

# Telomeres and the brain

– an investigation into the relationships of leukocyte telomere length with functional and structural attributes of the brain

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## Akademisk avhandling

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### **Abstract**

Telomeres are the outermost parts of linear chromosomes. They consist of tandemly repeated non-coding short nucleotide sequences (TTAGGG in all vertebrates), in humans spanning over the last 2 to 15 kilobase pairs of the chromosome. Due to the end-replication problem, telomeres shorten with each cellular division. A critically short telomere will trigger the cell to enter a state of cellular senescence or to apoptose. The rate of telomere shortening can be accelerated by factors such as oxidative stress and inflammation. Taken together, this contributed to making telomere length a candidate biomarker of health and aging. Studies have shown that leukocyte telomere length progressively shortens with age, and that it independent of age is associated with age-related morbidity, lifestyle factors, and mortality. This thesis was aimed at exploring the relationships of leukocyte telomere length with various functional and structural attributes of the brain.

In Paper I, telomere length was shown to be longer among non-demented carriers of the apolipoprotein E (APOE)  $\epsilon 4$  allele, a well-established risk factor for Alzheimer's disease. However, the rate of telomere shortening was greater among the  $\epsilon 4$  carriers, possibly due to the higher levels of oxidative stress and inflammation associated with this allele. Furthermore, performance on episodic memory tests was inversely related to telomere length among  $\epsilon 4$  carriers. The results may contribute to a better understanding of the pathophysiology related to the APOE  $\epsilon 4$  allele.

The volume of the hippocampus, a structure in the brain critical for episodic memory function, was in Paper II found to be inversely related to telomere length among non-demented APOE  $\epsilon 3/\epsilon 3$  carriers. No correlation between hippocampal volume and telomere length was discernible among  $\epsilon 4$  carriers, but they fit the pattern exhibited by the  $\epsilon 3/\epsilon 3$  carriers as they tended to have smaller hippocampi and longer telomere length compared with the  $\epsilon 3/\epsilon 3$  carriers. The results are possibly explained by a low proliferative activity among subjects with smaller hippocampi, which might also explain the inverse association between telomere length and episodic memory performance in Paper I.

In Paper III, we describe results corroborating earlier findings of shorter telomere length among individuals suffering from depression. Moreover, we found that the shorter telomere length among the patients to a large extent could be linked to a hypocortisolemic state; a state which has been associated with chronic stress. The findings corroborate the link between telomere length and stress, and underline the role of stress in depressive illness.

Two prominent manifestations of the aging brain are atrophy and white matter hyperintensities. In Paper IV, we report that white matter hyperintensities and cerebral subcortical atrophy were associated with shorter telomere length in aged non-demented individuals. Cortical atrophy was not associated with telomere length. Inflammation may be the underlying cause of the associations, as it is linked to telomere attrition, subcortical atrophy, and white matter hyperintensities.

Taken together, these results show that leukocyte telomere length has the potential of being used as a biomarker for structural and functional attributes of the brain. Furthermore, the findings can provide new insights into mechanisms of disease and aging of the brain.

### **Keywords**

APOE, aging, atrophy, brain, cognition, cortisol, depression, hippocampus, HPA axis, MRI, stress, telomere length, white matter hyper-intensities.

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