Selective age-related vulnerability in human perirhinal and lateral entorhinal cortices

https://neurodegenerationresearch.eu/survey/selective-age-related-vulnerability-in-human-perirhinal-and-lateral-entorhinal-cortices/

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Research Abstract

DESCRIPTION (provided by applicant): Episodic memory loss is one of the hallmarks of aging and is an important risk factor for dementia. Given the rapid rise in the aging population and the increased prevalence of Alzheimer’s disease (AD), understanding the neural basis of age-

related memory decline is of the utmost importance. The formation of memories is known to depend critically on brain regions within the medial temporal lobes (MTL). Prior aging research has focused on age-related changes in the hippocampus, but changes in extrahippocampal MTL cortices have garnered less attention. These cortices appear to be functionally segregated such that the perirhinal cortex (PRC) is primarily engaged by memory for items or objects, whereas the parahippocampal cortex (PHC) is engaged by memory for spatial configurations or contexts. Animal studies have further demonstrated that that this division of labor extends into the entorhinal cortex (EC), with the lateral portion (LEC) supporting object memory and the medial portion (MEC) supporting spatial memory. We designed a discrimination task taxing both object and spatial memory and used high-resolution functional MRI to not only replicate the dissociation between PRC and PHC, but also critically demonstrated key evidence of a similar object/spatial dissociation between LEC and MEC in humans. Related to these advancements, recent rodent models of neurocognitive aging have identified a selective vulnerability in the PRC/LEC pathway to pathology associated with cognitive decline. The LEC/PRC (transentorhinal) region is also the first to deposit tangle pathology in AD mouse models, which is also clear from postmortem tissue from AD patients (i.e. Braak Stage I). Building on our highly innovative approach to functionally segregate the human PRC/LEC and PHC/MEC networks, we propose a novel series of experiments to characterize the earliest behavioral deficits and functional aberrations in the PRC and LEC in older adults. Furthermore, we intend to probe for specific disruptions in structural connectivity between the hippocampal dentate (DG)/CA3 and upstream PRC/LEC, which project to the DG/CA3 via the lateral perforant path. We have previously reported perforant path degradation in older adults using cutting-edge ultrahigh-resolution diffusion imaging. Here, we will use novel techniques to segment the perforant path into medial and lateral portions and will test the hypothesis that this degradation is more severe in the lateral portion. The proposed project builds on the last five years of work from our lab, which successfully translates decades of animal and computational models to the human aging condition. We have identified aberrant conditions in the DG/CA3 associated with age-related memory loss using multimodal high-resolution MRI techniques. Our proposal here extends this work in an innovative direction both in terms of approach and hypothesis. This project is expected to significantly improve our understanding of the neurobiological bases of memory deficits in aging, and may yield highly selective neural targets for treatments and interventions.

Further information available at:

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