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Researchers say genes and vascular risk modify effects of aging on brain and cognition

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Efforts to understand how the aging process affects the brain and cognition have expanded beyond simply comparing younger and older adults.

"Everybody ages differently. By looking at genetic variations and individual differences in markers of vascular health, we begin to understand that preventable factors may affect our chances for successful aging," said Wayne State University psychology doctoral student Andrew Bender, lead author of a study supported by the National Institute on Aging of the National Institutes of Health and now in press in the journal *Neuropsychologia*.

The report, "Age-related Differences in Memory and Executive Functions in Healthy APOE ε4 Carriers: The Contribution of Individual Differences in Prefrontal Volumes and Systolic Blood Pressure," focuses on carriers of the ε4 variant of the apolipoprotein (APOE) gene, present in roughly 25 percent of the population. Compared to those who possess other forms of the APOE gene, carriers of the ε4 allele are at significantly greater risk for Alzheimer's, dementia and cardiovascular disease.

Many studies also have shown that nondemented carriers of the APOE ε4 variant have smaller brain volumes and perform less well on cognitive tests than carriers of other gene variants. Those findings, however, are

not consistent, and a possible explanation may come from examining interactions between the risky genes and other factors, such as markers of cardiovascular health. Prior research in typical samples of older adults has shown that indeed other vascular risk factors — such as elevated cholesterol, hypertension or diabetes — can exacerbate the impact of the APOE ε4 variant on brain and cognition, but it is unclear if such synergy of risks is present in healthy adults.

Thus, Wayne State researchers evaluated a group of volunteers from 19 to 77 years of age who self-reported as exceptionally healthy on a questionnaire that screened for a number of conditions, representing a "best case scenario" of healthy aging. The research project, led by Naftali Raz, Ph.D., professor of psychology and director of the Lifespan Cognitive Neuroscience Research Program at WSU's Institute of Gerontology, tested different cognitive abilities known for their sensitivity to aging and the effects of the APOE ε4 variant. Those abilities include speed of information processing, working memory (holding and manipulating information in one's mind) and episodic memory (memory for events).

Researchers also measured participants' blood pressure, performed genetic testing to determine which APOE variant participants carried, and measured the volumes of several critical brain regions using a high-resolution structural magnetic resonance imaging brain scan. Bender and Raz showed that for older APOE ε4 carriers, even minor increases in systolic blood pressure (the higher of the two numbers that are reported in blood pressure measures) were linked with smaller volumes of the prefrontal cortex and prefrontal white matter, slower speed of information processing, reduced working memory capacity and worse verbal memory. Notably, they said, that pattern was not evident in those who lacked the ε4 gene variant.

The study concludes that the APOE ε4 gene may make its carriers

sensitive to negative effects of relatively subtle elevations in systolic blood pressure, and that the interplay between two risk factors, genetic and physiological, is detrimental to the key brain structures and associated cognitive functions.

"Although genes play a significant role in shaping the effects of age and vascular risk on the brain and cognition, the impact of single genetic variants is relatively small, and there are quite a few of them. Thus, one's aging should not be seen through the lens of one's genetic profile," cautioned the study's authors. They continued, "The negative impact of many genetic variations needs help from other risk factors, and while there isn't much one can do about genes, a lot can be done about vascular risk factors such as blood pressure or cholesterol."

"Everybody should try to keep those in check, although people with certain genetic variants more so than others." Raz said. "Practically speaking, even with the best deck of genetic cards dealt to you, it still makes sense to reduce risk through whatever works: exercise, diet or, if those fail, medication."

Because the study is part of a longitudinal project, he and Bender said the immediate future task now is to determine how the interaction between risky genes and vascular risk factors affect the trajectory of age-related changes — not differences, as in this cross-sectional study — in brain and cognition.

Provided by Wayne State University