UMEÅ UNIVERSITET

The Architecture of the Aging Brain

Functional Reorganization, Structural Changes, and the Role of Dopamine Receptors

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Akademisk avhandling

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Abstract
Aging is associated with reorganization of functional brain architecture, potentially leading to cognitive decline in older age. However, the mechanisms responsible for alterations in functional brain architecture remain poorly understood. Using a combination of multimodal neuroimaging techniques and advanced statistical analyses in four independent studies, this thesis aims to contribute to our understanding of age-related alterations in functional brain architecture and cognitive decline. *Study I* demonstrated age-related decline in functional brain network segregation in a longitudinal setting. Age-related changes in network segregation were associated with concomitant losses of white matter integrity and domain-general cognitive function. *Study II* tested the hypothesis that older age and lower dopamine D1-receptor (D1DR) availability concomitantly are related to less segregated network structure in older age. The results supported the hypothesis, revealing that greater D1DR availability in older age is associated with a more youth-like functional architecture and greater working memory performance compared to age-matched counterparts with less D1DR. *Study III* further assessed the relationship between D1DR organization and functional architecture. Using a non-linear decomposition method, we demonstrate that the spatial co-expression and distribution of D1DRs are aligned with the principal organization of brain function. Individual differences in D1DR distribution were related to the degree of functional differentiation between unimodal and transmodal cortices. *Study IV* investigated age-related differences in the functional organization of the hippocampus, revealing three overlapping modes of organization. A medial-to-anterior and posterior mode largely corresponded to macroscale cortical organization of connectivity, aligned with local D1DR topography. Older age was associated with less distinct organization of cortico-hippocampal connectivity, and maintenance of youth-like hippocampal organization in older age was related to superior episodic memory function. Collectively, this thesis offers multiple lines of evidence for age-related alterations in functional brain organization, associations with white-matter integrity and cognitive function, in addition to a novel link between functional brain architecture and the D1DR system.

Keywords
brain architecture, functional connectivity, dopamine, aging, cognition, memory, functional magnetic resonance imaging, positron emission tomography, graph theory, Laplacian eigenmapping, gradient

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