Cells' protective DNA linked to size of brain region vital for memory

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(Medical Xpress)—A brain region that is vital for memory and shrinks in Alzheimer's disease patients also is likely to be smaller in those whose white blood cells have shorter DNA-protecting end caps – called telomeres – according to a study by Stanford and UC San Francisco researchers published online July 14, 2014 in the journal *JAMA Neurology*.

If the findings are confirmed in larger studies, the work is likely to fuel research on ways to manipulate cells to prevent aging of the brain and other organs, the researchers said.

UCSF telomere experts and Stanford researchers who specialize in studies of the hippocampus and aging found the link for the first time in humans. Previously, researchers studying mice found that lengthening telomeres can reverse brain aging.

In the new study the researchers studied 47 cognitively and physically healthy women ranging in age from 49 to 66. Nineteen of the 47 carry a gene called APO E4, which is associated with increased Alzheimer's disease risk. The association between telomere length and the size of the hippocampus was greatest among women without the risky APO E4 gene—and for reasons that are unclear—was obscured in the women with APO E4.

According to Emily Jacobs, PhD, the lead author of the study, who analyzed the data as a UCSF postdoctoral fellow, "Our findings highlight

how chromosomal aging is tied to broader aspects of physiological aging, in this case hippocampal volume. These data raise the possibility that leukocyte telomere length may provide an early marker of age-related neurodegeneration."

Previous studies have found that short telomere length in white blood cells predicts cognitive decline, Jacobs said.

Jacobs, now an instructor of psychiatry at Harvard Medical School, led the analysis as a postdoctoral fellow in the laboratory of Elissa Epel, PhD, a professor in the department of psychiatry at UCSF who studies the role of psychological stress in telomere length and chronic disease.

Natalie Rasgon, MD, PhD, professor of psychiatry and behavioral sciences at Stanford, the director of the Stanford Center for Neuroscience in Women's Health and the principal investigator for the new study, leads ongoing research on brain aging, which incorporates non-invasive magnetic resonance imaging to measure hippocampal volume.

While cautioning that this is a small study requiring replication, Rasgon said, "The results are very exciting and thought-provoking. It raises the possibility that we might be able to modulate telomere length to reduce vulnerability to dementia."

Elizabeth Blackburn, PhD, professor of biochemistry and biophysics at UCSF, who shared a Nobel Prize for her discoveries of how telomeres allow chromosomes to be copied in a complete way during cell divisions, and of how they protect chromosomes against degradation, is a study co-author. Jue Lin, PhD, an associate researcher who works in Blackburn's lab, also is a co-author.

Rasgon, Epel, Blackburn, Lin and colleagues intend to expand the

current cross-sectional findings by monitoring telomere and hippocampus status over time.

"The main importance of all of these efforts is for the early detection of vulnerable populations who may go on to develop cognitive decline and dementia," Rasgon said.

According to Epel, "Blood telomere length is a reliable predictor of diseases of aging, and it appears to relate to aspects of brain aging as well. Studies of stress reduction and lifestyle interventions suggest telomere length may be malleable. But it is still a big question as to whether increasing telomere length over time will actually prevent cognitive decline or other aging-related conditions."

The study co-authors, noting that chronic exposure of cells to inflammatory and oxidizing molecules and to glucocorticoid hormones can accelerate telomere shortening and lead to hippocampal atrophy, said it will be important to study cellular mechanisms in more detail to better understand how changes in telomere length—as well as changes in the activity of a telomere-lengthening enzyme called telomerase – either reflect or drive age-related cognitive decline.

More information: Jacobs EG, Epel ES, Lin J, Blackburn EH, Rasgon NL. "Relationship Between Leukocyte Telomere Length, Telomerase Activity, and Hippocampal Volume in Early Aging." *JAMA Neurol.* 2014;71(7):921-923. DOI: 10.1001/jamaneurol.2014.870.

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