Mediterranean diet, may ultimately need to be evaluated in a model system more closely related to humans – the nonhuman primate.

To test the hypothesis that long-term consumption of a Western, compared to Mediterranean, diet may relate to adverse health outcomes, Frye et al. conducted a longitudinal, randomized preclinical trial of 38 socially-housed, middle-aged female long-tailed (a.k.a. cynomolgus) macaques (*Macaca fascicularis*). Also known as crab-eating macaques, cynomolgus macaques in the wild span a broad geographical distribution across Asia, overlapping with human populations and sharing similarities in dietary breadth. Unlike rodents, which last shared a common ancestor with humans $>$ 75 million years ago, old world monkeys, including cynomolgus macaques, last shared a common ancestor with humans 25 million years ago. The resulting genetic, physiologic, immunologic, neurologic, and developmental similarities between macaques and humans provide unique translational opportunities to examine underlying neurobiological mechanisms linking the Mediterranean diet with improved neurobehavioral outcomes (Tarantal et al., 2022). This new paper extends ongoing studies from Shively and colleagues, exploring the hypothesis that long-term Western, compared to Mediterranean, diet consumption is associated with greater psychosocial stress reactivity and adverse health outcomes. Compared to animals fed a Western diet, those fed the Mediterranean diet exhibited enhanced stress resilience, higher microbial diversity in gut microbiome, altered mitochondrial function, and structural brain differences

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(Shively et al., 2023).

Preclinical models allow for highly controlled, comprehensive multisystem investigation, culminating in analyses of postmortem brain and body tissues that are essential for understanding cellular and molecular mechanisms that may underlie complex physiological processes associated with normal and pathological development and aging (Ryan and Bauman, 2022). This new paper provides mechanistic insight by evaluating RNAseq-generated transcriptional profiles in the lateral temporal cortex and their relationships with longitudinal changes in neuroanatomy, circulating monocyte (immune cell) gene expression, and observations of social isolation and anxiety. Diet resulted in differential expression of seven transcripts associated with inflammatory pathways. For example, cyclin dependent kinase 14 (CDK14), a proinflammatory regulator, was lower in the Mediterranean group, while the remaining six transcripts that are generally associated with anti-inflammatory/neuroprotective pathways were enriched in the Mediterranean group. Several of the differentially expressed cortex transcripts were associated with peripheral monocyte transcript levels, neuroanatomical changes determined by MRI, and behavioral outcomes, including social isolation and anxiety. These new findings provide compelling new evidence suggesting that the Mediterranean diet may confer protection against peripheral and central inflammation, which, in turn, impacts brain structure and neurobehavioral outcomes.

Importantly, the study focused on female macaques at middle age, a pivotal time for the early emergence of cognitive impairment and dementia. Despite greater susceptibility of women to some brain disorders, including AD (Livingston et al., 2017), relatively few preclinical studies have focused on female subjects, and women's health in aging remains a critically understudied area. Early developmental alterations can set the stage for lifelong health problems and age-related cognitive decline. Understanding relationships between lifestyle factors, such as diet and long-term health outcomes, is greatly enhanced by studying these variables in a model system more similar to humans in terms of lifespan development and social organization. However, nonhuman primates as research subjects are extremely costly, and it requires years of investment for animals to reach maturity. For practical as well as ethical considerations, there is a critical need to maximally leverage data from ongoing studies in nonhuman primate models. The paper by Frye and colleagues presents an excellent example of how precious tissue resources from nonhuman primate studies can be conscientiously utilized and compared to a wealth of data from these well-studied subjects, toward the goal of minimizing the number of animals required to yield meaningful insights into the neurobiology of healthy aging.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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